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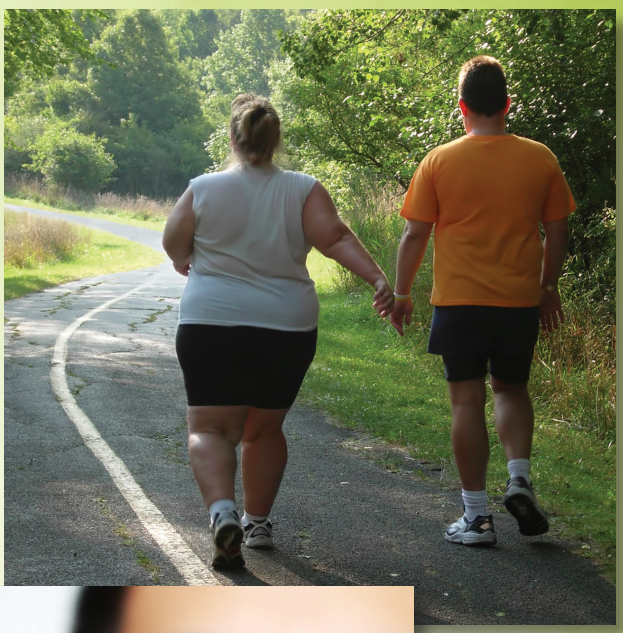

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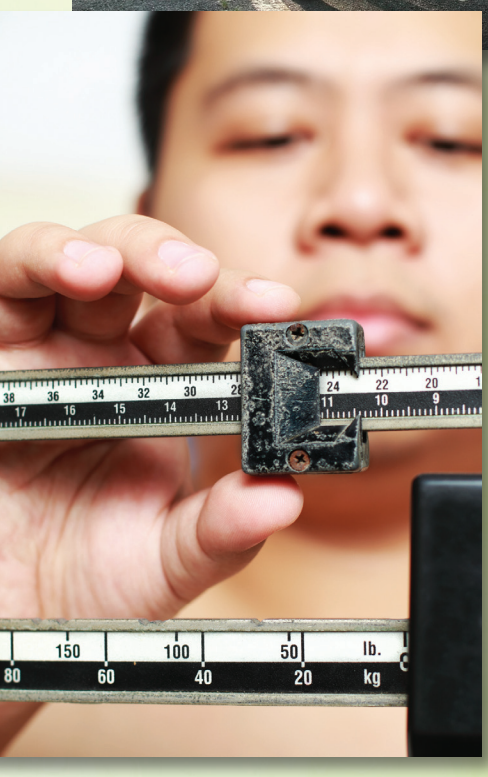

Management of Obesity in Adults

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LEARNING OBJECTIVES

1. Identify adults who are overweight or obese
2. Describe the benefits of weight loss in the obese
3. Describe terminology and strategies for discussing weight with patients
4. List key considerations for managing adults with obesity
5. Outline nutrition and physical activity goals and options
6. Identify the role of medications and bariatric surgery
7. Compare the safety and efficacy of medications approved for long-term use
8. Describe the safety and efficacy of medications in late stage development for obesity
9. Describe future directions in medical therapies for obesity

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INTRODUCTION

Management of Obesity in Adults

Stephen A. Brunton, MD, FAAFP

More than one-third of adults and one-sixth of children and adolescents in the United States are obese (ie, body mass index [BMI] ≥30 kg/m^2).[1] This is more than double the prevalence in 1994 (**FIGURE**).[2] Also of great concern, is that the prevalence of extreme obesity (BMI ≥40 kg/m^2) rose from 3.9% to 6.6% in the United States from 2000 to 2010, a 70% increase.[3] As primary care providers, family physicians contend on a daily basis with cardiovascular and other health consequences of this burgeoning epidemic.

However, despite the gloom that is associated with obesity there is good news. After a steady increase in the daily energy intake from 1955 kcal during 1971-1975 to 2269 kcal during 2003-2004, the daily energy intake has declined to 2195 kcal during 2009-2010.[4] After debate and discussion that spanned more than 2 decades, obesity is now recognized as a disease by most organizations.[5] In 2000, a National Institutes of Health panel was one of the first to describe obesity as a chronic disease.[6] More recently, the American Medical Association adopted a policy in June 2013 recognizing obesity as a disease, with the hope that doing so will help change how the medical community tackles this complex issue.[7]

To help tackle obesity, physicians now have more tools and support than ever before. In late 2011, the US Centers for Medicare and Medicaid Services (CMS) approved Medicare coverage for intensive behavioral therapy for obesity as a stand-alone billable service in the primary care setting.[8] Recognizing the need for long-term management, this action by the CMS is intended to promote sustained weight loss through intensive interventions of diet and exercise.

In 2012, after more than a decade without an approval, the US Food and Drug Administration (FDA) approved 2 medications as adjuncts to a reduced-calorie diet and increased physical activity for chronic weight management. Lorcaserin (Belviq) and phentermine/topiramate extended-release (Qsymia) are approved for use in adults with an initial BMI of ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least 1 weight-related comorbid condition (eg, hypertension, dyslipidemia, type 2 diabetes mellitus).[9,10]

In 2013, the American Heart Association/American College of Cardiology/The Obesity Society released guidelines and an algorithm to guide primary care providers in managing patients that are overweight or obese.[11] Although these guidelines do not include recommendations regarding pharmacotherapy, they provide specific recommendations regarding assessment, lifestyle intervention, and bariatric surgery that are applicable to the primary care setting.

These resources are important because they support the key role that family physicians can play in the management of overweight and obese patients. A recent systematic review and meta-analysis involving 207,226 people in the United States showed the positive impact of primary care physician advice on patient engagement in weight loss efforts (odds ratio, 3.85; $P < .01$) and weight loss.[12] Furthermore, the greater the support provided by physicians, and the health care team in general, and the better patients rated provider communication, the greater the weight lost.[12]

This supplement is intended to serve as an additional resource for family physicians to manage overweight and obese patients. In the first of 5 articles, Drs. Neil Skolnik and Donna Ryan provide a concise background of the pathophysiology and epidemiology of obesity in adults. Recommendations are also provided for patient assessment in a respectful and discrete manner. The importance of good communication with overweight and obese patients is emphasized by Dr. Carlos Campos. Tips are provided regarding how to initiate a discussion about weight with a patient, including the specific words preferred, as well as those found offensive, by patients. Suggestions are also made for assessing patient readiness

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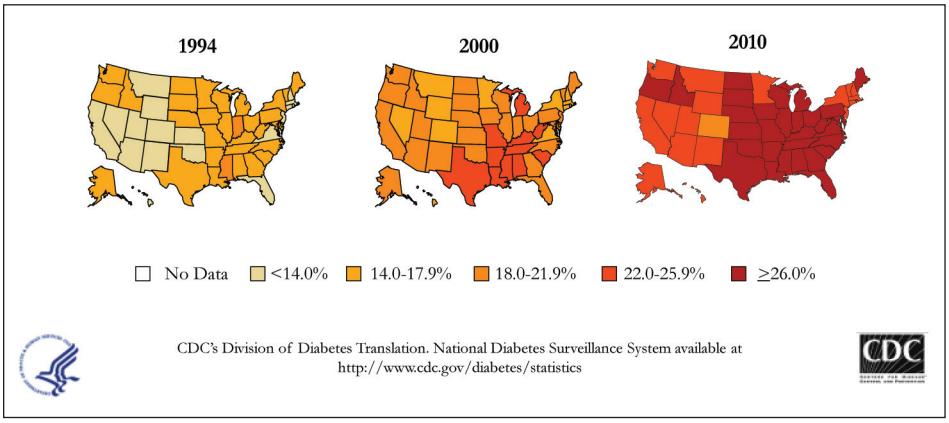
FIGURE Age-adjusted prevalence of obesity (BMI ≥30 kg/m²) among US adults ages ≥18 years[2]



Adapted from CDC's Division of Diabetes Translation National Diabetes Surveillance System, available at: http://www.cdc.gov/diabetes/statistics.

Abbreviation: BMI, body mass index.

to change and motivating patients, as well as setting up the office environment to better manage overweight and obese patients.

The principles and general considerations for managing overweight and obese patients are summarized by Drs. Robert Kushner and Denise Sur. Using a case-based approach, the nonpharmacologic management of patients is described, with details given about nutrition, physical activity, and behavioral therapy. The role of medications and the principles of pharmacologic management are provided by Dr. Donna Ryan, with a focus on the 3 medications approved for long-term use. The role and factors to be considered for bariatric surgery are also described. In the final article, Dr. Louis Aronne provides a look into the near future with a discussion of medications under review by the FDA or in phase III clinical trials for obesity. Also described are evolving approaches to treatment based on a greater understanding of obesity and its causes.

It is hoped that you find this supplement helpful as you provide care to the increasing number of overweight and obese patients in your practice. ●

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Pathophysiology, Epidemiology, and Assessment of Obesity in Adults

Neil S. Skolnik, MD; and Donna H. Ryan, MD

INTRODUCTION

The rising prevalence of obesity has generated extensive investigation into the consequences of, and diseases associated with, obesity. Much has also been learned about how food intake and satiety are regulated in humans and the pathophysiology associated with obesity. Both involve a complex network of central and peripheral pathways and mediators.

Before discussing these topics, as well as the assessment of obesity in adults in primary care, it is necessary to understand how obesity is defined. The accepted definition of overweight and obesity, worldwide, is based on body mass index (BMI), which is a better correlate of total body fat than body weight alone, especially on a population basis.[1] However, the relationship between BMI and percent body fat is less exact on an individual basis, particularly in men (especially those who are very muscular) and with increasing age.[2,3] "Overweight" is defined as having a BMI of 25.0 to 29.9 kg/m^2 and "obesity" applies to patients with a BMI ≥30.0 kg/m^2 (**TABLE 1**).

TABLE 1 Classifications for body mass index[1]

	Body mass index (kg/m^2)
Underweight	<18.5
Normal weight	18.5-24.9
Overweight	25.0-29.9
Obesity (class 1)	30.0-34.9
Obesity (class 2)	35.0-39.9
Extreme obesity (class 3)	≥40.0

REGULATION OF FOOD INTAKE

Obesity results from a chronic imbalance between energy intake and energy expenditure leading to storage of excess energy as fat, primarily in white adipose tissue.[4,5] This seemingly simple fact belies the complex underpinnings of the increasing obesity prevalence observed since 1980. In addition to environmental and behavioral factors, biologic factors influence both the amount and nutritional composition (ie, high-fat, high-sugar) of food ingested. Conventional wisdom ascribes the widespread availability of calorie-dense (ie, high-fat) food and sugary beverages as a major factor contributing to excess energy intake.[4,6]

Why then can't patients who need to lose weight just eat a little less and be a bit more active? Reducing food intake and increasing physical activity have served as the core management strategies for weight loss, but it is clear that instruction in eating less and exercising more is insufficient to produce and sustain weight loss in many patients. Patients struggle because of problems with appetite and metabolic adaptations to weight loss. Most currently available and many evolving treatments have, or are focused on, controlling appetite as a way to produce more weight loss and to sustain reduced weight. (See *The Pharmacological and Surgical Management of Adults With Obesity* and *Evolving Directions in Obesity Management* in this supplement.)

The physician's understanding of regulation of body weight is a critical first step to helping patients lose weight and sustain a reduced weight over the long term. Success at weight loss is determined not solely by motivation and will power, but also by strategies to affect appetite and the reduction in the metabolic rate that accompanies weight loss. This discussion on energy balance regulation serves as a foundation for clinical decision-making in helping patients with weight management.

Energy homeostasis is largely regulated by the brain, with input from the gastrointestinal (GI) tract, other organ systems, and adipose tissue to control food intake, satiety, and energy expenditure (**FIGURE 1**).[7] Current understanding

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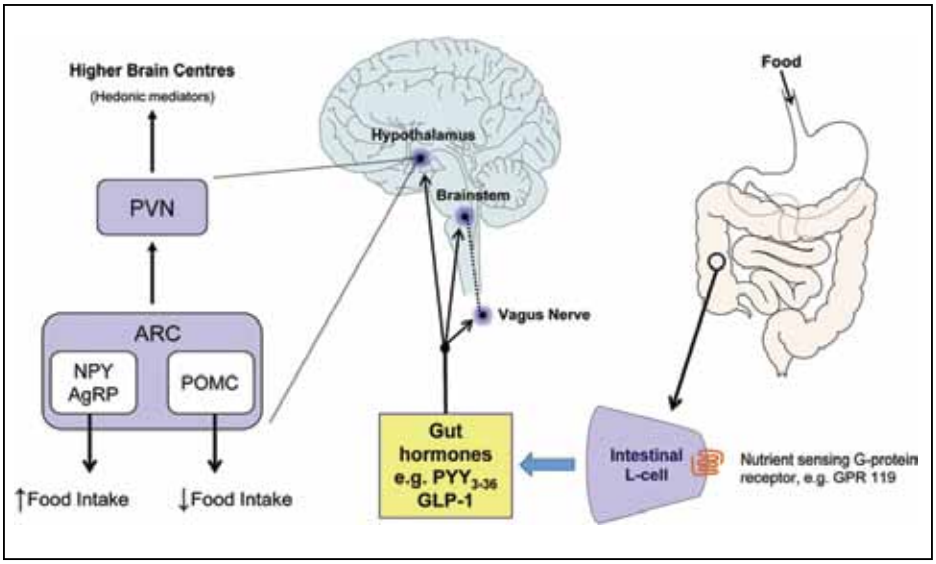
FIGURE 1 **The gut-brain axis regulation of food intake[7]**



Nutrients created by the digestion of food are proposed to activate G protein-coupled receptors on the luminal side of enteroendocrine cells (eg, the L-cell). This stimulates the release of gut hormones which may influence food intake at three sites: the vagus nerve, brainstem, and hypothalamus. Within the arcuate nucleus of the hypothalamus, two neuronal populations are thought to be critical conduits through which peripheral signals are integrated to alter the drive to eat, the orexigenic NPY/AgRP neurons, and the anorexigenic POMC neurons. Further connections between hypothalamic nuclei and higher brain centers may exist, which control the hedonic aspects of food ingestion.

Abbreviations: ARC, arcuate nucleus; AgRP, agouti related peptide; GLP-1, glucagon like peptide-1; NPY, neuropeptide Y; POMC, propiomelanocortin; PVN, paraventricular nucleus; PYY, peptide YY.

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suggests that this complex and highly redundant neurobiologic circuitry involves a variety of chemical mediators (eg, adipokines) and neurochemical pathways (eg, negative feedback regulation).[4,5,8] The way to conceptualize energy balance regulation is to consider peripheral signals (eg, leptin, ghrelin, and glucagon-like peptide-1 [GLP-1]) as informational to the brain on the status of food intake and energy stores. The brain receives these signals and through various neural circuits and neurotransmitters adjusts metabolic rate and appetitive behaviors to eat or stop eating.

