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Weight Loss Strategies for Treatment of Obesity

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ABSTRACT

Obesity is one of the most serious and prevalent non-communicable diseases of the 21st century. It is also a patient-centered condition in which affected individuals seek treatment through a variety of commercial, medical and surgical approaches. Considering obesity as a chronic medical disease state helps to frame the concept of using a three-stepped intensification of care approach to weight management. As a foundation, all patients should be counseled on evidence-based lifestyle approaches that include diet, physical activity and behavior change therapies. At the second tier, two new pharmacological agents, phentermine–topiramate and lorcaserin, were approved in 2012 as adjuncts to lifestyle modification. The third step, bariatric surgery, has been demonstrated to be the most effective and long-term treatment for individuals with severe obesity or moderate obesity complicated by comorbid conditions that is not responsive to non-surgical approaches. By using a medical model, clinicians can provide more proactive and effective treatments in assisting their patients with weight loss.

In June 2013, the American Medical Association (AMA) resolved that obesity should be considered a chronic medical disease state.[1] Although the *AMA* was not the first organization to do so,[2,3] it garnered the greatest media attention. One of the intentions of this declaration was to mobilize the medical community to take action regarding assessment and management of obese and overweight patients. Although there is ample evidence for the benefit of providing lifestyle interventions, pharmacotherapy and bariatric surgery for the treatment of obesity, survey data suggest that only a minority of clinicians provide such care.[4–7] Reasons for this clinical inertia include insufficient training in behavioral and lifestyle counseling, lack of familiarity and concern over safety with the use anti-obesity medications, unawareness of the indications and outcomes of bariatric surgery, and time restraints during a busy office practice among others.[6] Not all patients who are deemed obese by body mass index (BMI) alone need to be treated, as exemplified by the concepts of obesity paradox[8] or the metabolically healthy obese.[9] However, patients who present with obesity-related comorbidities and would benefit from weight loss intervention should be proactively managed. The purpose of this article is to review evidence-based weight loss strategies and expected outcomes.

The obesity care landscape

Obesity is primarily a consumer-oriented condition. That is, individuals typically select which treatment approach they feel most comfortable trying, fits into their budget, and is reasonably likely to be successful. The variety of treatment options is displayed in Fig 1. Note that the primary care provider is one of many choices. This is due, in part, to the

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Abbreviations and Acronyms

AMA = American Medical Association

BMI = body mass index

CV = cardiovascular

FDA = Food and Drug Administration

PA = physical activity

PHEN/TPM = phentermine and topiramate

LAGB = laparoscopic adjustable gastric banding

LSG = laparoscopic sleeve gastrectomy

RYGB = Roux-en-Y gastric bypass

T2D = type 2 diabetes

pervasiveness of marketing attractive products and services with wide accessibility, low cost and commitment, and the commercialization of obesity care. Nonetheless, several of these non-medical treatment options are evidence based and include selected commercial weight loss and Internet programs.[10] It is imperative that the clinicians education themselves about these programs and refer when indicated. Furthermore, with over 60% of the American adult population overweight and obesity,[11] it is prudent to include these selected programs as reasonable options since only a minority of physicians will likely provide comprehensive obesity care within the office setting. Although this proposed physician-commercial network to treat obesity appears pragmatic, there are currently no systems in place to facilitate bidirectional communication and ensure a standard of care.

Using a medical paradigm for obesity care

Considering obesity as a chronic medical disease state helps to frame the concept of using a stepped intensification of care approach to weight management (Fig 2). In this progression of care, all patients are provided guidance on lifestyle therapy which ranges from enrollment in an Internet or commercial group program to a participation in a physician-driven customized multidisciplinary program. If the patient is not able to achieve the weight and health goal by lifestyle alone and meets the indications for drug therapy, then addition of adjunctive pharmacotherapy should be considered. As a third step, bariatric surgery can be considered for patients with more severe disease and who meet its indications. Using this medical paradigm, clinicians and patients can advance through increasing intensities of treatments along with discussions of benefits and risks.

