

The Evidence for Semaglutide 2.4 mg in Obesity From a Managed Care Perspective

HIGHLIGHTS

- › Increasing Clinical Awareness of Obesity as a Serious, Chronic, Relapsing, and Treatable Disease
- › Patient Well-being and the Clinical and Economic Burdens Associated With Obesity in the United States
- › A Review of Current Guidelines for the Treatment of Obesity
- › Semaglutide 2.4-mg Injection as a Novel Approach for Chronic Weight Management
- › Managed Care Considerations of Weight Management Interventions for Obesity

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The Evidence for Semaglutide 2.4 mg in Obesity From a Managed Care Perspective

OVERVIEW

This supplement to *The American Journal of Managed Care*[®] describes the extensive body of literature on obesity, including current medical understanding of obesity as a serious, chronic, relapsing, and treatable disease associated with high clinical, economic, and patient well-being burdens. Current guidelines for treatment of adults with obesity are summarized, as are the Semaglutide Treatment Effect in People with Obesity (STEP) clinical trials of semaglutide 2.4 mg as a pharmacologic obesity treatment. Finally, opportunities and barriers to achieving clinically impactful weight loss are discussed from a managed care perspective.

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FACULTY

Anastassia Amaro, MD

Associate Professor of Clinical Medicine
Division of Endocrinology, Diabetes
and Metabolism

Medical Director
Penn Metabolic Medicine
University of Pennsylvania
Philadelphia, PA

Marc-André Cornier, MD

Director and Professor of Medicine
Division of Endocrinology, Diabetes
and Metabolic Diseases
Medical University of South Carolina
Charleston, SC

Michael Kaplan, DO

Associate Clinical Professor
Division of Internal Medicine
Division of Preventative Medicine
Stony Brook University Hospital
Stony Brook, NY

Janine Kyrillos, MD

Medical Director
Comprehensive Weight Management
Jefferson Health

Associate Professor of Clinical Medicine
Department of Medicine
Sidney Kimmel Medical College
at Thomas Jefferson University
Philadelphia, PA

Ethan Lazarus, MD

Owner and Physician
Clinical Nutrition Center
Greenwood Village, CO

Senior Clinical Instructor
University of Colorado Anschutz Medical Campus
Denver, CO

Danielle C. Massie, PharmD

Manager, Business Development
Clinical Pharmacy
Moda Health
Portland, OR

Shiara Ortiz-Pujols, MD, MPH

Medical Director of Obesity Medicine
MedExpress/Optum Health Services
Minneapolis, MN

FACULTY DISCLOSURES

These faculty have disclosed the following relevant commercial financial relationships or affiliations in the past 12 months.

Anastassia Amaro, MD

CONSULTANCIES OR PAID ADVISORY BOARDS
Novo Nordisk

GRANTS RECEIVED
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Marc-André Cornier, MD

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LECTURE FEES
Currax Pharmaceuticals, Novo Nordisk

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Increasing Clinical Awareness of Obesity as a Serious, Chronic, Relapsing, and Treatable Disease

Ethan Lazarus, MD; and Shiara Ortiz-Pujols, MD, MPH

Introduction

Understanding of obesity has changed dramatically since the American Medical Association (AMA) recognized it as a disease in 2013.¹ The many associations that have been identified between obesity-related genes and biologic processes highlight its physiologic basis.²⁻⁴ Intrinsic factors that lead to obesity are now meeting with an increasingly obesogenic environment, and obesity can be considered to be a global pandemic.⁵⁻⁷ The latest data from the World Health Organization demonstrate that globally, 13% of adults had obesity in 2016.⁸ This prevalence has almost tripled since 1975.^{7,8} In the United States, approximately 100 million people had obesity in 2016.⁹

As the burdens of this disease grow, so does the need for up-to-date review of clinical guidelines and scholarly research. This first article of the supplement reinforces current medical understanding of obesity as a serious, chronic, relapsing, and treatable disease. In the supplement's second article, Danielle C. Massie, PharmD, and others describe obesity's clinical and economic burden.¹⁰ Marc-André Cornier, MD, summarizes current guidelines for the treatment of adults with obesity in the supplement's third article, and, in the fourth article, Janine Kyrillos, MD, presents a novel anti-obesity medication (AOM) option in semaglutide 2.4-mg injection (Wegovy[®]; Novo Nordisk).^{11,12} Finally, in the fifth article of this supplement, Anastassia Amaro, MD, and colleagues discuss managed care considerations for obesity.¹³ Obesity affects people of all ages. This supplement addresses the management of obesity in adults.

Background on Obesity

Obesity meets AMA criteria for a disease: causing impairment of the normal functioning of part or parts of the body, possessing characteristic signs or symptoms, and leading to harm or morbidity.¹ The disease is associated with dysfunction of the tightly regulated energy homeostasis system, in that an accumulation of excess adipose tissue impairs normal hormonal and metabolic function through endocrine dysfunction; this causes dysregulated adipokine signaling, abnormal endothelial function, infertility, blood pressure elevation, nonalcoholic fatty liver disease, dyslipidemia, and

ABSTRACT

The American Medical Association recognized obesity as a disease in 2013. Obesity is influenced by genetic, environmental, physiologic, behavioral, and sleep factors and is associated with approximately 200 health conditions. Assessed using body mass index, body composition, and evaluation of weight-related complications, obesity is treated with lifestyle interventions, anti-obesity medications, and metabolic and bariatric surgery. The age-adjusted prevalence of overweight and obesity in US adults has increased substantially in the 21st century, from an estimated 56% in 1988-1994 to approximately 73.1% in 2017-2018. Nevertheless, there are substantial barriers to successful obesity treatment in the United States, including inadequate treatment coverage; a lack of acceptance by providers, patients, and employers that obesity is a disease; the perception that treatment is ineffective; and the belief that obesity is a behavioral concern related to a lack of willpower. Obesity is a serious, chronic, relapsing, and treatable disease associated with many related conditions; it requires long-term medical management and multimodal care strategies.

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For author information and disclosures, see end of text.

systemic and adipose tissue inflammation.^{1,14-16} The development of obesity is influenced by a variety of factors, including physiologic factors, genetics, associated health conditions, behavioral factors, race/ethnicity, gender, age, childbearing status, adverse childhood experiences, and social determinants of health including socioeconomic status and the built environment.^{1,15,17-20}

Physiologic factors

Body weight is normally regulated through a complex relationship of genetics, environment, appetite, metabolism, hormones, and energy expenditure.^{14,21,22} One of the main regulators of appetite is the hypothalamus, which coordinates signals from the brain, the peripheral circulation, and the gastrointestinal (GI) tract to regulate energy intake and expenditure.¹⁴ Peptide neurotransmitters in the hypothalamus's arcuate nucleus are associated with appetite; these peptides (ie, neuropeptide, agouti-related peptide, proopiomelanocortin, cocaine- and amphetamine-regulated transcript) induce or inhibit eating.¹⁴ Neurons that express these peptides communicate with signals from all over the body, including mechano- and chemoreceptors, nutrients (eg, glucose, amino acids, and fatty acids), GI peptide hormones (ie, cholecystokinin, ghrelin), hormones (eg, insulin, leptin, and adiponectin), and each other to influence hunger, feeding, and energy expenditure.¹⁴

GI hormones also are involved in appetite regulation. Gut hormones act on digestion and absorption of nutrients through GI motility and secretion.¹⁴ Gut peptides (eg, cholecystokinin, pancreatic polypeptide, peptide YY [PYY], glucagon-like peptide-1 [GLP-1], glucose-dependent insulinotropic polypeptide, oxyntomodulin, ghrelin) influence energy intake.^{14,23} Metabolic adaptations that occur after weight loss may result in increased signals for energy intake due to changes in appetite-regulating hormones.^{21,24} Metabolic adaptations can affect long-term weight loss maintenance; the “set-point” theory of body weight posits that the body has an internal physiologic mechanism to regulate metabolism and maintain body weight within a predetermined, stable range.^{14,24} Such changes may explain why many metabolic and bariatric surgeries, such as sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB), often are so successful at supporting weight loss—such procedures not only mechanically restrict the volume of food intake, but they also change underlying neuroendocrine function.^{14,24} Even bariatric and metabolic surgery, however, do not halt weight gain entirely. In the Longitudinal Assessment of Bariatric Surgery study, US adults who underwent RYGB regained 3.9% (95% CI, 3.4%-4.4%) of their baseline body weight between years 3 and 7 after surgery (at 7 years, 976 patients), and individuals who underwent laparoscopic adjustable gastric banding regained 1.4% (95% CI, 0.4%-2.4%) of baseline body weight during this time (at 7 years, 322 patients).²⁵ Findings from the Swedish Obese Subjects (SOS) study echoed these results—the mean change in body weight from baseline for patients who

underwent gastric bypass, vertical banded gastroplasty, or nonadjustable or adjustable banding decreased by 23% after 2 years, whereas the mean loss in body weight for this group was only 17% after 10 years (at 10 years, 1481 patients).²⁶

Additional hormonal drivers of obesity include both homeostatic (metabolic) and hedonic (nonmetabolic) regulators that manage food intake via a complex interplay between energetic and cognitive influences.²² Leptin, a homeostatic regulator, is a hormone that modulates food intake, energy expenditure, and glucose homeostasis under normal body conditions; in rodents, its disruption can result in severe diabetes.²⁷⁻²⁹ As obesity progresses, circulating levels of leptin increase, as well.^{27,28} Consistent with the hypothesis that disrupted leptin signaling partially underlies obesity, genetic deletion of the leptin receptor in hypothalamic neurons results in severe obesity and diabetes in the rodent model.²⁹ GLP-1 also serves as a homeostatic regulator; it has receptors in the hypothalamus and hindbrain. As a patient loses weight, the GLP-1 concentration decreases, which results in decreased satiety and increased hunger.^{21,30,31} In the presence of these physiologic abnormalities, if the patient has ready access to an energy source, an increase in calories consumed and an increase in weight can follow. Patients who undergo bariatric surgery and still struggle to lose weight report increased subjective hunger and lower satiety levels and have lower circulating PYY and GLP-1 and higher ghrelin levels when compared with postoperative patients who achieve expected weight loss.²⁴

Hormones and microbiota are part of the gut-brain connection, which, through both neural and endocrine routes, bidirectionally communicates nutritional composition and eating patterns between the gut and the brain.³² Metabolic and bariatric surgeries also alter the gut microbiome.²⁴ How microbiota affect metabolic processes in the gut is unknown, but these changes occur rapidly after RYGB and SG surgery, and rodent models suggest that they are crucial in weight loss.²⁴ More information about the gut-brain connection continues to be reported; in turn, the field of obesity treatment is rapidly expanding to seek out new methods to address this connection.³²

Obesity may relate bidirectionally with sleep disturbances, which may impact hormone production.³³ Sleep is implicated in insulin secretion, energy expenditure, and other weight-control pathways. A short sleep duration is associated with low levels of leptin, which decreases satiety, and high levels of ghrelin, which increases hunger.³³ Moreover, people who work outside of normal daytime working schedules may experience shift work-sleep disorder, in which desired sleep-wake schedules do not align with innate sleep-wake circadian rhythms.³³ Shift workers experience a greater frequency of overweight, obesity, and metabolic syndrome than do workers who have a traditional schedule.³³ As such, they are more predisposed to develop pathophysiologic alterations of glucose metabolism, lipid homeostasis, and appetite regulation, and

they may be susceptible to overeating, consuming poor nutrient diets, and having reduced physical activity because of daytime sleepiness.³³ In addition, obesity is a well-established risk factor for such sleep disorders as obstructive sleep apnea, insomnia, and restless leg syndrome.³³

Genetics

Genetic factors can contribute to the development of many diseases, including type 2 diabetes mellitus (T2D), various cancers, cardiovascular disease (CVD), and obesity.³⁴⁻³⁸ These factors also impact body mass index (BMI), a central measure of obesity that is calculated using a person's height and weight (see **Diagnosis and Treatment**). In twin and family studies, genetic factors account for 40% to 70% of interindividual differences in BMI.³⁷ The BMI of identical twins, including those separated at birth, are highly correlated. During childhood, they may be attributed to shared environment; in adulthood, however, nonshared experiences do not explain the continuing similarity.³⁷ The heritability of BMI (BMI-H) is age-related, peaking at 20 years of age, decreasing between the ages of 20 and 55 years, and then gradually increasing again after age 55 years; the BMI-H association increases with the average level of BMI.³⁹ The results of a 2017 study that compared the heritability of BMI across countries at various stages of economic development found that the proportionate increase in a child's BMI, which is associated with the parent's BMI, is approximately constant across countries and populations that are substantively different in epidemiologic terms.⁴⁰ The effect is nearly doubled when both parents are considered, suggesting that obesity is directly related to the process of intergenerational transmission of the disease within families from parents to children.⁴⁰

Furthermore, the results of a 2017 assessment of obesity-related genes found that the pathogenesis of obesity is related to intracellular signaling (eg, G-protein coupled receptors), cholesterol and lipid biology (eg, statin pathways), longevity, metabolism, immune mediators (eg, interleukin 7 [IL-7] signaling), feeding behaviors, cholesterol metabolic processes, glucose and cholesterol homeostasis, regulation of blood pressure, small-molecule metabolic processes, protein binding (including peptide hormone binding), hormone activity, steroid hormone receptor activity, insulin receptor binding, and enzyme binding.⁴¹ In the assessment, after obesity, the conditions most closely identified with the genes studied were noninsulin-dependent T2D, acquired metabolic disease, overnutrition, and disease of glucose metabolism.⁴¹ Most pathways and genes highly linked to obesity were related to insulin production, signaling, or related metabolic functions involving *IGF1*, *IRS1*, and *INS*, suggesting a physiologic link between obesity and diabetes.⁴¹ The many associations between obesity-related genes and biologic processes found in this study reinforce the physiologic complexity of this serious, chronic, relapsing, and treatable disease.²⁻⁴

Associated Health Conditions

Obesity is associated with approximately 200 health conditions, confounding its diagnosis and management.⁴² Massie et al examine this clinical burden in the second article of this series.¹⁰ Examples of weight-related diseases that are either caused or exacerbated by obesity include T2D, CVD, dyslipidemia, hypertension, polycystic ovary syndrome, infertility in women, hypogonadism in men, obstructive sleep apnea, asthma, osteoarthritis, mental depression, gastroesophageal reflux disease, nonalcoholic fatty liver disease, and urinary stress incontinence.¹⁵ In addition, 13 cancers and some infections, metabolic diseases, and obstetric conditions are associated with obesity.^{42,43} Most closely related to obesity is T2D; however, not all persons with overweight or obesity have T2D, and not all persons with T2D have overweight or obesity.¹⁵ Still, obesity can worsen existing insulin resistance and hasten the progression to diabetes.¹⁵

Although the relationship between obesity and CVD is complex, there is an association between overweight/obesity and CVD, with impact on mortality varying as a function of gender, ethnicity, age, and body fat distribution.^{15,44} Cancer also is prevalent in patients with obesity. In 2014, approximately 630,000 patients in the United States were diagnosed with overweight- or obesity-related cancers, capping a growth rate of 7% in the previous 9 years, when rates of cancers not related to obesity declined.⁴³

Another consideration in persons with obesity is the likelihood of weight gain associated with medications used to treat various comorbid conditions, which can lead to treatment nonadherence and worsening of comorbidities and obesity. Commonly used medications associated with weight gain include atypical antipsychotics, antidepressants (especially tricyclic antidepressants, but also serotonin reuptake inhibitors), some anti-epileptics, certain antidiabetic agents (eg, sulfonylureas, thiazolidinediones), glucocorticoids, progestin oral contraceptives, and β -blockers. Further research into the effects of gene variations on drug response (pharmacogenomics) may help optimize the use of AOMs while minimizing medication-induced weight gain.⁴⁵

Environment

Environmental factors that increase the risk for obesity development include, but are not limited to, unavailability of healthy food options, restrictive environmental access to safe physical activity, social isolation, poverty, and allostatic load.²⁰ Amaro et al explore these social determinants of health in the fifth article of this supplement series.¹³ In a statement, the Endocrine Society highlighted that the coupling of modern society's calorie-rich environment and sedentary culture with humans' evolutionary predisposition to conserve body fat represents a condition for widespread obesity.¹⁶

Large-scale economic factors can further promote an obesogenic environment. BMI-H positively correlates both with high

gross domestic product (GDP) per capita and with economic stagnation.³⁹ Food insecurity, advertisements, prices, and presence of food deserts all correlate with childhood obesity.²⁰ International trade agreements are another structural factor. In 1994, signing of the North American Free Trade Agreement increased the availability of soft drinks, processed foods, and meats in Mexico and preceded an obesity epidemic among the population of that country.⁴⁶ Lower financial capacity, as measured with the Economic Hardship Index, is also associated with higher rates of childhood obesity, and economic hardship is correlated with race.²⁰ Lower financial capacity can, for instance, limit access to personal transportation. Such obstacles can combine with limitations of the built environment—such as a lack of public transit and of a safe, walkable distance to grocery stores—to hinder families' access to quality food.²⁰

Environmental factors also influence response and access to anti-obesity treatment, including both lifestyle and medical interventions; starting as early as in childhood, these factors drive health disparities observed with obesity and other chronic diseases.⁴⁷ Moreover, adverse childhood experiences, defined as traumatic or stressful events and unsafe environments that occur in or are present for children under 18 years of age, are associated with the development of obesity in adulthood. The mechanisms by which adverse childhood experiences and obesity interact are not fully understood, but they may include chronic stress, mental health issues, social disruption, socioeconomic status, sleep disorders, and stress-induced overeating along with changes in the gut microbiome.¹⁹

Diagnosis and Treatment

In 2014, the American Heart Association (AHA), the American College of Cardiology (ACC), and The Obesity Society (TOS) published a clinical practice guideline for the management of overweight and obesity in adults.⁴⁸ In 2016, the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) released clinical practice guidelines that incorporated both BMI and weight-related complications into diagnosis and recommended that weight-related complications rather than a universal weight-loss target determine treatment selection.¹⁵ These guidelines represent the most current treatment guidelines for adults with obesity.

Obesity is diagnosed by a BMI measurement of at least 25 kg/m² (patients of Asian descent, ≥ 23 kg/m²) and the presence of 1 or more weight-related complications or a BMI measurement of at least 30 kg/m² (patients of Asian ethnicity, ≥ 25 kg/m²).¹⁵ A BMI of at least 25 kg/m² in any patient should prompt further evaluation, but a BMI of at least 23 kg/m² may prompt evaluation in individuals of South Asian, Southeast Asian, and East Asian ethnicity, as health risks associated with overweight and obesity are typically observed at lower BMIs in this population.^{15,48,49}

Obesity diagnosis should include assessment of both BMI and the degree to which excess adiposity negatively affects an individual patient's health.¹⁵ Age, sex, and body composition (eg, level of hydration, muscular composition) should also be considered.¹⁵ Excess accumulation of body fat is associated with signs and symptoms of obesity that include metabolic abnormalities, joint pain, immobility, sleep apnea, and low self-esteem.¹

The AHA/ACC/TOS guideline recommends that patients with obesity lose at least 5% of their body weight; the AACE/ACE advises a loss of at least 10% of body weight to ameliorate many weight-related conditions.^{15,48} To meet these targets and to simultaneously manage weight-related complications, patients and providers should work together.⁴⁸ A high-intensity lifestyle intervention program (≥ 14 sessions in 6 months) is recommended as the foundation of treatment for overweight or obesity.^{15,48}

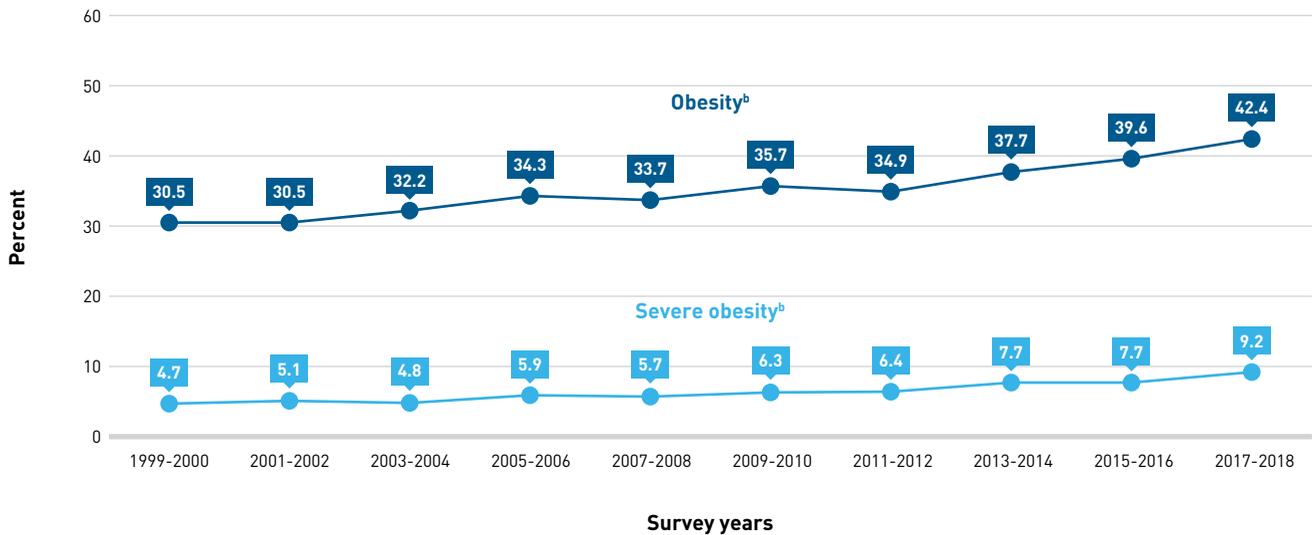
Pharmacotherapy or AOMs can be used with lifestyle modifications to produce greater and more sustained weight loss when compared with lifestyle modifications alone.^{15,48} The AACE/ACE guidelines recommend that this combination be considered for all individuals with a BMI of at least 27 kg/m² if lifestyle therapy fails to halt weight gain and is recommended for individuals with a BMI of at least 27 kg/m² and at least 1 severe weight-related condition.¹⁵

For patients with a BMI of at least 40 kg/m² and for those with at least 1 severe weight-related condition and a BMI of at least 35 kg/m², metabolic and bariatric surgery should also be considered.¹⁵ In patients with obesity, this surgery has led to the greatest weight loss, continuance of weight loss, and amelioration of weight-related complications and to decreased mortality.^{26,48}

Weight loss from lifestyle interventions, medical therapy, and bariatric surgery can effectively treat T2D and hypertension and substantially reduce early mortality, progression of T2D, and risk of CVD and stroke. However, for most patients, lifestyle interventions alone cannot reverse hormonal and metabolic abnormalities that come after weight loss; multiple interventions may be required for patients with obesity to sustain medically meaningful weight loss for the clinically significant period of 12 months or more.^{1,50} In a November 2022 guideline, the American Gastroenterological Association (AGA) emphasized the particular need for medical therapy. In evaluating safety and total body weight loss reported in randomized controlled trials across FDA-approved pharmacologic agents, the AGA guideline authors strongly recommend that an AOM be added to lifestyle intervention for all adults with obesity who have had insufficient response to lifestyle intervention alone.⁵⁰ They add that these agents generally need to be used chronically because of the chronic nature of obesity.⁵⁰ In the third article of this supplement series, Cornier explores the clinical guidelines for both diagnosis and treatment in greater detail.¹¹

The AACE/ACE guidelines do not recommend weight-loss therapy only to prevent cardiovascular events or prolong life in patients

FIGURE. Increasing Trend in Prevalence of Age-Adjusted Obesity and Severe Obesity Among Adults in the United States from 1999-2000 to 2017-2018^{a,54}



^aEstimates were age-adjusted by the direct method to the 2000 United States Census population using the age groups 20-39 years, 40-59 years, and ≥ 60 years.
^bSignificant ($P < 0.05$) linear trend. In this figure, obesity in adults is defined by a body mass index (BMI) ≥ 30 kg/m² and severe obesity by a BMI ≥ 40 kg/m².⁵⁴
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with CVD, but they underscore the need for further investigation.¹⁵ Since publication of the guidelines in 2016, such research has taken place. For example, in an SOS study of the effects of bariatric surgery on mortality and life expectancy in patients with obesity, patients who underwent surgery ($n = 2007$) were 30% less likely to die from CVD than were patients in the control group ($n = 2037$; HR, 0.70 [95% CI, 0.57-0.85]).⁵¹

A lower rate of obesity-related cancer in patients noted among patients who underwent bariatric surgery underscores the relationship between obesity and cancer. A large, retrospective, observational, matched cohort study followed 30,318 patients with obesity in the United States; after 10 years, among 5510 patients, individuals who underwent RYGB or SG ($n = 939$) were 32% (95% CI, 13%-47%) less likely to have obesity-related cancer than were those who received usual care ($n = 4571$).⁵²

Growing Prevalence and Burden of Obesity

Following global trends, the prevalence of this serious medical condition in adults in the United States increased markedly during the 21st century. According to data from the National Health and Nutrition Examination Survey (NHANES), the age-adjusted prevalence of overweight and obesity in US adults rose from an estimated 56% in 1988-1994 to approximately 73.1% in 2017-2018.⁵³ Data gathered in recent years reinforce this trend: the proportion of US adults with obesity increased from 30.5% in 1999-2000 to 39.6%

in 2016 and then to 42.4% in 2018.⁵³ From 1999-2000 to 2017-2018, the prevalence of severe obesity (BMI ≥ 40 kg/m²) increased from 4.7% to 9.2% (Figure).⁵⁴ Weight gain, which propels obesity, also increases with age. A 2022 study using 2011-2018 NHANES data on 13,802 US adults found that the mean 10-year weight gain was 6.6% (SE, $\pm 0.2\%$) of initial body weight.⁵⁵

Trends by patient gender, age, race, and ethnicity show clearly where overweight and obesity most affect American adults.⁵⁴ In particular, patterns for severe obesity illustrate demographic differences. In 2017-2018, women had a significantly higher prevalence of severe obesity (11.5%) than did men (6.9%).⁵⁴ Adults aged 40 to 59 years (11.5%) had the highest prevalence of severe obesity; those aged 20 to 39 years had the next-highest prevalence (9.1%); and adults 60 years and over had the lowest (5.8%).⁵⁴ Non-Hispanic Black adults experienced the highest prevalence of severe obesity (13.8%); non-Hispanic White adults, Hispanic adults, and non-Hispanic Asian adults experienced lower prevalence (9.3%, 7.9%, and 2.0%, respectively).⁵⁴ Trends in weight gain reflect some of these demographic differences. A 2022 study of US adults that used NHANES data reported that women gained 2.4 times more weight over a 10-year period than did men (when considering percentage weight gain); non-Hispanic Black adults had the largest weight gain during this period, and non-Hispanic Asian patients had the smallest weight gain.⁵⁵

The COVID-19 pandemic exacerbated the obesity pandemic. Infection with SARS-CoV-2 is associated with persistent myocardial

injury, worsening control of blood glucose level in T2D, reduced ability to be physically active, increased mental depression and anxiety, and effects on food consumption and purchasing bias; all of these may affect weight and weight control activities.⁶ In turn, obesity increases the risk for mortality, severe morbidity, and lasting COVID-19–related complications among those infected with SARS-CoV-2.^{56,57} The growing prevalence of overweight and obesity in the United States and the association of these medical problems with increased morbidity and mortality underscore the need for clinical intervention.