Central Regulation

While several areas of the brain are important in regulating feeding, current concepts consider circuitry as being the proper way to conceive appetite regulation. These circuits include the homeostatic systems regulating hunger and satiety, the reward system, and addiction.

The hypothalamus is the regulating center of appetite and energy homeostasis and receives input from all peripheral organs, as well as neural pathways from mainly the brainstem.[8,9] Orexigenic and anorexigenic peptides are the primary integrators of various nutritional information. Both types of peptides are directly and differentially sensitive to hormones such as leptin, insulin, and ghrelin, but also to metabolites, including glucose, fatty acids, and amino acids.[8]

The nonhomeostatic (ie, reward or hedonic) system also plays a major role in feeding behavior. In obesity, hedonic responses generated in mesolimbic dopamine structures override homeostatic regulation to alleviate deficits in reward signaling, resulting in sustained and escalated overeating. Consequently, despite normal or excessive energy storage, palatable foods are over consumed for their pleasurable effects.[8,10]

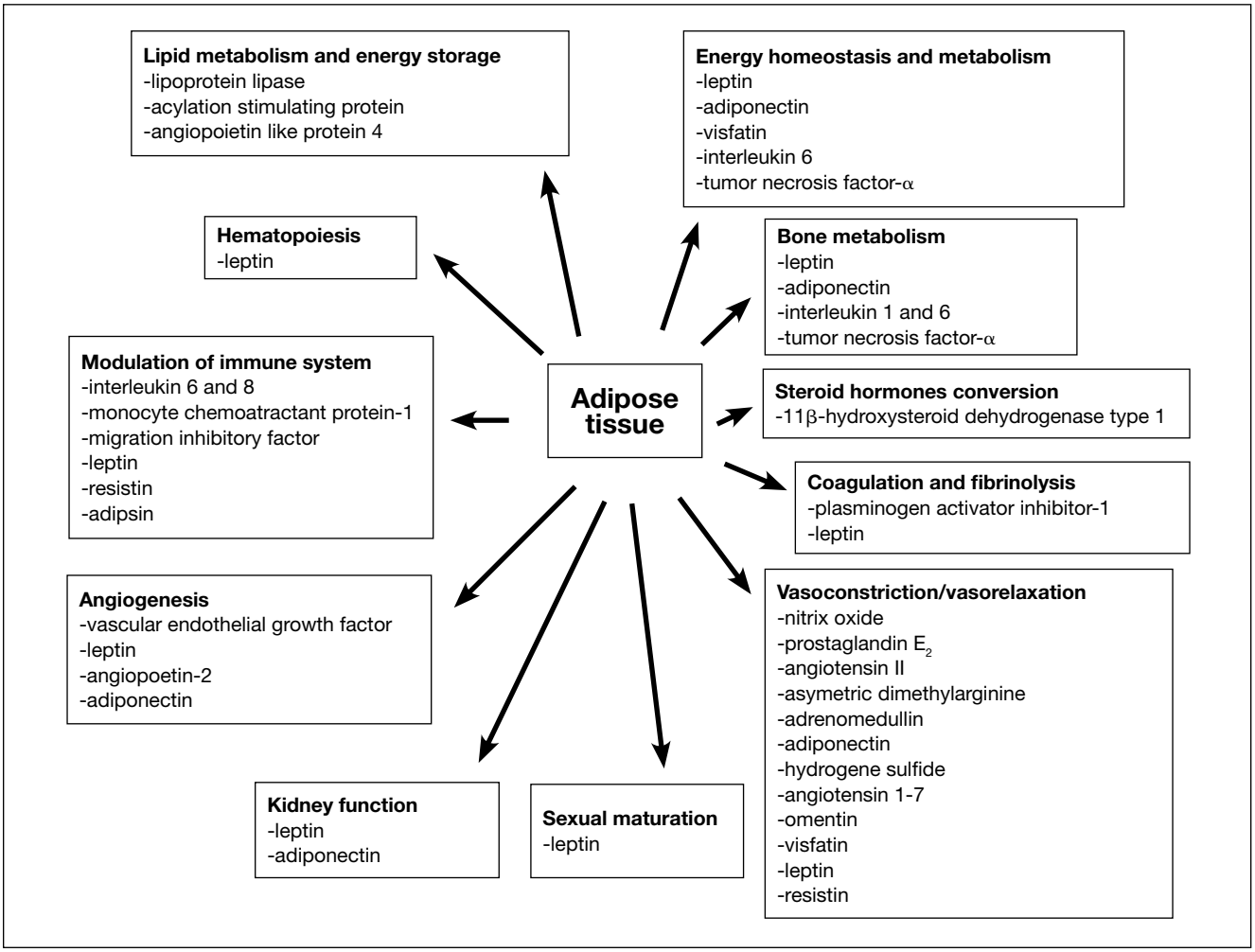
Obesity appears to share some properties observed with drug addiction. Among these properties, impairment in dopaminergic pathways appears to be involved, although it is unclear if the homeostatic or reward system—or both—is affected. Alterations in self-control, conditioning, stress reactivity, and interoceptive awareness have been observed.[11,12]

Peripheral Signals

Adipose tissue is extensively involved in bodily functions by exerting endocrine, paracrine, and autocrine actions (**FIGURE 2**).[13] While brown adipose tissue is mainly involved in thermogenesis, white adipose tissue serves diverse functions.[13] Among these is the production of numerous adipokines such as leptin and adiponectin, both of which play roles in obesity, as well as having important cardiometabolic effects (**TABLE 2**).[13-15]

Leptin is synthesized and secreted in direct proportion to body fat mass, while the level of adiponectin is decreased in obese individuals.[14,15] Leptin is involved in the regulation of food intake and energy expenditure, partly in concert with insulin. Leptin suppresses insulin secretion in a negative feedback loop, whereas insulin stimulates the release of leptin.[15] Deficiency of, and/or resistance to, insulin or leptin is associated with severe obesity, while administration of either directly into the arcuate nucleus suppresses appetite and reduces food intake.[16] Because leptin levels correlate with

FIGURE 2 **The major physiological functions of adipose tissue secretory products[13]**



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body fat stores, and obese individuals have very high levels of leptin as well as hyposensitivity to leptin, clinical trials with leptin did not demonstrate efficacy, even at extremely high doses because of tolerance/resistance.[9,15-18] The leptin level fluctuates throughout the day, with a decreased level correlating with food intake.

The role of adiponectin in obesity is unclear, but appears to involve feedback loops with insulin and pro-inflammatory cytokines. Adiponectin exerts beneficial effects on insulin action in peripheral tissues and promotes pancreatic β-cell function and survival.[14,15] Gut microbiota also appear to play a direct role in regulating weight; they may also act indirectly through GI peptides.

Several hormones secreted in the gut have anorexigenic effects, including cholecystokinin (CCK), pancreatic polypeptide, peptide tyrosine-tyrosine (PYY), GLP-1, and oxyntomodulin, whereas ghrelin has an orexigenic effect.[9] The clinically relevant example of the impact of these hormones on appetite and body weight is with surgical bypass, associated with reduction in ghrelin and increases in GLP-1 and other gut anorexigenic peptides. Cholecystokinin serves as a satiation signal as it is released in response to luminal fat and protein, but not glucose.[8] Indeed, obese women have been shown to have a low fasting CCK level and blunted postprandial response suggesting that CCK may play a role in the pathogenesis of obesity.[10]

Glucagon-like peptide-1 and PYY are secreted through direct luminal stimulation by all 3 macronutrients as well as

TABLE 2 Selected metabolic effects of leptin and adiponectin[13-15]

Mediator	Metabolic effects
Leptin	↓ Food intake ↓ Adipose tissue mass ↑ Insulin sensitivity and improvement of type 2 diabetes ↑ Energy expenditure
Adiponectin	↓ Plasma free fatty acids and muscle triglycerides ↓ Hepatic triglycerides and fatty liver ↑ Hepatic insulin action ↑ Glucose-stimulated insulin secretion ↓ Visceral adipose tissue ↓ Inflammation

neural reflexes originating in the upper small intestine.[8,10] Whereas satiety appears to be the most important action of PYY, GLP-1 has potent effects on suppression of food intake, gastric emptying and motility, and regulation of blood glucose levels by stimulating insulin secretion. Suppression of food intake by GLP-1 occurs locally through vagal afferents and centrally through brain neurons arising from the hindbrain that maintain synaptic connections with the hypothalamus.[8,10] GLP-1 also acts directly on the hypothalamus resulting in reduced food intake.[19] Serving as a signal to initiate food intake, levels of the orexigenic hormone ghrelin rise before the onset of a meal, but are rapidly suppressed upon food ingestion.[10] Gut microbiota also appear to play a direct role in regulating weight; they may also act indirectly through GI peptides.[10]

Many of the hormones and pathways discussed earlier, as well as others, are being investigated as possible targets for therapeutic intervention for either weight loss and/or maintenance (see *Evolving Directions in Obesity Management* in this supplement).

Adaptations in intake regulation to weight loss

Once weight is lost, a variety of compensatory changes occur in several biological pathways involved in the utilization and storage of energy and the regulation of appetite, which together predispose to weight regain.[20] A reduction in resting energy expenditure is observed, perhaps as an adaptive mechanism to protect lean body mass.[21] Adiposity-related signals, such as leptin and insulin, fall during weight loss and remain significantly reduced after 1 year compared with baseline. Conversely, ghrelin levels rise and remain elevated.[17,22] These changes appear to contribute to enhanced hunger and reduced satiety.[21-23] Significant differences from baseline to 1 year in the mean levels of other mediators of appetite have also been observed, including PYY, CCK, and pancreatic polypeptide.[22] In fact, most measures of appetite appear to be enhanced and measures of satiety reduced in the weight-reduced state.[23,24]

Changes in substrate metabolism also occur. For example, weight-stable formerly obese people have lower fasting or 24-hour rate of fat oxidation compared with controls. They may also have an altered ability to appropriately increase fat oxidation in response to a high-fat diet.[24] These changes may stimulate feeding to restore glycogen reserves. These and other adaptations explain the difficulty many persons have in maintaining weight loss long-term. Knowledge of them helps inform a strategy for maintenance of reduced weight, with emphasis on physical activity, vigilance, and reinitiating successful strategies when gain is documented.

Socioecological factors

Many socioecological factors contribute to obesity with a final common pathway of an increase in energy intake relative to energy expenditure. These range from individual factors (age, sex, socioeconomic status, race) to behavioral settings (communities, work, health care, home) to other factors, such as education, media, food-and-beverage industry, and entertainment, and evolving social norms and values.[25] From 1971-1974 to 2005-2008, total caloric intake increased from 2450 kcal/day to 2656 kcal/day in males ages ≥20 years and from 1542 kcal/day to 1811 kcal/day in females ages ≥20 years. The increases were due to ~10% increase in percent of energy from carbohydrates.[26] Factors contributing to the increase in caloric intake in adults are an increase in portion size—particularly of soft drinks, fruit drinks, and fast food—as well as excess availability of calorie-dense food and increased consumption of food outside the home.[25]

On the other side of the energy balance equation, insufficient physical activity remains an issue. Although participation in leisure-time aerobic and muscle-strengthening activities that meet the 2008 federal Physical Activity Guidelines increased from 1998 to 2010 for men and women, only 1-in-5 adults met both the aerobic activity and muscle-strengthening guideline while 1-in-2 adults met neither guideline in 2010.[26]

COMORBIDITIES ASSOCIATED WITH OBESITY

As suggested earlier, adipocytes may play a major role in cardiovascular disease and other comorbidities associated with obesity. White adipose tissue constitutes the largest single endocrine organ and secretes a wide variety of pro-inflammatory and anti-inflammatory substances.[15,27] The pro-inflammatory state resulting from obesity promotes insu-

lin resistance, endothelial dysfunction, hypertension, and dyslipidemia that culminate to increase the likelihood of type 2 diabetes mellitus (T2DM) and promote atherogenesis, coronary heart disease, stroke, and congestive heart failure.[27,28]

Overall, the risk of multimorbidity, ie, the co-occurrence of long-term conditions (such as T2DM and depression), rises with increasing BMI in both men and women. For example, the prevalence of multimorbidity is 23% in normal weight men and 28% in women, rising to 44% and 51% in men and women, respectively, with BMI ≥40 kg/m^2.[29] The risk of T2DM increases with the degree and duration of being overweight or obese as well as with increasing levels of visceral adiposity.[30] The Nurses Health Study showed that persons with a BMI of 25 to 26.9 kg/m^2 were 2.3 times more likely to develop T2DM than those with BMI 23 to 24.9 kg/m^2, while those with BMI ≥31 kg/m^2 were 5.8 times more likely.[31,32] The National Health and Nutrition Examination Survey 2007-2010 showed that adults who are abdominally obese (waist circumference ≥102 cm [40 inches] for men and ≥ 88 cm [35 inches] for women) were more likely to be hypertensive (odds ratio [OR], 1.51; 95% confidence interval [CI], 1.27-1.81).[33] Even those with normal BMI, but with abdominal obesity, were more likely to be hypertensive than those with normal BMI and no abdominal obesity (OR, 1.81; 95% CI, 1.28-2.57).