Lifestyle treatment

The foundation of obesity care is assisting patients in making healthier dietary and physical activity (PA) choices that will lead to a net negative energy balance. The initial goal is to achieve a 5% to 10% weight loss over the initial 6 months of treatment.[12] Caloric reduction is the most important component in achieving weight loss whereas increased and sustained PA is particularly important in maintaining the lost weight.[13–15] Weight loss is primarily dependent on reducing total caloric intake, not the proportions of carbohydrate, fat, and protein in the diet.[16] The macronutrient composition (i.e. proportion of calories from carbohydrate, fat and protein) will ultimately be determined by the patient's taste preferences, cooking style and culture. However, the patient's underlying medical problems are also important in guiding the recommended dietary composition. The dietary prescription will vary according to the patient's metabolic profile and risk factors.[17–21] A consultation with a registered dietitian for medical nutrition therapy is particularly useful[22] along with the importance of emphasizing collaborative care and self-management of chronic disease.[23] Incorporating meal replacements into the diet is another useful strategy. Meal replacements are foods that are designed to take the place of a meal or snack while at the same time providing nutrients and good taste within a fixed caloric limit.[24,25] An alternative dietary strategy is to refer the patient to one of several commercial weight loss programs that have demonstrated weight loss outcomes.[26,27]

In addition to reducing caloric intake, patients are also encouraged to burn more calories. There is a distinction between PA and exercise. Whereas PA consists of any bodily movement that increases energy expenditure, e.g. activities of daily living like walking, climbing stairs, gardening, etc., *exercise* is defined as planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness.[28] Weight loss counselling should encourage both aspects as part of treatment. Studies have demonstrated that lifestyle activities are as effective as structured exercise programs in improving cardiorespiratory fitness and weight loss.[29] The most useful strategy in achieving lifestyle goals is to include self-monitoring. Patients are asked to track their food intake, PA, and weight throughout treatment.[30] The benefits of tracking include having real-time data on dietary intake as it relates to caloric and other nutritional goals, allows reflection and planning of diet, introduces restraint, and provides information to share with the provider. Similar benefits are achieved by tracking PA by recording time or steps. Finally, it is important to remember that lifestyle management is one component of a comprehensive approach to the patient with obesity and cardiovascular disease. Control of glucose, blood pressure and lipid levels along with secondary prevention of recurrent events is optimized with the use of concurrent medication management.[31]

Pharmacotherapy

According to current Food and Drug Administration (FDA) guidance, pharmacotherapy is approved for patients with a BMI $\geq$30 kg/m^2 or $\geq$27 kg/m^2 when complicated by an obesity–comorbidity. Despite the logic of using medication to enhance weight loss, less than 3% of individuals who are obese are being treated by prescription medication.[32] The reasons for