Clinical, Economic, and Humanistic Burden

Massie et al explore fully the clinical, economic, and humanistic burden of obesity in the second article of this supplement series; however, some highlights are discussed here. The impact of obesity has an enormous effect on health care spending. The direct health care costs of chronic diseases linked to the risk factors of overweight and obesity in 2016 amounted to \$480.7 billion, and indirect costs from lost economic productivity accounted for another \$1.24 trillion. In total, costs associated with chronic diseases related to obesity and overweight totaled \$1.72 trillion, or 9.3% of that year's GDP.^{9,10}

Obesity is associated with a substantial burden apart from physical comorbidities. This burden includes mental disorders, mood disorders, anxiety, and major depression.^{58,59} In both men and women, a bidirectional relationship exists between mental depression and body weight. In people with obesity, symptoms of depression may be caused by their negative body image. Obesity is also a risk factor for a variety of comorbidities (eg, T2D, CVD) associated with the development of depression. In turn, modified eating patterns or reduced physical activity related to depression may impact body weight.⁵⁹ Emotions, stress, and cultural food cues often prompt disordered eating, which occurs frequently in patients with obesity.⁵⁸ Further, obesity negatively affects self-esteem, body image, quality of life, and level of anxiety in social situations, and it can increase exposure to social, educational, employment, and health care stigma and discrimination.⁵⁸

Advancements in National Policy Due to Medical Acceptance

In designating obesity as a disease, the AMA joined several major medical organizations, including the AACE, the ACC, the Endocrine Society, the American Society for Reproductive Medicine, and the American College of Surgeons.^{1,15} As Amaro et al detail in the fifth article of this supplement series, patient, provider, and employer stigma and misperceptions surrounding obesity and lack of treatment coverage pose significant barriers to treatment.¹³ However, several key advancements in policy led to the AMA's 2013 designation of obesity as a disease, which, in itself, led to new and proposed policies supporting those who have obesity or overweight.^{17,60}

The Treat and Reduce Obesity Act is proposed legislation calling for expansion of Medicare coverage of intensive behavioral therapy for people with obesity and coverage of medications used for obesity or weight loss management under Medicare's prescription drug benefit.⁶⁰ Additional strides have been made in reducing social stigma and in increasing legal protections of persons with obesity and overweight. The Equal Employment Opportunity Commission has won court cases involving obesity as a protected disability under the Americans with Disabilities Act, and employment law firms have printed opinions warning employers that discrimination suits could be brought to court for obesity discrimination.¹⁷ These advances show the positive effect of classifying obesity as a chronic disease, yet structural barriers to obesity therapy remain. For example, the US Department of Health and Human Services Healthy People 2030 program acknowledges the need for public health interventions and culturally appropriate programs and policies to foster healthy eating, physical activity, and maintenance of a healthy weight.⁶¹ Strong support from the AMA may bolster national policy. For instance, the AMA recently declared that it would lead a comprehensive initiative to advance the study, prevention, and treatment of obesity and to involve state and national medical societies in this effort.⁶²

Conclusions

That obesity is a serious, chronic, relapsing, and treatable disease associated with multiple comorbidities and requiring long-term medical management underscores the need for multimodal care strategies.^{1,63}

Since development of the 2 comprehensive, US-based guidelines from the AHA/ACC/TOS and AACE/ACE, the management of obesity has changed considerably. Over the few years after critical questions were chosen for the AHA/ACC/TOS guideline, the FDA approved 4 AOMs for the long-term treatment of this disease.^{15,48,64-67} Since publication of the AACE/ACE guidelines, another long-term AOM was approved, an AOM was withdrawn from the market, and several procedures and devices for weight loss were recommended by the American Society for Metabolic and Bariatric Surgery (ASMBS) or became regulated by the FDA.^{64,68-70} Moreover, updated clinical practice recommendations have been provided by organizations such as the Obesity Medicine Association, which updates the Obesity Algorithm and published its inaugural issue of a peer-reviewed, evidence-based journal for clinicians in March 2022.^{4,71} Further, the ASMBS and the International Federation for the Surgery of Obesity and Metabolic Disorders issued a joint statement in November 2022 that broadens the population for whom it recommends metabolic and bariatric surgery.⁷² A need exists for new collaborative guidelines that incorporate recent research and that are inclusive of guidance on current therapies.

Regardless, evidence has shown that lifestyle intervention alone may not be enough to achieve and maintain medically meaningful

weight loss for the clinically significant period of 12 months or more.^{1,50} FDA-approved treatments for chronic weight management have helped affected persons to achieve and sustain significant weight loss and other health benefits.¹⁵ In particular, pharmacotherapy and a multifaceted approach that involves intensive lifestyle/behavioral therapy is effective, and this strategy should be considered for eligible individuals.^{15,73} ■

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Author Affiliations: Clinical Nutrition Center and University of Colorado Anschutz Medical Campus (EL), Greenwood Village and Denver, Colorado; MedExpress/Optum Health Services (SOP), Minneapolis, MN.

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Address Correspondence to: Ethan Lazarus, MD, Clinical Nutrition Center, 5995 Greenwood Plaza Blvd, Ste 150, Greenwood Village, CO 80111. Email: ethanlazarus@gmail.com

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Patient Well-being and the Clinical and Economic Burdens Associated With Obesity in the United States

Danielle C. Massie, PharmD; Anastassia Amaro, MD; and Michael Kaplan, DO

Introduction

The prevalence of obesity among US adults has steadily increased since the late 1970s, growing from 15.0% in 1976-1980 to 42.8% in 2017-2018 among those aged 20 to 74 years.^{1,2} Defined by a body mass index (BMI) of at least 30 kg/m², obesity is the most substantial risk factor for chronic disease in the United States and is associated with nearly 200 related complications.³⁻⁷ The 2016 American Association of Clinical Endocrinology/American College of Endocrinology obesity treatment guidelines clarified that, as part of a larger diagnostic staging process, overweight and obesity should be assessed not just by BMI, but also by measurement of waist circumference, patient examination, and clinical interpretation of weight-related comorbidities.³ In the third article of this supplement, Marc-Andre Cornier, MD, discusses the guideline-recommended evaluation, classification, and treatment of overweight and obesity in adults.⁸ This article explores the patient and health care resource burden of obesity and certain related comorbidities (eg, metabolic disorders, cardiovascular disease [CVD], some cancers) that pose the greatest burden on global health.⁷ The escalating prevalence of obesity may be the precursor for future clinical, well-being, and economic burdens.

Clinical Burden of Obesity

Some of the most notable complications either caused or exacerbated by excess adiposity include type 2 diabetes (T2D), CVD, dyslipidemia, hypertension, polycystic ovary syndrome, female infertility, male hypogonadism, obstructive sleep apnea, asthma, osteoarthritis, depression, gastroesophageal reflux disease, nonalcoholic fatty liver disease, and urinary stress incontinence.³ Although a comprehensive description of the relationships between obesity and the full array of related comorbidities is beyond the scope of this article, the following describes several common and prominent comorbidity clusters that exert a substantial clinical burden upon individuals with obesity.

Cardiometabolic Disease

Cardiometabolic disease describes a group of related cardiovascular and metabolic disorders; these include T2D, dyslipidemia, hypertension, coronary artery disease (CAD), venous thromboembolic

ABSTRACT

Obesity is a serious, progressive, chronic disease that is associated with a spectrum of complications and poor outcomes (eg, premature death, diminished quality of life) and is a risk factor for several other diseases. Obesity increases the risk of developing type 2 diabetes, cardiovascular disease, and certain cancers. More recently, obesity was recognized as a risk factor for poor outcomes in patients with COVID-19. When experienced concurrently with a serious disease, obesity may increase the risk of negative health outcomes. Furthermore, individuals with obesity are more likely to experience social stigma and discrimination at work and in educational and health care settings; these may impact mental and physical health and contribute to increased adiposity. In the United States, the economic burden of obesity is immense—according to estimates, hundreds of billions of dollars are spent annually on direct medical needs and lost productivity associated with obesity. More severe classes of obesity greatly impact both the health of individuals and health care expenditures. As obesity becomes more prevalent, policy makers, health care professionals, and payers must consider its clinical, social, and economic implications.

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disease, and stroke.^{3,9,10} The mechanistic relationships between obesity, insulin resistance, and cardiometabolic disease are not yet fully understood. Still, obesity can be associated with increased insulin resistance, and both obesity and weight gain are associated with poor glucose control in patients with T2D.³ Waist circumference, abdominal obesity, and ectopic adiposity are associated with CVD independent of BMI; furthermore, obesity and increased BMI are associated with overt atherosclerotic lesions, amplified risk of atrial fibrillation, incident CAD, venous thromboembolism, pulmonary embolism, and sudden cardiac death.⁹⁻¹² The risk factors for CVD in obesity function in complex, interrelated, and bidirectional relationships.¹³ For example, the pathophysiologic mechanisms related to development of hypertension via endothelial dysfunction—including inflammation, oxidative stress, and activity of adipokines (ie, cytokines secreted by adipose tissue) and the renin-angiotensin-aldosterone system—also are linked to diseases affecting cardiovascular, cerebrovascular, and renal function, and they can be exacerbated by increases in adiposity.^{3,10,13,14} Excess weight, and particularly visceral adiposity, is the principal cause for 60% to 70% of adult hypertension.³ In addition, abnormal adiposity may induce insulin resistance, which is associated with the cardinal characteristics of dyslipidemia: increased plasma triglyceride, total cholesterol, and low-density lipoprotein (LDL) cholesterol levels and reduced high-density lipoprotein (HDL) cholesterol levels.^{3,9,10}

BMI ranges are used to categorize weight into classes from underweight through class 3 obesity (Table).^{3,4} In a study published in 2015, investigators developed a model from National Health and Nutrition Examination Survey (NHANES) data (2003-2010) to compare estimates of life expectancy in non-Hispanic White US adults; data extracted from US national life tables and the Framingham Heart Study were used to calculate the effects of excess weight by class on loss of healthy life-years (defined as years without CVD or diabetes).¹⁵ Compared with normal weight, excess weight (grouped into overweight, class 1 obesity, and class 2 or 3 obesity categories) had a

clear impact on the number of healthy life-years lost in both men and women, with greater losses seen among younger individuals (Figure 1).^{3,15} For example, among men and women aged 20 to 39 years, those with overweight lost approximately 6 more healthy life-years than did those with normal weight, whereas those with class 1 obesity lost approximately twice that, and those with class 2 or 3 obesity lost approximately 3 times that; this trend continued to a lesser degree among men and women aged 40 to 59 years and 60 to 79 years.¹⁵ In all age groups studied, excess body weight correlated with early development of CVD and T2D. Furthermore, the results showed relationships between BMI class and risk of hypertension; elevated serum glucose, triglyceride, and total and LDL cholesterol levels; and reduced HDL cholesterol levels.¹⁵

A retrospective analysis of cross-sectional data gathered from the 2018 National Health and Wellness Survey (NHWS) investigated correlations between adult obesity and comorbidities derived from a representative random sampling of 69,742 US adults; results showed that patients in higher obesity classes had higher rates of T2D. Rates of T2D were significantly higher among patients with class 3 obesity (25.3%) versus those with class 2 obesity (19.7%), individuals with class 2 obesity versus those with class 1 obesity (15.2%), people with class 1 obesity versus persons with overweight (9.1%), and those with overweight versus individuals of normal weight (3.3%; all comparisons, $P < .05$). The cross-sectional design of the NHWS, the use of bivariate statistics, and the reliance on BMI categories were limitations of this analysis.¹⁶

Cancer

Substantial associations have been established between higher BMI and increased risk of developing certain types of cancer.¹⁷ This pathophysiologic relationship may be explained partially by the association of obesity with a decrease in fat cell precursors maturing into adipocytes, which may indirectly result in increased levels of local and circulating proinflammatory cytokines and proangiogenic factors.¹⁸ A positive feedback loop then occurs, wherein the proinflammatory factors impair adipocyte maturation; this may result in conditions that favor tumor growth, both in the adipose microenvironment and, perhaps, at distant sites.¹⁸ Results of a meta-analysis showed that even a 5-kg/m² increase in BMI was strongly associated with an increased risk of certain cancers, including thyroid and colon cancers in men, endometrial and gallbladder cancers in women, and esophageal adenocarcinoma and renal cancers in both sexes.¹⁹ The highest relative risk (RR) per 5-kg/m² increase in BMI was shown for endometrial cancer in women (RR, 1.59; $P < .0001$) and for esophageal adenocarcinoma in men (RR, 1.52; $P < .0001$) and women (RR, 1.51; $P < .0001$). Another analysis of over 1000 epidemiologic studies found that when compared with individuals with a normal BMI, those with an elevated BMI had a greater risk of certain cancers of the gastric cardia, colon, rectum,

TABLE. Overweight and Obesity Classification by BMI from CDC^{4,a}

BMI range	Weight class
< 18.5 kg/m ²	Underweight
18.5 to < 25 kg/m ²	Normal weight
25.0 to < 30 kg/m ²	Overweight
30 to < 35 kg/m ²	Class 1 obesity
35 to < 40 kg/m ²	Class 2 obesity
≥ 40 kg/m ²	Class 3 obesity

BMI, body mass index.

^aBMI is screening tool, but it does not diagnose excess adiposity or provide a health assessment.

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liver, gallbladder, pancreas, kidney, breast (in postmenopausal women), uterus, ovary, and thyroid, as well as esophageal adenocarcinoma, meningioma, and multiple myeloma.¹⁷ In this analysis, comparison of the risk of cancer development among individuals with class 3 obesity versus those with normal weight showed that the RR was highest for endometrial cancer (RR, 7.1; 95% CI, 6.3-8.1) and esophageal adenocarcinoma (RR, 4.8; 95% CI, 3.0-7.7).¹⁷

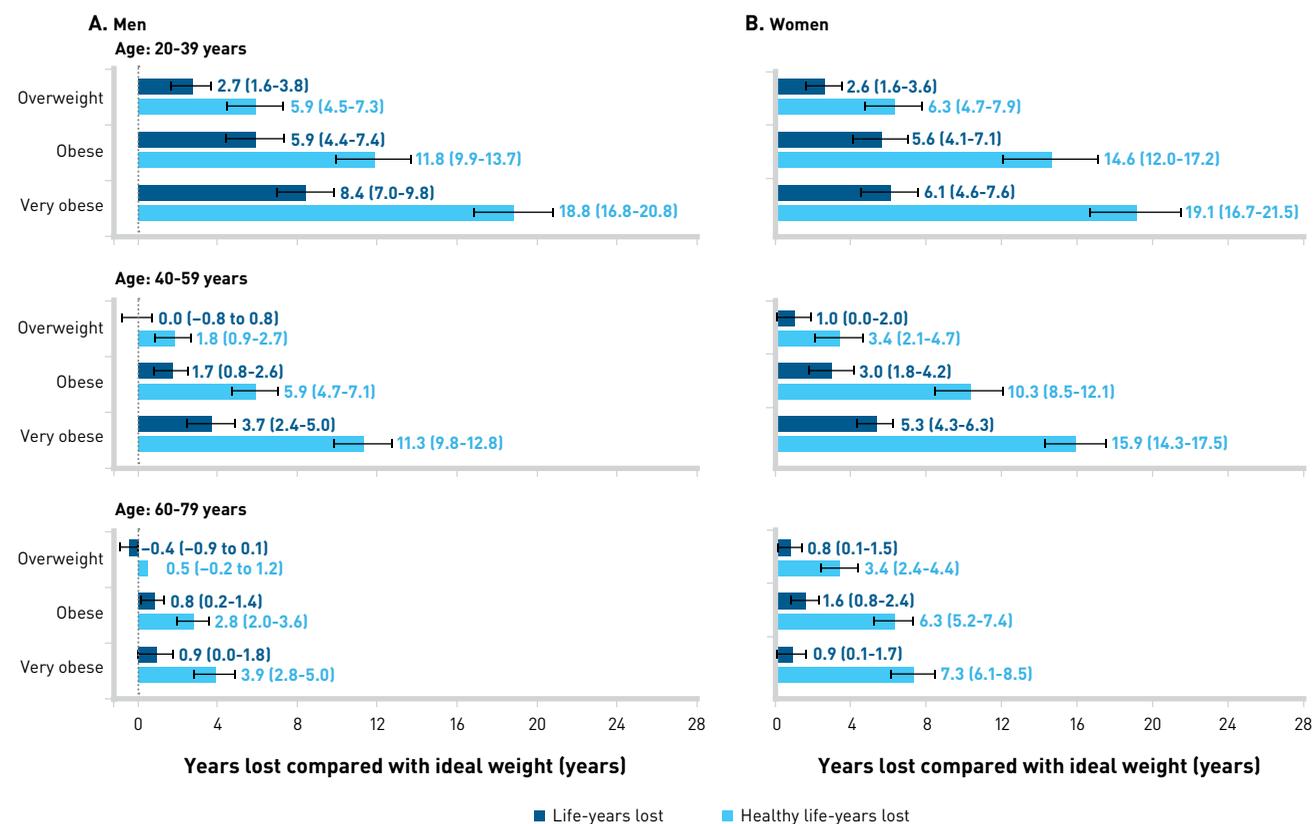
Furthermore, the results of a 2017 report from the Centers for Disease Control and Prevention (CDC) indicated that the prevalence of overweight- and obesity-related cancers (excluding colorectal cancer) increased by 7% among US adults (age, ≥20 years) from 2004 to 2015, whereas the prevalence of cancers not known to be related to overweight or obesity decreased by 13%.²⁰ Analyzed data compiled from the 2005-2014 US Cancer Statistics data set excluded

colorectal cancer due to increased use of screening tests that likely contributed to its steep decline (-23%) over the period. The increase of adiposity-related cancer incidence mirrors the approximate 7% increase in obesity among US adults noted from 2003-2004 (32.2%) to 2015-2016 (39.6%).¹

COVID-19

Obesity has emerged as a significant risk factor for morbidity and mortality among patients with COVID-19, with risk generally increasing in patients with higher BMIs. Investigators from the CDC analyzed the relationship between BMI and COVID-19 outcomes using data from the Premier Healthcare Database Special COVID-19 Release (PHD-SR). The data set included nearly 150,000 patients in US hospitals who were diagnosed with COVID-19 between March

FIGURE 1. Calculated Years of Life Lost and Healthy Life-years Lost in Men (A) and Women (B) Compared With Those With an Ideal Body Weight^{3,15,a,b}



BMI, body mass index.

^aIdeal body weight refers to a BMI of 18.5 to < 25 kg/m²; overweight refers to a BMI of 25 to < 30 kg/m²; obese refers to a BMI of 30 to < 35 kg/m²; very obese refers to a BMI ≥ 35 kg/m². Data based on cardiometabolic risk factors in US adults in the National Health Examinations and Nutrition Survey data from 2003-2010. Error bars show 95% CI for each estimate.

^bThe names of BMI categories represented here differ from those used throughout this article. The "obese" category represents class 1 obesity, and the "very obese" category represents a combination of class 2 and class 3 obesity.

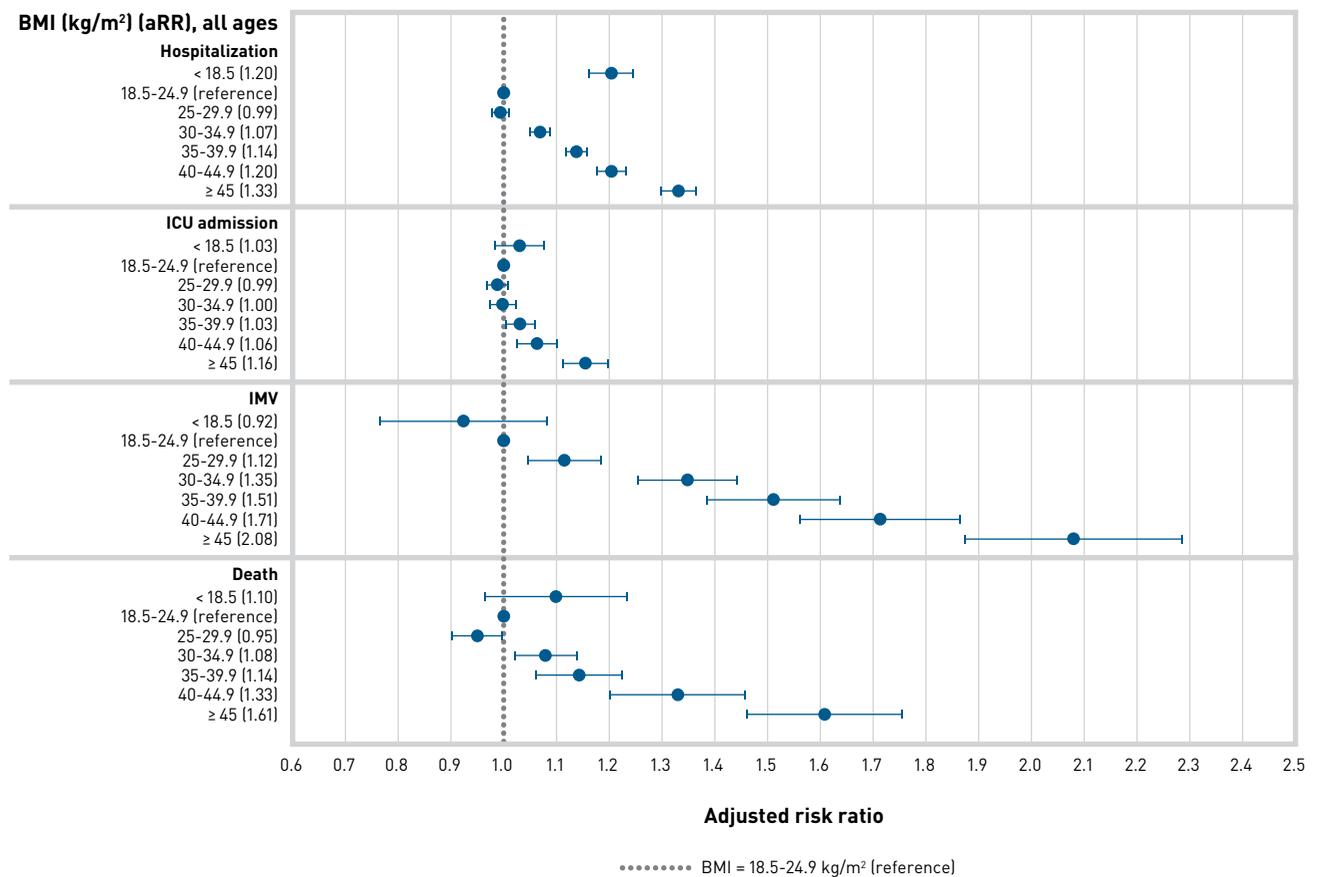
Reprinted from The Lancet Diabetes & Endocrinology, Vol 3/2, Grover SA, Kaouache M, Rempel P, et al., Years of life lost and healthy life-years lost from diabetes and cardiovascular disease in overweight and obese people: a modelling study, Pages No. 14-122, Copyright (2015), with permission from Elsevier.