When all-cause mortality is considered, the association of BMI, and especially BMI categories, can be a cause for confusion. What is abundantly clear is that when BMI is considered as a continuous variable in evaluating population associations with all cause mortality, there is a steady increase in risk, with the nadir usually being a BMI of 22 kg/m^2. When BMI is categorized as overweight and by grade of obesity, being overweight may not always be associated with an increased risk and sometimes will be associated with decreased risk for all cause mortality. What is important for clinicians is that population studies evaluate population risks and do not always inform about individual risks. For this reason, the guidelines issued by the American Heart Association/American College of Cardiology/The Obesity Society (AHA/ACC/TOS) in 2013 utilize BMI as a screening tool.[34]

Weight loss is only indicated for overweight patients with one or more risk factors. Obesity is associated with other health problems, including musculoskeletal conditions, sleep apnea, cholesterol gallstone disease, and GI disorders, such as hiatal hernia, reflux disease, and Barrett esophagus.[27,28,30] There is also an association between obesity and cancer of the breast, cervix, colon, endometrium, esophagus, kidney, liver, ovaries, prostate, and rectum.[27,28,30,35] In women, obesity is associated with depression, menorrhagia, amenorrhea, stress incontinence, polycystic ovary syndrome, and infertility. During pregnancy, obesity is associated with higher rates of maternal complications and health care expenditures as well as negative fetal outcomes.[27,30]

Children who are obese are more likely to suffer from asthma and musculoskeletal pain, injuries, and fractures, and experience impaired psychological functioning than normal weight children.[36-38]

BENEFITS OF WEIGHT LOSS

The benefits of modest weight loss (5%-10%) in obese persons have been clearly demonstrated.[39-47] The Look AHEAD trial (N = 5145) demonstrated benefits in those who had a mean weight loss of 8.6% at 1 year in an intensive lifestyle intervention group compared with those who had a weight loss of 1% in a diabetes support group.[48] Respective improvements from baseline in the lifestyle versus support group were: glycated hemoglobin (HbA_{1c}) (–0.6% vs –0.1%; $P < .001$), systolic blood pressure (BP) (–7 mm Hg vs –3 mm Hg; $P < .001$), diastolic BP (–3 mm Hg vs –2 mm Hg; $P < .001$), low-density lipoprotein cholesterol (–5 mg/dL vs –6 mg/dL; $P = .49$), high-density lipoprotein cholesterol (3 mg/dL vs 1 mg/dL; $P < .001$), and triglycerides (–30 mg/dL vs –15 mg/dL; $P < .001$). Reductions in the use of medications for diabetes, hypertension, and dyslipidemia were also significantly greater in the lifestyle group. At 1 year, patients in the lifestyle group were more likely to experience improvements in symptoms of depression, obstructive sleep apnea, and sexual dysfunction, while fewer developed symptoms of urinary incontinence.[49-52] At 4 years, patients in the lifestyle group were more likely to experience diabetes remission (7% vs 2%, respectively; $P < .001$) and a reduction in the risk of loss of mobility.[39,53] However, the primary endpoint of Look AHEAD was a composite of cardiovascular events. The study was stopped after a median follow-up of 9.6 years because the primary endpoint, though lower in the intervention group compared to the control group, did not show statistical significance. The issue was the low event rates in both groups.[54]

A reduction in the development of T2DM was also observed in persons with impaired glucose tolerance in several studies, most notably the Diabetes Prevention Program (DPP) (N = 3234) and the Da Qing IGT and Diabetes Study (N = 577).[46,55] At mean follow-up of 2.8 years and 10 years in the DPP, the lifestyle intervention group reduced the incidence of T2DM by 58% and 34%, respectively, compared with placebo.[47] In the Da Qing study, the risk of developing T2DM was reduced 31% in the diet intervention group, 46% in the exercise intervention group, and 42% in the diet-plus-exercise intervention group after 6 years of intervention.[55] After an additional 14 years of follow-up, the risk of developing T2DM was reduced 43% in the diet-plus-exercise intervention group.[56]

ATTITUDES AND EXPECTATIONS

The overall management of patients with obesity is complex and often viewed as frustrating by primary care providers (PCPs).[57,58] Many PCPs report limited success in helping obese patients lose weight.[57-59] If physicians view their role in helping patients as simply a matter of telling them to "lose weight," "eat less and exercise more," or "exercise your will power," then frustration for the patient is inevitable. To successfully achieve and maintain weight loss, patients must develop the required skill set. We know that it takes coaching by providers for patients to be successful.

The centerpiece of the 2013 AHA/ACC/TOS guidelines is the recommendation for patients to have access to "comprehensive lifestyle intervention (diet, exercise and behavioral modification), with at least 14 sessions with an interventionist in 6 months and continued follow-up for at least a year."[34] This level of intervention coaching is necessary for patients to achieve the skill set of complex behaviors required to achieve and sustain weight loss. In theory, this coaching could be done by the physician, but the reality is that this is usually most efficiently done by another member of the care team, or through outside referral.

The first step is in setting a weight loss goal. The limited success in helping patients lose weight may reflect unrealistic expectations of physicians and patients in the amount of weight to be lost. Some physicians believe that a 10% reduction in body weight is insufficient to significantly improve obesity-related health complications.[57] Patients often have greater weight loss expectations, as high as 38%.[60-63] In fact, nearly 2 decades ago, Foster and colleagues[64] showed that nearly half of obese women (BMI of 36.3 kg/m^2) did not achieve a weight loss of 17 kg (17% of body weight) after 48 weeks of treatment. Prior to the study, participants had indicated that a weight loss of 17 kg or less would be disappointing. The provider's function is to help the patient shift from cosmetic objectives to health targets and to set achievable goals to meet those health targets.

Not all patients will succeed with intensive comprehensive lifestyle intervention. The AHA/ACC/TOS guidelines endorse medications and bariatric surgical procedures as aids to comprehensive lifestyle intervention for patients who struggle with weight loss and weight loss maintenance.[34] If physicians view their patients' struggles as having a biologic basis, the rationale for these approaches is obvious.

Feelings of dissympathy and discomfort toward obese persons are common among PCPs.[57,58,65] The purpose of understanding the etiology and pathogenesis of obesity and to understand the science behind body weight regulation is to see the patient's struggle with weight as physicians see other diseases. Excess body weight is not a personal choice; it's the result of complex interaction of genetics and environment. Weight loss is not a matter of will power; it is hard work that requires constant vigilance against factors that promote regain.

ASSESSMENT

Screening for obesity is recommended by the US Preventive Services Task Force and the AHA/ACC/TOS for all adults since treatment of obese individuals is associated with improvements in glucose tolerance and other physiologic risk factors for cardiovascular disease.[34,66] The 5 A's model (ask, advise, assess, assist, and arrange) has been found useful to discuss weight with patients and to provide assistance (http://www.drsharma.ca/the-five-as-approach-to-oebsity-counseling.html).[67]

For practical purposes, BMI is a reasonable surrogate measure of total body fat and should be measured annually or more frequently. In addition, waist circumference should be measured annually or more frequently in overweight and obese adults.[34] A waist circumference >35 inches (88 cm) in women and >40 inches (102 cm) in men is considered a cardiovascular risk factor.[1] Patients with BMI or waist circumference above normal should be advised of their greater risk of cardiovascular disease and obesity-related comorbidities as described above.

Assessment of other risk factors for obesity-related comorbidities is essential as they define the level of cardiometabolic risk and mechanical complications and should influence decisions about treatment.[68] To measure physical activity, a variety of tools are available, including activity trackers, smart phone applications, questionnaires, diaries/logs, accelerometer, pedometer, and observation. Among the questionnaires, the Exercise Vital Sign and the Activity Vital Sign are particularly useful for primary care.[69-71] Additional risk factors include elevated BP, lipids, and glucose, as well as established atherosclerotic disease and sleep apnea.[1] Risk assessment tools, such as the Edmonton Obesity Staging System (http://www.drsharma.ca/wp-content/uploads/edmonton-obesity-staging-system-pocket-card.pdf), can be used to guide intervention.[72]

Because of the importance of behavior as an etiologic factor for obesity, a brief behavioral assessment is recommended as well. Employing the transtheoretical model "stage of change" (http://www.uri.edu/research/cprc/transtheoretical.htm) may be helpful to identify a patient's readiness to change (see *Tips for Communicating With Overweight and Obese Patients* in this supplement).[73] Motivational interviewing (http://www.motivationalinterview.org/) may be used to assist patients to move to a new stage of change. When a patient seeks medical assistance with weight loss, the reasons should be identified. Determination should also be made of past weight loss attempts, treatments utilized, and

reasons and barriers for success or failure. Patients should also be screened for the presence of an eating disorder.

SUMMARY

Obesity is a multifactorial disease that results from a combination of both physiological, genetic, and environmental inputs. Obesity is associated with adverse health consequences, including T2DM, cardiovascular disease, musculoskeletal disorders, obstructive sleep apnea, and many types of cancer. The probability of developing adverse health outcomes can be decreased with maintained weight loss of 5% to 10% of current body weight. Body mass index and waist circumference are 2 key measures of body fat. A wide variety of tools are available to assess obesity-related risk factors and guide management. ●

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Tips for Communicating With Overweight and Obese Patients

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INTRODUCTION

A chronic disease such as obesity is primarily managed by the patient who will make decisions on a daily basis that affect their health outcomes. To effectively self-manage their disease, overweight and obese patients must have the necessary knowledge, skills, and motivation to implement a treatment plan that should be developed in collaboration with their health care team.[1] A 2013 survey of overweight patients and their physicians found that only half of these patients reported ever having discussed weight with their physicians. Yet, all physicians indicated they counsel their overweight and obese patients about diet and exercise.[2] These findings, which are relatively unchanged from a 2008 survey, indicate a disconnect in the patient-provider relationship, and suggest an opportunity to improve patient-provider communication regarding excess weight.[3]

The importance of good patient-provider communication cannot be overemphasized due to its significant impact on patient weight and attitudes related to weight management.[4-6] Moreover, a study of 824 patients who completed a previsit and postvisit questionnaire pertaining to their physician's consultation style showed that patients valued 3 elements of the office encounter: communication, partnership, and health promotion.[7]

This article describes various communication techniques that can be implemented in the primary care setting to foster good patient-provider communication as part of a collaborative decision-making process. The goal is to improve patient self-management and motivation, and to achieve better health outcomes. Although patient-provider relationships in conjunction with their health system influence patient-centered communication, the empahsis in this article is on provider factors involving a patient's weight management.[8]

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DISCLOSURES
Dr. Campos discloses that he is on the advisory boards and speakers' bureaus for Bristol-Myers Squibb Company; Eli Lilly and Company; Novo Nordisk, Inc.; and Janssen Pharmaceuticals, Inc.

DISCUSSING WEIGHT WITH PATIENTS

The societal stigma often associated with excess weight means that terms related to weight status may be offensive, misunderstood, and can disrupt the patient-provider relationship.[9] Thus, an initial challenge that the primary care provider faces when managing overweight and obese patients is how to begin the discussion and what terminology to use.

Initiating the discussion

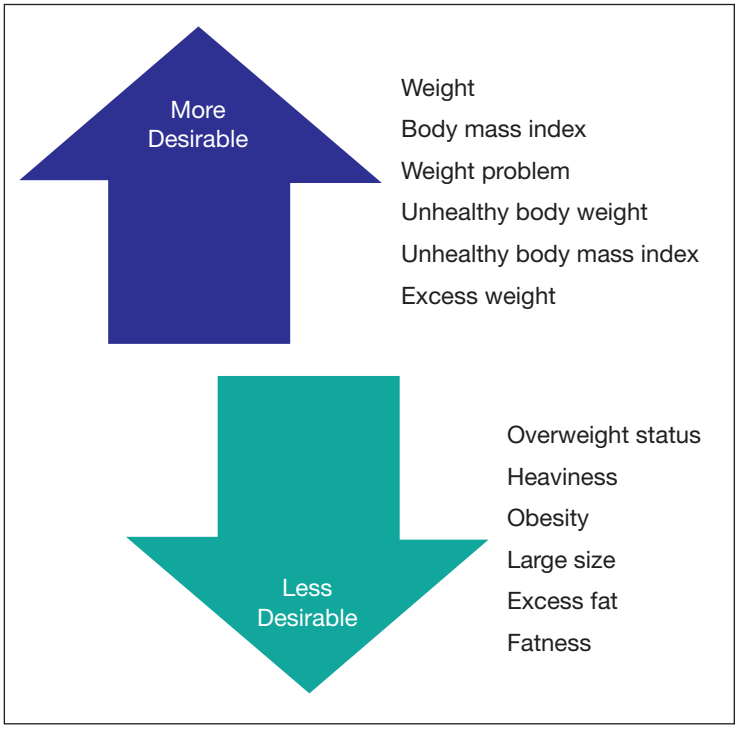
There is no definitive approach when initiating a discussion about a patient's weight, since there are many factors to be considered. These factors include the reason for the patient's visit; whether the patient is new to the practice or they are an existing patient; their overall health status; and lastly, culture, age, and health literacy. For example, the reason for the patient's visit should be addressed first, even if it's unrelated to their weight. By addressing the patient's concerns first, the health care provider conveys the importance of the patient being heard while, at the same time, strengthening the patient-provider relationship.

Once the patient's concerns have been addressed, the topic of weight can be broached by asking if he or she would be comfortable discussing general health care issues such as weight. In some cases, a more direct approach can be taken. For example, if the patient's overall health status is adversely affected by being overweight or the patient has a weight-related condition, such as type 2 diabetes mellitus or hypertension, then the health care provider may want to ask, "Do you think your weight is contributing to your health problems?" or, "Do you have any concerns about your weight?" Both questions can open the way for a constructive dialogue.[10-12] Patients who do not understand that their weight is problematic and that it poses a health risk are unlikely to change their behaviors or even engage in a discussion about losing weight. It is, therefore, important that patients be educated about the health risks associated with obesity (see *Pathophysiology, Epidemiology, and Assessment of Obesity in Adults* in this supplement).[12]

The initial goals for a discussion with the patient about weight are to inform the patient about his or her body weight related to health standards; clearly convey the health risks associated with excess weight; explore the patient's motivation and readiness to engage in weight control; identify previous attempts at weight loss; recognize the barriers to behavioral change; and lastly, establish practical lifestyle changes and short-term goals.[11]

When initiating the discussion about weight, it is helpful to be empathetic and communicate a nonjudgmental attitude that differentiates the weight problem from the patient with the problem. An example might be, "I know it is difficult to lose weight, but it is important for your long-term health." Such an approach establishes a rapport with the patient and demonstrates an interest in understanding the patient's situation, perspective, and feelings. This can be especially important for overweight patients because of their experiences with social stigmatization and personal frustration with previous attempts at weight loss. Empathy also promotes diagnostic accuracy, therapeutic adherence, and patient and provider satisfaction.[10,12]

FIGURE Patient ratings of terms to describe excess weight[13,14]



The importance of terminology

The old adage that words can hurt or heal definitely applies to obesity. The question is which words can heal? That is, which words are preferred by patients and will enable meaningful discussion about weight management? To answer this question, several investigations have been conducted that assesses the responses of overweight and obese patients to terms related to obesity that are commonly used by primary care physicians.[9,13,14] Similar findings were observed among each of the studies. Words such as weight and body mass index (BMI) were preferable vs adjectives that describe excess weight, particularly excess fat and fatness (**FIGURE**).[13,14] Patient ratings generally did not differ according to BMI, gender, or race and ethnicity, athough Caucasians rated the term "obesity" as significantly more undesirable than did African-American patients.[13,14]

ASSESSING MOTIVATION AND READINESS TO CHANGE

An assessment of the patient's motivation for weight loss and readiness to implement and continue with an agreed upon treatment plan is essential. The assessment should include the patient's reasons and motivation to lose weight; previous attempts at weight loss; expected support from family and friends; understanding the risks and benefits of weight loss; level of and attitudes toward physical activity; and potential barriers and previous difficulties or successes with weight loss.[10]

There are several techniques that can be employed to assess the patient's motivation and readiness to change. One is to simply ask the patient on a scale of 1 to 10 (with 10 being ready to take immediate action), how ready he or she is to lose weight. An answer ≤4 indicates that that the patient has very little intention of losing weight. An answer that rates between 5 and 7 indicates ambivalence about taking action to lose weight. In either case, the patient could be asked "What would have to happen for you to be more ready?" or "What would it take to increase your score?" The patient's response should lead the discussion toward identifying and addressing concerns or barriers. An answer between 8 and 10 indicates that the patient is very willing to take action to lose weight.[10]

Motivational interviewing (MI) is a technique increasingly used to assess and strengthen a person's motivation and commitment to change.[15,16] A central concept of MI is the identification, examination, and resolution of ambivalence about changing the patient's behavior. As such, MI does not impose change but rather supports change in a manner compatible with the person's values and concerns.[16] Three key principles of MI are collaboration (vs confrontation), evoca-

TABLE Sample MI questions for discussions with overweight patients[17]

Purpose	Examples of questions[a]
Assess ambivalence and motivation for lifestyle change	How ready do you feel to change your eating patterns and/or lifestyle behaviors?
	What kinds of things have you done in the past to change your eating?
	How much of you is not wanting to change?
	What makes you feel like you can continue to make progress if you decide to?
Readiness to change	People differ in how ready they are to make these kinds of changes. What about you?
	How would you like your health to be different?
	Some people don't want to talk about their weight at all, whereas some people don't mind at all. How do you feel about this?
Importance of change	Tell me how things would be different for you if you ___ (were at a healthier weight, etc).
	What would have to happen before you seriously considered changing?
	What concerns do you have about ___ (losing weight, eating healthier, exercising more)?
Building confidence	What would make you more confident about making these changes?
	How can I help you succeed?
	What are some practical things that you need to do to achieve this goal?
Barriers	What things stand in the way of your taking a first step?
	What barriers might impede success (eg, child care, transportation, distance, cost, accessibility)?