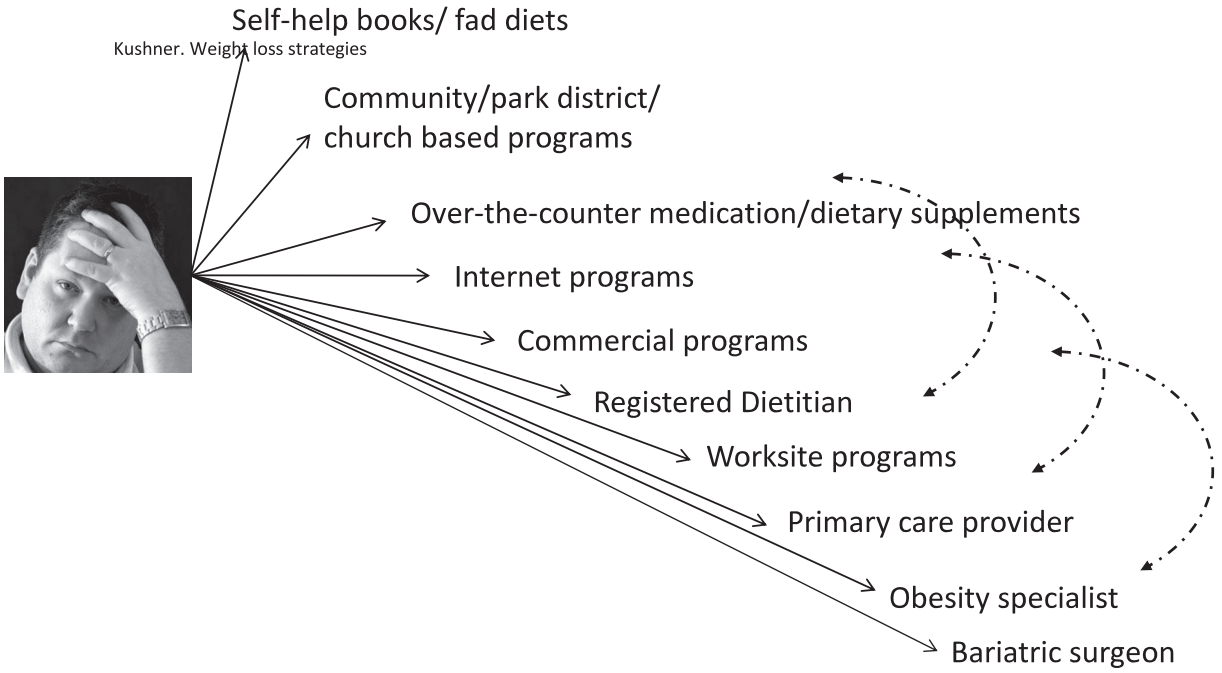

Fig 1 – Patient-centric approach to seeking weight loss options that range from commercial to medical and surgical treatment approaches.

this low prescription rate include lack of training and concern over safety with the use anti-obesity medications, the availability of few medications, and biased attitudes regarding obesity. A legacy effect about safety is somewhat justified since this class of drugs has been plagued by removal of several drugs from the marketplace: fenfluramine and dexfenfluramine in 1997 and sibutramine in 2010 from the FDA, and rimonabant from European Agency for the Evaluation of Medicinal Products in 2009. However, two new medications were approved by the FDA in 2012 that demonstrate favorable