2020 and December 2020. Obesity was found to be a risk factor for COVID-19 hospitalization, intensive care unit (ICU) admission, and invasive mechanical ventilation; furthermore, risk of hospitalization and death increased with increasing BMI class (Figure 2).²¹ These risk estimates were calculated entirely from adults receiving care at a hospital and may not be generalizable to all adults with COVID-19 or representative of the US patient population as a whole.²¹

A separate retrospective analysis of patients with COVID-19 seen in the Cleveland Clinic Health System between March 11, 2020, and July 30, 2020, reinforced trends seen in the previous CDC analysis relating to increased risk of hospitalization among those within the

highest BMI classes. Among 2839 patients who recovered from acute infection and who did not require ICU admission, those with class 2 or class 3 obesity had a significantly higher risk for hospitalization (HR, 1.28 [95% CI, 1.05-1.56] and HR, 1.30 [95% CI, 1.06-1.59], respectively) compared to patients with normal BMI ($P = .006$), although admission rates of patients with overweight or class 1 obesity versus those with normal BMI were comparable. Notably, during a median follow-up time of 8 months through January 27, 2021, the analysis revealed that patients with obesity had an increased risk for post-acute sequelae of COVID-19 (PASC). The investigators could adjust outcomes by age, sex, race, and smoking status; however, adjustments

FIGURE 2. Association Between BMI and Severe COVID-19–Associated Illness^a Among Adults (Aged ≥ 18 Years) in the United States, March–December 2020^{21,b,c}



aRR, adjusted risk ratio; BMI, body mass index; ICU, intensive care or stepdown unit; IMV, invasive mechanical ventilation; PHD-SR, Premier Healthcare Special COVID-19 Release.

^aIllness requiring hospitalization, ICU admission, or IMV or resulting in death

^bData from the PHD-SR, formerly known as the PHD COVID-19 Database, are released every 2 weeks [release date: March 2, 2021; access date: March 3, 2021].

^cEach panel contains the results of a single logit model, adjusted for BMI category, age, sex, race/ethnicity, payer type, hospital urbanicity, hospital US Census region, and admission month as control variables. Age group (ie, 18-39 [reference], 40-49, 50-64, 65-74, and ≥ 75 years) was used as a control variable. Risk for hospitalization was estimated in the full sample; risk for ICU admission, IMV, and death were estimated in the hospitalized sample. Patients who died without requiring ICU admission or IMV were excluded from the sample when estimating the model with outcome of ICU admission or IMV, respectively.

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according to preexisting medical conditions, laboratory values, and use of pharmacologic agents were precluded by a lack of information. Results of this study were further limited by the retrospective study design, use of electronic medical record (EMR) data from a single health system, and absence of records detailing why patients were hospitalized, underwent diagnostic testing, or died; these events, therefore, could have been unrelated to SARS-CoV-2 infection. Data on mild PASC that did not require diagnostic testing or hospitalization were not captured, nor were data on PASC in patients with asymptomatic COVID-19 who were not tested.²²

Mortality

The relationship between obesity and mortality is multifaceted. Higher BMI correlates with an increased risk for certain leading causes of death (eg, cardiometabolic and cerebrovascular diseases, certain types of cancer) in the United States, and BMI greater than 40 kg/m² can be a risk factor for premature death independent of comorbidities.^{3,13,17,23-25}

This complexity was further demonstrated in a retrospective cohort study which used EMR data from 39,735 adult patients seen at the Mayo Clinic in Rochester, Minnesota, between January 1, 2000, and January 1, 2005 (median follow-up, 9.2 years). The residual mortality risk attributed to BMI showed a U-shaped distribution, in which individuals with very low BMI (< 15 kg/m²) or a very high BMI (\geq 45 kg/m²) had an elevated mortality risk not explained by comorbidities. Although baseline comorbidities were better predictors of mortality risk overall, the independent association between elevated BMI and mortality risk emerged clearly among patients with few or no comorbidities. The possibility of inaccurate or incomplete EMR data and other limitations generally associated with observational retrospective cohort studies should be considered when interpreting these results. Furthermore, data on patient smoking status were limited and nonstandard, so this variable was not considered. Generalizability of results may be limited due to data retrieved from a single medical center and the likely underrepresentation of healthy individuals.²³

The association between BMI and mortality was further explored in the previously discussed modeling study using 2003-2010 NHANES data in non-Hispanic White US adults, which examined not only loss of healthy life-years but also average life expectancy losses due to overweight and obesity.¹⁵ For both men and women, the effect of excess weight on lost life-years was most pronounced among the younger population (those aged 20-39 years), underlining the cumulative effect of obesity on reducing lifespan (Figure 1).^{3,15}

A separate retrospective cohort study examined the relationship between baseline BMI and mortality over more than 30 years of follow-up; results were based upon data from 273,843 patients who underwent health examinations at the Kaiser Foundation Health Plan of Northern California. Patients initially were seen between 1964-1973 or 1978-1985

and were followed through December 2012. In all, 103,218 deaths were recorded over the course of the study. Compared with patients with normal weight, the adjusted odds ratio (OR) for total mortality was 1.14 (95% CI, 1.11-1.17) for those with overweight, 1.49 (95% CI, 1.43-1.55) for those with class 1 obesity, 2.09 (95% CI, 1.93-2.26) for those with class 2 obesity, and 2.70 (95% CI, 2.40-3.03) for those with class 3 obesity was ($P < .001$ for all). Among both men and women, mortality risk progressively increased for patients with class 2 and class 3 obesity when compared with individuals with normal weight. Because this study only used a single baseline measure of BMI and covariates, changes in weight either before or after baseline were not analyzed. Additionally, the study only captured deaths that occurred in California, and it did not examine diabetes, hypertension, or blood lipid measures. Data also were not controlled for certain relevant factors (eg, diet, exercise) that may impact mortality, and the absence of detailed adiposity-related data hindered efforts to account for sex and race disparities.²⁶

The relationships between CVD-associated mortality and 5 factors that included obesity were analyzed in a study using mortality data from the 2000-2015 Surveillance, Epidemiology, and End Results data set; results based on 2012-2015 data revealed greater age-standardized mortality rates due to CVD premature death in US counties having higher rates of obesity.²⁷ The results of another study showed that individuals in higher BMI categories had a greater risk of cardiovascular-related death than did those with normal weight.²⁶ The OR for CVD death was 1.37 ($P < .001$) for those with overweight and 1.99 ($P < .0001$) for those with class 1 obesity. This trend continued among those with class 2 and class 3 obesity. Furthermore, results of The Atherosclerosis Risk in Communities study of 14,941 Black and White men and women (age, 45-64 years) showed that patients with greater BMI experienced a significantly increased risk of sudden cardiac death ($P = .01$).¹¹ Thus, not only may obesity increase the risk of mortality due to CVD, but that risk may be higher among those with more severe obesity.

Current evidence also supports an association between obesity and increased mortality in patients with certain cancers. A meta-analysis of 203 studies from EMBASE, PubMed, and the Cochrane Library from database inception through September 2020 examined the association between obesity and cancer outcomes among adult patients with solid tumors overall and with specific cancer types.²⁵ Compared to those with normal weight, patients with obesity had significant reductions in both overall survival (OS) (HR, 1.14 [95% CI, 1.09-1.19]) and cancer-specific survival (CSS) (HR, 1.17 [95% CI, 1.12-1.23]) (both $P < .001$). Significant reductions in OS related to breast, colorectal, and uterine cancers were noted among patients with obesity (breast: HR, 1.26 [95% CI, 1.2-1.33] and colorectal: HR, 1.22 [95% CI, 1.14-1.31] [both $P < .001$]; uterine: HR, 1.20 [95% CI, 1.04-1.38] [$P = .01$]). Similarly, CSS was decreased in patients with obesity and breast, colorectal, prostate, and pancreatic cancers (breast: HR, 1.23 [95% CI, 1.15-1.32] and colorectal: HR, 1.24 [95%

CI, 1.16-1.32] [both $P < .001$]; prostate: HR, 1.26 [95% CI, 1.08-1.47] and pancreatic: HR, 1.28 [95% CI, 1.05-1.57] [both $P = .01$]). Although obesity was associated with increased mortality only in certain cancers, the overall trends support a link with increased cancer- and noncancer-related deaths. Limitations of the analysis include the heterogeneous designs of studies analyzed and the inability to calculate an effect per BMI unit increase. Across studies, the use of patient self-reported height and weight measurements may have affected the accuracy of BMI data. In addition, data from patients with obesity were compared to the combined data of patients with normal and overweight. Finally, the authors noted that included studies rarely adjusted outcomes based on private insurance status. Obesity can increase costs for cancer treatment and lead to complications. Patients of lower socioeconomic status may have less access to medical facilities and treatments, rehabilitation, or follow-up intensity and, therefore, may experience worse health outcomes.²⁵

Obesity also has been associated with an increased risk of mortality among patients with COVID-19. The CDC study using PHD-SR data observed a positive correlation between BMI category and risk of COVID-19–related death. The adjusted RR for mortality ranged from 1.08 (95% CI, 1.02-1.14) in patients with class 1 obesity to 1.61 (95% CI, 1.47-1.76) in those with a BMI of 45 kg/m² or greater. Notably, when considering only patients younger than 65 years with BMI of 45 kg/m² or greater, the adjusted RR for COVID-19–related death rose to 2.01 (95% CI, 1.72-2.35), indicating the increased mortality risk experienced by younger adults with very high BMI.²¹

Quality of Life and Social Burdens of Obesity

Obesity's association with poor outcomes extends beyond clinical diseases and conditions. Affected individuals may experience weight-related stigma and diminished physical, mental, and social quality of life (QOL) that can impact their well-being.^{16,28-30}

The Awareness, Care, and Treatment in Obesity Management (ACTION) study included an online survey of 3008 US adults with class 1 obesity or higher. Investigators assessed health-related QOL (HRQOL) across obesity classes using 2 different measures. Both measures showed significantly lower HRQOL with increasing obesity class across all measured domains, including physical function, general health, mental health, sexual life, work, self-esteem, public distress, and social functioning (all differences between obesity classes, $P < .05$). Although patients can best share their own experiences related to these domains, the reliance on patient-reported outcomes and use of an online survey methodology may have limited the results of this analysis.²⁹

Similarly, results from the previously discussed study of 2018 data from the NHWS assessed the relationship between BMI and QOL using patient-reported outcomes from 69,742 US adult survey respondents with normal or greater weight. Compared to respondents with normal weight, those with obesity reported lower HRQOL

scores, with the largest reductions in HRQOL seen in mental and physical component scores for patients with class 2 and class 3 obesity. There were significantly lower scores across all domains for patients with class 2 versus class 1 obesity and for individuals with class 3 versus class 2 obesity; domains studied included physical and mental component scores, as well as individual scores for physical functioning, bodily pain, social functioning, mental health, vitality, general health, physical role limitations, and emotional role limitations (all $P < .05$).¹⁶

Stigma

Individuals with overweight and obesity face social stigmatization and discrimination, and they may be burdened by negative stereotypes about behavioral and moral characteristics based on the assumption of complete personal responsibility for excess weight. A consensus statement produced by a multidisciplinary international expert panel addressed the challenges of stigma faced by people with obesity in health care, workplace, and educational settings.³⁰ Health care professionals may hold negative biases regarding obesity that can negatively affect the quality of health care provided to those with excess adiposity. Further, patients with obesity may be less likely to pursue or receive appropriate treatment for obesity or other conditions due to external or internalized weight-based stigma.³⁰ The panel noted that women are more likely to experience weight-based discrimination than are men; furthermore, the consequences of stigma from both external sources and internalized beliefs and attitudes about obesity can combine to negatively impact an individual's self-esteem and mental health and increase the individual's susceptibility to depression, anxiety, stress, and substance abuse.^{30,31} Moreover, individuals in higher BMI classes may face greater prevalence of perceived weight discrimination.³¹ The panel also stated that those who experience this stigma are less likely to engage in physical activity and exercise and are more likely to have unhealthy diets and sedentary behaviors that may increase adiposity, creating a positive feedback loop and compounding the negative effects of weight-based discrimination.³⁰

Economic Burden of Obesity

The high economic burden associated with obesity and related comorbidities represents an outsized proportion of health care costs in the United States. Direct comparisons between studies that seek to assess the direct and indirect costs of obesity are limited by methodological heterogeneity; nonetheless, these studies generally estimate a very large cost burden of excess adiposity and associated diseases to health care systems and society.^{6,32} The following summarizes data from recently published US-based studies.

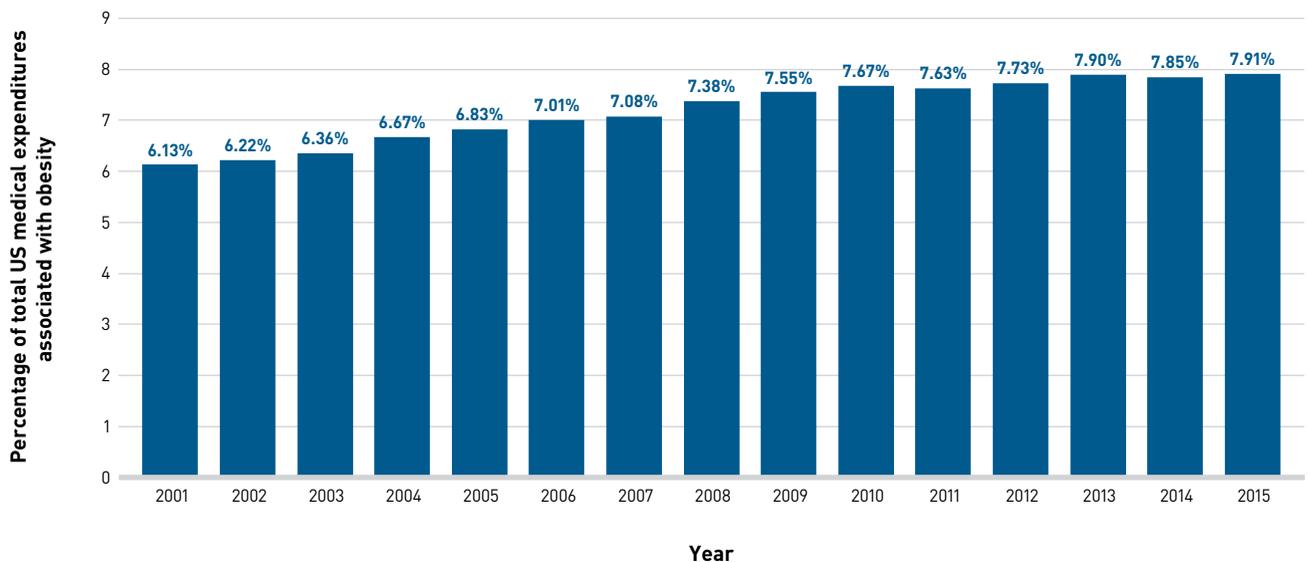
An analysis of medical literature on weight-related costs and data from the Medical Expenditure Panel Survey (MEPS) from the Milken Institute estimated that in 2016, chronic diseases

associated with overweight and obesity caused \$480.7 billion in direct medical costs and \$1.24 trillion in indirect costs (2016 US\$ for both) due to lost economic productivity, representing 47.1% of all direct and indirect chronic disease costs in the United States that year.⁶ The result was a total cost of \$1.72 trillion, or approximately 9.3% of the US gross domestic product in 2016. A separate analysis of 2001-2015 MEPS data sought to determine the proportion of costs correlated with obesity to total US medical costs over time based on medical expenditures (2015 US\$) from 334,297 adults, comparing excess expenditures among those with obesity (n=99,377; 29.7% of sample) versus those of matched controls.³³ A steady and significant increase in the proportion of national medical expenditures associated with people with obesity was observed (6.13% to 7.91%), representing a 29% increase over the 15-year period ($P < .05$) (Figure 3).³³ This followed the gradual increase in the prevalence of obesity seen in the United States over time (2001-2002, 30.5%; 2015-2016, 39.6%).^{1,33} On average, between 2010 and 2015, obesity expenditures accounted for 9.21%, 6.86%, and 8.48% of expenditures for private insurers, Medicare, and Medicaid, respectively.³³ This study's methodology allowed for a correlative, but not causal, determination of costs, although previous analyses indicated that correlative studies consistently underestimate the causal relationship between obesity and medical costs.

In a 2021 study, researchers investigated the causal effects of obesity on direct medical expenditures, employing a 2-part model to correct for both that segment of the population with zero

expenditures and the positive-skewing of those with expenditures (2017 US\$), since a small proportion of the latter group represents an outsized proportion of costs. The study, an analysis of a pooled cross-sectional sample of 2001-2016 MEPS data, only examined adult patients (N = 63,508) with at least 1 biological child to factor in the influence of inheritability of a propensity for weight gain in their analysis. Compared with those with normal weight, adults with obesity experienced a doubling in total annual medical care expenditures (\$2504 vs \$5010), with increases in expenditures of 68% for class 1 obesity (\$1713), 120% for class 2 obesity (\$3005), and 234% for class 3 obesity (\$5850). The incremental cost per unit of BMI was \$201 (90% CI, \$149.37-\$251.89). Persons with obesity experienced increased costs for every category of care—inpatient, outpatient, and prescription drugs—and higher obesity classes were significantly associated with greater expenditures in each category. The largest increases were seen for inpatient care, with class 1 obesity incurring 178% higher costs and class 3 obesity incurring 924% higher costs. Over the study period, total direct costs associated with obesity more than doubled from \$124.2 billion in 2001 to \$260.6 billion in 2016; in 2016, private health insurance paid \$139.4 billion, public health insurance paid \$57.9 billion, while patients paid \$20.0 billion in out-of-pocket costs. The limitations of the study included possible errors associated with assumptions used in the 2-part cost model to predict the causal effect of BMI on medical expenditures; among these assumptions were that child BMI is not correlated with residual parental medical expenditures

FIGURE 3. Trend in Share of Estimated US All-Payer Direct Expenditures Associated With Obesity from 2001-2015^{33,a,b}



^aPercentages significantly different from 0 at all time points ($P < .05$)

^bFor comparability, annual medical expenditures were converted to year 2015 US\$ using the United States Bureau of Labor Statistics Consumer Price Index.

and that the effect of parental BMI on other outcomes does not affect child BMI. Both parts of the model were controlled for a number of variables (including race/ethnicity, gender and age of respondent and child, education level, location, employment and marital status, and health insurance coverage), but the authors acknowledged that BMI is a limited measure of adiposity and that child BMI may have been correlated with unknown factors for which the model could not account. Additionally, generalizability of results were limited by the inclusion criterion that patients have at least 1 biological child, which narrowed the age range of the study population.³⁴

Projecting Future Direct Costs and Health Care Resource Utilization

A 2018 study employed 2000-2012 MEPS data to develop a model for projecting direct medical expenditures through 2025, with the MEPS data being reweighted to match a historical and a projected national population using data from NHANES and the US Census Bureau. The projection model sought to calculate health care use and expenditures (2010 US\$) for different classes of obesity. Total health care expenditures are expected to more than double between 2000 and 2025; they are estimated to increase by 69% in patients with normal weight, 76% in those with class 2 obesity, and 93% in those with class 3 obesity. Use of all health care services except outpatient care is calculated to increase; the number of outpatient visits is projected to rise only among people with class 3 obesity. Patients with normal or overweight show stabilizing or even decreasing trends in use of inpatient and outpatient care, whereas use of nearly all health care services for those with class 2 and 3 obesity are expected to increase over time. Of note, MEPS data depend on self-reported information supplemented with administrative data for many of its results; this may have led to an underestimation of future health care expenditures.³⁵

Indirect Costs

Obesity's economic impact extends beyond direct medical costs. The considerable indirect economic burden of obesity on individuals, employers, and the government must be considered. A study employing a Markov-based microsimulation model that combined 2005-2012 NHANES data and 2008-2012 MEPS data determined the indirect US economic burden arising from obesity through a comparison with normal-weight controls matched by demographic and insurance type. Over a 10-year time horizon, the per-person estimated indirect burden of obesity included \$6800 in lost income due to lack of labor force participation; \$17,100 in lower earnings despite labor force participation; \$2200 in lost productivity to employers due to work absenteeism; and an additional \$1300 in Supplemental Security Income (SSI) payments received (2013 US\$). Furthermore, indirect costs due to loss of personal income, lower earnings, and SSI payments increased with increasing BMI class.

The model made assumptions using data from multiple sources due to the lack of a single longitudinal data source with a large enough population over time; in addition, confidence intervals could not be calculated, because certain data applied to the model either lacked standard error data or were inherently subjective.³⁶

The results of a separate study indicated that absenteeism and productivity losses rose with increasing classes of obesity. Investigators employed a 2-part instrumental variables model (including only patients with a biological child in the household) that applied 2001-2016 MEPS data from 50,789 employed adults (age, 20-65 years) to estimate the dollar value of lost productivity due to job absenteeism. Workers with normal weight lost an average of 2.34 days per year; annual absenteeism was 2.07 days higher (88.5%) in people with class 1 obesity, 3.67 days higher (156.8%) in those with class 2 obesity, and 7.13 days (304.7%) higher in those with class 3 obesity, averaging 3.0 workdays of job absenteeism annually associated with obesity. Furthermore, each additional unit of BMI was associated with 0.24 extra days/year of missed work. Per-worker annual productivity losses also increased with BMI category, ranging from \$186.65 to \$373.31 for those with class 1 obesity, to \$331.66 to \$663.32 for individuals with class 2 obesity, and \$643.27 to \$1286.54 for those with class 3 obesity. On a national level, obesity may have accounted for productivity losses in the billions of dollars, with aggregate losses increasing over the study period. The study's limitations related both to its use of a model for which validity cannot be proven and to its exclusion of those who did not have a biological child living at home, which narrowed the study population and possibly limited the generalizability of results. Further, the model could only account for employed individuals and did not consider presenteeism costs; in addition, BMI estimates were calculated from self-reported data, and authors acknowledged that BMI itself does not directly measure fat or body composition.³⁷

Conclusions

The effects of obesity and weight-related comorbidities in the United States are considerable and multifaceted. Patients with overweight and obesity may experience a higher risk of morbidity and mortality, decreased QOL, and increased stigma and discrimination. Furthermore, obesity and related comorbidities are associated with substantial medical and indirect costs at the individual and national level, and these costs may rise with increasing BMI. The growing prevalence of overweight and obesity in the United States and the increase in health care resources that may be required to meet the needs of patients create an urgent problem. Providers, health care decision makers, and payers should consider this important population health issue and ensure the continuation or implementation of plans and programs to support diagnosis and appropriate treatment for those with excess adiposity. ■

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Author Affiliations: Moda Health (DCM), Portland, Oregon; University of Pennsylvania (AA) Philadelphia, PA; Stony Brook University Hospital (MK), Stony Brook, NY.

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Authorship Information: Concept and design (DCM, AA, MK); analysis and interpretation of data (AA); drafting of the manuscript (DCM, MK); and critical revision of the manuscript for important intellectual content (DCM, AA, MK).

Address Correspondence to: Danielle C. Massie, PharmD, Moda Health, 601 SW 2nd Ave, Portland, OR 97204. Email: danielle.massie@modahealth.com

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A Review of Current Guidelines for the Treatment of Obesity

Marc-André Cornier, MD

Introduction

In 2013, the American Medical Association (AMA) designated obesity as a chronic disease.¹ In 2014, the American College of Cardiology (ACC), the American Heart Association (AHA), and The Obesity Society (TOS) published clinical practice guidelines for the management of overweight and obesity in adults.² In 2016, the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published evidence-based clinical practice guidelines that built upon the AMA's designation, the AACE's novel diagnostic paradigm that incorporated both body mass index (BMI) and weight-related complications, and the AACE's framework that suggested that weight-related complications rather than a universal weight-loss target determine treatment modality selection.³ These 2 comprehensive documents remain the most accepted guidelines for the treatment of obesity.