Abbreviation: MI, motivational interviewing.

[a]Reproduced with permission of Yale University Rudd Center for Food Policy & Obesity.

tion (vs imposing ideas), and autonomy (vs authority). Examples of specific questions to ask a patient with excess weight using MI are shown in the **TABLE**.[17] Motivational interviewing can also be used by the provider explicitly taking the negative (status quo) side of ambivalence by stating, "Am I correct in thinking that your current behavior is so important to you that you won't give it up—regardless of the cost?"[16]

While extensive implementation of MI may not be possible in the typical primary care practice, use of MI-consistent behaviors (asking permission, affirming, evoking change, providing support, and emphasizing patient control) is associated with greater patient confidence to improve nutrition and greater weight loss than use of MI-inconsistent behaviors by primary care providers.[4-6] The use of MI has also been shown to lead to significant improvement in weight-related behavior and obesity-related anthropometric measures over 14 weeks in obese children.[18] In a study, persistent benefits have been observed at 12 months of follow-up in some patients. In the study, patients were provided with standard exercise and nutrition information and they also participated in ≤5 face-to-face MI sessions that were delivered by a physical activity specialist and registered dietitian over 6 months.[19]

SETTING UP THE OFFICE ENVIRONMENT

Because the care of overweight patients often requires long-term multimodal therapy that is provided by a team of health care professionals—a systems approach is needed to fully support patients' needs for self-management. The systems approach may include support outside of the office environment, such as support groups, community-based programs, and community-based allied health care professionals. To be successful, the systems approach requires good communication between all providers and staff who have contact with patients. From the front door to the examination room, all team members must provide the same message and level of support. To do so, a system that supports good communication among team members is essential.

Communication with patients can occur outside the examination room and take place before or after the patient's visit. Using telephone, email, or other evolving technologies, patients can be sent reminders about treatment and be provided with 24/7 support. In addition, video-based education can be used in the waiting room using programs such as Emmi (http://www.emmisolutions.com/) that are available via the internet. If a spouse, partner, or family member is involved with buying and preparing the patient's food, it is useful for them to be included in any educational activities.

Another way to facilitate good communication, as well as patient education, is group medical visits. The use of group medical visits is an evolving way to support patients with better self-management of their obesity by enabling them to share their experiences with and learn from other patients, as well as the health care team. Group medical visits work particularly well when there is a mix of experi-

ence among the participants. As with other types of patient education, involvement of the family in group medical visits can facilitate good communication (see *Principles and Nonpharmacologic Management of Obesity in Adults* in this supplement).

CONCLUSION

Good communication between patient and provider, and the health care team in general, is important for effective patient self-management of obesity. The initial goals for a discussion about weight are the following: inform the patient about his body weight related to health standards; clearly convey the health risks associated with excess weight; explore the patient's motivation and readiness to engage in weight control; identify previous attempts at weight loss; elicit barriers to behavioral change; and establish practical lifestyle changes and short-term goals. Motivational interviewing is a valuable strategy to assess motivation and readiness to change and is associated with several weight management-related benefits. An office environment that supports the patient in the long-term management of obesity is essential. Good patient communication can also occur outside of the office visit and can be facilitated through the use of evolving technologies and group medical visits. ●

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Principles and Nonpharmacologic Management of Obesity in Adults

Robert F. Kushner, MD, MS, FACP; and Denise K. Sur, MD

INTRODUCTION

Over a decade ago, guidance for the management of patients with excess body weight became available from recommendations developed by the US National Institutes of Health (NIH).[1] Many of those recommendations remain valid today. In 2013, the American Heart Association (AHA), American College of Cardiology (ACC), and The Obesity Society (TOS) jointly developed and released updated guidelines that were designed for the management of overweight and obese patients in the primary care setting. These guidelines include a detailed algorithm focusing on the assessment and early management of such patients.[2]

CASE STUDY

CW is a 37-year-old female diagnosed with type 2 diabetes mellitus (T2DM) 7 months ago. Her glycated hemoglobin (HbA_{1c}) was 6.8% and fasting plasma glucose was 135 mg/dL. She has made multiple attempts over the past 20 years to lose weight—mostly without physician involvement—and has tried the Atkins diet, and the Weight Watchers and NutriSystem programs. In addition, she has tried various exercise approaches, such as a gym membership and walking at lunch time. She reports that her weight has ranged from 212 to 237 lb with a body mass index (BMI) of 34 to 38 kg/m^2 over the past 20 years. Her current weight is 230 lb, with a BMI of 37 kg/m^2 and a height of 5'6" and a waist circumference of 40.6 inches (103 cm). CW is taking metformin 1000 mg twice daily, and her current HbA_{1C} is 6.1%.

Since being diagnosed with T2DM, CW has become depressed because she knows that diabetes can cause kidney damage and "other bad things." She is partially aware of the link between diabetes and obesity and says she wants to lose at least 50 lb, approximately 22% of her current body weight. She asks her primary care provider to help her.

The primary care provider tells CW he will be glad to help her, and congratulates her on her commitment to losing weight. Recognizing that CW understands some of the consequences of obesity, he decides to talk with CW about the many benefits of losing weight and adopting a healthy lifestyle (see *Pathophysiology, Epidemiology, and Assessment of Obesity in Adults* in this supplement). He also talks with CW about realistic goals and her experiences with previous attempts at weight loss.

GOALS

According to the 2000 NIH and 2013 AHA/ACC/TOS guidelines, there are 2 broad goals for weight management: (1) diminishing the risk of obesity-related comorbidities by reducing body weight, and (2) reducing and maintaining the desired body weight over the long-term.[1,2] Achieving and maintaining a body weight goal is consistent with the treat-to-target approach used for other chronic diseases, such as diabetes and hypertension.

The 2000 NIH guidelines include a recommendation for an initial weight loss of 10% of a patient's body weight over 6 months in order to reduce disease risk factors.[1] The 2013 AHA/ACC/TOS panel examined the relationship between the amount of weight lost in individuals who are overweight or obese, and its impact on cardiovascular (CV) risk factors, CV events, and health and psychological outcomes.[2] In general, the greater the weight loss and the longer weight loss is maintained, the greater the reduction in the risk of developing T2DM and the greater the improvement in glycemic control, high-density lipoprotein-cholesterol, triglycerides, and blood pressure (BP).[2] For example, in overweight and obese adults with T2DM, a weight loss of 5% to 10% at 1 year is associated with HbA_{1c} reduction of 0.6% to 1.0%, as well as a

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DISCLOSURES

Dr. Kushner discloses that he is on the advisory boards for Novo Nordisk, Inc.; Retrofit, Inc.; Takeda Pharmaceuticals U.S.A., Inc.; and VIVUS, Inc. He has intellectual property rights in Retrofit, Inc., and does contracted research for Aspire Bariatrics and Weight Watchers International, Inc.

Dr. Sur discloses that she has no real or apparent conflicts of interest to report.

reduced need for glucose-lowering medications. A 5% weight loss for up to 3 years in overweight or obese adults with CV risk factors reduces systolic and diastolic BP approximately 3 and 2 mm Hg, respectively.

While 5% to 10% weight loss is associated with several benefits, patients often indicate a desire to lose 20% or more of their body weight.[3-7] While these weight loss goals are not practical for most patients, setting realistic goals generally does not lead to more favorable weight loss outcomes. However, not addressing unrealistic patient expectations may lead to patient disappointment.[3,5,8,9]

GENERAL CONSIDERATIONS

Several general considerations regarding the management of overweight and obese patients should be kept in mind. Obesity and being overweight is a chronic, primarily self-managed disease that requires long-term intervention and support. Because patients who are overweight or obese are at an increased health risk—and lifestyle intervention is effective in reducing CV-related risk with no significant adverse consequences—comprehensive lifestyle intervention is a cornerstone of initial as well as long-term management. Lifestyle intervention consisting of proper nutrition, physical activity, and behavior therapy should be encouraged and provided by a multidisciplinary team of medical, nutrition, and behavior experts, as well as other appropriately trained health care professionals in collaboration with the patient. This collaborative approach is consistent with the chronic disease management model and is key in supporting patient self-management, motivation, and adherence.

Lack of patient motivation is reported by many primary care providers as the greatest barrier to weight loss. This indicates that individualizing treatment by identifying barriers to treatment and what will motivate the patient are important when developing a treatment plan.[10-12]

Therefore, it is critical that the health care team provide education and coaching to ensure that patients acquire the knowledge, skills, and self-efficacy needed for self-management.[13,14] Involving the spouse or parents of children in ongoing education is highly recommended.[15] One additional action that should be implemented, is to periodically review all of the medications and supplements that a patient is taking in order to identify any of those that may contribute to weight gain, and then adjust or make substitutions accordingly.

To reduce body weight, a moderate daily energy deficit of approximately 500 to 1000 kcal is generally the goal. This means that the patient must consume 500 to 1000 kcal per day less than the energy expended. Thus, the level of physical activity is as important as caloric intake in determining the daily energy deficit.[16] Validated equations and tools are available to quantify a patient's energy balance and can be used in a primary care setting, or by another provider such as a registered dietitian. For most patients, an energy deficit of approximately 500 to 1000 kcal can be accomplished based upon a daily caloric intake determined by using the **TABLE**.[17]

A very low calorie diet (VLCD), ie ≤800 kcal per day, can be considered for patients with a BMI >30 kg/m^2 who have significant comorbidities or patients who have failed nutritional approaches to weight loss.[16] However, because of the potential for health complications, a VLCD should be used in limited circumstances and only under the supervision of trained clinicians in a medical care setting where medical monitoring and high-intensity lifestyle interventions can be provided.[2]

In primary care, an alternative approach to creating an energy deficit is achieved by restricting the intake of high-carbohydrates and low-fiber or high-fat foods.[1,2] Creating a moderate energy deficit typically results in a weight loss of 1 to 2 pounds per week over the first few months. However, clinicians should not be alarmed by more rapid weight loss if a greater energy deficit is created. Rapid weight loss is not associated with poorer long-term weight-loss outcomes compared with gradual weight loss.[18] Rapid weight loss has been shown to result in significantly greater weight loss after 6 and 18 months.[19,20]

Weight loss often plateaus around 6 months with lifestyle interventions—as well as pharmacologic intervention—due to changes in the resting metabolic rate, muscle efficiency, and patient difficulties with treatment adherence.[1,2] If further weight loss is desired, treatment should be modified to recreate an energy deficit. This may require referral to an obesity, nutrition, or behavior specialist or may include initiation of pharmacotherapy. The addition of either more intensive behavioral therapy or pharmacotherapy has been shown to be more effective in achieving greater weight loss than lifestyle intervention alone.[2,21,22]

Bariatric surgery is an option for patients with a BMI ≥40 kg/m^2 or a BMI ≥35 kg/m^2 that is associated with serious obesity related comorbidities such as T2DM, hypertension, obstructive sleep apnea, and debilitating arthritis.[1,23] If further weight loss is not possible despite combination therapy, treatment should transition to weight maintenance and avoidance of weight regain. Further weight loss can be attempted after a period of weight maintenance, if desired.

Finally, the high likelihood of weight regain following the initial period of weight loss makes it clear that long-term treatment is necessary to prevent or at least reduce the amount of weight regain.[2] Thus, if pharmacotherapy has been initiated, it should be continued long-term, if tolerated (see *The Pharmacological and Surgical Management of Adults With Obesity* in this supplement).[1] The effectiveness

TABLE Recommended caloric intake by sex, age, and activity level[17]

Age (y)	Female (calories)		Male (calories)	
	Sedentary[a,b]	Active[a,c]	Sedentary[a,b]	Active[a,c]
2-3	1000	1000-1400	1000	1000-1400
4-8	1200-1400	1400-1800	1200-1400	1600-2000
9-13	1400-1600	1800-2200	1600-2000	2000-2600
14-18	1800	2400	2000-2400	2800-3200
19-30	1800-2000	2400	2400-2600	3000
31-50	1800	2200	2200-2400	2800-3000
51-70	1600	2000-2200	2000-2200	2600-2800
≥71	1600	2000	2000	2400-2600

[a]Calorie levels are based on the Estimated Energy Requirements (EER) and activity levels from the Institute of Medicine Dietary Reference Intakes Macronutrients Report, 2002.

[b]Sedentary = <30 minutes a day of moderate physical activity in addition to daily activities.

[c]Active = ≥60 minutes a day of moderate physical activity in addition to daily activities.

of long-term treatment beyond 6 to 12 months in providing sustained weight loss has been demonstrated in a recent systematic review and meta-analysis.[24]

CASE STUDY (continued)

CW and her primary care provider agree that a weight loss goal of 5% (12 lb) at 6 months is reasonable. The primary care provider helps CW understand that her weight problem is largely under her control and that the choices she makes each day regarding diet and physical activity affect her body weight. CW says that the self-management of her weight is now clear to her, but that she needs specific directions related to her diet and physical activity that she can follow. CW agrees to meet with a registered dietitian to determine which diet and exercise approaches would be best for her. CW is scheduled for a follow-up visit in 6 weeks.

NONPHARMACOLOGIC MANAGEMENT

The adoption of a healthy lifestyle consisting of proper nutrition, regular physical activity (≥150 minutes per week), appropriate sleep time (≥6 hours per night), and time for recreation or play, stress reduction, and happiness is foundational for weight loss and weight maintenance.[16] Proper nutrition requires that the patient or the responsible family member receive education about meal planning, reading food labels, food purchasing, and food preparation, all in consideration of the patient's culture and food preferences. Similarly, the patient should receive education about types and intensity of physical activity, with individualization based on comorbid conditions. Behavioral therapy should be implemented to support the development and continuation of a healthy lifestyle.