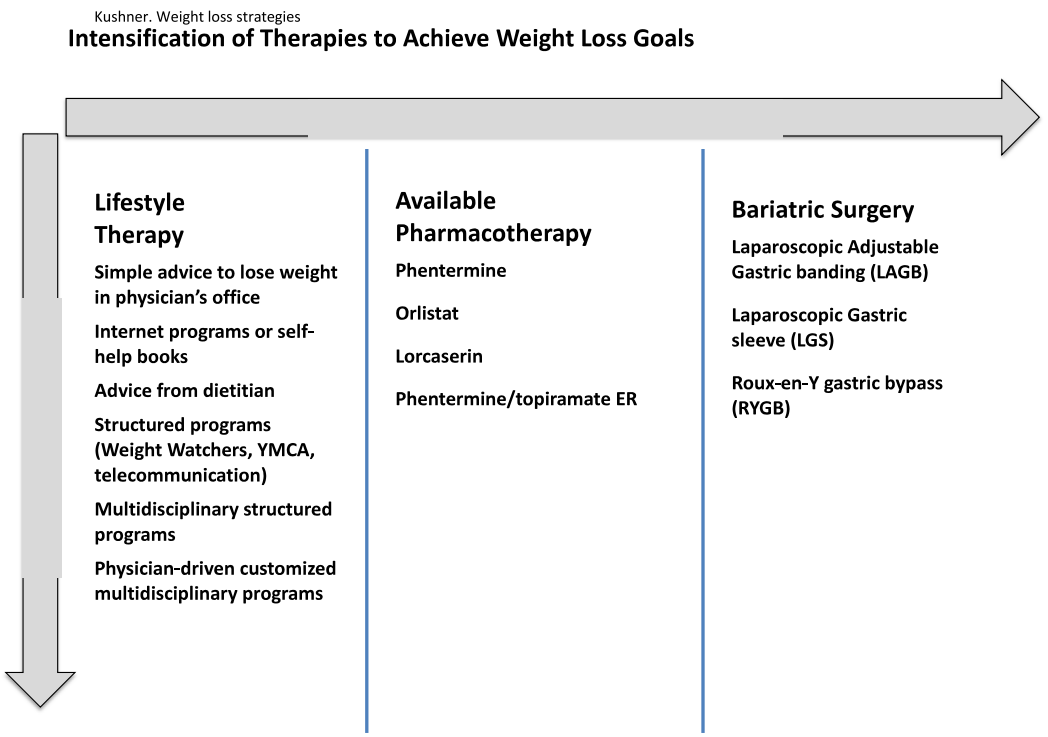

Fig 2 – Three-stepped intensification of care approach to weight management.

benefit to risk ratios, thus providing more options for pharmacologic treatment for the patient with obesity.

Medications approved prior to 2012

Medications for obesity have traditionally fallen into two major categories: appetite suppressants or anorexiants, and gastrointestinal fat blockers. Appetite suppressing medications have targeted three monoamine receptor systems in the hypothalamus: noradrenergic, dopaminergic and serotonergic.[33] In the 1930s, amphetamines were first introduced as anorexiants. However, amphetamine was addictive and had euphoric side effects. By modifying the side chain of amphetamine's β-phenylethylamine structure, the anorectic effect of the parent compound was retained while reducing the stimulatory properties and potential for addiction. Among the centrally acting adrenergic agents that have been marketed for the treatment of obesity, five compounds—phentermine, benzphetamine, phendimetrazine, diethylpropion and mazindol—have been most commonly used. By 1960 all five of the sympathomimetic amines were approved as adjuncts in the management of obesity. These medications are labeled as scheduled drugs by the Drug Enforcement Agency. Among the anorectics, phentermine is the most commonly prescribed agent and there are limited long-term data on its effectiveness. A 2002 review of six randomized controlled trials using phentermine for weight control found that patients lost 0.6–6.0 additional kilograms of weight compared to placebo over 2–24 weeks of treatment.[34] A study by Munro et al.[35] demonstrated the effectiveness of intermittent or continuous use of phentermine over 36 weeks with both active groups losing an average of 20.5% of initial body weight compared to 6% loss in the placebo group. The most common side effects of the amphetamine-derived anorexiants are restlessness, insomnia, dry mouth, constipation, and increased blood pressure and heart rate.

Orlistat was approved by the FDA in 1999 as the first lipase inhibitor for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. Based on its safety profile, the medication was approved as an over-the-counter medication in the United States in 2007 at half the prescription dose. The drug is a synthetic hydrogenated derivative of a naturally occurring lipase inhibitor, lipostatin, produced by the mold *Streptomyces toxytricini*. Orlistat is a potent slowly reversible inhibitor of pancreatic, gastric, and carboxylester lipases and phospholipase A_2, which are required for the hydrolysis of dietary fat in the gastrointestinal tract into fatty acids and monoacylglycerols.[36] Orlistat is minimally (<1%) absorbed from the gastrointestinal tract and primarily eliminated in the feces. When taken as directed (120-mg capsule three times per day with meals or up to 1 hour after a meal), the drug blocks the digestion and absorption of ~30% of dietary fat. Multiple randomized, 1- to 2-year double-blind, placebo-controlled studies have shown that after 1 to 2 years, mean weight loss averages ~2.7 to 3.19 kg greater than placebo-treated patients.[37–39] Categorically, more subjects randomized to orlistat compared to placebo lose >5% (average 55% vs. 33%) and >10% (average 34% vs. 16%) of body weight.