However, much has changed since the development of these 2 guidelines. After the critical questions of the ACC/AHA/TOS guideline were chosen and before the AACE/ACE guidelines were published, the FDA approved 4 new medications for the long-term treatment of obesity.²⁻⁷ Further, since publication of the AACE/ACE guidelines, another long-term anti-obesity medication (AOM) was approved, an AOM was withdrawn from the market, and several procedures and device types for weight loss and weight management were recommended or FDA-approved.^{4,8-11} These guidelines remain cornerstones for treatment for obesity. However, since their publication, input from the Centers for Disease Control and Prevention and several professional organizations—including the Endocrine Society, the National Institute of Diabetes and Digestive and Kidney Diseases, the American Society for Metabolic & Bariatric Surgery (ASMBS), the Obesity Medicine Association, and the American Society of Anesthesiologists—have advanced our understanding of the disease.¹²⁻¹⁴

This article summarizes and synthesizes the 2013 ACC/AHA/TOS guideline and the 2016 AACE/ACE guidelines and supplements that foundation with recent guidance from the aforementioned organizations. It also highlights consensus that obesity is a serious, progressive, and chronic disease.^{2,15,16}

ABSTRACT

Two guidelines—one by the American College of Cardiology (ACC)/American Heart Association (AHA)/The Obesity Society (TOS), and the other by the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE)—remain the standard of care in the management of overweight and obesity in adults. However, since the publication of the ACC/AHA/TOS document, several relevant pharmacotherapies have been approved by the FDA, a medication was withdrawn from the market, and several procedures and device types for weight loss have been recommended or FDA-approved. Simultaneously, research in obesity treatment has advanced, and leaders in the field have issued complementary guidance. This article summarizes and synthesizes the 2013 ACC/AHA/TOS and the 2016 AACE/ACE guidelines and includes updates from more recent professional association guidance. Measurement of body mass index is recommended to initiate evaluation for overweight and obesity and determine disease classification. To stage disease severity, weight-related conditions should be assessed. Although lifestyle therapy remains the cornerstone of treatment for this disease, both pharmacotherapy and metabolic and bariatric surgery produce greater and more sustained weight loss in treatment-approved populations as compared with lifestyle modifications alone. An ongoing partnership between the patient and clinician is highly recommended to manage this serious, progressive, chronic disease.

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For author information and disclosures, see end of text.

Screening and Diagnosis

Both guidelines recommend that all adults be screened annually using a body mass index (BMI) measurement (body weight [kg]/height [m²]) to initiate evaluation for overweight and obesity.^{2,3} The guidelines recommend that although a BMI of at least 25 kg/m² in any patient prompts further evaluation, a BMI of at least 23 kg/m² may herald the need for such evaluation in patients of South Asian, Southeast Asian, and East Asian genetic heredity, as health risks associated with overweight and obesity typically are observed at lower BMIs in these populations.^{2,3,17}

To diagnose obesity, both measurement of BMI and clinical assessment of weight-related complications are recommended.³ A BMI of 30 kg/m² to 34.9 kg/m² defines class 1 obesity, of between 35 kg/m² and 39.9 kg/m² constitutes class 2 obesity, and of at least 40 kg/m² marks class 3 obesity (Table 1).^{2,3,12} However, age, sex, level of hydration, muscular composition, presence of fluid in noncirculatory (“third”) space, and presence of sarcopenia, edema, and high-volume tumors all should be considered before a classification is made.³ Classes 1, 2, and 3 are sometimes referred to as mild, moderate, and severe obesity, respectively.^{12,18-20} The AACE/ACE guidelines use these classes to indicate that a patient is at moderate, severe, or very severe risk of weight-related disease.³

Waist circumference also should be considered in patients having a BMI of 25 kg/m² to 35 kg/m². Waist circumferences of at least 102 cm (approximately 40 in.) in men and of at least 88 cm (approximately 35 in.) in women indicate abdominal obesity, which is associated with increased risk for adiposity-related disease.^{2,3} Lower thresholds (eg, ≥94 cm [≈37 in.] in men and ≥80 cm [≈32 in.] in women) are used outside of the United States; consideration of ethnicity and use of region-specific thresholds also may be used to measure disease risk.^{2,3} For instance, in patients of South Asian, Southeast Asian, and East Asian heredity, waist circumference of at least 85 cm (≈34 in) in men and at least 74 cm to 80 cm (29-32 in.) in women should be used to identify abdominal obesity.^{3,17}

Clinical Assessment of Weight-Related Complications

Patients with overweight or obesity should be screened for prediabetes, type 2 diabetes mellitus (T2D), dyslipidemia, hypertension, metabolic syndrome, cardiovascular disease, nonalcoholic fatty liver disease, osteoarthritis, and mental depression. These patients also should be evaluated for obstructive sleep apnea, asthma and reactive airway disease, and gastroesophageal reflux disease (Table 2).^{2,3}

Women with overweight or obesity should be screened for urinary incontinence, and those who are premenopausal should be screened for reproductive abnormalities (eg, polycystic ovary syndrome). When suitable, women with overweight or obesity also should be advised of their heightened risk of infertility and of the lower success rates for assisted reproduction; a large body of

evidence also correlates higher BMI with gestational diabetes and other obstetric and fetal complications.^{3,21} Men with obesity or an elevated waist circumference should be assessed for hypogonadism.³

Establishing Prevention and Treatment Targets

Measuring weight, assessing lifestyle, and taking a thorough and accurate medical history are key to assessing risk for overweight or obesity, determining whether and to what effect comprehensive lifestyle intervention and/or adjunctive therapies have been used, and evaluating therapeutic options.^{2,3} Patients with normal (healthy) weight (BMI, 18.5 to <25 kg/m²) should be counseled on the health benefits of avoiding weight gain.^{2,12} Patients whose genetics, biomarkers, family history, ethnicity, cultural practices, or individual behaviors put them at high risk for overweight or obesity should be counseled to avoid weight gain and educated in healthy meal planning and physical activity.³

The presence and extent of weight-related complications should be evaluated among those with a BMI of at least 25 kg/m² to establish prevention and treatment targets for each patient.^{2,3} Like the Edmonton Obesity Staging System, which incorporates weight-related complications into its staging of the disease, the AACE/ACE guidelines stage overweight and obesity based upon BMI and the presence, extent, and severity of these complications (Table 2).^{3,22} The treatment targets for patients with overweight stage 0 are to avoid additional weight gain or to lose weight and prevent both progression to obesity and development of complications.^{2,3}

According to the ACC/AHA/TOS, patients with obesity should be assessed for their readiness to make lifestyle changes.² Those who are ready should formulate with a clinician weight loss goals and complementary lifestyle treatment strategies.² The recommended therapeutic targets for patients with obesity stage 0 are weight loss or prevention of additional weight gain coupled with prevention of complications.^{2,3} For patients with obesity stage 1 or obesity stage 2, weight loss is recommended; however, the AACE/ACE guidelines set complication-specific treatment targets (each of which includes weight loss and other clinical outcomes), whereas the ACC/AHA/TOS guideline recommends determining weight-loss

TABLE 1. Classification of Obesity by BMI in Adult Patients^{2,3,12}

BMI, ^a (kg/m ²)	Classification
18.5-24.9	Normal weight
25-29.9	Overweight
30-34.9	Class 1 obesity
35-39.9	Class 2 obesity
≥ 40	Class 3 obesity

BMI, body mass index.

^aBMI values are not dependent upon age or sex. Values may not correspond to the same amount of adiposity in different populations, including certain ethnic groups (specifically, South Asian, Southeast Asian, and East Asian adults).

goals in collaboration with the patient rather than according to weight-related complication.^{2,3}

To prevent the progression, or lower the burden, of weight-related complications, both guidelines recommend that patients with obesity stage 1 or stage 2 lose at least 5% of their body weight; the AACE/ACE guidelines recommend a loss of at least 10% of body weight for many complication-specific targets.^{2,3} Because early weight loss helps predict sustained weight reduction, the AACE/ACE recommend targeting 2.5% weight loss within 1 month for all patients with

overweight or obesity.³ The ACC/AHA/TOS guideline recommends that all patients with overweight or obesity achieve the realistic and meaningful goal of 5% to 10% weight loss within 6 months.²

Treatment

Managing obesity requires the ongoing partnership of a committed patient and informed clinicians.² In patients given a diagnosis of overweight or obesity, adiposity and weight-related complications should be evaluated at regular intervals.³ Individuals with overweight

TABLE 2. Diagnosis and Medical Management of Adult Patients With Obesity: AACE/ACE Framework³

Diagnosis		Staging and treatment	
BMI, ^a kg/m ² Anthropometric component	Clinical component ^b	Disease stage	Suggested therapy (based on clinical judgment)
< 25 < 23 in patients of certain ethnicities; waist circumference below regional/ethnic cutoffs		Normal weight (no obesity)	<ul style="list-style-type: none"> • Healthy lifestyle: Healthy meal plan/physical activity
25-29.9 23-24.9 in patients of certain ethnicities	Evaluate for presence or absence of adiposity-related complications and severity of complications <ul style="list-style-type: none"> • Metabolic syndrome • Prediabetes • Type 2 diabetes • Dyslipidemia • Hypertension • Cardiovascular disease • Nonalcoholic fatty liver disease • Polycystic ovary syndrome • Infertility (women) • Hypogonadism (men) • Obstructive sleep apnea • Asthma/reactive airway disease • Osteoarthritis • Urinary stress incontinence • Gastroesophageal reflux disease • Mental depression 	Overweight stage 0 (no complications)	<ul style="list-style-type: none"> • Lifestyle therapy: Reduced-calorie healthy meal plan/physical activity/behavioral interventions
≥ 30 ≥ 25 in patients of certain ethnicities		Obesity stage 0 (no complications)	<ul style="list-style-type: none"> • Lifestyle therapy: Reduced-calorie healthy meal plan/physical activity/behavioral interventions • Anti-obesity medications^c: Consider if lifestyle therapy fails to prevent progressive weight gain (BMI ≥ 27)
≥ 25 ≥ 23 in patients of certain ethnicities		Obesity stage 1 ^d (1 or more mild to moderate complications)	<ul style="list-style-type: none"> • Lifestyle therapy: Reduced-calorie healthy meal plan/physical activity/behavioral interventions • Anti-obesity medications^c: Consider if lifestyle therapy fails to achieve therapeutic target or initiate concurrently with lifestyle therapy (BMI ≥ 27)
≥ 25 ≥ 23 in patients of certain ethnicities		Obesity stage 2 ^d (at least 1 severe complication)	<ul style="list-style-type: none"> • Lifestyle therapy: Reduced-calorie healthy meal plan/physical activity/behavioral interventions • Add anti-obesity medication^c: Initiate concurrently with lifestyle therapy (BMI ≥ 27) Consider bariatric surgery: (BMI ≥ 35)

AACE, American Association of Clinical Endocrinology; ACE, American College of Endocrinology; BMI, body mass index.

^aBMI values are not dependent upon age or sex. However, values may not correspond to the same amount of adiposity in different populations (including certain ethnic groups).

^bStaging of a complication as mild, moderate, or severe is based on criteria specific to each particular complication.

^cThe 2016 guideline uses the term "weight-loss medications." "Anti-obesity medications" is now preferred.

^dNote that a diagnosis of obesity stage 1 or stage 2 may be given to an individual classified as overweight by BMI but who has weight-related complications.

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or obesity who have lost weight should be advised to participate in a comprehensive weight loss maintenance program for at least 1 year.² Weight-related complications should be managed in parallel with any treatment for overweight or obesity.² Such management may or may not require additional therapy.³

Treatment for overweight and obesity

Weight management and weight loss are fundamental goals in treating overweight and obesity. Because an energy deficit is required for weight loss, a reduction in caloric intake forms the foundation of any weight-loss strategy.^{2,3} According to both guidelines, individuals with overweight or obesity who intend to lose weight should be prescribed aerobic exercise and resistance training along with a reduced-calorie diet, their active leisure-time pursuits should be promoted, and their sedentary time should be reduced.^{2,3} In addition, both guidelines recommend that patients pursue behavioral interventions that foster adherence to physical activity and meal plan prescriptions.^{2,3} Such interventions can include activities conducted by the individual (eg, goal setting, self-monitoring of food intake and physical activity), 1:1 sessions with clinicians (eg, cognitive behavioral therapy, dietary education), and group meetings (eg, gatherings with peers, use of social support structures).³ These interventions are often multidisciplinary, and they can include psychologists, psychiatrists, and dietitians; they can also be conducted remotely via telephone or Internet.³ The AACE/ACE guidelines recommend that behavioral interventions be escalated for patients who do not achieve 2.5% weight loss within 1 month of starting treatment.³

A structured and comprehensive lifestyle intervention program designed for weight loss (lifestyle therapy) that includes a healthy meal plan, physical activity, and behavioral intervention is recommended for all patients with overweight or obesity seeking to lose weight.^{2,3} An in-person, high-intensity program (≥ 14 sessions in 6 months) is recommended as the most effective behavioral treatment for overweight or obesity. The recommendation is based upon treatment efficacy; participation in such high-intensity programs produces approximately 5% to 10% body weight loss, on average, over 6 months.² Especially when in-person, high-intensity intervention programs are not available, alternative programs (eg internet- or phone-based) with proven efficacy or referral to a nutrition professional may be prescribed.²

To improve adherence and outcomes, calorie-restricted diet, physical activity prescription, and behavioral lifestyle intervention should be individualized to each patient.^{2,3}

Pharmacological treatment

Pharmacotherapy or AOMs used with lifestyle modifications produce greater and more sustained weight loss when compared with lifestyle modifications alone.^{2,3} The AACE/ACE guidelines recommend

that this combination be considered for all individuals with a BMI of at least 27 kg/m² if lifestyle therapy fails to halt weight gain; it is also recommended for individuals with obesity stage 2 (Table 2).³ AOM use and selection should be individualized based on clinical weight loss goals, weight-related conditions, and drug cautions and warnings.^{2,3}

FDA-Approved Medications for the Long-Term Treatment of Obesity

At the time that the ACC/AHA/TOS guideline was being developed, only orlistat (Xenical; H-2 Pharma; OTC: Alli; GlaxoSmithKline) was FDA-approved for chronic weight management.² Subsequently, AACE/ACE guidelines authors could offer guidance for orlistat, phentermine combined with topiramate (Qsymia; VIVUS), naltrexone combined with bupropion (Contrave; Currax Pharmaceuticals), liraglutide (Saxenda[®]; Novo Nordisk), and lorcaserin (Belviq; Arena Pharmaceuticals/Eisai), the last 4 of which had then been approved by the FDA for this indication.³ The Endocrine Society's 2015 clinical practice guideline for the pharmacological management of obesity, to which the AACE/ACE guidelines refer, also considers orlistat, phentermine-topiramate, naltrexone-bupropion, liraglutide, and lorcaserin.^{3,23} In 2020, however, lorcaserin was withdrawn from the market due to concerns regarding adverse effects found with its use.⁴ In June 2021, the FDA approved semaglutide injection 2.4 mg subcutaneously once weekly (Wegovy[®]; Novo Nordisk) as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in patients with a BMI of at least 27 kg/m² who have at least 1 weight-related complication or a BMI of at least 30 kg/m².⁹ Thus, at the time of this publication, 5 drugs retain FDA approval for the long-term treatment of obesity (Table 3).^{3,5-8,23-29} A sixth medication, setmelanotide (Imcivree; Rhythm Pharmaceuticals), is only indicated for patients with 1 of 3 rare genetic disorders (POMC, PCSK1, or LR deficiency) as confirmed by genetic testing or those with Bardet-Biedl syndrome.^{13,30}

In November 2022, the American Gastroenterological Association (AGA) issued a new clinical practice guideline on pharmacological interventions for adults with obesity.³¹ Authors developed this guideline in response to the underuse of AOMs relative to mounting evidence from RCTs for the agents' efficacy and to the increasing prevalence of obesity and related health conditions.³¹ In particular, the guideline advances those evidence-based recommendations from the ACC/AHA/TOS, the AACE/ACE, and the Endocrine Society discussed in this article with updated direction on currently available AOMs.³¹

The AGA guideline authors strongly recommend that an AOM be added to lifestyle intervention for adults with obesity who have had insufficient response to lifestyle intervention alone.³¹ Reiterating that AOM selection should be based on each patient's needs, authors highlight that AOMs are generally used chronically to treat the chronic disease of obesity.³¹ Noting that total body weight loss

TABLE 3. FDA-Approved Medications for the Long-Term Treatment of Obesity, and Phentermine Hydrochloride^{3,5-8,23-29,a,b,c}

Medication	Drug class	Indication ^d	Dosing	Common adverse events
Semaglutide injection (Wegovy [®] ; Novo Nordisk) ⁸	GLP-1 receptor agonist	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² in the presence of ≥ 1 weight-related comorbid condition (eg, hypertension, T2D, dyslipidemia)	0.25 mg SC once weekly for 4 wk to start, followed by dosage escalations as per package labeling to a maintenance dose of 2.4 mg SC once weekly Give on the same day each week, at any time of day, with or without meals.	Nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia in T2D, flatulence, gastroenteritis, GERD ^e
Liraglutide injection (Saxenda [®] ; Novo Nordisk) ⁷	GLP-1 receptor agonist	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² in the presence of ≥ 1 weight-related comorbid condition (eg, hypertension, T2D, dyslipidemia)	0.6 mg SC for 1 wk to start, followed by dose escalations as per package labeling to a recommended dose of 3 mg SC once daily	Nausea, diarrhea, constipation, vomiting, injection site reaction, headache, hypoglycemia in T2D, dyspepsia, fatigue, dizziness, abdominal pain, increased lipase, upper abdominal pain ^f
Phentermine HCl and topiramate extended-release capsules (Qsymia; VIVUS) ⁵	Combination sympathomimetic amine anorectic/anti-epileptic analogue	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² in the presence of ≥ 1 weight-related comorbidity (eg, hypertension, T2D, dyslipidemia)	One 3.75-mg phentermine HCl/2-mg topiramate extended-release cap PO once daily in the morning for 14 d to start Continue on a dose-escalation schedule based on BMI; give with or without food.	Paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth ^g
Naltrexone HCl and bupropion HCl extended-release tablets (Contrave; Currax Pharmaceuticals) ⁶	Combination opioid antagonist/aminoketone antidepressant	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² in the presence of ≥ 1 weight-related comorbidity (eg, hypertension, T2D, dyslipidemia)	One 8-mg naltrexone HCl/90-mg bupropion HCl extended-release tab PO once daily in the morning for 1 wk to start Continue on a dose-escalation schedule, up to 2 extended-release tabs PO twice daily.	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea ^h
Orlistat (Xenical; H2-Pharma) ²⁴	Lipase inhibitor	Obesity management, including weight loss and weight maintenance when used with a reduced-calorie diet Reduction of risk for weight regain after prior weight loss For use in patients with an initial BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² in the presence of other risk factors (eg, hypertension, T2D, dyslipidemia)	One 120-mg cap PO 3 times/d with each main meal containing fat (during or up to 1 h after the meal)	GI symptoms ⁱ : <ul style="list-style-type: none"> • Oily spotting • Flatus with discharge • Fecal urgency • Fatty/oily stool • Oily evacuation • Increased defecation • Fecal incontinence

(continued)

reported in RCTs has ranged from 3.0% to 10.8% depending upon the pharmacological agent, AGA guideline authors identified that semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine-topiramate extended release, and naltrexone-bupropion extended release had a balance of weight loss over harm that favored their use.³¹

AGA guideline recommendations are made for each AOM, and numbered.³¹ Table 3 reflects this order. The guideline states, “given the magnitude of net benefit, semaglutide 2.4 mg may be prioritized over other approved AOMs for the long-term treatment of obesity for most patients.”³¹ The guideline recommends against the use of orlistat.³¹

FDA-Approved Medications for Short-Term Weight Loss

Four drugs are currently available in the United States for short-term weight loss: phentermine (eg, Adipex-P; Teva Pharmaceuticals [37.5-mg capsules or tablets], and Lomaira; KVK Tech [8-mg capsules or tablets]), benzphetamine, diethylpropion, and phendimetrazine.^{13,32} Although the AACE/ACE guidelines recommend against use of these treatments, the Endocrine Society guideline considers the off-label use of phentermine for long-term treatment of obesity (Table 3).^{3,5-8,23-29} Phentermine has a relatively low cost and a low addiction potential and has shown efficacy and safety, and it is widely prescribed; the guideline provides a

TABLE 3. (Continued) FDA-Approved Medications for the Long-Term Treatment of Obesity, and Phentermine Hydrochloride^{3,5-8,23-29,a,b,c}

Medication	Drug class	Indication ^d	Dosing	Common adverse events
Orlistat (Alli; GlaxoSmithKline [OTC]) ^{25,26}	Lipase inhibitor	Weight loss in overweight adults (age, ≥ 18 y) when used with a reduced-calorie and low-fat diet	One 60-mg cap PO with each meal containing fat, not to exceed 3 caps/d	GI symptoms ¹ : <ul style="list-style-type: none"> • Fatty/oily stool • Fecal urgency • Oily spotting • Flatus with discharge • Increased defecation • Infections and infestations • Upper respiratory tract infection
Not FDA-Approved for Long-Term Treatment^b				
Phentermine HCl (eg, Adipex-P; Teva Pharmaceuticals [37.5-mg caps or tabs], and Lomaira; KVK TECH [8-mg caps or tabs]) ^{27-29,b}	Sympathomimetic amine anorectic	As a short-term (few weeks) adjunct to exercise, behavioral modification, and caloric restriction for exogenous obesity in adults with an initial BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² in the presence of other risk factors (eg, hypertension, T2D, hyperlipidemia)	Individualized to obtain adequate response with lowest effective dose. <i>37.5-mg caps or tabs</i> : usually, 37.5 mg/d PO before or 1 to 2 h after breakfast. <i>8-mg tabs</i> : usually, 8 mg PO 3 times daily, 30 min before meals. Dosage may be adjusted to patient need.	Primary pulmonary hypertension and/or regurgitant cardiac valvular disease, effect on ability to engage in potentially hazardous tasks, withdrawal effects after prolonged high-dose administration, cardiac palpitation, tachycardia, elevation of blood pressure, ischemic events, overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, psychosis, dryness of mouth, unpleasant taste, diarrhea, constipation, other GI disturbances, urticaria, impotence, changes in libido

AE, adverse event; BMI, body mass index; cap, capsule; CNS, central nervous system; d, day(s); GERD, gastroesophageal reflux disease; GI, gastrointestinal; h, hour(s); HCl, hydrochloride; min, minute(s); PO, orally; SC, subcutaneous(ly); T2D, type 2 diabetes; tab, tablet; wk, week(s); y, year(s).
^aSetmelanotide SC injection (Imcivree; Rhythm Pharmaceuticals) is FDA-approved for chronic weight management in patients ≥ 6 y with obesity due to POMC, PCSK1, or LR deficiency, as confirmed by genetic testing, or Bardet-Biedl syndrome.³⁰ Due to the rarity of these disorders, setmelanotide is not listed in this table.
^bPhentermine hydrochloride (phentermine monotherapy) is not FDA-approved for long-term management of obesity. Although the American Association of Clinical Endocrinologists and American College of Endocrinology guideline also recommends against use of short-term medications like this for long-term treatment,³ the Endocrine Society guideline considers its use off-label. In particular, noting the relatively low cost of the drug, its low addiction potential, its efficacy, its safety, and its widespread prescription, the Endocrine Society guidelines provide a qualified endorsement of prescribing phentermine long-term that is contingent upon several conditions being met.²³
^cInformation on dosing is limited and for reference only. For complete information on dosing and schedules, please refer to product package labeling.
^dOnly indications for adults are listed. For pediatric indications, please refer to product package labeling.
^eBased on the results of 3 randomized, double-blind, placebo-controlled trials, occurring in ≥ 2% of treated patients and more frequently than in those given placebo.⁹
^fBased on the results of 5 double-blind, placebo-controlled trials. Reported in ≥ 5% of treated adults and ≥ 8% of treated pediatric patients and more frequently than in those given placebo.⁷
^gAEs that occurred at a rate ≥ 5% and at a rate ≥ 1.5 times that of placebo. Based on treatment with phentermine and topiramate extended-release in two 1-year, randomized, double-blind, placebo-controlled, multicenter clinical trials and two phase 2 supportive trials.⁵
^hBased on the results of 5 double-blind placebo-controlled trials. AEs occurred in ≥ 2% of treated patients and were more common than in those given placebo.⁶
ⁱGI symptoms were the most commonly observed treatment-emergent AEs associated with the use of orlistat, based on first- and second-year data from 7 double-blind, placebo-controlled clinical trials. Commonly observed is defined as an incidence of ≥ 5% and an incidence in the orlistat 120-mg group that was at least twice that of the placebo group.²⁴

qualified endorsement of long-term prescription of phentermine that is contingent upon several conditions being met.²³ The AGA guideline also provides a qualified endorsement of long-term prescription of phentermine, noting a low quality of evidence for this recommendation.³¹