Nutrition

Numerous dietary approaches are available to achieve the desired daily caloric deficit, with each approach resulting in beneficial weight loss. Generally, caloric restriction rather than macronutrient composition (ie, carbohydrates, fats, and protein) is the key determinant of weight loss as most diets commonly used are similarly effective in reducing body weight. The greater the caloric restriction, the greater the weight loss over the short-term.[2] Evidence suggests that Mediterranean, low-carbohydrate, low-glycemic index, and high-protein diets result in greater improvement in glycemic control compared with other diets such as low-fat, American Diabetes Association, European Association for the Study of Diabetes, and low-protein diets (LPD).[25]

The use of commercially available programs and foods, such as Jenny Craig, NutriSystem, and Weight Watchers, are reasonable approaches because of their convenience and support systems. In addition, their use generally provides weight loss of up to 5% to 10% with no greater risks than other approaches to nutrition.[26-31] Thus, the patient's choice of diet is best determined by their preferences and comorbid conditions. Therefore, the diet that produces weight loss and helps the patient adhere to their weight loss is the ideal diet.[32]

Despite their benefits, low-calorie diets are not appropriate for all patients.[16] They should be avoided in pregnant or lactating women, those with serious or unstable psychiatric illnesses (eg, bulimia nervosa and anorexia nervosa), and those with serious health conditions where caloric restriction may worsen their illness (eg, active malignancy, unstable angina, or a recent cardiac or cerebrovascular event).[16] In addition, patients should be educated about possible complications (eg, constipation, hypotension, loss of muscle

mass, cold intolerance, poor wound healing) and psychological symptoms (eg, depression and irritability), loss of libido, menstrual irregularity, and osteoporosis.[16]

Physical activity

Energy expenditure associated with physical activity is an important determinant of the energy deficit and is directly associated with the amount of weight lost. However, since most patients have difficulty in maintaining the moderate or high level of physical activity required, physical activity as the only intervention typically results in <3% weight loss.[33,34] Consequently, discussion about a patient's level of, and interest in, physical activity should be assessed prior to implementing a change. The patient should also be assessed to determine the type and level of physical activity in which the patient can safely engage in excercise. In addition, if the patient's history is uncertain or incomplete, patients should complete the Physical Activity Readiness Questionnaire in order to identify medical conditions that may pose a concern (http://nasm.org/docs/pdf/nasm_par-q-(pdf-21k).pdf).

In addition to contributing to weight loss, increased physical activity is an important determinant of weight maintenance, particularly when continued in combination with diet modification and behavior therapy.[35-37] Beyond weight loss, physical activity is also associated with numerous health benefits. These benefits, which are independent of weight, include improvement in systolic and diastolic blood pressure, resting heart rate, blood lipid levels, blood glucose, hepatic and peripheral insulin sensitivity, aerobic capacity, and mood.[38-42]

Physical activity should include the following components: strengthening, endurance, and flexibility. Moderately intense physical activity of 150 to 250 minutes per week is recommended by the American College of Sports Medicine as sufficient to produce modest weight loss and prevent weight regain of >3% in most adults.[34] For patients who have been physically inactive or have significant comorbidity, initiating physical activity at a lower level such as walking at a pace slower than brisk walking 2 or 3 times a week for 30 minutes is reasonable. The Frequency, Intensity, Time, and Type (FITT) Principle can be used to guide the initiation of physical activity (http://www.collegeofwellness.com/files/file/11%20FITT%20Principle.pdf).

CASE STUDY (continued)

At the 6-week follow-up visit, CW reports that she has had good success in following the treatment plan developed with the registered dietitian that consists of a Mediterranean diet of 1450 kcal per day and physical activity that includes 30 minutes of brisk walking 5 days a week. CW has lost 6 lb. She indicates that her greatest difficulty is avoiding cookies and snack foods since she likes to have something sweet after lunch and dinner and during her afternoon break. The provider praises CW for resisting the urge and suggests substituting fresh fruit or a rare treat in a reduced amount on occasion. They discuss other possibilities for behavior modification.

Behavioral therapy

Behavioral therapy is a key component of treatment for overweight and obese patients. The goal should be to help the patient develop long-term behaviors that provide a balance between nutrition and physical activity. Intensive behavioral therapy (IBT) is implemented to promote sustained weight loss through high-intensity interventions with diet and physical activity and is reimbursable by the US Centers for Medicare and Medicaid Services when provided to Medicare beneficiaries who are obese.[43] To be reimbursable, each IBT for obesity must be consistent with the 5 A's approach (**FIGURE**).[43]

Most clinical trials have shown that behavioral interventions related to diet and physical activity are effective, leading to an average of 4% weight loss at 12 to 18 months.[22] As with physical activity, the amount of weight lost is directly related to the number of behavioral interventions. Behavioral interventions found to be effective include self-monitoring through the use of food diaries, a physical activity log and weight records, stimulus control, stress management to reduce life stressors, cognitive restructuring (ie, changing

FIGURE Five A's approach for obesity[43]

1. **Assess:** Ask about or assess behavioral health risk(s) and factors affecting choice of behavior change goals or methods.
2. **Advise:** Give clear, specific, and personalized behavior change advice, including information about personal health harms and benefits.
3. **Agree:** Collaboratively select appropriate treatment goals and methods based on the beneficiary's interest in, and willingness to, change the behavior.
4. **Assist:** Using behavior change techniques (self-help and/or counseling), aid the beneficiary in achieving agreed-upon goals by acquiring the skills, confidence, and social or environmental supports for behavior change, supplemented with adjunctive medical treatments when appropriate.
5. **Arrange:** Schedule follow-up contacts (in person or by telephone) to provide ongoing assistance or support and to adjust the treatment plan as needed, including referral to more intensive or specialized treatment.

negative thought patterns), and problem solving (eg, preparing strategies to deal with challenging situations).[44]

Patients often identify one or more of their behaviors that contributes to improper nutrition on their low level of physical activity, but they may have difficulty in identifying specific steps to change their behavior. This requires the primary care provider to investigate and identify specific challenges that may be encountered by a patient when attempting to change obesity-related behaviors. Thus, motivational interviewing, the 5 A's, or another approach may be helpful (see *Tips for Communicating with Overweight and Obese Patients* in this supplement).

Moreover, these techniques can be used to motivate patients to change and resolve feelings of ambivalence. When supported by appropriate patient education, strategies to change behaviors should be implemented in a stepwise manner to avoid overwhelming the patient. Successful modification of obesity-related behaviors enables the patient to build on a series of modest successes, thereby gaining confidence and motivation for further, perhaps more difficult changes. Stepwise implementation also provides the primary care provider with the opportunity to more easily modify the treatment plan when needed.

One approach for educating patients about weight-related issues is to learn from other patients. However, patients should be cautioned about patient success stories and testimonials that appear in the lay press and on the internet. Patient stories that have been vetted are available from the National Weight Control Registry (http://www.nwcr.ws/stories.htm).

Another approach is a group medical visit. Not to be confused with a class or group therapy session, a group medical visit includes a group educational session as well as most components of individual patient visits, including one-on-one medical evaluations conducted by a health care provider. Among the many reported benefits of group medical visits are improved health behaviors, increased patient satisfaction, increased physician productivity, improved medication adherence, increased self-efficacy, and decreased health service utilization.[45-47]

In addition to clinical staff, office staff should be available to provide the same functions as with regular office visits (eg, collecting payment and privacy forms, scheduling follow-up visits). Group medical visits require extensive planning—recommendations for preparing and conducting a group medical visit related to obesity are available from the American Academy of Family Physicians (http://www.transformed.com/resources/group_visits.cfm). Other means of providing education and support, such as via internet or telephone, have been successfully implemented, although with less favorable results than with the traditional face-to-face office visit.[2]

CASE STUDY (continued)

At the 6 month follow-up, the physical examination showed that CW achieved her weight loss goal by losing 13 lb (5.7%) of her weight. She experienced a reduction in her BMI of 2.0 kg/m^2 and her waist circumference has decreased by 2 inches (5 cm). Her current HbA_{1c} is 5.8%. CW is pleased with her success, but admits that it has been difficult. She has found it easier to increase her level of physical activity than modify her diet, especially when she gets together with friends or relatives or eats outside of the home. Her provider asks how he can help CW sustain her lifestyle changes. They also discuss further weight loss and the available medications for long-term use.

CONCLUSION

As a chronic and primarily self-managed disease, obesity requires a multimodal intervention provided by a multidisciplinary healthcare team. These interventions have to be realistic, individualized, and monitored. Lifestyle intervention consisting of proper nutrition and physical activity supported by behavioral therapy is the cornerstone of long-term management. Creating an energy deficit of 500 to 1000 kcal per day generally results in 5% to 10% weight loss over 6 to 12 months. Caloric restriction rather than macronutrient composition is the key determinant of weight loss. Once weight loss has plateaued, further weight loss is possible for some by adjusting treatment. For others, weight maintenance with continued provider support for patient self-management is the long-term goal. ●

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The Pharmacological and Surgical Management of Adults With Obesity

Donna H. Ryan, MD

INTRODUCTION

Maximal weight loss for most patients treated with lifestyle intervention is usually achieved on average at 6 months. With the best of lifestyle interventions, the average weight loss, according to the Look AHEAD (Action for Health in Diabetes) study, was 8 kg (approximately 5%-10%) in 6 months.[1] But not all patients are successful in achieving even 5% weight loss due to compensatory mechanisms involving appetite and metabolic rate. Thirty-two percent of patients that were managed with intensive lifestyle intervention in the Look AHEAD study did not achieve 5% weight loss after 1 year.[1] Furthermore, the usual pattern after 6 months is a period of weight stabilization; weight regain occurs gradually over time in many patients.[2]

For patients who do not meet their target weight or weight-related treatment goals with initial lifestyle intervention, or who regain their weight, intensification of therapy is needed. Options for intensification include: additional behavioral therapy; switching to an alternate diet including options for meal replacement; referral to a dietitian; the addition of pharmacotherapy that promotes weight loss; or referral for bariatric surgery.[2] Pharmacotherapy or bariatric surgery can also be considered during the initiation of lifestyle intervention for those patients who have previously participated in a comprehensive lifestyle intervention, but who have been unable to lose weight or sustain weight loss.[2]

This article explores the efficacy, safety, and other factors to be considered regarding the use of medications for chronic weight management. The benefits and risks of bariatric surgery are also discussed.

Rationale for using medications and surgery

Prescription medications serve as an adjunct to lifestyle changes in order to produce the negative energy balance that is required for weight loss. Medication does not work on its own—however, it does suppress the appetite to help the patient ingest fewer calories. With less hunger, more satiety, and the ability to resist food cues induced by medications that act on central appetite centers, patients will be better able to adhere to their diet. Indeed, in clinical studies of approved medications where all patients who are trying to lose weight through lifestyle change, substantially more patients are able to achieve 5% to 10%, or even 15% weight loss when taking active medication compared with placebo. In practice, the weight loss goal for a patient is approximately 5% to 15%. If achieved, these modest and moderate weight loss targets are well known to improve health indices, with greater weight loss yielding more benefits.[2]

Bariatric surgical procedures produce weight loss by restricting the size of a meal (all procedures) and by their effects on gut hormones that affect appetite, such as gastric bypass and gastric sleeve. These procedures have been shown to not only produce weight loss, but to have a positive impact on diabetes, hypertension, dyslipidemia and even mortality.[2]

Barriers to medications and surgery

Despite advances in understanding the science behind obesity, numerous barriers exist that have limited the widespread implementation of obesity pharmacotherapy. Since reimbursement for medication that is used for chronic obesity management is not common, the out-of-pocket cost for this medication can be substantial. Furthermore, in the past, safety has been a major concern leading to withdrawal or non-approval of several medications, including most recently, sibutramine and rimonabant. Similarly, barriers to bariatric surgery include cost, with reimbursement a challenge, and residual concerns among physicians and patients about the safety of these procedures.[3]

PHARMACOTHERAPY FOR WEIGHT LOSS

General considerations

The role of medications for weight loss is as adjunctive therapy to lifestyle intervention in patients with a body mass index (BMI) ≥30 kg/m^2 or ≥27 kg/m^2 who have other risk

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DISCLOSURES
Dr. Ryan discloses that she is on the advisory boards for Eisai Inc.; Janssen Pharmaceuticals, Inc.; Novo Nordisk, Inc.; Takeda Pharmaceuticals U.S.A., Inc.; and VIVUS, Inc. Dr. Ryan has ownership interest in Scientific Intake.

factors or diseases, such as hypertension, dyslipidemia, cardiovascular disease, type 2 diabetes mellitus (T2DM), fatty liver disease, and obstructive sleep apnea.[4] Medications are best suited for patients who are motivated to lose weight and adherent to lifestyle intervention since the combination is more effective than lifestyle intervention or pharmacotherapy alone.[5,6] While a wide variety of medications have been utilized to promote weight loss, only those shown to be effective and approved by the US Food and Drug Administration (FDA) for chronic obesity management should be utilized. Some older medications are approved for short-term use, ie, only a few weeks, but their use results in modest weight loss.

Since obesity requires long-term management, this article will focus on those medications approved for long-term use (ie, 1 year or longer). If the patient does not respond with a reasonable weight loss (1 pound per week) within a few weeks, adherence to the medication, lifestyle intervention, and behavior therapy should be considered. If adherence is verified and the patient remains unresponsive to the medication, or serious adverse effects occur, the medication should be discontinued.[4] Otherwise, unless the weight is regained, the long-term use of medication for weight loss is most effective when continued indefinitely.[4]

The patient should be monitored periodically to measure weight, BMI, waist circumference, blood pressure, heart rate, identify adverse events, answer patient questions, and provide ongoing support. When considering the initiation of pharmacotherapy for weight loss, it is also a good time to review the other medications that the patient is taking and discontinue those associated with weight gain or substitute with a weight neutral medication, if possible.[4]

Medications for long-term use

Three medications are currently available in the United States for long-term obesity management: lorcaserin, orlistat, and phentermine/topiramate extended-release (ER). Available in the United States since 1999, orlistat, a reversible inhibitor of lipase enzymes in the gastrointestinal (GI) tract, reduces fat absorption from the GI tract. Lorcaserin, a serotonin-2C receptor agonist, and phentermine/topiramate ER, a combination of a sympathomimetic and gamma-aminobutyrate agonist, both approved in 2012, are thought to suppress appetite and promote satiety.[7-9] Lorcaserin has been shown to reduce body weight through the reduction of energy intake without influencing energy expenditure.[10] Both lorcaserin and phentermine/topiramate extended-release (ER) are scheduled intravenous (IV) controlled substances. However, lorcaserin, at supratherapeutic doses, is associated with distinct, primarily negative, subjective effects and has low abuse potential.[11] Beyond abuse potential, scheduling medications for obesity is a method of limiting misuse for cosmetic purposes.

Clinical Efficacy and Safety

Orlistat

Orlistat in combination with lifestyle intervention, such as a moderate-fat, calorie-reduced diet, resulted in weight loss of 3.9 kg to 10.6 kg after 1 year and 4.6 kg to 7.6 kg after 2 years of treatment.[4] Orlistat is also associated with reductions in low-density lipoprotein cholesterol (LDL-C) with reductions that are greater than would be expected due to its effect on weight, which is probably due to the low-fat diet the patient is recommended to follow while on the drug.

A 4-year, double-blind, randomized, placebo-controlled trial with orlistat included 3304 overweight patients, 21% of whom had impaired glucose tolerance.[12] In the first year, their mean weight loss was 9.6% below baseline in the orlistat-treated group and 5.6% below baseline in the placebo-treated group. Over the remaining 3 years of the trial, there was a small regain in weight and at the end of 4 years, the orlistat-treated patients were 5.2% below baseline, compared with 2.7% for those receiving placebo. In study patients with impaired glucose tolerance, there was a 37% reduction in the conversion from impaired glucose tolerance to diabetes. In patients with normal glucose tolerance at baseline, 2.6% of patients taking orlistat and 2.7% of patients taking placebo progressed to T2DM over 4 years.

The safety profile of orlistat is good. It is the only obesity medication approved for use in adolescents and is available both by prescription (120 mg 3 times daily) and over the counter (60 mg 3 times daily). However, gastrointestinal adverse events (oily spotting, flatulence, and fecal urgency) limit patient acceptance, although these symptoms are generally mild and transient. Kidney stones may occur in patients at risk for renal insufficiency and in rare cases serious liver injury have been reported with orlistat.[4,13]

Lorcaserin and phentermine/topiramate ER

The clinical efficacy and safety of lorcaserin and phentermine/topiramate ER have been investigated in several randomized, double-blind, placebo-controlled, multicenter, phase 3 clinical trials (**TABLE**).[14-19] Lorcaserin should be discontinued after 12 weeks if the patient has not lost ≥5% of body weight. Similarly, if the patient has not lost ≥3% of body weight after 12 weeks of treatment with phentermine/topiramate ER 7.5 mg/46 mg, the drug should be discontinued or the dose increased. If the dose is increased and the patient has not lost ≥5% of the baseline weight after an additional 12 weeks on a daily dose of phentermine/topiramate ER 15 mg/92 mg, the patient should gradually discontinue use.[9]

TABLE Phase III clinical trials of lorcaserin and phentermine/topiramate ER

Study description	Treatment	Efficacy outcomes[a]	
		Weight-related	Other
Lorcaserin			
Smith et al[14] Adults 18-65 years N = 3037 BMI 30-45 kg/m^2 or 27-45 kg/m^2 with HTN, DL, CVD, IGT, SA	Energy deficit of 600 kcal/day + 30 minutes moderate PA/day and: Lorcaserin 10 mg BID (group A) Or Placebo BID (group B) X 1 year	Weight change, kg: –5.8[b] vs –2.2 Weight loss ≥5%, %: 47.5[b] vs 20.3 Weight loss ≥10%, %: 22.6[b] vs 7.7 Waist circumference, inches: –2.7[b] vs –1.5 BMI, kg/m^2: –2.1[b] vs –0.8	BP, mm Hg: –1.4[c]/–1.1[d] vs –0.8/–0.6 TC, %: -0.9[b] vs 0.6 LDL-C, %: 2.9[c] vs 4.0 HDL-C, %: 0.05 vs –0.2 TG, %: –6.2[b] vs –0.1 HbA_{1c}, %: –0.04[b] vs 0.03
	Then group A randomized (2:1) to: Lorcaserin 10 mg BID Or Placebo While Group B (placebo BID) continued X 1 year	Weight change, kg: 2.5 vs 4.8 vs 1.0 Waist circumference, inches: 0.7 vs 1.4 vs 0.2 BMI, kg/m[b]: 0.9 vs 1.7 vs 0.4	BP, mm Hg: 0.3/0.4 vs 2.6/0.7 vs 0.7/0.7 TC, %: 2.5 vs 3.8 vs 1.9 LDL-C, %: 3.8 vs 5.5 vs 3.4 HDL-C, %: 0 vs 0.4 vs –0.7 TG, %: 10.9 vs 15.0 vs 8.1
Fidler et al[15] Adults 18-65 years N = 4008 BMI 30-45 kg/m^2 or 27-45 kg/m^2 with HTN, DL, CVD, IGT, SA	Energy deficit of 600 kcal/day + 30 minutes moderate PA/day and: Lorcaserin 10 mg BID Or Lorcaserin 10 mg QD Or Placebo X 1 year	Weight change, kg: –5.8[b] vs –4.7[b] vs –2.9 Weight change, %: –5.8[b] vs –4.7[b] vs –2.8 Weight loss ≥5%, %: 47.2[b,e] vs 40.2[b] vs 25.0 Weight loss ≥10%, %: 22.6[b,e] vs 17.4[b] vs 9.7 Waist circumference, inches: –2.5[b] vs –2.3[b] vs –1.6 BMI, kg/m[b]: –2.1[b] vs –1.7[b] vs –1.0 Total body fat, %: –9.9[d] vs –6.1 vs –4.6	BP, mm Hg: –1.9/–1.9 vs –1.3/–1.1 vs –1.2/–1.4 TC, %: –0.7 vs –1.3[c] vs 0 LDL-C, %: 0.3 vs –0.1 vs 1.7 HDL-C, %: 3.7[b] vs 3.5[d] vs 1.3 TG, %: –4.3[c] vs –5.5[d] vs –0.9 HbA_{1c}, %: –0.19 vs –0.17 vs –0.14
O'Neil et al[16] Adults 18-65 years diagnosed with T2DM and treated with metformin, SU, or both N = 603 BMI 27-45 kg/m[b]	Energy deficit of 600 kcal/day + 30 minutes moderate PA/day and: Lorcaserin 10 mg BID Or Lorcaserin 10 mg QD Or Placebo BID X 1 year	Weight change, kg: –4.7[b] vs –5.0[b] vs –1.6 Weight change, %: –4.5[b] vs –5.0[b] vs –1.5 Weight loss ≥5%, %: 37.5[b] vs 44.7[b] vs 16.1 Weight loss ≥10%, %: 16.3[b] vs 18.1[b] vs 4.4 Waist circumference, inches: –2.2[b] vs –2.0 vs –1.3 BMI, kg/m^2: –1.6[b] vs –1.7[b] vs –0.6	BP, mm Hg: –0.8/–1.1 vs 0.6/0.3 vs –0.9/–0.7 TC, %: –0.7 vs 1.4 vs –0.1 LDL-C, %: 4.2 vs 4.2 vs 5.0 HDL-C, %: 5.2[f] vs 4.4 vs 1.6 TG, %: –10.7 vs –5.5 vs –4.8 HbA_{1c}, %: –0.9[b] vs –1.0[b] vs –0.4
Phentermine/topiramate ER			
Gadde et al[17] Adults 18-70 years N = 2487 BMI 27-45 kg/m^2 and ≥2 comorbidities[g]	Diet and lifestyle counseling and: Phentermine/topiramate ER 7.5 mg/46 mg QD Or Phentermine/topiramate ER 15 mg/92 mg QD Or Placebo X 56 weeks[h]	Weight change, kg: –8.1[i] vs –10.2[i] vs –1.4 Weight loss ≥5%, %: 62[i] vs 70[i] vs 21 Weight loss ≥10%, %: 37[i] vs 48[i] vs 7 Waist circumference, inches: –3[i] vs –3.6[i] vs –0.9	BP, mm Hg: –4.7[b]/–3.4 vs –5.6[i]/–3.8[f] vs –2.4/–2.7 TC, %: –4.9[c] vs –6.3[i] vs –3.3 LDL-C, %: –3.7 vs –6.9[d] vs –4.1 HDL-C, %: 5.2[i] vs 6.8[i] vs 1.2 TG, %: –8.6[i] vs –10.6[i] vs 4.7 HbA_{1c}, %: 0[i] vs –0.1[i] vs 0.1

CONTINUED

Lorcaserin

The BLOOM,[14] BLOSSOM,[15] and BLOOM-DM[16] trials involved 7648 overweight or obese patients. Results of the 3 trials showed that the combination of lorcaserin with lifestyle intervention resulted in significantly greater reductions in body weight, BMI, and waist circumference than the

TABLE Phase III clinical trials of lorcaserin and phentermine/topiramate ER *(continued)*

Study description	Treatment	Efficacy outcomes[a]	
		Weight-related	Other
Garvey et al[18] 52-week extension of the above trial N = 676	Diet and lifestyle counseling and: Phentermine/topiramate ER 7.5 mg/46 mg QD Or Phentermine/topiramate ER 15 mg/92 mg QD Or Placebo X 52 weeks	From baseline to week 108: Weight change, kg: –9.6[i] vs –10.9[i] vs –2.1 Weight change, %: –9.3[i] vs –10.5[i] vs –1.8 Weight loss ≥5%, %: 75.2[i] vs 79.3[i] vs 30.0 Weight loss ≥10%, %: 50.3[i] vs 53.9[i] vs 11.5 Waist circumference, inches: –3.9[i] vs –4.2[i] vs –1.4	From baseline to week 108: BP, mm Hg: –4.7/–3.7 vs –4.3/–3.5 vs –3.2/–3.9 LDL-C, %: –4.6[d] vs –5.6[d] vs –10.7 HDL-C, %: 7.3 vs 11.9[i] vs 4.7 TG, %: –12.5[d] vs –13.7[i] vs 0.4 HbA_{1c}, %: 0.01 vs 0.00 vs 0.2
Allison et al[19] Adults 18-70 years N = 1263 BMI ≥35 kg/m^2	Energy reduction of 500 kcal/day + PA and: Phentermine/topiramate ER 3.75/23 mg QD Or Phentermine/topiramate ER 15/92 mg QD Or Placebo X 56 weeks[h]	Weight change, %: –5.1[i] vs –10.9[i] vs –1.6 Weight loss ≥5%, %: 44.9[i] vs 66.7[i] vs 17.3 Weight loss ≥10%, %: 18.8[i] vs 47.2[i] vs 7.4 Waist circumference, inches: –2.2[b] vs –4.3[i] vs –1.2	BP, mm Hg: –1.8[f]/–0.1 vs –2.9[j]/–1.5[j] vs 0.9/0.4 TC, %: –5.4 vs –6.0[f] vs –3.5 LDL-C, %: –7.7 vs –8.4[c] vs –5.5 HDL-C, %: 0.5 vs 3.5[j] vs 0 TG, %: 5.2 vs –5.2[f] vs 9.1

BID, twice daily; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DL, dyslipidemia; ER, extended-release; FBG, fasting blood glucose; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; PA, physical activity; QD, once daily; SA, sleep apnea; SU, sulfonylurea; T2DM, type diabetes mellitus; TC, total cholesterol; TG, triglycerides; URI, upper respiratory infection.

[a]Mean values

[b]$P \leq .001$ vs placebo

[c]$P \leq .05$ vs placebo

[d]$P \leq .01$ vs placebo

[e]$P < .01$ lorcaserin QD vs lorcaserin BID

[f]$P \leq .005$ vs placebo

[g]Systolic BP 140-160 mm Hg (130-160 mm Hg if diabetic); diastolic BP 90-100 mm Hg (85-100 mm Hg if diabetic); taking ≥2 antihypertensive medications; TG 200-400 mg/dL; taking ≥2 lipid-lowering medications; fasting blood glucose >100 mg/dL; 2-h postprandial glucose >140 mg/dL; T2DM managed with lifestyle intervention or metformin; or waist circumference ≥40 inches (men) or ≥35 inches (women)

[h]all patients had dose titration during the initial 4 weeks starting at phentermine/topiramate ER 3.75 mg/23 mg, or placebo, with weekly increases in phentermine/topiramate ER 3.75 mg/23 mg until achieving the assigned dose, which were then maintained for 52 weeks

[i]$P \leq .0001$ vs placebo

[j]$P \leq .0005$ vs placebo

combination of placebo with lifestyle intervention. Mean reductions in body weight ranged from 4.7 kg to 5.8 kg over 1 year for lorcaserin 10 mg twice daily, the dose approved by the FDA. Significantly more patients lost ≥5% of their body weight with lorcaserin than placebo (37.5% to 47.5% vs 16.1% to 25.0%, respectively).

Lorcaserin led to significant improvement in some secondary efficacy endpoints compared with placebo, although improvements did not meet statistical significance in all 3 studies. Lorcaserin did show significant improvement on glycemic parameters across the studies. In the BLOOM-DM trial, which included only patients with diabetes, lorcaserin 10 mg once or twice daily led to significant improvement in the glycated hemoglobin (HbA_{1c}) compared with placebo (-1.0% vs -0.9% vs -0.4%, respectively; P <.001 for both doses of lorcaserin vs placebo).[16] Quality of life improved significantly in the BLOOM and BLOSSOM trials.[14,15]

Lorcaserin has been shown to have a favorable tolerability profile. The most commonly observed adverse events with lorcaserin included: headache, upper respiratory infection, nausea, dizziness, and fatigue.[14-16] The 1-year completion rates ranged from 55.4% to 69.5% in the lorcaserin group and 45.1% to 62.1% in the placebo group. Discontinuation due to an adverse event related to lorcaserin occurred in 7.1% to 8.6% of patients compared with 4.3% to 6.7% of placebo patients. Headache and dizziness were com-

mon reasons for discontinuation. Across the 3 trials, new valvulopathy occurred in 2.37% of lorcaserin patients and 2.04% of placebo patients (risk ratio, 1.16; 95% confidence interval, -0.46 to 1.13).[20] One concern is the use of lorcaserin with other serotonergic drugs since there is a possible risk of serotonin syndrome. Examples of serotonergic drugs include: selective serotonin reuptake inhibitors; serotonin-norepinephrine reuptake inhibitors; monoamine oxidase inhibitors; triptans; bupropion; dextromethorphan; and St. John's Wort.[8]

Phentermine/topiramate ER

The CONQUER,[17] SEQUEL,[18] and EQUIP[19] trials involved 4426 overweight or obese patients. Results of the 3 trials showed that the combination of diet and lifestyle intervention with phentermine/topiramate ER (at doses of 3.75 mg/23 mg, 7.5 mg/46 mg, or 15 mg/92 mg once daily) led to significantly greater reductions in body weight and waist circumference than the combination of diet and lifestyle intervention with placebo. The mean weight loss ranged from 5.1% with phentermine/topiramate ER 3.75 mg/23 mg once daily to 10.9% with phentermine/topiramate ER 15 mg/92 mg once daily; weight loss was 1.6% with the addition of placebo.[19] Significantly more patients with phentermine/topiramate ER at all 3 dose levels experienced weight loss ≥5% than placebo patients (ranging from 44.9% to 79.3% for phentermine/topiramate ER and 17.3% to 30.0% for placebo). Weight loss associated with phentermine/topiramate ER has been shown to result in improvements in symptoms related to obstructive sleep apnea in obese patients.[21]

Compared with placebo, significant improvements were observed in other endpoints with phentermine/topiramate ER at once-daily doses of 7.5 mg/46 mg and 15 mg/92 mg. A subanalysis of the CONQUER trial showed that the dose-related weight loss induced by phentermine/topiramate ER was accompanied by significant improvements with cardiovascular risk factors in patients who had dyslipidemia or hypertension at baseline.[22] Two-year results of the SEQUEL trial showed that there was minimal change in the HbA_{1c} (0.01% vs 0.0%) and fasting glucose (0.1 vs -1.2 mg/dL) levels with phentermine/topiramate ER 7.5 mg/46 mg and 15 mg/92 mg, respectively.[18] The annualized incidence rates for progression to T2DM among patients without T2DM at baseline were 1.7%, 0.9%, and 3.7% in the phentermine/topiramate ER 7.5 mg/46 mg and 15 mg/92 mg and placebo groups, respectively.