Surgical Procedures and Devices for Weight Management

The ASMBS acknowledges the impact that language may have on weight bias and on treatment for obesity.³³ To accurately reflect how encompassed procedures impact weight, metabolic health, and weight-related conditions, the ASBMS uses the term “metabolic and bariatric surgery” for what has been called “weight-loss surgery.”³⁴ In patients with obesity, these procedures have led to the greatest weight loss, continuance of weight loss, and amelioration of weight-related complications and to decreased mortality.^{2,35} These procedures should be considered for patients with a BMI of at least

40 kg/m² and for those with at least 1 severe weight-related condition and a BMI of at least 35 kg/m² when therapeutic goals cannot be attained using structured lifestyle change and pharmacotherapy alone.^{3,14,36} Patients should be thoroughly evaluated before being recommended for a bariatric procedure.^{3,14} Risk, patient preferences, individualized therapy goals, and available procedural expertise should be considered when selecting a bariatric procedure.¹⁴

The AACE/ACE guidelines draw recommendations from the 2013 AACE/TOS/ASMBS clinical practice guidelines for support of the bariatric surgery patient.³ These bariatric surgery support guidelines were updated in 2019; they feature ASMBS-endorsed procedures, FDA-regulated devices, and emerging procedures and devices.¹⁴ Since then, the ASMBS has updated its recommended procedures (Table 4).^{10,14}

The ACC/AHA/TOS, AACE/ACE, and bariatric surgery support guidelines all recommend consideration of bariatric procedures for individuals with a BMI of at least 40 kg/m² or a BMI of at least

TABLE 4. ASMBS-Endorsed and/or FDA-Approved Procedures for Weight-Loss^{10,14,a,b}

Procedure	Target weight loss, %	Favorable aspects	Unfavorable aspects
Laparoscopic adjustable gastric banding	20%-25%	No anatomic alteration Removable Adjustable	High explant rate Erosion Slip/prolapse
Sleeve gastrectomy	25%-30%	Easy to perform No anastomosis Reproducible Few long-term complications Metabolic effects Versatile for challenging patient populations	Leaks difficult to manage Little data beyond 5 yr 20%-30% GERD
Roux-en-Y gastric bypass	30%-35%	Strong metabolic effects Standardized techniques < 5% major complication rate Effective for GERD Can be used as second stage after sleeve gastrectomy	Few proven revisional options for weight regain Marginal ulcers Internal hernias possible Long-term micronutrient deficiencies
Biliopancreatic diversion with duodenal switch	35%-45%	Very strong metabolic effects Durable weight loss Effective for patients with very high BMI Can be used as second stage after sleeve gastrectomy	Malabsorptive 3%-5% protein-calorie malnutrition GERD Potential for hernias Duodenal dissection Technically challenging Higher rate of micronutrient deficiencies than roux-en-Y gastric bypass

(continued)

35 kg/m² with weight-related complications when such techniques would not place the patient at excessive risk.^{2,3,14} The AACE/ACE obesity guidelines and 2019 bariatric procedure guidelines add that patients with a BMI of at least 30 kg/m² and T2D for whom glycemic levels remain insufficiently controlled after lifestyle therapy and pharmacotherapy also should be considered for a bariatric procedure.^{3,14}

In a November 2022 statement, the ASMBS, along with the International Federation for the Surgery of Obesity and Metabolic Disorders, recommended that providers consider bariatric procedures for a larger patient population, including all patients with a BMI of 30 kg/m² who do not attain and sustain desired weight loss or improvement in weight-related conditions.³⁷ However, at the time that the current article was being written, the ACC, AHA, TOS, AACE, and ACE had not commented upon this statement. Whether other leading societies will endorse expanding eligibility for bariatric procedures remains to be seen.

Conclusions

Although much has changed in the field of obesity treatment since development of the most accepted guidelines, consensus remains: all adults should be screened annually for overweight and obesity using BMI, and weight-related complications should be assessed to formulate a diagnosis and to establish treatment targets.^{2,3} Lifestyle therapy that includes a healthy meal plan, physical activity, and behavioral intervention is the foundation of obesity treatment.^{2,3} In conjunction with lifestyle modifications, pharmacotherapy and metabolic and bariatric surgery produce greater and more sustained weight loss in treatment-approved populations when compared with lifestyle modifications alone.^{2,3} A sustained partnership between the patient and the clinician is necessary to manage the chronic disease of obesity.² ■

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TABLE 4. (Continued) ASMBS-Endorsed and/or FDA-Approved Procedures for Weight-Loss^{10,14,a,b}

Procedure	Target weight loss, %	Favorable aspects	Unfavorable aspects
Single anastomosis duodeno-ileal bypass with sleeve gastrectomy	35%-45%	Single anastomosis Simpler to perform than biliopancreatic diversion with duodenal switch Strong metabolic effects Low early complication rate	Little long-term data Nutritional and micronutrient deficiencies possible Duodenal dissection
Intragastric balloon	10%-12%	Endoscopic or swallowed Good safety profile	Temporary (6 mo) therapy Temporary nausea/vomiting, pain Early removal rate of 10%-19%
One-anastomosis gastric bypass	35%-40%	Simpler to perform than roux-en-Y gastric bypass More malabsorptive Strong metabolic effects No mesenteric defects	Potential for bile reflux Malabsorptive (long biliopancreatic limb) Little experience in the United States
Transpyloric bulb	14%	Endoscopic Delays gastric emptying	6-mo data Gastric ulcers
Aspiration therapy	12%-14%	Endoscopic Changes eating behavior	1-yr therapy Tube-related problems/complications 26% early removal
Vagal nerve blocking therapy	8%-9%	No anatomic changes Low complication rate (4%)	Pain at neuroregulatory site Explant required for conversion to another procedure

ASMBS, American Society of Metabolic and Bariatric Surgery; BMI, body mass index; GERD, gastroesophageal reflux disease; mo, month; vBloc, vagal nerve-blocking device; yr, year.

^aASMBS also endorses bariatric reoperative procedures.¹⁰

^bIn a 2019 clinical practice guidelines update, the American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, ASMBS, Obesity Medicine Association, and American Society of Anesthesiologists also discussed use of primary obesity surgery endoluminal, Gelesis100 ingested hydrogel capsules (Genesis), and endoscopic sleeve gastroplasty.¹⁴ Endorsements for these procedures and this device do not appear in ASMBS' most recent update.¹⁰

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Address Correspondence to: Marc-Andre Cornier, MD, 96 Jonathan Lucas St, CSB 822, MSC 624, Charleston, SC 29425. Email: cornier@muscc.edu

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Semaglutide 2.4-mg Injection as a Novel Approach for Chronic Weight Management

Janine Kyrillos, MD

Introduction

In 2017 and 2018, approximately 42.4% of adults in the United States had obesity (defined as a body mass index [BMI] ≥ 30 kg/m²), according to data from the 2017-2018 National Health and Nutrition Examination Survey.¹ Although a reduced-calorie diet, exercise, and behavioral modifications form the cornerstone of guideline-recommended obesity treatment, these lifestyle interventions alone are associated with moderate weight loss and with weight regain.^{2,3} Pharmacotherapy for weight loss in conjunction with lifestyle interventions produces greater weight loss sustained over time than does lifestyle intervention alone.^{2,3} Individuals with a BMI greater than 30 kg/m² (ie, obesity) and those with a BMI of at least 27 kg/m² (ie, overweight) who have a weight-related comorbidity should be considered for add-on treatment with pharmacotherapy.⁴ Bariatric surgery should be considered when therapeutic goals cannot be attained using structured lifestyle change and pharmacotherapy alone, or in conjunction with lifestyle therapy and pharmacotherapy.^{5,6}

The FDA-approved medications for the long-term treatment of obesity have provided patients in the general adult population with mean weight loss from 4.0% to 10.9% of body weight after 1 year of treatment.⁷ A mean weight loss target of at least 5% is the lowest body weight reduction recommended to mitigate certain weight-related complications; however, achievement of greater weight loss is necessary for clinically significant improvements in some comorbidities.² Weight loss of 15% would meet or exceed the recommended targets for all weight-related complications considered in the most widely accepted guidelines for obesity treatment.² Therefore, there is a need for pharmacotherapeutic strategies that can provide sustained, long-term weight loss of 15%.

The glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA) class has emerged with the potential to meet this need. Several GLP-1RA medications, such as liraglutide (Victoza®; Novo Nordisk), have been FDA-approved for the treatment of type 2 diabetes (T2D).⁸⁻¹⁰ Liraglutide is also FDA-approved as a daily 3.0-mg injection to be used with lifestyle intervention for the treatment of patients with a BMI greater than 30 kg/m² and for those with a BMI of at least 27 kg/m² who have a weight-related comorbidity (Saxenda®; Novo

ABSTRACT

Anti-obesity medications used with lifestyle intervention produce greater and more sustained weight loss than does lifestyle intervention alone. However, until 2021, FDA-approved medications for the long-term treatment of obesity in the general adult population had not demonstrated the sustained loss of 15% body weight needed to meet or exceed all guideline-recommended targets for weight-related complications. To meet this need, investigators launched the Semaglutide Treatment Effect in People with obesity (STEP) program of phase 3 clinical trials to assess the safety and efficacy of a weekly 2.4-mg subcutaneous injection of semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA). Following the results of STEPs 1 to 4, the FDA approved semaglutide therapy in patients with obesity. This article examines the design, efficacy, and safety of semaglutide therapy as revealed by the results of STEPs 1 to 4. These trials included adults with obesity who reported at least 1 unsuccessful attempt to reduce body weight by means of diet. STEP 2 studied effects on patients who also had type 2 diabetes (T2D); STEPs 1, 3, and 4 excluded patients with this condition. STEP 3 examined the effect of this pharmacotherapy plus intensive behavioral therapy and a 2-step, intensively restricted dietary plan. STEP 4 assessed the effects of continuing semaglutide 2.4 mg vs switching to placebo after an initial treatment period. In the trials comparing the effects of semaglutide 2.4-mg treatment with those of placebo across 68 weeks and in patients with no T2D (ie, STEPs 1 and 3), patients treated with semaglutide achieved a mean -14.9% to -16.0% weight change. This far exceeds the 4.0% to 10.9% weight loss seen with other approved antiobesity medications. In STEPs 2 and 4, the estimated treatment differences between the semaglutide 2.4-mg and placebo arms were -6.2% and -14.8%, respectively. Safety and tolerability of this treatment in STEPs 1 to 4 was consistent with those of other GLP-1RA-based therapies. Ultimately, the results of the first 4 STEP trials demonstrated that semaglutide 2.4 mg is a safe, well-tolerated, and highly effective treatment to promote weight loss, avoid weight regain, and mitigate the effects of the prevalent, chronic disease of obesity. In November 2022, based upon the results of STEPs 1 to 3 and other trials, the American Gastroenterological Association recommended that semaglutide 2.4 mg "be prioritized over other approved [anti-obesity medications] for the long-term treatment of obesity for most patients."

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For author information and disclosures, see end of text.

Nordisk).¹¹ Treatment with 3.0-mg liraglutide was associated with clinically significant weight loss in clinical trials; however, in a large (n = 3731), randomized clinical trial (RCT) assessing the impact of liraglutide 3.0 mg upon weight loss in patients with obesity, patients in the liraglutide arm experienced a mean weight loss of only 8.0% (SD, ± 6.7%) at 56 weeks.⁷

Semaglutide has 94% sequence homology to human GLP-1 and acts as a GLP-1RA that selectively binds to and activates the GLP-1R.¹² It was initially approved by the FDA for the treatment of T2D as a weekly subcutaneous injection at doses up to 2 mg (Ozempic®; Novo Nordisk) and in tablet form at doses up to 14 mg daily (Rybelsus®; Novo Nordisk).^{13,14} However, in a 52-week, randomized, phase 2 trial of patients with obesity (BMI ≥ 30 kg/m²) but without T2D, daily treatment with semaglutide 0.4 mg was associated with greater mean weight loss than that associated with daily liraglutide 3.0 mg and placebo (−13.8% vs −7.8% and −2.3%, respectively).¹⁵

Based on these promising results, the Semaglutide Treatment Effect in People with obesity (STEP) program of phase 3 clinical trials was initiated to investigate the safety and efficacy of once-weekly subcutaneous semaglutide 2.4-mg injection for chronic weight management.¹⁶ In STEPs 1 (NCT03548935) and 3 (NCT03611582), use of semaglutide demonstrated a mean weight loss of −14.9% to −16.0% across a broad population of patients with obesity after 68 weeks.^{17,18}

In 2021, based on the results of these 2 trials and those of STEPs 2 (NCT03552757) and 4 (NCT03548987), weekly semaglutide 2.4-mg subcutaneous injection was FDA-approved as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of 30 kg/m² or greater or for patients with a BMI of 27 kg/m² or greater in the presence of at least 1 weight-related condition.^{12,16,19}

The Semaglutide Treatment Effect in People with Obesity (STEP) Program

The STEP program involves 7 completed and 5 ongoing phase 3, double-blind, randomized trials evaluating the safety and efficacy of semaglutide 2.4-mg subcutaneous injection as an adjunct to lifestyle therapy compared with either placebo, semaglutide 1.0 mg, semaglutide 1.7 mg, or liraglutide 3.0 mg (Table 1).^{16-18,20-33} Treatment efficacy and safety have been or are being studied over several time intervals, ranging from 44 weeks (STEP 7 [NCT04251156]) to 104 weeks (STEP 5 [NCT03693430]). One trial (STEP 4) compared the efficacy and safety of continued treatment with semaglutide 2.4 mg vs switch to placebo after initial treatment with semaglutide.

The STEP program enrolled patient populations with a range of comorbid conditions, including those with and without T2D; those with prediabetes, heart failure, or knee osteoarthritis; patients from East Asia; and individuals largely from China. STEP 1 also included an extension phase, which is not summarized within this article; the results were published after FDA approval (Table 1).^{16-18,20-33}

This article reviews the study design and findings from the phase 3, randomized, placebo-controlled STEP 1, 2, 3, and 4 trials that were used for FDA approval of semaglutide.^{12,16,19}

Trial Design for the STEP 1, 2, 3, and 4 Trials

For more information regarding the study design, treatment arms, inclusion/exclusion criteria, primary end points, and confirmatory secondary end points of the STEP 1, 2, 3, and 4 trials, please see Table 1.^{16-18,20-33}

Patient Population

Across the 4 trials, patient enrollment criteria included an age of at least 18 years, at least 1 self-reported unsuccessful attempt to reduce body weight by means of diet, and a BMI of at least 27 kg/m². Patients who had gained or lost over 5 kg (11 lb) in the 90 days leading up to screening were excluded from all trials. An additional exclusion criterion was treatment with an anti-obesity medication (AOM) during this 90-day period.^{16-18,22}

Treatment Arms and Dosing

In STEPs 1 to 4, patients received lifestyle intervention in combination with either placebo, subcutaneous semaglutide 1.0 mg, or semaglutide 2.4 mg for 68 weeks. The trials included a 7-week follow-up period. In patients randomly assigned to receive semaglutide 2.4 mg, the medication was initiated at a dose of 0.25 mg. The dose was escalated every 4 weeks (0.5 mg, 1.0 mg, 1.7 mg, 2.4 mg) over a 16-week period; this was followed by a 52-week period at the maintenance dose of semaglutide 2.4 mg (Figure).^{16-18,22,23} STEPs 1 to 3 assessed outcomes across this 68-week treatment period. To determine the effects of semaglutide 2.4 mg on sustained weight management, patients in STEP 4 received semaglutide on a dose escalation schedule for 20 weeks and then were randomly assigned to either continue active treatment or switch to placebo for the duration of the study.¹⁶

Lifestyle Intervention

Lifestyle intervention included nonmonetary incentives to promote physical activity (eg, jump ropes and kettle bells), support from a multidisciplinary team that included a dietitian or similarly qualified provider, and periodic counseling.¹⁶ Lifestyle intervention for STEPs 1, 2, and 4 was defined as prescription of both a daily deficit of 500 kcal (relative to estimated caloric expenditure at randomization) and 150 min/wk of physical activity, plus counseling and support to bolster adherence to this regimen.¹⁶

Individual Trial Characteristics

Patients with T2D were excluded from STEPs 1, 3, and 4, which assessed semaglutide 2.4 mg compared with placebo as an adjunct to lifestyle intervention in a general population of patients with a BMI of at least 27 kg/m² plus 1 or more weight-related (non-T2D)

SEMAGLUTIDE 2.4-MG INJECTION FOR CHRONIC WEIGHT MANAGEMENT

TABLE 1. Overview of the STEP Trials of Semaglutide 2.4-mg Injection^{16-18,20-33}

Trial	Additional trial design elements ^a	Study arms	Additional inclusion criteria ^b	Treatments	Primary end points	Confirmatory secondary end points
Phase 3a STEP trials (completed)						
STEP 1: WM (NCT03548935) ^{16,17,20,21}	Included a 45-week extension phase (N=327) ^{c,d}	N=1961 Sema 2.4 (n=1306) Placebo (n=655)	<ul style="list-style-type: none"> BMI, 27-29.9 kg/m² and ≥1 WRC (not T2D) <i>or</i> BMI ≥30 kg/m² 	For 68 weeks: <ul style="list-style-type: none"> Sema 2.4 or placebo Lifestyle intervention 	<ul style="list-style-type: none"> Δ in BW (%) ≥5% loss of BW 	<ul style="list-style-type: none"> ≥10% loss of BW ≥15% loss of BW Δ in WC and systolic BP Δ in PF
STEP 2: WM in T2D (NCT03552757) ^{16,22}	Double-dummy superiority trial	N=1210 Sema 2.4 (n=404) Sema 1.0 (n=403) Placebo (n=403)	<ul style="list-style-type: none"> BMI, ≥27 kg/m² HbA_{1c}, 7%-10% (53-86 mmol/mol) T2D diagnosis ≥180 days before screening 	For 68 weeks: <ul style="list-style-type: none"> Sema 2.4, Sema 1.0, or placebo Lifestyle intervention 	<ul style="list-style-type: none"> Δ in BW (%) ≥5% loss of BW 	<ul style="list-style-type: none"> ≥10% loss of BW ≥15% loss of BW Δ in WC and systolic BP Δ in PF Δ in HbA_{1c} Δ in BW (Sema 2.4 vs Sema 1.0)
STEP 3: WM with intensive behavioral therapy (NCT03611582) ^{16,18}	None	N=611 Sema 2.4 (n=407) Placebo (n=204)	<ul style="list-style-type: none"> BMI, 27-29.9 kg/m² ≥1 WRC (not T2D) <i>or</i> BMI ≥30 kg/m² 	For 68 weeks: <ul style="list-style-type: none"> Sema 2.4 or placebo Intensive behavioral therapy lifestyle intervention (including meal replacements and 30 counseling sessions) 	<ul style="list-style-type: none"> Δ in BW (%) ≥5% loss of BW 	<ul style="list-style-type: none"> ≥10% loss of BW ≥15% loss of BW Δ in WC and systolic BP
STEP 4: Sustained WM (NCT03548987) ^{16,23}	Withdrawal trial	Week 0 N=902 Sema 2.4 (n=902) Week 20 N=803 Sema 2.4 (n=535) Placebo (n=268)	<ul style="list-style-type: none"> BMI, 27-29.9 kg/m² and ≥1 WRC (not T2D) <i>or</i> BMI ≥30 kg/m² 	Weeks 0-20: <ul style="list-style-type: none"> Sema 2.4 Lifestyle intervention Weeks 21-68: <ul style="list-style-type: none"> Sema 2.4 or placebo Lifestyle intervention 	From weeks 20-68: <ul style="list-style-type: none"> Δ in BW (%) 	From weeks 20-68: <ul style="list-style-type: none"> Δ in WC and systolic BP
Phase 3b STEP trials						
STEP 5: Long-term WM (NCT03693430) [completed] ^{16,24}	None	N=304 Sema 2.4 (n=152) Placebo (n=152)	<ul style="list-style-type: none"> BMI, 27-29.9 kg/m² and ≥1 WRC (not T2D) <i>or</i> BMI ≥30 kg/m² 	For 104 weeks: <ul style="list-style-type: none"> Sema 2.4 or placebo Lifestyle intervention 	<ul style="list-style-type: none"> Δ in BW (%) ≥5% loss of BW 	<ul style="list-style-type: none"> ≥10% loss of BW ≥15% loss of BW Δ in WC and systolic BP
STEP 6: WM in patients from East Asia (NCT03811574) [completed] ^{25,30}	Double-dummy superiority trial	N=401 Sema 2.4 (n=199) Sema 1.7 (n=101) Placebo (n=101)	<ul style="list-style-type: none"> From east Asia BMI ≥35 kg/m² and ≥1 WRC <i>or</i> BMI ≥27 kg/m² and ≥2 WRCs^e 	For 68 weeks: <ul style="list-style-type: none"> Sema 2.4, Sema 1.7, or placebo Lifestyle intervention 	<ul style="list-style-type: none"> Δ in BW (%) ≥5% loss of BW 	<ul style="list-style-type: none"> ≥10% loss of BW ≥15% loss of BW Δ in WC
STEP 7: WM (mostly in China) (NCT04251156) [ongoing] ²⁶	None	N=375	<ul style="list-style-type: none"> BMI 27-29.9 kg/m² and ≥1 WRC <i>or</i> BMI ≥30 kg/m² 	For 44 weeks: <ul style="list-style-type: none"> Sema 2.4 or placebo Lifestyle intervention 	<ul style="list-style-type: none"> Δ in BW (%) ≥5% loss of BW 	(Not published) ^f

[continued]

TABLE 1. (Continued) Overview of the STEP Trials of Semaglutide 2.4-mg Injection^{14-18,20-33}

Trial	Additional trial design elements ^a	Study arms	Additional inclusion criteria ^b	Treatments	Primary end points	Confirmatory secondary end points
Phase 3b STEP trials (continued)						
STEP 8: WM – Sema 2.4 vs Lira 3.0 (NCT04074161) (completed) ²⁷	Open-label, but the 2 active treatment arms are double-blinded against placebo	N=338 Sema 2.4 (n=126) Lira 3.0 (n=127) Placebo (pooled) (n=85)	<ul style="list-style-type: none"> BMI 27-29.9 kg/m² and ≥ 1 WRC (not T2D)^g or BMI ≥ 30 kg/m² 	For 68 weeks: <ul style="list-style-type: none"> Sema 2.4, Lira 3.0, or placebo Lifestyle intervention 	<ul style="list-style-type: none"> Δ in BW (%) 	<ul style="list-style-type: none"> ≥ 10% loss of BW ≥ 15% loss of BW ≥ 20% loss of BW
STEP 9: Patients with knee OA (NCT05064735) (ongoing) ^{28,29}	None	N=375	<ul style="list-style-type: none"> BMI ≥ 30 kg/m² Clinical diagnosis of knee OA^h Pain due to knee OA 	For 68 weeks: <ul style="list-style-type: none"> Sema 2.4 or placebo Lifestyle intervention 	<ul style="list-style-type: none"> Δ in BW (%) Δ in WOMAC pain score 	(Not published) ^f
STEP 10: Patients with prediabetes (NCT05040971) (ongoing) ³¹	Quadruple-blind trial	N=201	<ul style="list-style-type: none"> BMI ≥ 30 kg/m² HbA_{1c} of 6.0%-6.4% (42-47 mmol/mol) or FPG of 5.5-6.9 mmol/L (99-125 mg/dL) 	For 52 weeks: <ul style="list-style-type: none"> Sema 2.4 or placebo Lifestyle intervention 	<ul style="list-style-type: none"> Δ in BW (%) Glycemic level, Δ to normoglycemia (HbA_{1c} < 6.0% and FPG < 5.5 mmol/L) 	(Not published) ^f
STEP HFpEF (NCT04788511): Patients with HFpEF (ongoing) ³²	None	N=516	<ul style="list-style-type: none"> BMI ≥ 30 kg/m² NYHA classes II-IV LVEF ≥ 45% 	For 52 weeks: <ul style="list-style-type: none"> Sema 2.4 or placebo Lifestyle intervention 	At 52 weeks: <ul style="list-style-type: none"> Δ in KCCQ clinical summary score Δ in BW (%) 	(Not published) ^f
STEP HFpEF DM (NCT04916470): Patients with HFpEF and T2D (ongoing) ³³	Quadruple-blind trial	N=610	<ul style="list-style-type: none"> BMI ≥ 30 kg/m² NYHA classes II-IV LVEF ≥ 45% Diagnosed with T2D ≥ 90 days before screening HbA_{1c} ≤ 10% 	For 52 weeks: <ul style="list-style-type: none"> Sema 2.4 or placebo Lifestyle intervention 	At 52 weeks: <ul style="list-style-type: none"> Δ in KCCQ clinical summary score Δ in BW (%) 	(Not published) ^f

Δ, change; BMI, body mass index; BP, blood pressure; BW, body weight; CVD, cardiovascular disease; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; HFpEF, heart failure with preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; Lira 3.0, once-daily subcutaneous injection of liraglutide 3.0 mg; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OA, osteoarthritis; PF, physical function; Sema 1.0, once-weekly subcutaneous injection of semaglutide 1.0 mg; Sema 1.7, once-weekly subcutaneous injection of semaglutide 1.7 mg; Sema 2.4, once-weekly subcutaneous injection of semaglutide 2.4 mg; STEP, Semaglutide Treatment Effect in People with obesity; T2D, type 2 diabetes; WC, waist circumference; WL, weight loss; WM, weight management; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; WRC, weight-related condition.