The most commonly observed adverse events with phentermine/topiramate ER were dry mouth, constipation, paresthesia, and dysgeusia.[17-19] The carbonic anhydrase inhibitory effects of topiramate contribute to the paresthesias and altered taste sensations with carbonated beverages. The percentage of patients who completed the trials ranged from 58.3% to 82.9% for phentermine/topiramate ER to 46.9% to 86.3% for placebo. Discontinuation due to an adverse event occurred in 4.5% to 16.7% for phentermine/topiramate ER and 3.1% to 8.9% for placebo. The most common adverse events leading to discontinuation were: insomnia, irritability, anxiety, headache, disturbance in attention, depression, dry mouth, and nephrolithiasis.[19] Psychiatric adverse events (eg, depression, anxiety, irritability) and cognitive adverse events (eg, disturbance in attention) generally occurred early with treatment, resolved on discontinuation, and were dose-dependent.[17] A small increase in heart rate was observed (0.3 to 1.7 beats per minute), although more phentermine/topiramate ER patients had increases of more than 10 beats per minute at 2 consecutive visits. Consequently, the patient's heart rate should be closely monitored.

The recommended dose of phentermine/topiramate ER is 7.5 mg/46 mg, although dose escalation from 3.75 mg/23 mg is required. The recommended dose is chosen because of a more favorable tolerability and near equal weight loss. Dose escalation for nonresponse may occur as noted above. No congenital malformations were observed in the 20 pregnancies that occurred in the 3 trials; however, topiramate is associated with a higher risk of orofacial cleft.[23] Therefore, phentermine/topiramate ER is contraindicated in pregnancy. The use of contraception with pregnancy testing before and during the use of phentermine/topiramate ER is advised.[9]

SURGERY FOR WEIGHT LOSS

The effectiveness of bariatric surgery for promoting significant weight loss and health improvements was shown in the Swedish Obese Subjects (SOS) study[24] and confirmed in a systematic review conducted in the development of the American Heart Association/American College of Cardiology/The Obesity Society (AHA/ACC/TOS) guidelines, as well as 2 recent systematic reviews and meta-analyses.[25,26] It has been demonstrated that weight loss at 2 to 3 years varies from a mean of 20% to 35% depending on the procedure.[2] In the SOS study, the cumulative overall mortality rate at 16 years of follow-up was lower in the surgical group compared with the conventional treatment group (hazard ratio, 0.76; $P = .04$).[24] Weight loss was similar for gastric bypass and sleeve gastrectomy, with less weight loss occurring from adjustable gastric banding.[2,26] Biliopancreatic diversion is an uncommon procedure in the United States and produces weight loss similar to bypass.

Compared with nonsurgical treatment, bariatric surgery was found to lead to higher remission rates of T2DM and metabolic syndrome, greater improvements in quality of life, and reductions in use of medications.[2,25] Based on these findings, the AHA/ACC/TOS panel strongly recommended the following to primary care providers: "Advise adults with a BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with obesity-related comorbid conditions who are motivated to lose weight and who have not responded to behavioral treatment with or without pharmacotherapy with sufficient weight loss to achieve targeted health outcome goals that bariatric surgery may be an appropriate option to improve health and offer referral to an experienced bariatric surgeon for consultation and evaluation."[2] This is the strongest recommendation yet for primary care providers to refer appropriate patients for bariatric surgery.

The decision to undertake a bariatric surgical procedure must be made with the understanding of potential complications, which should be discussed with the patient by the bariatric surgeon. Complications vary by procedure and patient-related risk factors, and may include requirement for reoperation, wound infection, deep vein thrombosis, nutritional deficiencies, and death. For the primary care provider who will encounter patients who have had bypass and band procedures, knowledge of nutritional management of these patients over the long term is paramount. Gastric bypass patients require supplementation with iron, multivitamins, minerals, calcium, and vitamin D. Practitioners must be alert to an increased risk for vitamin B_{12} deficiency, thiamine deficiency, and osteoporosis. For detailed discussion and recommendations regarding nutritional monitoring and treatment following bariatric surgery, the updated guidelines by the American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery are a valuable resource.[27]

CONCLUSION

Primary care providers face an imperative responsibility to aid their obese and overweight patients with achieving sustained weight loss for the attainment of health benefits. Obesity is the underlying driver of many chronic diseases and modest or moderate weight loss can improve health, particularly cardiometabolic factors. Providers must deploy tools to help their patients who are struggling to make lifestyle changes, create a negative energy balance and sustain weight loss. Among those tools are medications and bariatric surgical procedures. The new AHA/ACC/TOS guidelines urge physicians to use available treatment options to help their patients succeed at lifestyle changes that produce and sustain weight loss. ●

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Evolving Directions in Obesity Management

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INTRODUCTION

Over the past decade, treatment for obesity has been limited because of an incomplete understanding of the pathophysiology of obesity, lack of recognition of it as a disease, and limited efficacy of treatment options. Safety concerns related to medical and surgical approaches for obesity have also been a major barrier.[1] The challenging nature of obesity management is reflected in a survey of primary care physicians which indicated that treating patients with obesity can be as difficult as treating patients with nicotine or alcohol dependence.[2]

Several medications are under review by the US Food and Drug Administration (FDA) or in phase II and III clinical trials, and this may add to the medication options available for the long-term treatment of obesity (see *The Pharmacological and Surgical Management of Adults With Obesity* in this supplement). Some of these treatments include the glucagon-like peptide receptor agonist liraglutide, the centrally-acting combination naltrexone sustained release (SR)/bupropion SR, and the injectable methionine aminopeptidase 2 (MetAP2) inhibitor beloranib. Additionally, enhanced understanding of the genetics and factors regulating eating behavior has led to a rather robust pipeline of medications in earlier development. This article discusses the emerging treatment options and approaches for obesity.

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DISCLOSURES

Dr. Aronne discloses that he is a contract researcher for Aspire Bariatrics; GI Dynamics, Inc.; Medical University of South Carolina (MUSC); and Novo Nordisk, Inc. He is a consultant for Eisai Inc.; Ethicon Endo-Surgery Inc.; Novo Nordisk, Inc.; VIVUS, Inc.; and Zafgen Inc. He has ownership interest in Cardiometabolic Support Network, LLC; Myos Corporation; and Zafgen, Inc. He is on the board of directors for Myos Corporation.

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FUTURE MEDICAL THERAPIES

Currently, the medications that are available target appetite suppression through potentiation of neurotransmitter activity in the central nervous system, or intestinal lipase inhibition.[1] Enhanced understanding of the pathogenesis of obesity and observation of the effects of weight loss from these available medications have led to the investigation of several medications for evaluation of their potential efficacy and safety for the treatment of obesity (**TABLE**). [1,3-11]

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide receptor (GLP-1R) agonists mimic GLP-1, an incretin gut hormone secreted when a meal is ingested. GLP-1 lowers glucose by increasing insulin output and decreasing glucagon secretion, both in a glucose-dependent manner. GLP-1Rs are expressed in the periphery and in several areas in the brain that are implicated in the regulation of appetite. Both central and peripheral administration of GLP-1 has been shown to reduce appetite and food intake.[12,13]

Although GLP-1 administration in humans slows gastrointestinal (GI) motility, recent data derived from testing rats suggests that the slowing of the gastric emptying rate is not inducing weight loss.[14] Furthermore, the effect of the GLP-1R agonist liraglutide on slowing the gastric emptying rate was diminished following 14 days of dosing. In obese adults without diabetes, liraglutide-induced weight loss was shown to be mediated by a reduction in appetite and energy intake rather than increased energy expenditure.[15] Liraglutide has demonstrated significant dose-dependent weight loss in studies of patients with type 2 diabetes mellitus (T2DM) and has led to its investigation and recent submission to the FDA for approval for the treatment of obesity.[4-6,16]

In a 20-week, dose-finding, phase II trial, patients with obesity were randomized to liraglutide 1.2 mg, 1.8 mg, 2.4 mg, 3.0 mg or to placebo once daily, or orlistat 3 times daily (**TABLE**).[4] Patients also followed a 500 kcal per day energy-deficit diet and increased their physical activity. In addition to significantly greater weight loss with liraglutide after 20 weeks, liraglutide 1.8 mg, 2.4 mg, and 3 mg reduced prediabetes by 84% to 96%. Metabolic syndrome was reduced by 60% from baseline at the 2.4 mg and 3 mg doses, compared

with 38% and 13% for placebo and orlistat, respectively.[4] A post-hoc analysis revealed a greater probability of a normal glucose tolerance test at week 20 in the liraglutide groups compared with placebo or orlistat ($P < .01$ for all doses).[4] Systolic blood pressure (BP) was 3.4 mm and 1.4 mm Hg lower with liraglutide 2.4 mg and 3.0 mg vs orlistat at follow-up.

Following completion of the 20-week trial, patients could continue randomized treatment for 1 year, after which liraglutide or placebo-treated patients were switched to liraglutide 2.4 mg. Between weeks 70 and 96, patients were switched from liraglutide 2.4 mg to 3.0 mg because 1-year results showed that the 3.0 mg dose was more favorable. At 2 years, patients who received liraglutide 2.4 mg or 3.0 mg (ie, combined liraglutide 2.4 mg and 3.0 mg group) lost significantly more weight than those treated with orlistat (**TABLE**).[5] Reductions from screening (2-year completer population) in systolic BP (12.5 mm vs 9.9 mm Hg) and diastolic BP (6.9 vs 6.9) were similar in the combined liraglutide 2.4 mg with 3 mg group and orlistat groups, respectively.[5,6] At 2 years, the proportion with prediabetes was 32% in the orlistat group and 16% in the liraglutide 2.4/3 mg group ($P < .001$).[5]

Other components of metabolic syndrome were also impacted at 2 years. Triglycerides trended toward a larger reduction in the liraglutide 2.4/3 mg group with 3 mg group (–9.8 vs –0.9mg/dL; $P = .053$), and high density lipoprotein cholesterol (HDL-C) increased 2.3 mg/dL with liraglutide 2.4/3 mg and 3 mg, but decreased 0.4 mg/dL with orlistat ($P = .03$).[5] These studies indicate that liraglutide effectively reduces body weight, and has the potential to reduce the risk of prediabetes and elements of metabolic syndrome compared with orlistat. The most frequent drug-related adverse events were mild to moderate, transient nausea and vomiting. Patients with nausea (24%-48% vs 7%, respectively) and vomiting (5%-15% vs 2%, respectively) occurred more often with liraglutide than with placebo. The overall withdrawal rates for patients in year 2 were 14% to 19% in the liraglutide groups, 11% in the orlistat group, and 15% in the placebo group.

A phase III study randomized patients with obesity but without diabetes who had lost at least 5% of their screening body weight during a run-in phase with a low-calorie diet and physical activity.[10] Patients (N = 422) lost a mean 6.0% of screening weight during run-in. Patients continued diet and physical activity therapy and were randomized to liraglutide 3.0 mg or placebo once daily for 56 weeks. Liraglutide was initiated at 0.6 mg once daily, increasing weekly by 0.6 mg once daily to the 3.0 mg dose. Over the 56 weeks of treatment, patients treated with liraglutide lost significantly more weight, and significantly more liraglutide-treated patients lost ≥5% or ≥10% of randomization weight (**TABLE**). A follow-up at week 12 showed those who had received liraglutide maintained a 4.1% reduction in randomization weight compared with a gain of 0.3% for placebo-treated patients ($P < .0001$).

Compared with placebo, liraglutide-treated patients achieved significantly greater decreases in body mass index (BMI) (–2.1 kg/m^2 vs 0 kg/m^2; $P < .0001$) and glycated hemoglobin A1c (-0.1% vs 0.1%; $P < .0001$) during 56 weeks of treatment. Mean systolic and diastolic BP and pulse rate increased at 1 or more times above randomization values in both treatment groups. At week 56, the increase in systolic BP was significantly less in the liraglutide vs the placebo group (0.2 mm vs 2.8 mm Hg; $P = .007$), with no significant differences between groups for diastolic BP and pulse rate. A small increase or no change was observed in most lipid levels without significant differences between groups except for triglycerides where there was no change with liraglutide and an increase with placebo (0 vs 9 mg/dL; $P = .03$). Gastrointestinal disorders were the most common adverse events in the liraglutide group occurring in 74% compared with 45% in the placebo group. Most GI disorders were mild or moderate in nature, and most incidents of nausea occurred during the first 4 weeks of treatment, and coincided with dose escalation.

The results of this phase III trial showed that liraglutide, with dietary restriction and physical activity, helped maintain weight loss that was achieved by caloric restriction and contributed to further weight loss over 56 weeks. Improvements in some cardiovascular disease risk factors were also observed, and without unexpected adverse events.