^aThe STEP program is a series of phase 3 trials performed to evaluate the efficacy and safety of semaglutide 2.4 mg administered SC weekly in persons with obesity or overweight.¹⁴ All trials are or were randomized, placebo-controlled, multicenter, parallel group studies. All were at least double-blind. In STEP 8, Sema 2.4 vs Lira 3.0 is open-label, but the 2 active treatment arms are double-blinded against placebo. STEP 10 was quadruple-blinded.

^bAll patients in the STEP trials were at least 18 years of age. For STEP 6, patients in Japan were at least 20 years of age. All patients in the STEP trials also reported at least 1 previous dietary effort to lose weight. Exceptions are the STEP 9, STEP 10, STEP HFpEF, and STEP HFpEF DM trials, for which WL effort was not reported as an inclusion criterion.

^cTreatments were neither actively administered nor forbidden during the extension phase.²¹

^dThe extension's end points were all exploratory. They related to 2 broad objectives: examining the effects of treatment withdrawal and comparing the after-effect of treatment with placebo.²¹

^eFor all patients, at least 1 WRC must be hypertension or dyslipidemia or (in Japan only) T2D.

^fPublished trial data list secondary end points but do not indicate which are confirmatory (vs exploratory).

^gWith at least 1 WRC being hypertension, dyslipidemia, obstructive sleep apnea, or CVD

^hWith moderate radiographic changes

complications or a BMI of at least 30 kg/m².^{16,17,23} STEP 2, which included patients with T2D and BMI of at least 27 kg/m², assessed the superiority of semaglutide 2.4 mg over semaglutide 1.0 mg as well as over placebo. For patients receiving semaglutide 1.0 mg, the dose escalation period (0.5-1.0 mg every 4 weeks) ceased 8 weeks after treatment initiation.

Lifestyle intervention in STEP 3 was unique relative to that of the other trials in the STEP program. STEP 3 included an intensive behavioral therapy component consisting of a low-calorie diet (1000-1200 kcal/d) for the first 8 weeks in the form of provided meal replacements; for the remaining 60 weeks, they were prescribed a hypocaloric diet (1200- 1800 kcal/d) in the form of conventional food. Patients were also prescribed weekly physical activity to be performed across 4 to 5 days: 100 minutes at the time of randomization and 25 additional minutes every 4 weeks until patients achieved 200 min/wk. Patients in STEP 3 also received 30 behavioral therapy sessions, which is approximately 13 more than received by participants in the other trials.^{17,18,22,23}

Efficacy of Semaglutide 2.4 mg in STEPS 1 to 4
Weight Change Outcomes

The percentage change in body weight from baseline to end of treatment (EOT) was a primary end point across the trials. In STEP 4, baseline was week 20 (when patients were randomly assigned to continue semaglutide or switch to placebo) to assess the sustained effects of semaglutide 2.4 mg after an acute weight loss. Across STEPS 1 to 4, the mean percentage change in body weight from baseline to EOT was significantly greater in patients treated with semaglutide 2.4-mg injection vs those given placebo (*P* < .001 for all) (Table 2).^{16-18,22}

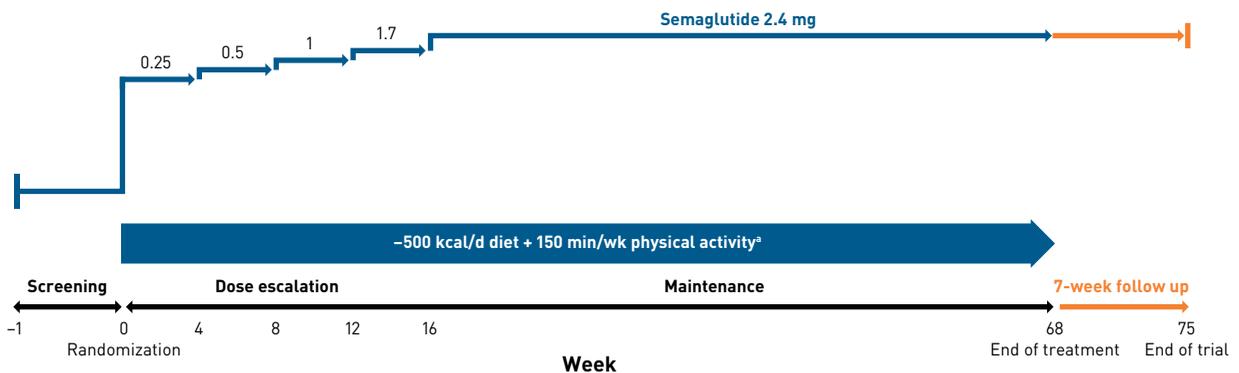
The estimated treatment differences between the semaglutide 2.4 mg and placebo arms ranged from -6.2% (95% CI, -7.3% to -5.2%) in STEP 2 to -14.8% (95% CI, -16.0% to -13.5%) in STEP 4.^{22,23}

STEPS 1 to 3 included a co-primary end point of at least 5% weight loss from baseline to EOT. Semaglutide 2.4-mg treatment given for 68 weeks was associated with a significantly greater likelihood of 5% or greater body weight reduction vs placebo (*P* < .001 for all). Odds ratios (ORs) for achieving at least a 5% weight reduction with semaglutide vs placebo ranged from 4.9 (95% CI, 3.6-6.6) in STEP 2 to 11.2 (95% CI, 8.9-14.2) in STEP 1.^{17,18,22,23} STEPS 1 to 3 also included confirmatory secondary end points of at least 10% weight loss and of at least 15% weight loss from baseline to EOT. Patients treated with semaglutide 2.4 mg were significantly more likely to lose at least 10% and 15% of their body weight at EOT than were patients treated with placebo (*P* < .001 for all). ORs for 10% body weight loss ranged from 7.4 (95% CI, 4.9- 11.0) in STEP 3 to 14.7 (95% CI, 11.1-19.4) in STEP 1. ORs for 15% body weight loss ranged from 7.7 (95% CI, 4.1-14.2) in STEP 2 to 19.3 (95% CI, 12.9-28.8) in STEP 1.

As a confirmatory secondary end point in STEP 2, change in body weight at EOT from baseline in the group receiving semaglutide 2.4 mg was compared with that in the group receiving semaglutide 1.0 mg.^{16-18,22} Significantly greater weight loss was achieved by patients given semaglutide 2.4 mg vs those given semaglutide 1.0 mg; the estimated treatment difference was -2.65 (95% CI, -3.66 to -1.64; *P* < .0001).²²

These weight management results suggest that treatment with semaglutide 2.4 mg can help patients with obesity (both with and without T2D) achieve weight loss that meets or exceeds recommended targets.

FIGURE. Dose Titration of Semaglutide 2.4-mg Injection in the STEP 1, 2, 3, and 4 Trials^{16-18,22,23}



d, day; min, minutes; wk, week.

*STEP 3 included intensive behavioral therapy in which patients were prescribed a low-calorie diet [1000-1200 kcal/d] for the first 8 weeks in the form of provided meal replacements; for the remaining 60 weeks, they were prescribed a hypocaloric diet [1200- 1800 kcal/d] in the form of conventional food. Patients were also prescribed weekly physical activity to be performed across 4 to 5 days: 100 minutes at the time of randomization and 25 additional minutes every 4 weeks until patients achieved 200 min/wk.^{17,18,22,23}

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Cardiometabolic Risk Outcomes

Changes in 2 cardiometabolic risk factors—waist circumference (cm) and systolic blood pressure (mm Hg)—were evaluated as confirmatory secondary end points across STEPs 1 to 4.^{16,17} Other cardiometabolic risk factors including diastolic blood pressure (mm Hg) and lipid levels were measured as supportive or exploratory end point; these results are not summarized here, as they were not controlled for multiplicity.^{17,18,22,23}

Compared with patients given placebo, patients given semaglutide 2.4-mg treatment had significantly greater reductions in waist circumference from baseline to EOT across STEP trials 1, 2, 3, and 4 ($P < .001$ for all). The between-group differences in waist circumference ranged from -4.9 cm (95% CI, -6.0 to -3.8 cm) in STEP 2 to -9.7 cm (95% CI, -10.9 to -8.5) in STEP 4. Additionally,

the semaglutide 2.4-mg arm experienced significant reductions in systolic blood pressure vs the placebo arm across these trials ($P \leq .0016$); between-group differences also varied across trials from -3.4 mm Hg (95% CI, -5.6 to -1.3 mm Hg) in STEP 2 to -5.1 mm Hg (95% CI, -6.3 to -3.9 mm Hg) in STEP 1.^{17,18,22,23}

Additionally, STEP 2 included the change in glycated hemoglobin (HbA_{1c}) level from baseline to EOT as a confirmatory secondary end point; it showed that patients treated with semaglutide 2.4 mg experienced significantly greater reductions in HbA_{1c} levels compared with patients given placebo. The HbA_{1c} percentage change difference between groups was -1.2% (95% CI, -1.4%; $P < .0001$).^{16,22}

These results suggest that semaglutide 2.4 mg provides improvements in key measures of metabolic risk by lowering blood pressure

TABLE 2. Key Efficacy Results from the STEP 1, 2, 3, and 4 Trials of Semaglutide 2.4-mg Injection^{16-18,22}

From baseline to EOT ^a	STEP 1: WM (NCT03548935) ^{16,17}				STEP 2: WM in T2D (NCT03552757) ^{16,22}				
	Sema 2.4 (n=1306)	Placebo (n=655)	Treatment comparison (95% CI)	P value	Sema 2.4 (n=404)	Sema 1.0 (n=403)	Placebo (n=403)	Treatment comparison (95% CI)	P value
PRIMARY END POINTS									
Δ in BW (%)	-14.9	-2.4	ETD, -12.4 (-13.4 to -11.5)	<.001	-9.6	—	-3.4	ETD, -6.2 (-7.3 to -5.2)	<.0001
≥5% loss BW (participants, %)	86.4 ^b	31.5 ^b	OR, 11.2 (8.9 to 14.2) ^b	<.001 ^b	68.8	—	28.5	OR, 4.9 (3.6 to 6.6)	<.0001
CONFIRMATORY SECONDARY END POINTS									
≥10% loss BW (participants, %)	69.1 ^b	12.0 ^b	OR, 14.7 (11.1 to 19.4) ^b	<.001 ^b	45.6	—	8.2	OR, 7.4 (4.9 to 11.2)	<.0001
≥15% loss BW (participants, %)	50.5 ^b	4.9 ^b	OR, 19.3 (12.9 to 28.8) ^b	<.001 ^b	25.8	—	3.2	OR, 7.7 (4.1 to 14.2)	<.0001
Δ in WC, cm	-13.5	-4.1	ETD, -9.4 (-10.3 to -8.5)	<.001	-9.4	—	-4.5	ETD, -4.9 (-6.0 to -3.8)	<.0001
Δ in systolic BP, mm Hg	-6.2	-1.1	ETD, -5.1 (-6.3 to -3.9)	<.001	-3.9	—	-0.5	ETD, -3.4 (-5.6 to -1.3)	.0016
Δ in physical function, SF-36v2 score	2.2	0.4	ETD, 1.8 (1.2 to 2.4)	<.001	2.5	—	1.0	ETD, 1.5 (0.4 to 2.6)	.0061
Δ in physical function, IWQOL-Lite-CT score	14.7	5.3	ETD, 9.4 (7.5 to 11.4)	<.001	10.1	—	5.3	ETD, 4.8 (1.8 to 7.9)	.0018
Δ in HbA _{1c} , %	—	—	—	—	-1.6	—	-0.4	ETD, -1.2 (-1.4 to -1.0)	<.0001
Δ in HbA _{1c} , mmol/mol	—	—	—	—	-17.5	—	-4.1	ETD, -13.5 (-15.5 to -11.4)	<.0001
Δ in BW, % (Sema 2.4 vs Sema 1.0)	—	—	—	—	-9.6	-7.0	—	ETD, -2.7 (-3.7 to -1.6)	<.0001

(continued »)

and reducing mean waist circumference.¹⁷ Additionally, semaglutide 2.4 mg also supports HbA_{1c} improvement in patients with T2D and obesity.²²

Physical Function Outcomes

STEPS 1 to 4 included patient-reported outcomes as confirmatory secondary end points; these were assessed using the Short Form 36 v2 Health Survey, Acute Version (SF-36v2). Patients treated with semaglutide 2.4 mg reported improvements in measures of physical functioning on the SF-36v2 from baseline to EOT compared with placebo-treated patients. The greater change in SF-36v2 physical functioning score between groups was significant in STEPS 1, 2, and 4 (STEP 2, *P* = .0061; STEP 1 and 4, *P* < .001). However, this change was not significant in STEP 3 (*P* = .12).^{17,18,22,23}

STEPS 1 and 2 also included a confirmatory secondary end point of change in physical functioning score on the Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT) measure. By this measure, physical functioning improved significantly more for patients treated with semaglutide 2.4 mg than it did for patients treated with placebo (STEP 1, *P* < .001; STEP 2, *P* = .0018).^{17,22}

Overall, treatment with semaglutide 2.4 mg was associated with improvements in physical functioning and quality of life.^{17,18,22,23}

Safety and Tolerability of Semaglutide 2.4 mg in STEPS 1 to 4

Safety results reported across STEPS 1 to 4 are shown in **Table 3**.^{16-18,22,23} Overall, the safety profile of semaglutide 2.4 mg was consistent with previous reports for use of GLP-1RAs in clinical trials and with

TABLE 2. (Continued) Key Efficacy Results from the STEP 1, 2, 3, and 4 Trials of Semaglutide 2.4-mg Injection^{16-18,22}

From baseline to EOT ^a	STEP 3: WM with intensive behavioral therapy (NCT03611582) ^{16,18}				STEP 4: Sustained WM (NCT03548987) ^{a,16,23}			
	Sema 2.4 (n = 407)	Placebo (n = 204)	Treatment comparison (95% CI)	<i>P</i> value	Sema 2.4 (n = 535)	Placebo (n = 268)	Treatment comparison (95% CI)	<i>P</i> value
PRIMARY END POINTS								
Δ in BW (%)	-16.0	-5.7	ETD, -10.3 (-12.0 to -8.6)	< .001	-7.9%	6.9%	ETD, -14.8 (-16.0 to -13.5)	< .001
≥ 5% loss BW (participants, %)	86.6	47.6	OR, 6.1 (4.0 to 9.3)	< .001	—	—	—	—
CONFIRMATORY SECONDARY END POINTS								
≥ 10% loss BW (participants, %)	75.3	27.0	OR, 7.4 (4.9 to 11.0)	< .001	—	—	—	—
≥ 15% loss BW (participants, %)	55.8	13.2	OR, 7.9 (4.9 to 12.6)	< .001	—	—	—	—
Δ in WC, cm	-14.6	-6.3	ETD, -8.3 (-10.1 to -6.6)	< .001	-6.4	3.3	ETD, -9.7 (-10.9 to -8.5)	< .001
Δ in systolic BP, mm Hg	-5.6	-1.6	ETD, -3.9 (-6.4 to -1.5)	.001	0.5	4.4	ETD, -3.9 (-5.8 to -2.0)	< .001
Δ in physical function, SF-36v2 score	2.4	1.6	ETD, 0.8 (-0.2 to 1.9)	.12	1.0	-1.5	ETD, 2.5 (1.6 to 3.3)	< .001
Δ in physical function, IWQOL-Lite-CT score	—	—	—	—	—	—	—	—
Δ in HbA _{1c} , %	—	—	—	—	—	—	—	—
Δ in HbA _{1c} , mmol/mol	—	—	—	—	—	—	—	—
Δ in BW, % (Sema 2.4 vs Sema 1.0)	—	—	—	—	—	—	—	—

BP, blood pressure; BW, body weight; EOT, end of treatment; ETD, estimated treatment difference; HbA_{1c}, glycated hemoglobin; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite Clinical Trials Version; OR, odds ratio; Sema 1.0, once-weekly subcutaneous injection of semaglutide 1.0 mg; Sema 2.4, once-weekly subcutaneous injection of semaglutide 2.4 mg; SF-36v2, Short Form 36 v2 Health Survey, Acute Version; STEP, Semaglutide Treatment Effect in People with obesity; T2D, type 2 diabetes; WC, waist circumference; WM, weight management.

^aFor the STEP 1, STEP 2, and STEP 3 trials, baseline was week 0. For the STEP 4 trial, baseline was week 20.²³ EOT for all was 68 weeks.

^bDenominators for the percentage of participants observed to have BW reduction of at least 5%, at least 10%, at least 15%, and at least 20% at week 68 are the numbers of participants with available data at the week 68 visit (semaglutide group: n = 1212; placebo group: n = 577).¹⁷

known effects of rapid weight loss; no new safety concerns emerged in analyses of safety data from STEPs 1 to 4.^{17,18,22,23} Investigators used the *Medical Dictionary for Regulatory Activities* to identify additional safety areas of interest or focus based on regulatory feedback and requirements and the therapeutic experience previously reported with GLP-1RA treatments.^{17,18,22,23}

Results of STEPs 1, 3, and 4 demonstrated the safety of semaglutide 2.4 mg when used in patients without T2D. Similar rates of adverse events (AEs) were reported in the semaglutide 2.4-mg and placebo arms across the 68-week STEP 1 and 3 trials.^{17,18} In STEP 4, a greater percentage of patients who continued use of semaglutide 2.4 mg after 20 weeks reported AEs compared with those who switched to placebo (81.3% and 75.0%, respectively).²³ In the STEP 2 trial, which included patients with T2D, a larger percentage of patients reported AEs in the semaglutide 2.4-mg group (87.6%) compared with the semaglutide 1.0-mg (81.8%) or placebo (76.9%) groups.²²

Gastrointestinal (GI) disorders were the most frequently reported AEs across STEPs 1 to 4. In STEP 3, which reported the highest rates of GI AEs, 82.8% of patients treated with semaglutide 2.4 mg reported GI AEs vs 63.2% in the placebo arm. Across the trials, nausea, diarrhea, vomiting, and constipation were the most common GI AEs noted, and they occurred more frequently in patients receiving semaglutide 2.4 mg than in patients receiving placebo or semaglutide 1.0 mg. In the semaglutide arm of STEP 3, nausea was reported

in 58.2% of patients (vs 22.1% in placebo arm), diarrhea in 36.1% (vs 22.1%), and vomiting in 27.3% (vs 10.8%). In the trials, GI AEs were generally mild to moderate in severity; for the most part, they did not result in treatment discontinuation. The highest rate of discontinuation due to GI AEs (4.5%) was seen in the semaglutide arm of STEP 1.^{17,18,22,23}

Throughout STEPs 1 to 4, serious AEs were reported more frequently with semaglutide 2.4 mg than with semaglutide 1.0 mg or placebo. These were seen in up to 9.8% of patients receiving semaglutide treatment (STEP 1). Treatment discontinuations related to AEs were mostly due to GI disorders; they occurred at a higher incidence in the semaglutide 2.4-mg groups than in the semaglutide 1.0-mg and placebo groups. The highest rate of these discontinuations was seen in STEP 1—7.0% of the semaglutide arm discontinued due to AEs. One death was reported in each of the study groups in STEPs 1, 2, and 4 (placebo, semaglutide 2.4 mg, and semaglutide 1.0 mg [STEP 2]). No deaths were reported in the STEP 3 trial.^{17,18,22,23}

American Gastroenterological Association Recommendation of Semaglutide 2.4-mg Injection

In November 2022, the American Gastroenterological Association (AGA) issued a new clinical practice guideline on pharmacological interventions for adults with obesity.³⁴ Responding to growing evidence from RCTs about AOMs, to the increasing prevalence of

TABLE 3. Key Safety Results from the STEP 1, 2, 3, and 4 Trials of Semaglutide 2.4-mg Injection^{16-18,22,23}

	STEP 1: WM (NCT03548935) ^{16,17}		STEP 2: WM in T2D (NCT03552757) ^{16,22}			STEP 3: WM with intensive behavioral therapy (NCT03611582) ^{16,18}		STEP 4: Sustained WM (NCT03548987) ^{16,23}	
	Sema 2.4 (n = 1306)	Placebo (n = 655)	Sema 2.4 (n = 403)	Sema 1.0 (n = 402)	Placebo (n = 402)	Sema 2.4 (n = 407)	Placebo (n = 204)	Sema 2.4 (n = 535)	Placebo (n = 268)
AEs, %	89.7	86.4	87.6	81.8	76.9	95.8	96.1	81.3	75.0
Serious AEs, %	9.8	6.4	9.9	7.7	9.2	9.1	2.9	7.7	5.6
AEs leading to treatment discontinuation, %	7.0	3.1	6.2	5.0	3.5	5.9	2.9	2.4	2.2
GI events leading to treatment discontinuation, %	4.5	0.8	4.2	3.5	1.0	3.4	0	—	—
GI AEs, %	74.2	47.9	63.5	57.5	34.3	82.8	63.2	41.9	26.1
Nausea, %	44.2	17.4	33.7	32.1	9.2	58.2	22.1	14.0	4.9
Diarrhea, %	31.5	15.9	21.3	22.1	11.9	36.1	22.1	14.4	7.1
Vomiting, %	24.8	6.6	21.8	13.4	2.7	27.3	10.8	10.3	3.0
Gallbladder-related disorders, % ^a	2.6	1.2	0.2	1.0	0.7	4.9	1.5	2.8	3.7

AE, adverse event; GI, gastrointestinal; Sema 1.0, once-weekly subcutaneous injection of semaglutide 1.0 mg; Sema 2.4, once-weekly subcutaneous injection of semaglutide 2.4 mg; STEP, Semaglutide Treatment Effect in People with obesity; T2D, type 2 diabetes; WM, weight management.

^aPrimarily cholelithiasis^{17,18,23}

obesity and associated conditions, and to the need for guidance on currently available AOMs, guideline authors advanced the evidence-based recommendations of leading societies, including those recommendations discussed by Marc-André Cornier, MD, in the third article of this supplement.^{34,35}

Citing the results of STEPs 1 to 3, STEPs 6 and 8, and other RCTs studying the effects of this agent, AGA guideline authors recommended that semaglutide 2.4 mg “be prioritized over other approved AOMs for the long-term treatment of obesity for most patients.”³⁴

Conclusions

Across STEPs 1 to 4 among adults with obesity with or without T2D, once-weekly subcutaneous semaglutide 2.4 mg demonstrated superiority to placebo and (in STEP 2) to once-weekly subcutaneous semaglutide 1.0 mg as an adjunct to lifestyle modification with respect to weight loss. Semaglutide 2.4 mg provided substantial weight loss that was both clinically and statistically significant, and its safety and tolerability profiles appeared to be similar to those of other GLP-1RAs.

In STEP 1, adults with obesity and without T2D who received semaglutide 2.4 mg had a mean weight loss of 14.9%, which exceeded placebo-based therapy by 12.4%.¹⁷ Although semaglutide 2.4 mg was not investigated in head-to-head trials with other AOMs, the 14.9% reduction seen in STEP 1 was considerably larger than the 4.0% to 10.9% reductions in body weight seen across phase 3 development programs of other agents.⁷ Moreover, 86% of the semaglutide treatment group of this trial lost 5% or more of their baseline body weight, which is the minimum recommended loss to mitigate certain weight-related complications.^{2,17} Importantly, as compared with patients treated with placebo, those treated with semaglutide also were significantly more likely to lose the 10% to 15% of baseline body weight that is recommended to mitigate many weight-related complications.² Semaglutide-treated patients were 14.7 times more likely to lose at least 10% of their baseline body weight and 19.3 times more likely to lose at least 15% of their body weight than were placebo-treated patients.¹⁷

In STEP 1, waist circumference and blood pressure also were reduced to a significantly greater degree for patients receiving semaglutide than they were for those receiving placebo. The semaglutide treatment group lost a mean 9.4 cm more in waist circumference and dropped 5.1 mm Hg more in blood pressure than did the placebo group.¹⁷ Finally, as compared to treatment with placebo, treatment with semaglutide was associated with improved physical functioning and quality of life—the mean SF-36v2 and IWQOL-Lite-CT physical functioning scores for the semaglutide treatment group were higher than they were for the placebo group.¹⁷

Results of STEPs 2 to 4 corroborated the efficacy and safety seen in STEP 1, across patients with T2D (STEP 2) and patients also receiving intensive behavioral therapy (STEP 3), and in comparison to patients

who were withdrawn from semaglutide therapy at 20 weeks (STEP 4). Results of STEP 2 also demonstrated that patients treated with semaglutide 2.4 mg had significantly greater reductions in HbA_{1c} levels than did patients given placebo and significantly greater weight loss than did patients given semaglutide 1.0 mg or placebo.²²

The FDA approval of once-weekly subcutaneous semaglutide 2.4 mg was based upon the results of the STEP 1 to 4 trials, which demonstrate that semaglutide 2.4-mg injection is a safe, well tolerated, and highly effective treatment to promote weight loss, avoid weight regain, and reduce risk factors associated with obesity. As shown in Table 1, the full STEP program seeks to demonstrate the degree to which semaglutide 2.4 mg SC is associated with weight loss recommended to ameliorate comorbidities, as well as its safety and efficacy relative to other GLP-1RAs and other AOMs.^{16-18,20-33} Based on results from the STEP trials and other RCTs of this agent, the AGA recommends that semaglutide 2.4-mg injection be prioritized for the long-term treatment of obesity for most patients.³⁴ ■

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Author Affiliations: Jefferson Health and Sidney Kimmel Medical College at Thomas Jefferson University (JK), Philadelphia, PA.

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Address Correspondence to: Janine Kyrillos, MD, 225 East City Ave, Balu Cynwyd, PA 19004. Email: janine.kyrillos@jefferson.edu

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Managed Care Considerations of Weight Management Interventions for Obesity

Anastassia Amaro, MD; Michael Kaplan, DO; and Danielle C. Massie, PharmD

Introduction

A 2013 resolution passed by the American Medical Association House of Delegates recognized obesity as a chronic medical disease and recommended that providers receive “appropriate financial support and payment from third-party payers” for the medical management of obesity and overweight.¹ Since then, the age-adjusted prevalence of obesity among US adults 20 years or older increased from 37.7% in 2013-2014 to 42.4% in 2017-2018.² With the rising prevalence of obesity comes the greater importance of treatments to combat this serious chronic disease. However, barriers in perception and practice and social determinants of health may hinder access to obesity interventions for clinically meaningful weight loss. Other articles in this supplement cover the extensive body of literature on obesity, including current medical understanding of obesity as a serious, chronic, and treatable disease; the clinical, economic, and patient well-being burdens associated with obesity; the guideline-recommended standard of care in the management of overweight and obesity; and the Semaglutide Treatment Effect in People with obesity (STEP) clinical trials of semaglutide 2.4 mg as a pharmacologic treatment for obesity.³⁻⁶ This article will discuss barriers and opportunities, from a managed care perspective, for achieving clinically impactful weight loss in individuals with excess adiposity.

Clinical Targets for Obesity Treatment

Effective obesity treatment may include lifestyle intervention, metabolic and bariatric surgery, and use of anti-obesity medications (AOMs).^{7,8} Marc-Andre Cornier, MD, further explores guideline recommendations for treatment of obesity and weight-related comorbidities in the third article of this supplement.⁵ Regardless of treatment modality, relatively small reductions in body weight can be effective in achieving clinically significant therapeutic goals for managing obesity and associated diseases.^{7,9}

In 2016, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) published clinical practice guidelines for the medical care of patients with obesity based on clinical characteristics and disease burden.⁷ According to these guidelines, reducing body weight by approximately

ABSTRACT

The growing prevalence of obesity in the United States has presented an opportunity to increase knowledge about optimal treatment approaches based on a better understanding of patient and provider biases, health care coverage and practices, and social determinants of health. Guideline-recommended obesity treatment begins with lifestyle intervention, and weight management may be enhanced by metabolic and bariatric surgery or anti-obesity medication (AOM) use. However, patient and provider perceptions surrounding obesity and different treatment modalities may present barriers to discussion and uptake of these interventions. Furthermore, it is uncommon for all effective obesity treatments (particularly AOMs) to be covered by insurance. Limited patient access to these treatments carries the potential for negative health consequences and higher health care costs. For these reasons, managed care decision makers are encouraged to improve access to effective obesity treatments, including coverage of AOMs such as semaglutide 2.4 mg.

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For author information and disclosures, see end of text.

5% to 15% in individuals with a body mass index (BMI) of at least 25 kg/m² can be sufficient for preventing or delaying the onset of type 2 diabetes (T2D) in at-risk individuals or for inducing clinically meaningful improvements in patients with other weight-related diseases.⁷ This guidance reinforces a report from a 2014 expert multidisciplinary working group panel organized by the National Institutes of Health citing medical evidence that weight loss of 5% to 10% can produce clinically significant health improvements.⁹ The panel noted that maintenance of long-term weight loss and associated downstream benefits on comorbidities is more likely when there is a greater degree of weight loss during the initial intervention period.⁹ Thus, even small amounts of weight loss in individuals with obesity or overweight can be associated with clinically meaningful improvements, and greater degrees of weight loss may confer larger health benefits.⁸

A full exploration of the effects of weight loss on health outcomes in patients with excess adiposity is beyond the scope of this article. However, decreased weight can also reduce the risks of, and improve health outcomes related to, comorbidities other than metabolic disorders and cardiovascular disease (CVD). For example, modest weight loss in patients with obesity and overweight is linked to a decreased risk of total knee replacement in osteoarthritis, increased asthma control, and reduced reflux symptoms and esophageal acid exposure in gastroesophageal reflux disease.^{7,10-12}

Efficacy and Safety of Recommended Obesity Treatment Modalities

A variety of inherited and external factors (eg, genetics, family history, ethnicity, cultural practices, environment, use of certain prescribed medications) can put a person at increased risk for obesity and weight gain.^{7,13} Treatment guidelines for obesity recommend several approaches to weight management; these involve lifestyle intervention and, when lifestyle intervention alone is insufficient, additional treatment modalities, such as pharmacologic or surgical therapies.^{7,8} This article briefly covers the vast literature on safety and efficacy of recommended obesity interventions, focusing mainly on the managed care considerations of obesity treatment.

Lifestyle Intervention

Lifestyle intervention represents the initial standard of care for obesity treatment among patients with overweight or obesity; it also is an essential component of surgical and pharmacologic interventions used in patients who require additional treatment. The 3 primary facets of lifestyle intervention are reduced caloric intake, increased physical activity, and behavioral modifications.^{7,13}

The US Preventive Services Task Force (USPSTF) completed a systematic review of data (published by August 2018) concerning the benefits and harms of interventions for weight loss and maintenance in adults with overweight and obesity.¹⁴ Across 89 trials,

patients who received lifestyle intervention generally lost more weight, were more likely to achieve at least 5% weight loss, and maintained greater weight loss for up to 36 months. Rates of adverse events (AEs) often were not reported in these trials, yet the review found no serious harm related to lifestyle intervention.¹⁴ A separate meta-analysis of randomized clinical trials (RCTs) from 1980 through 2018 examined the results of lifestyle intervention in adults with obesity and overweight.¹⁵ Results from 31 trials involving a wide variety of lifestyle interventions showed that weight loss was greater in the intervention groups than in the control groups at 1 year, although the difference had decreased somewhat by 3 years. The study authors noted that reliable information about the impact of lifestyle intervention on mortality was difficult to gather due to low mortality rates in such studies; still, based on limited data, mortality was lower in the lifestyle intervention arms than in the control arms, although the difference was not significant.¹⁵ As the standard of care, lifestyle interventions are an important component of management for obesity and overweight, and they may help in achieving clinically meaningful weight-loss goals; however, some patients may need adjunctive therapy to lose weight or maintain weight loss.^{7,8}

Bariatric Surgery

Bariatric surgery can be highly effective for weight loss in eligible patients, and it is recommended for patients with severe obesity, as discussed in the third article of this supplement.^{5,7} The results from a meta-analysis of 45 studies on the efficacy of bariatric surgery found that 1 year after surgery, patients who underwent any type of procedure showed superior percentages of excess weight loss vs controls, and this trend remained at 2 and 3 years after surgery for certain procedures.¹⁶ Further, results of an ongoing, prospective, controlled Swedish study assessing long-term (median, > 20 years) mortality outcomes associated with bariatric surgery in patients with obesity showed that bariatric surgery was associated with a significantly lower risk of mortality ($P < .001$) and a decreased risk of mortality due to CVD or cancers than was conventional obesity care.¹⁷

In November 2022, the American Society for Metabolic and Bariatric Surgery released a joint statement with the International Federation for the Surgery of Obesity and Metabolic Disorders that recommends bariatric surgery for individuals with a BMI of at least 35 kg/m² regardless of weight-related complications, for patients with a BMI of at least 30 kg/m² who have T2D, and for those with a BMI of 30 kg/m² to 34.9 kg/m² who have not achieved “substantial and durable” weight loss or improvement in complications using nonsurgical methods.¹⁸ The statement notes that the definition of obesity via BMI thresholds does not apply similarly to all populations, and access to bariatric surgery should not be denied based on BMI criteria alone. At the time of writing, this statement has not been evaluated by authors of the 2016 AACE/ACE treatment guidelines,

which state that bariatric surgery should only be considered for patients with a BMI of at least 40 kg/m² or those with a BMI of at least 35 kg/m² and at least 1 weight-related complication.⁷ Thus, in practice, bariatric surgery may not be an option for those with overweight or with obesity and a lower BMI. Various bariatric surgery procedures may also be associated with short- or long-term AEs, such as pain, development of hernias, wound infection, bleeding, ulcers, band slippage or erosion, gallstone formation, nausea and vomiting, strictures, malnutrition, dumping syndrome, need for revision surgeries, and gastrointestinal (GI) obstruction, leakage, or perforation.^{16,19} For the large proportion of patients with obesity and overweight who do not qualify for, or who are unwilling to consider, bariatric surgery, use of AOMs or other treatment options should be considered.

Pharmacotherapy

The AACE/ACE treatment guidelines for obesity suggest that patients with a BMI of at least 27 kg/m² are eligible for weight management with AOMs.⁷ The guidelines also state that all FDA-approved AOMs, when combined with lifestyle intervention, produce greater and more sustained weight loss when compared with lifestyle intervention alone, and the degree of weight loss achieved with the addition of these medications is associated with greater health benefits.⁷ In November 2022, the American Gastroenterological Association (AGA) released new guidelines on pharmacologic treatment for adults with obesity to support decision-making by patients and health care providers (HCPs) about currently available AOMs.²⁰ The panel considered the benefits and harms derived from a systematic review and meta-analysis of RCTs published through the end of 2021 on subcutaneous injection of semaglutide 2.4 mg (Wegovy[®]; Novo Nordisk) and liraglutide 3.0 mg (Saxenda[®]; Novo Nordisk), as well as the following oral agents: phentermine-topiramate extended release (ER) (Qsymia; VIVUS), naltrexone-bupropion ER (Contrave; Currax Pharmaceuticals), orlistat, phentermine, diethylpropion, and Gelesis100 superabsorbent hydrogel (Plenity; Gelesis).²⁰⁻²⁵ The AGA guidelines strongly recommend AOMs plus lifestyle intervention in patients with obesity or overweight with comorbidities who have not responded adequately to lifestyle intervention alone; further, they note that chronic use of AOMs is generally necessary.²⁰ With the exceptions of orlistat (recommendation against) and Gelesis100 oral superabsorbent hydrogel (no recommendation due to a gap in knowledge), all treatments analyzed were recommended over lifestyle intervention alone in eligible patients. The authors affirmed that “the selection of the medication...should be based on the clinical profile and needs of the patient, including, but not limited to, comorbidities, patients’ preferences, costs, and access to the therapy.”²⁰

A 2022 report from the Institute for Clinical and Economic Review (ICER) reviewed the efficacy and safety of 4 AOMs: semaglutide, liraglutide, phentermine-topiramate ER, and naltrexone-bupropion ER.²⁶

Results showed that use of any of the AOMs in combination with lifestyle intervention produced significantly greater mean weight loss than did placebo with diet and exercise counseling at 1 year ($P < .05$). However, AOMs also were associated with higher discontinuation rates than was placebo.²⁶ Furthermore, the USPSTF systematic review assessing the effectiveness of orlistat, naltrexone-bupropion, phentermine-topiramate, liraglutide, or oral lorcaserin (Belviq; Eisai) compared with control found that AOM groups lost more weight, were more likely to lose 5% of their weight, and generally maintained greater weight loss compared with control groups, although some studies had high dropout rates and short follow-up durations.^{14,27} Rates of serious AEs were generally similar between arms; however, AOMs were associated with more frequent drop-out and higher AE rates than was placebo treatment.¹⁴ However, this study did not review data published after March 2018, and the results do not reflect the withdrawal of lorcaserin from the US drug market in 2020.²⁷

According to prescribing information for AOMs with indications for chronic weight management in patients with obesity or with overweight in the presence of at least 1 weight-related complication, GI AEs are the most reported; other common AEs include paresthesia, dizziness, dysgeusia, insomnia, dry mouth, headache, injection site reaction, fatigue, and, in patients with T2D, hypoglycemia.^{21-24,28} Despite potential AEs, the guidelines clearly recommend that AOMs be available for eligible patients.^{7,8}

Barriers to Treatment

The currently recommended clinical treatment guidelines for obesity involve therapeutic options based on a foundation of lifestyle intervention (including behavioral modification, healthy meal plans, and increased physical activity) in addition to other modalities, including bariatric surgery and AOMs.^{7,8}

However, effective obesity treatment can be hindered by patient and HCP perceptions of obesity and associated treatments, low insurance coverage, social determinants of health that impact accessibility, challenges with treatment adherence, and other factors.

Patient Perceptions

Barriers to effective screening and diagnosis of overweight and obesity may include patient feelings of discomfort or stigmatization in health care settings, prior negative experiences, or the belief that seeking help indicates personal failure.²⁹ Although 65% of people with obesity surveyed as part of the Awareness, Care and Treatment In Obesity Management (ACTION) study (NCT03223493) believed that obesity was a disease, 82% agreed that their weight loss was completely their responsibility, and 44% of those who did not seek help from HCPs for weight loss cited personal responsibility as a reason.³⁰ This survey explored the perceptions of and potential barriers to obesity care based on responses from patients with

obesity (n = 3008) and HCPs (n = 606) in the fall of 2015. Most people with obesity agreed that improved eating habits/calorie reduction and increased physical activity were “completely effective” for long-term weight management (80% and 81%, respectively); however, they perceived lower efficacy for bariatric surgery (40%) and AOMs (27%).³⁰ According to the authors, these perceptions may impact uptake of proven effective weight management interventions, and HCPs have an opportunity to facilitate discussions about obesity with patients who believe that they are completely responsible for their weight loss. However, self-reported data (such as BMI measures) gleaned from the ACTION surveys may prove unreliable, and selection of respondents may have been skewed due to the survey response rate (10%-20%) and average length of time needed to complete the survey (> 37 minutes).³⁰

Patients are often receptive to HCP counseling on weight management, and they may be more likely to engage in a weight-loss attempt or to seriously consider bariatric surgery if their HCP advises them to do so.^{29,31,32} However, not only may patients perceive different levels of effectiveness for various obesity interventions, but patient characteristics are associated with differences in openness to or consideration of discussion about obesity and treatments with HCPs. Results from 1 survey of adult patients with overweight and obesity found that compared with White respondents, those from other racial/ethnic backgrounds were more likely to want weight-related discussions with their HCPs.³³ Results from a different survey of adult patients with a BMI greater than 35 kg/m² showed that compared with women and White patients, men and African American patients were less likely to seriously consider undergoing bariatric surgery.³²

Provider Perceptions

Most HCPs surveyed in the ACTION study agreed that dietary (81%) and physical activity (79%) improvements were “completely effective” for weight loss, yet fewer believed the same of bariatric surgery (62%) or AOMs (30%).³⁰ A separate online survey examined obstacles to obesity management perceived by HCPs in an academic Michigan health system.³⁴ Although most reported addressing BMI during clinic visits, only about half of the providers had discussed weight loss during over 50% of visits with patients with obesity. Among treatments offered, counseling on lifestyle changes was almost universally reported, and discussion about bariatric surgery or AOMs with eligible patients was lower. Reported barriers to offering bariatric surgery included concerns about AEs and surgical risk, lack of either comfort with initiating discussion of surgery or experience with timing for offering surgery, and limited knowledge about bariatric surgery or long-term outcomes. Over 80% of respondents did not offer AOMs to patients with obesity; reported barriers to prescribing AOMs included lack of experience with or awareness of medications, concerns about AEs, high costs or issues with

prior authorizations, and perceived lack of efficacy. Limitations of this study included a small sample size (N = 111), use of a non-validated questionnaire, and a survey population of only primary care providers and endocrinologists.³⁴

In both surveys, HCPs most often cited lack of time during an appointment as an obstacle to initiating discussions of weight loss with patients, and some providers also reported discomfort with broaching the subject.^{30,34} HCPs indicated that they do not provide guideline-recommended counseling on weight management because of inadequate training and counseling skills, lack of time or clinic space and resources, low confidence in efficacy of obesity counseling, and reimbursement challenges.²⁹ Further, authors of a survey study examining weight-related care experiences in adult patients with overweight and obesity posited that providers' lack of comfort with or biases against bariatric surgery or AOM use may have contributed to results showing that most eligible patients received no information about bariatric surgery or AOM treatment.³³ Indeed, an analysis of 2009-2015 data from 8 different health networks showed that 8.3% of prescribers wrote approximately 90% of all filled AOM prescriptions; the authors noted that this trend may have resulted from such prescribing barriers as provider biases, concerns about safety and efficacy, and a lack of uniform and consistent treatment coverage.³⁵

Treatment Coverage

In 2002, the Internal Revenue Service issued a ruling including expenses for obesity treatment as deductible medical expenses.³⁶ That same year, the Social Security Administration determined that obesity was a valid medical source of impairment for disability claims, further supporting the financial needs of patients with obesity and overweight.³⁶ In 2006, the Centers for Medicaid & Medicare Services (CMS) began providing coverage for bariatric surgery under Medicare, removing a significant barrier for patients with obesity who were seeking surgical care.³⁶ However, health plans for federal employers still could exclude obesity care by characterizing obesity as a lifestyle or cosmetic condition.³⁶ This continued until 2014, when the federal Office of Personnel Management issued guidance to health plans that prohibited the practice for federal employers, acknowledging that AOMs can assist adults with obesity who “do not achieve weight loss goals through diet and exercise alone.”^{36,37} States were encouraged to follow suit in 2015, when the National Conference of Insurance Legislators released a resolution urging state legislators, health departments, and other state agencies and institutions to prioritize the prevention and treatment of obesity, including “coverage of the full range of obesity treatments, particularly new innovative measures such as pharmacotherapy and bariatric surgery” to decrease the direct and indirect negative effects of obesity on patient health and quality of life and the US economy.^{36,38}

Current legislation is pending to expand protections for persons with obesity and overweight and to encourage treatment availability and access. The Treat and Reduce Obesity Act of 2021, proposed in the US Senate in March 2021, would update Medicare's rules to expand the list of HCPs (eg, physicians, physician assistants, nurse practitioners, registered dietitians) qualified to provide covered intensive behavioral treatment and to expand Medicare Part D coverage to include AOMs for those with obesity or overweight and 1 or more comorbidities.³⁹

However, current insurance coverage often does not align with obesity treatment guidelines. Providers using evidence-based clinical treatment guidelines to treat patients with obesity face the challenge that private and public health insurers often do not cover certain treatments, as noted in a recent consensus statement from an international expert panel.^{40,41} Only 13% of employed people with obesity in 1 study reported that their employers offered "insurance coverage for the medical treatment of obesity," although the study did not provide details about coverage for specific obesity treatment modalities.³⁰

Coverage of Lifestyle Intervention

Lifestyle intervention forms the foundation of obesity treatment, and long-term counseling can improve long-term weight loss and maintenance.^{7,8,29} However, coverage of behavioral counseling for weight loss can vary based on a patient's insurance coverage and specific diagnoses.

As of November 29, 2011, CMS offers insurance coverage for intensive behavioral therapy for patients with a BMI of at least 30 kg/m² to promote prevention and early detection of associated illness and disability. Intensive behavioral therapy includes obesity screening, dietary assessment, and intensive behavioral counseling and therapy to promote long-term weight loss through high-intensity diet and physical activity interventions.⁴²

In 2018, the USPSTF recommended that "intensive, multicomponent behavioral interventions (ie, behavior-based weight loss and weight loss maintenance interventions)" be offered to or referred for adults with a BMI of 30 kg/m².⁴³ This recommendation was given a grade "B" rating, indicating moderate net benefit. The Patient Protection and Affordable Care Act (ACA) requires group health plans and health insurance issuers that offer group or individual health insurance coverage to cover and impose no cost sharing requirements on services and treatments related to USPSTF recommendations that receive a grade "A" or "B" rating.⁴⁴ However, Medicare currently covers behavioral therapy only in the primary care setting, and nutritional counseling is only covered for patients with certain comorbidities (eg, diabetes, kidney disease); in both cases, Medicare may not cover the frequency or specific services an HCP recommends, and patients may still have out-of-pocket costs.^{40,45,46}

Coverage of Bariatric Surgery

Coverage of bariatric surgery for qualifying individuals is generally high, although only certain patients with obesity are eligible. Since February 21, 2006, CMS offers coverage for several bariatric surgery procedures for Medicare beneficiaries with a BMI of at least 35 kg/m² and at least 1 weight-related complication who have been unsuccessful with other medical treatments for obesity. However, CMS will not cover bariatric surgery to treat obesity in patients without associated comorbidities.⁴⁷

Private insurers often provide conditional coverage for bariatric surgery, as well. In a survey of bariatric surgery coverage policies from the 64 private insurance companies with the highest US market shares using policies that were updated between 2017 to 2018 or collected by phone from company representatives, 61 companies (95%) had defined medical policies for bariatric surgery coverage, whereas the 3 remaining companies did not provide coverage. Among private payers, coverage varied for different procedure types. Further, 56 companies (92%) required that patients meet a criterion of a BMI of at least 40 kg/m² or of at least 35 kg/m² with at least 1 weight-related complication, and 53 companies (87%) required completion of a supervised medical weight management program. A minority of insurers required an obesity diagnosis 1 to 5 years before surgery, and some insurers required the presence of particular comorbidities (eg, T2D, hypertension, obstructive sleep apnea, coronary artery disease). All policies also required prior authorization and covered very few or no out-of-network costs.⁴⁸

Coverage of Pharmacotherapy

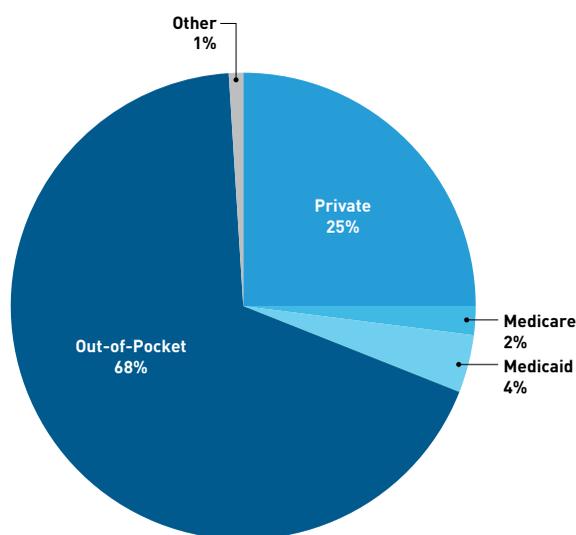
As of 2021, only Virginia and New Mexico mandated AOM coverage for health benefits under the ACA.⁴⁰ In 2014, considering the Federal Employees Health Benefits Program's widespread exclusion of medications for weight management, the US Office of Personnel Management published a supplemental guidance stating that federal coverage of AOMs cannot be denied based on the notion that obesity is a "lifestyle" condition or that obesity treatment is "cosmetic."³⁷ In addition, it emphasized that there is no prohibition of carriers extending coverage to include AOMs. However, insurance coverage of AOMs remains highly variable.