Naltrexone SR/bupropion SR

The central nervous system regulates food intake by affecting appetite and energy using the hypothalamic melanocortin system, as well as regulating reward and goal-oriented behavior via the mesolimbic system.[8] Due to compensatory mechanisms, medications that target only one of these systems have demonstrated limited efficacy.[7] The combination of naltrexone SR and bupropion SR simultaneously stimulates hypothalamic pro-opiomelanocortin neurons and blocks opioidmediated pro-opiomelanocortin autoinhibition. This combination also has the potential to modulate the mesolimbic reward system and regulate dopamine midbrain areas to reduce food intake.[8]

Phase II and III trials of naltrexone SR and bupropion SR are summarized in the **TABLE**.[7-9, 11] In a phase II trial, the combination of naltrexone SR and bupropion SR produced greater weight loss than either agent alone or placebo. The placebo group demonstrated a 24-week weight loss of –3.5% to –4.6%.[7] The addition of naltrexone SR 32 mg/bupropion SR 360 mg per day along with intensive behavior modifica-

TABLE Efficacy of liraglutide and naltrexone SR/bupropion SR in phase II and III trials for obesity

Design/population/previous therapy	Treatment	Efficacy outcomes
Astrup et al[4] M, DB, P, R, OL Duration: 20 weeks N = 564 Adults with BMI 30-40 kg/m^2, stable body weight (<5% change in 3 months) given 500 kcal per day energy deficit, diet, and increased physical activity starting at a 2-week run-in where all received placebo starting 1 week after screening, then a 4-week dose titration phase (initial dose liraglutide 0.6 mg) after randomization and a 16-week constant dose phase.	Liraglutide 1.2 mg once daily (n = 94)	*Change from baseline at 20 weeks:* Weight: –4.8 kg Weight loss ≥5%: 52.1%[a] Weight loss >10%: 7.4%
	Liraglutide 1.8 mg once daily (n = 90)	Weight: –5.5 kg Weight loss ≥5%: 53.3%[a] Weight loss ≥10%: 18.9%
	Liraglutide 2.4 mg once daily (n = 92)	Weight: –6.3 kg Weight loss ≥5%: 60.8%[b] Weight loss ≥10%: 22.8%
	Liraglutide 3 mg once daily (n = 92)	Weight: –7.2 kg Weight loss ≥5%: 76.1%[c] Weight loss ≥10%: 28.3%
	Placebo injection (n = 98)	Weight: –2.8 kg Weight loss ≥5%: 29.6% Weight loss ≥10%: 2%
	Orlistat 120 mg TID (open-label) (n = 95)	Weight: –4.1 kg Weight loss ≥5%: 44.2% Weight loss ≥10%: 9.5%
Astrup et al[5,6] M, DB, P, R, OL N = 398	Liraglutide 2.4mg/3mg combined (n = 92)	*Change from baseline at 2 years:* Weight: –5.3 kg[d] Weight loss ≥5%: 52%[d] Weight loss ≥10%: 26%[e] Waist: –6.2 cm
2-year extension of the above study	Orlistat 120 mg TID (open-label) (n = 95)	Weight: -2.3 kg Weight loss ≥5%: 29% Weight loss ≥10%: 16% Waist: -4.5 cm
Wadden et al[10] M, R, DB, P Duration: 56 weeks N = 422 Adults with BMI ≥30 kg/m^2 or ≥27 kg/m^2 with dyslipidemia and/or HTN but not T2DM who lost ≥5% of their initial body weight with a 1200-1400 kcal/day diet and exercise during a 4 to 12 week run-in. At randomization, subjects were prescribed a 500 kcal/day deficit diet plus physical activity. Liraglutide was initiated at 0.6 mg once daily, increasing weekly by 0.6 mg once daily to the 3.0 mg dose.	Liraglutide 3 mg once daily (n = 212)	*Change during run-in:* Weight: –5.9% *Change from week 0-56:* Weight: –6.2%[b] Weight loss ≥5%: 50.5%[b] Weight loss ≥10%: 26.1%[b] Waist: –4.7 cm[b]
	Placebo injection (n = 210)	*Change during run-in:* Weight: -6.0% *Change from week 0-56:* Weight: –0.2% Weight loss ≥5%: 21.8% Weight loss ≥10%: 6.3% Waist: –1.2 cm

CONTINUED

TABLE Efficacy of liraglutide and naltrexone SR/bupropion SR in phase II and III trials for obesity *(continued)*

Design/population/previous therapy	Treatment	Efficacy outcomes
Greenway et al[7] M, R, DB, P, OL Duration: 24 weeks, extension to 48 weeks N = 419 Adults with BMI 30-40 kg/m^2	Naltrexone IR 48 mg daily (n = 56) for 24 weeks, then crossed over to open-label extension Naltrexone IR 32 mg daily with Bupropion SR 400 mg daily	*Change from baseline at 24 weeks (ITT):* Weight: –1.2% Weight loss ≥ 5%: 10% Weight loss ≥ 10%: 2%
	Bupropion SR 400 mg daily (n = 60)	*Change from baseline at 24 weeks (ITT):* Weight: –2.7% Weight loss ≥5%: 26% Weight loss ≥10%: 7% *Change from baseline at 48 weeks (ITT):* Weight: –2.7% Weight loss ≥5%: 33% Weight loss ≥10%: 12%
	Naltrexone IR 16 mg daily with bupropion SR 400 mg daily (n = 64)	*Change from baseline at 24 weeks (ITT):* Weight: –5.4%[f] Weight loss ≥5%: 52%[f] Weight loss ≥10%: 17%[g] *Change from baseline at 48 weeks (ITT):* Weight: –5.5%[h] Weight loss ≥ 5%: 50% Weight loss ≥10%: 22%
	Naltrexone IR 32 mg daily with bupropion SR 400 mg daily (n = 63)	*Change from baseline at 24 weeks (ITT):* Weight: –5.4%[f] Weight loss ≥5%: 51%[f] Weight loss ≥10%: 19%[g] *Change from baseline at 48 weeks (ITT):* Weight: –6.6%[h] Weight loss ≥5%: 51% Weight loss ≥10%: 25%
	Naltrexone IR 48 mg daily with bupropion SR 400 mg daily (n=61)	*Change from baseline at 24 weeks (ITT):* Weight: –4.3%[f] Weight loss ≥5%: 39%[g] Weight loss ≥10%: 15%[g] *Change from baseline at 48 weeks (ITT):* Weight: –5% Weight loss ≥5%: 39% Weight loss ≥10%: 20%
	Placebo/placebo (n = 85) for 24 weeks, then crossed over to open-label extension Naltrexone IR 32 mg daily with Bupropion SR 400 mg daily	*Change from baseline at 24 weeks (ITT):* Weight: –0.8% Weight loss ≥5%: 15% Weight loss ≥10%: 2%

CONTINUED

TABLE Efficacy of liraglutide and naltrexone SR/bupropion SR in phase II and III trials for obesity *(continued)*

Design/population/previous therapy	Treatment	Efficacy outcomes
Greenway et al[8] M, R, DB, P Duration: 56 weeks N = 1742 (1482 women, 260 men) Adults age 18-65 years, BMI 30-45 kg/m^2 with uncomplicated obesity, or BMI 27-45 kg/m^2 and controlled HTN and/or dyslipidemia, received a quarter of the assigned dose, increased weekly to a full-dose by week 4. All patients were assigned a 500 kcal per day deficit and mild advice was given on lifestyle modification (lifestyle compliance not assessed)	Naltrexone SR 16 mg per day with bupropion SR 360 mg per day, taken as two 4mg/90mg tablets BID (n = 578)	*Change from baseline at 56 weeks:* Weight: –4.9kg[b] Weight loss ≥5%: 39%[b,i] Weight loss ≥10%: 20%[b]
	Naltrexone SR 32 mg per day with bupropion SR 360 mg per day, taken as two 8mg/90mg tablets BID (n = 583)	Weight: –6.1kg[b] Weight loss ≥5%: 48%[b,i] Weight loss ≥10%: 25%[b]
	Placebo BID (n = 581)	Weight: –1.4kg Weight loss ≥5%: 16% Weight loss ≥10%: 7%
Wadden et al[9] M, R, DB, P Duration: 56 weeks N = 793 Adults age 18-65 years, BMI 30-45 kg/m^2 with uncomplicated obesity, or BMI 27-45 kg/m^2 and controlled HTN and/or dyslipidemia, received a quarter of the assigned dose, increased weekly to full-dose by week 4. All patients were assigned intensive multidisciplinary group behavioral modification, exercise, and a calorie-restricted diet.	Naltrexone SR 32 mg per day with Bupropion SR 360 mg per day, taken as two 8mg/90mg tablets BID (n = 591)	*Change from baseline at 56 weeks (mITT-LOCF):* Weight: –9.3%[j] Weight loss ≥5%: 66.4%[j] Weight loss ≥10%: 41.5%[j] Waist: –10.0 cm[d] IWQOL: +13.4[j]
	Placebo (n = 202)	Weight: –5.1% Weight loss ≥5%: 42.5% Weight loss ≥10%: 20.2% Waist: –6.8 cm IWQOL: +10.3
Apovian et al[11] M, R, DB, P Duration: 56 weeks N = 1496 Adults 18-65 years, BMI 30-45 kg/m^2, or BMI 27-45 kg/m^2 and controlled HTN and/or dyslipidemia. Naltrexone SR/Bupropion SR was escalated weekly over the first 3-4 weeks. All subjects were prescribed a 500 kcal/day deficit diet plus physical activity and behavior modification.	Naltrexone SR 32 mg per day with Bupropion SR 360 mg per day, in divided doses BID (n = 1000) Subjects with <5% weight loss at visits between weeks 28 and 44 were randomized to continue same treatment (n = 128) or increase to Naltrexone SR 48 mg per day with Bupropion SR 360 mg per day (n = 123), in divided doses BID.	*Change from baseline at 56 weeks (mITT-LOCF):* Weight: –6.4%[d] Weight loss ≥5%: 50.5%[d] Weight loss ≥10%: 28.3%[d] Waist: –6.7 cm[d]
	Placebo BID (n = 493)	Weight: –1.2% Weight loss ≥ 5%: 17.1% Weight loss ≥ 10%: 5.7% Waist: –2.1 cm

Abbreviations: AE, adverse events; BID, twice daily; BMI, body mass index; CI, confidence interval; CO, cross-over; DB, double-blind; HTN, hypertension; IR, immediate-release; ITT, intention to treat; IWQOL, impact of weight on quality of life; LSM, least squares mean; M, multicentered; mITT-LOCF, modified intention to treat-last observation carried forward; NA, not applicable; OL, open-label; P, placebo; R, randomized; SD, standard deviation; SE, standard error; SR, sustained-release; T2DM, type 2 diabetes mellitus; TID, three times per day; Wt, weight.

[a]*P* value versus placebo: $P = .002$

[b]*P* value versus placebo: $P < .0001$

[c]*P* value versus orlistat or placebo: $P \leq .0001$

[d]*P* value versus orlistat: $P < .001$

[e]*P* value versus orlistat: $P = .04$

[f]*P* value versus placebo or naltrexone 48mg or bupropion 400mg: $P < .05$

[g]*P* value versus placebo or naltrexone 48mg: $P < .05$

[h]*P* value versus bupropion 400mg: $P < .05$

[i]*P* value versus naltrexone/bupropion: $P = .0099$

[j]*P* value versus placebo: $P < .001$

tion, dietary restriction, and physical activity has been investigated in obese adults with controlled dyslipidemia and/or hypertension in 2 phase III trials over 56 weeks.[9,11] In the study by Apovian et al,[11] patients who were initially randomized to naltrexone SR 32 mg/bupropion SR 360 mg with <5% weight loss at visits between weeks 28 and 44 were rerandomized to continue at the current dose or escalate to naltrexone SR 48 mg/bupropion SR 360 mg. In both studies, patients treated with the addition of naltrexone SR/bupropion SR lost significantly more weight than those treated with placebo ($P < .001$). The proportions of patients who achieved ≥5%, ≥10%, and ≥15% reductions in baseline body weight were greater with naltrexone SR/bupropion SR than with placebo ($P <.001$ for all comparisons).[9] Naltrexone SR/bupropion SR at the 32 mg or 48 mg doses of naltrexone SR, relative to placebo, reduced triglycerides (–9.8% to –16.6% vs –0.5% to –8.5%; $P < .005$), increased HDL-C (3.6% to 9.4% vs –0.9% to 2.8%; $P < .001$), and improved impact of weight on quality of life (IWQOL) scale score (10.9 to 13.4 points vs 6.4 to 10.3 points, 0-100 point scale; $P < .001$).[9,11] Small changes in BP and pulse rate were observed.[8,9]

Primarily because of adverse events, the completion rate was low in these phase III trials with rates ranging from 54% to 58% in both treatment groups.[9,11] Adverse events that were significantly more common with naltrexone SR and bupropion SR relative to placebo included: nausea, headache, constipation, dizziness, vomiting, dry mouth, tremor, abdominal pain, bronchitis, and tinnitus. The most common reason for discontinuation of treatment was nausea.

The results of these 2 phase III trials showed that naltrexone SR/bupropion SR, along with lifestyle management that consisted of behavior modification, dietary restriction, and increased physical activity, resulted in greater weight loss over 56 weeks than with lifestyle management alone. Improvements in some cardiovascular disease risk factors were also observed, without unexpected adverse events.

Other mechanisms targeted for drug development

Beloranib is a novel injectable antiobesity agent which inhibits MetAP2. Inhibition of MetAP2 is thought to promote intracellular reduction in fat biosynthesis and increased fat oxidation and lipolysis.[17] A preliminary 4-week dose-finding study demonstrated a median weight loss of –3.8 kg with beloranib 0.9 mg/m^2 (95% CI, –5.1 to –0.9) vs -0.6 kg with placebo (95% CI –4.5 to –0.1). The most frequent adverse effects that were reported included headache, infusion site injury, nausea, and diarrhea; nausea and infusion site injury occurred more frequently in the beloranib group. Beloranib 0.9 mg/m^2 produced significantly greater changes compared with placebo in hunger (–40.8% vs –2.2%; $P < .01$), triglycerides (–42% vs 15.2%; $P <.01$), and low-density lipoprotein cholesterol (LDL-C) (–18.4% vs 2.3%; $P < .05$). Overall, significant improvements were observed with factors related to obesity.[17]

FUTURE DIRECTIONS IN MEDICAL THERAPIES

Enhanced understanding of the neurochemicals and mediators that regulate food intake, as well as genetic targets associated with obesity, are leading to greater understanding of the differences in etiology between adults and children. In addition, there is a more robust pipeline of pharmacologic agents available.[1,18-20] These neurochemicals and mediators include agouti-related protein, leptin, neuropeptide Y5, dopamine 3, and pancreatic polypeptide analog.[21] As agents that act on these targets are investigated, it seems likely that optimal treatment may require combination therapy that addresses different pathophysiologic mechanisms.

Other approaches are increasingly available to individualize treatment. For example, one way is to evaluate a patient's current medication regimen and carefully consider the patient's medical history when adding new medications, since some medications may contribute to weight gain. Particularly in psychiatric illness, avoidance of medications with a high potential for weight gain could lead to the prevention of the onset of significant additional health problems.[19] This approach also has a potential benefit for patients with diabetes, since many medications used to treat diabetes are associated with weight gain.[22]

Because of the complexity and cost of the current approach to obesity management and multimodal therapy, there is a need to develop more convenient, low-cost, sustainable programs for weight loss.[23] Recent studies have focused on incorporating technology into the primary care setting as well as the patient's home. These interventions include telephone coaching, web-based goal setting and tracking, and personal digital assistants that provide active decision support such as smartphone applications that include *Lose It!*, *My Fitness Pal*, and *Fooducate*, in addition to standard group therapy and counseling. Many of these interventions have demonstrated favorable weight loss results.[24-26] Undoubtedly, the ideal intervention for each patient will continue to require a combination of options.

Beyond focusing on the amount of weight lost, even greater consideration is being given to establishing the impact on cardiometabolic and other key outcome endpoints such as myocardial infarction and stroke, rather than surrogate endpoints such as BP and LDL-C.[27,28] In addition, a longer-term follow-up of existing studies may provide additional insights into cardiovascular health and other risks and

benefits of these weight loss medications, especially when they have disparate effects on BP and LDL-C.[28]

CONCLUSION

Obesity is a common disease with few effective and safe long-term treatment options. An increased understanding of the multiple mechanisms that contribute to obesity has resulted in new treatment targets. Various medications are under investigation, and several of these treatments have completed phase III trials and are under review by the FDA. Other approaches to treatment are being investigated too, with the strong possibility of new approaches for combination therapy becoming available. ●

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