Medicare excludes medications for weight management, including for noncosmetic weight loss, from the definition of a Part D drug. Medicare Part D plans may choose to provide enhanced alternative coverage plans that cover AOMs as a supplemental benefit; however, beneficiaries who opt for a Part D plan offering supplemental benefits must pay the full premium, as Medicare does not subsidize these benefits. An in-depth investigation into the expenditures on, prescriptions for, and insurance coverage of 9 AOMs (phentermine, diethylpropion, benzphetamine, phendimetrazine, orlistat, lorcaserin, phentermine-topiramate ER, liraglutide, and naltrexone-bupropion ER) from the US Government Accountability

Office (GAO) found that only 555 claims from 209 beneficiaries were reimbursed for AOMs in 2017 under this enhanced alternative coverage. Further, coverage of AOMs is optional for state Medicaid and Medicaid managed care plans. The GAO report was based on a review of literature from January 2012 through January 2019, including analyses of federal agency data and interviews with stakeholders from 3 medical associations and 5 advocacy groups. It showed that among states that reimbursed for AOMs in 2017, approximately half covered fewer than 100 claims; further, more than half of all AOM reimbursements were for generic phentermine, which is approved only for short-term use (generally, ≤ 12 weeks).⁴⁹

According to the GAO report's assessment of private employer-sponsored and individually purchased health plans, a substantial proportion of plans provided coverage for AOMs in principle, but many had requirements (prior authorization, determination of medical necessity) that inevitably reduced access. Some plans offered no coverage at all, whereas others covered AOMs as a nonformulary option after a patient tried other treatment options

FIGURE. Average Annual Estimate of Payment Distribution for AOMs by Insurance Type⁴⁹



AOMs, anti-obesity medications.

*"Other" payments include those made by TRICARE, the Veterans Administration, or other federal government sources, such as the Indian Health Service and military treatment facilities.

†The relative SE > 30% for the payment estimate.

‡"Out-of-pocket" payments include payments made by the patient or the patient's family, including insurance co-payments and deductible amounts, and payments for AOMs not covered by insurance.

Source: Agency for Healthcare Research and Quality's estimates from the Medical Expenditure Panel Survey, 2012–2016. Adapted from: US Government Accountability Office. August 2019. Accessed July 22, 2022. <https://www.gao.gov/assets/gao-19-577.pdf>

(eg, behavioral intervention). Overall, older AOMs were more likely to be covered, and newer drugs were more likely to be associated with prior authorizations or higher co-pays.⁴⁹

The GAO also reported that between 2012 and 2016, more than two-thirds (68%) of all money spent on AOMs in the United States involved out-of-pocket payments made by patients (Figure).⁴⁹ These results may indicate the extent to which private and public insurers may not meet the coverage needs of patients. Implications of this report were limited by the analysis of only 9 AOMs approved by the FDA as of June 2019 for short- or long-term treatment of obesity and the imprecise estimates of payments. In addition, reimbursement data included coverage by Medicaid managed care organizations that could provide coverage for AOMs not covered by state plans; Medicaid and Medicare plans that covered an AOM but had no enrolled beneficiaries fill such a prescription were not captured.⁴⁹

Treatment Adherence

Adherence to weight management interventions may be difficult for patients with overweight or obesity. A systematic review and meta-analysis of 27 RCTs and observational studies (2004–2015) on lifestyle intervention adherence found that the overall adherence rate was 60.5%.⁵⁰

Sustaining lifestyle or behavioral changes increases the chance of weight loss. However, adherence to nutritional and physical activity regimens can be difficult to maintain and may often wane after the initial period of weight loss.⁹ This trend may result from the perception that the physical and cognitive efforts required during initial weight loss feel less worthwhile when maintaining achieved weight loss. Additionally, achievement of weight loss outcomes may vary, and weight loss early in the intervention can be predictive of long-term success. These factors serve as elements of a larger physiologic feedback loop, wherein weight loss induces biologic changes that lead to increased appetite and disproportionately decreased energy expenditure.⁹ Additionally, metabolic alterations enhance the body's use and storage of nutrients and encourage the use of carbohydrates, rather than fat, for energy production. These adaptive responses typically do not reset when a reduced body weight is achieved, and they may even become exacerbated over time, promoting weight regain. Thus, although lifestyle intervention is the foundation of obesity treatment, psychological and physiologic barriers may be obstacles to successful and sustained weight loss via lifestyle intervention alone.^{9,13}

Recommended postoperative care for patients undergoing bariatric surgery includes regular follow-up appointments to monitor metabolism and nutrition, consistent physical activity, and evaluation of vitamin levels and need for supplementation in patients at risk for deficiencies.^{51,52} Increased adherence to these measures is associated with improved outcomes. However,

dietary and physical adherence after surgery is often low (< 50%), and adherence to follow-up visits drops substantially over time.⁵²

For patients who receive a prescription for an AOM, ongoing use—required to maintain treatment benefits—can be challenged by the poor rates of medication adherence.⁵³⁻⁵⁵ More than half of patients prescribed long-term AOMs may discontinue or switch treatment within 6 months of initiation (often within the first month), although risk of discontinuation varies with use of different AOMs.^{54,55}

Social Determinants of Health as Obstacles to Treatment

Social determinants of health (SDOH) include a network of interrelated issues that may impact a person's health, including socioeconomic, geographic, occupational, educational, and environmental factors. SDOH can impact weight control through conditions that influence related behaviors; these include income and debt, employment opportunities and health insurance, access to education and nutritious food choices, cost of housing, and characteristics of the neighborhood or locality in which a person resides. Populations negatively impacted by SDOH may face substantial obstacles to achieving weight loss due to associated health inequities.^{56,57}

Sociodemographic criteria may impact the risk of experiencing obesity and patient access to obesity treatments. The results of a Centers for Disease Control and Prevention analysis of National Health and Nutrition Examination Survey data from 2011 to 2014 found that adults in lower income brackets generally had a greater risk of obesity (BMI \geq 30 kg/m²) compared with those in the highest income bracket, as did adults with lower educational levels compared with those with higher educational levels.⁵⁸ HCPs who treat patients with obesity should consider that these groups may be at greater risk for obesity and may have less access to or understanding of health care due to social determinants.⁵⁷⁻⁵⁹ Indeed, patients with lower educational attainment and those living below the poverty level may have lower levels of health literacy, defined as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.”^{57,59}

Clinical guidelines represent what may be considered the ideal for obesity treatment; however, patients negatively impacted by SDOH may not have the capacity or resources necessary to follow such comprehensive treatment plans. Thus, providers should weigh patient preferences and practical considerations to individualize obesity treatment. For example, financial security may influence access to resources that promote healthy weight (eg, gyms and trainers, nutritious foods, and health insurance coverage).^{7,57,60} People with higher family incomes are more often insured, and they tend to have higher rates of private health insurance coverage.⁶⁰ Results from the previously mentioned meta-analysis of studies on adherence to lifestyle intervention found that higher socioeconomic

status was associated with higher adherence.⁵⁰ Further, according to data from a separate international meta-analysis of 9 studies involving nearly 65 million eligible adult patients, those with private insurance were 2.5 times more likely to receive bariatric surgery than were those with nonprivate insurance.⁶¹ Finally, in a study analyzing National Ambulatory Medical Care Survey data (2011-2016) on AOM mentions, individuals with private insurance were significantly more likely to have an AOM mention than were those with public insurance (eg, Medicare, Medicaid), other coverage (including workers' compensation, no charge, or charity), or missing insurance information or self-pay patients, regardless of patient obesity status ($P < .0001$).⁶² Authors of the study posited that this disparity may be due to low public health insurance coverage of these drugs, although they noted that the study design may have led to an underestimation of AOM mentions (ie, consideration of only orlistat, phentermine, diethylpropion, benzphetamine, phendimetrazine, liraglutide, lorcaserin, naltrexone-bupropion ER, or phentermine-topiramate ER).⁶²

Payers are encouraged to examine procedural requirements for coverage of obesity treatment. For example, requiring weekly personalized weight management sessions may create unnecessary barriers to care (eg, cost-prohibitive treatment, patient lack of transportation or inability to get time off work). Payers that will not cover AOMs or bariatric surgery for patients unable to participate in an intensive lifestyle intervention should consider the possible burden of such restrictions on socially or economically disadvantaged patients.

Managed Care Considerations

In the second article of this supplement, Danielle C. Massie, PharmD, and colleagues discuss the clinical burden of obesity, including how many common diseases (eg, T2D, CVD, osteoarthritis, asthma, depression, certain cancers) may be associated with or exacerbated by excess adiposity.⁴ In addition, the risk for weight-related complications can increase in proportion with duration of sustained obesity, demonstrating the profound health consequences that may result from obesity treatment barriers. Investigators on the Coronary Artery Risk Development in Young Adults (CARDIA) multicenter longitudinal cohort study (NCT00005130) analyzed the risk of CVD based on years of obesity or overweight (\geq 25 kg/m²) in 4061 eligible Black and White adult participants.⁶³ The results indicated that greater degree and longer duration of obesity predicted the risk of CVD development in a dose-dependent manner.⁶³ For example, sustaining a BMI of 30 kg/m² for 8 years (equivalent to 50 excess BMI-years) carried a 20% increased risk of CVD, 25% increased risk of coronary heart disease, and 45% increased risk of heart failure.⁶³ Similarly, investigators in an analysis of pooled data from 20,746 participants in 3 long-term birth cohort studies in the United Kingdom assessed the effects of obesity duration over the life course on cardiometabolic

disease risk factors in mid-adulthood.⁶⁴ Serial BMI measurements (total, 5-6) were recorded for each participant from age 10 to 40 years; this was followed by a single biomedical analysis (measurements of blood pressure, lipids, and hemoglobin A_{1c} [HbA_{1c}]) when participants had reached their 40s or 50s. Longer obesity duration was associated with higher HbA_{1c} levels, increased systolic and diastolic blood pressure measurements, increased risk of hypertension, and lower high-density lipoprotein cholesterol levels compared with those of patients who never had obesity ($P < .001$ for all trends).⁶⁴

Investigators on another study analyzed the risk of developing T2D associated with cumulative duration of overweight and obesity over nearly 2.5 million person-years of follow-up in 2 cohorts of women who were registered nurses in the United States.⁶⁵ Results specific to obesity showed that for every 2 years of sustained obesity, T2D risk increased by 14%. Further, among women who had obesity for more than 9 years, the risk of developing T2D was nearly 5 times greater than seen among women who never had obesity, including those with normal or overweight (risk ratio, 4.82; 95% CI, 4.31-5.38).⁶⁵ Finally, the results of a multicenter longitudinal study examined the relationship between sustained overweight or obesity duration and development of obesity-related cancer (cancer of the breast [postmenopausal], colon, rectum, liver, gallbladder, pancreas, endometrium, ovary, kidney, or thyroid) in 73,913 postmenopausal women who were cancer-free at baseline.⁶⁶ Results specific to obesity showed that for every 10 years of obesity, there was a 10% increased risk of developing an obesity-related cancer.

Reported health consequences should be interpreted in the context of study limitations (eg results may not be generalizable due to limited study populations, presence of confounding due to observational study design or differences in height and weight measurement protocols, reliance on self-reports for some data, and risk of missing data inherent in such longitudinal studies).⁶³⁻⁶⁶ Overall, however, the results support that the health consequences of obesity compounded over time. Therefore, timely access to obesity treatment may prevent complications in the long term, and patients may benefit from achieving weight loss regardless of how long they live with obesity.

Quality Measures in Obesity

CMS has tied quality measures to fee-for-service payments to incentivize quality of health outcomes over quantity of procedures. A search of quality measure databases and professional societies conducted in October 2016 and in January 2017 revealed 11 quality measures focused on obesity or BMI in US adults.⁶⁷ Only 2 of 11 measures were actively used within CMS programs at the time of analysis. The measure Adult BMI Assessment calculated the percentage of patients aged 18 to 74 years who had an outpatient visit and whose BMI was documented in the previous 2 years; however, this measure was retired in 2020.^{67,68} The measure Preventive Care and Screening:

BMI Screening and Follow-Up focuses on percentage of adult patients with BMI documentation during the current encounter or within the previous 12 months and with a documented follow-up plan when BMI is outside of the normal weight parameters.⁶⁹ For this measure, the follow-up plan may include documentation of education, referral to an HCP for lifestyle or behavioral therapy, pharmacologic interventions, dietary supplements, and physical activity or nutrition counseling.⁶⁹ Thus, health care systems that encourage HCPs to implement appropriate treatment may be less likely to receive reduced CMS reimbursement.

Additional quality measures in obesity treatment have been investigated. A recent observational study investigated the performance of obesity quality measures using retrospective quantitative data; results showed that the measure Documentation of Obesity Diagnosis—the percentage of adult patients (age, 18-79 years) with at least 1 ambulatory visit during the measurement year, BMI of at least 30 kg/m², and a documented obesity diagnosis—was feasible (performance rates at different sites, 9.8%-35.0%) and reliable (reliability score [scale, 0.0-1.0], 0.996). Although validity of this measure was supported, further testing is needed to improve content validity and scalability of measures focused on improving and documenting obesity care.⁷⁰

Rates of obesity diagnoses in eligible patients attending normal clinic visits could be improved. In the ACTION study, only 55% of patients with obesity who had discussed their weight with their HCP over the previous 5 years reported receiving a diagnosis of obesity.³⁰ In an analysis of 2015 electronic health records in patients 20 years or older at the Cleveland Clinic, only 48% of patients with a BMI of at least 30 mg/m² (n = 134,488) had a documented diagnosis of obesity.⁷¹

Receiving a formal diagnosis of obesity is associated with increased odds of having an obesity management plan or losing weight.²⁹ Thus, documented, confirmed obesity diagnoses can facilitate discussion between HCPs and patients about obesity, patient engagement in weight management interventions, and patient weight loss.⁷⁰ A quality measure that encourages documentation of obesity diagnoses in patient claims or electronic health records may promote positive outcomes in individuals with obesity, and it also can provide information for population identification and planning of larger health initiatives.⁷⁰

Potential Health Care Costs Savings with Obesity Treatments

Obesity and overweight are risk factors for several chronic diseases.⁷² Estimated direct medical costs of treating these conditions total in the hundreds of billions of dollars annually; when considering the indirect costs due to lost economic productivity, the total cost of chronic diseases due to obesity increases into the trillions of dollars.⁷² However, clinically significant weight loss (5%-10% of body

weight) can improve clinical markers of weight-related conditions and lower patient risk of certain comorbidities.^{7,9} Therefore, obesity treatments that can help patients achieve therapeutic weight loss may, by extension, reduce health care costs.

Nonsurgical weight management treatments include lifestyle intervention and AOMs.^{7,73} These may be associated with significant short-term (2 years) health care cost savings ($P < .05$) for patients achieving sustained clinically meaningful weight loss, according to the results of a retrospective analysis of electronic medical record data in over 15,000 patients with obesity between 2012 and 2018.^{7,9,73}

A study modeling Medicare savings calculated that moderate (50%) or extensive (67%) expansion of coverage for lifestyle intervention with or without AOM use would increase treatment utilization and result in billions of dollars in savings over 10 years.⁷⁴ A separate study modeling the economic effects of potential patient weight loss associated with 100% AOM uptake on Medicare, Medicaid, and disability payments estimated that despite increased retirement payouts due to increased survival, the US government would save billions of dollars over 10 years and, potentially, hundreds of billions of dollars over 75 years.⁷⁵ When estimating health care costs across the United States over the long term, widespread coverage of lifestyle intervention and AOMs is modeled to result in substantial cost savings.

Bariatric surgery is highly effective for weight loss in patients with severe obesity, and it may be associated with long-term cost savings.^{7,76} For example, the results of a systematic review and meta-analysis of pooled data from bariatric surgery cost-utility research published through July 2019 in high-income countries (including the United States) found that despite high variability of study results, bariatric surgery can be cost-effective vs usual care (ie, pharmacotherapy and/or lifestyle intervention) over 10 years and over a lifetime horizon.⁷⁶ Unfortunately, there is a dearth of similar studies modeling the long-term cost impact of bariatric surgery on the US health care system, specifically. Surgical weight management procedures can be associated with substantial upfront costs in the United States, including the high inpatient costs associated with bariatric surgeries, and limited US data suggest that this modality may not produce significant long-term direct health care cost savings over 6 to 10 years.⁷⁷⁻⁷⁹ However, these results fail to consider the potential effects of bariatric surgery on indirect costs associated with obesity (eg, premature morbidity and mortality, income and productivity losses, higher disability payments)⁷⁹⁻⁸¹ or on lifetime health care costs for patients and payers.

Semaglutide 2.4 mg for Obesity— Clinical Evidence and Place in Therapy

The third article in this supplement discusses the broader treatment landscape of AOMs and their guideline-recommended place

in therapy. There are currently 5 AOMs FDA-approved for long-term treatment of obesity. The newest is semaglutide 2.4 mg.⁵

Semaglutide is a GLP-1 receptor agonist that promotes weight management by limiting energy intake, increasing satiety, and reducing hunger.^{24,82} In 2021, semaglutide 2.4 mg delivered via subcutaneous injection received FDA approval as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of at least 30 kg/m² or at least 27 kg/m² and in the presence of 1 or more weight-related complications (eg, hypertension, T2D, or dyslipidemia).^{24,83} Efficacy and safety results cited in the prescribing information come from 4 randomized phase 3a trials—STEP 1 (NCT03548935), STEP 2 (NCT03552757), STEP 3 (NCT03611582), and STEP 4 (NCT03548987)—in which patients with overweight or obesity received semaglutide 2.4 mg plus behavioral intervention over 68 weeks.^{24,82} The study populations for STEPs 1, 3, and 4 included either patients with obesity (BMI ≥ 30 kg/m²) or patients with overweight (BMI ≥ 27 kg/m²) and at least 1 non-T2D weight-related complication, whereas the study population for STEP 2 consisted of patients with a BMI of at least 27 kg/m² and T2D.⁸²

In all 4 trials, mean weight loss from baseline was significantly superior to that achieved by patients in the control arms (Table).⁸⁴⁻⁸⁷ Furthermore, in STEPs 1, 2, and 3, patients treated with semaglutide were significantly more likely to achieve at least 5% weight loss from baseline than were control patients (all $P < .001$; STEP 4 did not assess statistical significance of this measure).⁸⁴⁻⁸⁶

Thus, semaglutide 2.4 mg showed clinically meaningful reductions in weight.⁷ Reduced body weight was achieved with semaglutide 2.4 mg, regardless of patient age, sex, race, ethnicity, baseline body weight, or renal function.²⁴ Further, because the trials analyzed AOM use plus lifestyle intervention, the results support the utility of this treatment option for patients who do not achieve meaningful weight loss on lifestyle intervention alone and who are unwilling or unable to undergo bariatric surgery.⁸² In the fourth article of this supplement, Janine Kyrrillos, MD, explores results from the STEP trials in further detail.⁶

Evidence on the place for semaglutide 2.4 mg in therapy is evolving rapidly. In its 2022 guidance, the AGA states that “given the magnitude of net benefit, semaglutide 2.4 mg may be prioritized over other approved AOMs for the long-term treatment of obesity for most patients.” The panel also notes that uncertainty and variability in patient values and preferences on benefits and harms of treatment led to this recommendation being conditional.²⁰

The previously mentioned ICER report analyzed the efficacy, safety, and cost-effectiveness of lifestyle intervention plus semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine-topiramate ER, or naltrexone-bupropion ER. Use of semaglutide and phentermine-topiramate ER was associated with greater weight loss than was treatment with liraglutide or naltrexone-bupropion ER, and

semaglutide therapy appeared to be associated with lower rates of discontinuation due to AEs than were the other drugs. In addition, the combination of semaglutide and lifestyle intervention was more effective, but more costly, than both phentermine-topiramate ER and naltrexone-bupropion ER. To meet typical cost-effectiveness thresholds, pricing of semaglutide would require considerable wholesale acquisition cost discounts; however, semaglutide has shown higher efficacy, a lower AE burden, and greater cost-effectiveness than has liraglutide.²⁶

A separate study modeled the cost-effectiveness of semaglutide 2.4 mg vs other long-term use AOMs (ie, liraglutide 3.0 mg, phentermine-topiramate ER, naltrexone-bupropion ER) as an adjunct to lifestyle intervention in patients with overweight and obesity from a US third-party payer perspective. At a willingness-to-pay threshold of \$150,000 per quality-adjusted life-year gained over a 30-year horizon, semaglutide was deemed to be more cost-effective than no treatment, lifestyle intervention alone, and use of other long-term AOMs. Model parameters were often based on trial data, and that may have limited generalizability of results to the real world, including the course of the disease and the patient population with obesity. Further, lifestyle intervention was modeled after individual counseling provided in the semaglutide STEP 1 trial to support calorie reduction and increased physical activity, which may not represent real-world lifestyle intervention. Finally, treatment efficacy was based upon naïve comparisons of respective pivotal trial data, as indirect or direct head-to-head comparisons of treatments were not available at the time of study completion.⁸⁸

Conclusions

Social and practical barriers, patient and HCP biases, and health care affordability challenge implementation of widespread obesity

treatment. However, views of obesity are changing. Since the official recognition of obesity as a chronic disease in 2013, implementation of the ACA has increased coverage for some obesity treatments. Furthermore, there is increasing evidence and awareness that certain treatment approaches may be more appropriate than others for individual patients. Lifestyle intervention is the foundation of effective weight management initiatives; alone, however, it may not result in successful weight loss or maintenance for a substantial proportion of people with excess adiposity. The addition of bariatric surgery or AOM use may aid in clinically meaningful weight loss that improves health and well-being. Future research should focus on the long-term clinical and economic outcomes associated with use of different interventions and the effects of providing access to and coverage of the full range of obesity treatments for eligible patients. Such research will inform treatment and coverage decisions at the population level, as obesity is a chronic disease that will require long-term individualized treatment. Despite being recommended by obesity treatment guidelines and showing the potential for long-term cost-effectiveness based on current evidence, AOMs—now including semaglutide 2.4 mg—largely are not covered by either public or private insurers. From a managed care perspective, successful treatment of obesity to improve health outcomes and reduce health care costs must take advantage of all available evidence-based modalities for achieving weight loss. ■

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Author Affiliations: University of Pennsylvania (AA), Philadelphia, PA; Stony Brook University Hospital (MK), Stony Brook, NY; Moda Health (DCM), Portland, OR.

TABLE. Primary Efficacy Results from the STEP 1, 2, 3, and 4 Trials of Semaglutide 2.4 mg Injection⁸⁴⁻⁸⁷

From baseline to EOT ^c	STEP 1: WM (NCT03548935) ^{84,a}			STEP 2: WM in type 2 diabetes (NCT03552757) ^{85,b}			STEP 3: WM with intensive behavioral therapy (NCT03611582) ⁸⁶			STEP 4: Sustained WM (NCT03548987) ⁸⁷		
	Sema 2.4 mg (n = 1306)	Placebo (n = 655)	P value	Sema 2.4 mg (n = 404)	Placebo (n = 403)	P value	Sema 2.4 mg (n = 407)	Placebo (n = 204)	P value	Sema 2.4 mg (n = 535)	Placebo (n = 268)	P value
PRIMARY END POINTS												
Δ in BW (%)	-14.9%	-2.4%	<.001	-9.6%	-3.4%	<.0001	-16.0%	-5.7%	<.001	-7.9%	-6.9%	<.001
≥5% loss BW (participants, %)	86.4%	31.5%	<.001	68.8%	28.5%	<.0001	86.6%	47.6%	<.001	—	—	—

BW, body weight; EOT, end of treatment; Sema 2.4, once-weekly subcutaneous injection of semaglutide 2.4 mg; STEP, Semaglutide Treatment Effect in People with obesity; WM, weight management.

^aDenominators for the percentage of participants observed to have BW reduction of ≥5%, ≥10%, ≥15%, and ≥20% at week 68 are the numbers of participants with available data at the week 68 visit (semaglutide group: n = 1212; placebo group: n = 577).⁸⁴

^bThis study included a semaglutide 1.0-mg arm not shown here for conciseness.

^cFor STEPs 1, 2, and 3, baseline was week 0. For STEP 4, baseline was week 20. EOT for all was 68 weeks.⁸⁷

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Address Correspondence to: Michael Kaplan, DO, Long Island Weight Loss Institute, 329 East Main Street, Suite 9, Smithtown, NY 11789. Email: drkaplan@LIWLI.com

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