Since orlistat is minimally absorbed from the gastrointestinal tract, it has no systemic side effects. Tolerability to the drug is related to the malabsorption of dietary fat and subsequent passage of fat in the feces. Six gastrointestinal tract adverse effects have been reported to occur in at least 10% of orlistat-treated patients; oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, and increased defecation. The events are generally experienced early, diminish as patients control their dietary fat intake, and infrequently cause patients to withdraw from clinical trials.

Medications approved in 2012

Two medications were approved by the FDA in 2012: lorcaserin (Belviq, Arena Pharmaceuticals GmbH, Zofingen, Switzerland) and phentermine–topiramate extended release (Qsymia, VIVUS, Inc, Mountain View, CA USA). Both of these medications met the requirements of the 2007 FDA draft guidance for approval which required conducting a prospective, randomized, double-blind study with a total of approximately 3000 subjects randomized to active doses of the drug and no fewer than 1500 subjects randomized to placebo for 1 year of treatment, and predetermined effectiveness as measured by either ≥5% mean percent weight loss or superior categorical weight loss of drug versus placebo.[40] Both medications were approved with a requirement to conduct a post-marketing long-term cardiovascular (CV) outcomes trial.

Lorcaserin

Lorcaserin is a selective 5-HT2C receptor agonist with a functional selectivity of approximately 15 times that for the 5-HT2A receptors and 100 times that for the 5-HT2B receptors.[41] This selectivity is important since the drug-induced valvulopathy seen from two other serotonergic agents previously removed from the market, fenfluramine and dexfenflurame, was due to activation of the 5-HT2B receptors expressed on cardiac valvular interstitial cells.[42] By activation of the 5-HT2C receptor, lorcaserin is thought to decrease food intake through the pro-opiomelanocortin system of neurons.

Lorcaserin has undergone two pivotal randomized, placebo-controlled, double-blind trials to assess efficacy and safety. In the Behavioral Modification and LOrcaserin for Overweight and Obesity Management (BLOOM) and Behavioral modification and LOrcaserin Second Study for Obesity Management (BLOSSOM) studies, subjects were randomized to receive lorcaserin 10 mg bid versus placebo (BLOOM)[43] or lorcaserin 10 mg bid or qd, or placebo (BLOSSOM).[44] All subjects received diet and exercise counseling. Subject number, eligibility, characteristics, and weight loss outcomes are displayed in Table 1. Overweight or obese subjects have at least one coexisting condition (hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance or sleep

Table 1 – Comparison of 1-year prospective, randomized, double-blind trials for lorcaserin (BLOOM and BLOSSOM) and phentermine–topiramate extended release (EQUIP and CONQUER).

	BLOOM	BLOSSOM [a]	EQUIP [b]	CONQUER
Number of subjects (ITT_LOCF)	3182	4008	1230	2448
Age (yrs)	18–65	18–65	≥35	27–45
BMI (kg/m^2)	27–45	27–45	18–70	18–70
Comorbid conditions (cardiovascular and metabolic)	At least 1	At least 1	At least 1	≥2
Mean % weight loss compared to placebo	5.8% vs 2.2%	4.8% vs 2.8%	11% vs 1.6%	10.4% vs 1.8%
Placebo-subtracted weight loss (%)	3.6%	2.0%	9.4%	8.6%
Categorical change in 5% weight loss compared with placebo	47.5% vs 20.3%	47.2% vs 25%	67% vs 17%	70% vs 21%
Completion rate	55.4% lorcaserin; 45.1% placebo	55.5%	59.9%	62%

[a] Lorcaserin 10-mg bid dose.
[b] Phentermine–topiramate extended release 15-mg/92-mg dose.

apnea), medical conditions that reflect practical use in the office setting. Intention-to-treat 1-year placebo-subtracted weight loss was 3.6% and 2.0%, respectively, for the BOOM and BLOSSOM trials. This difference did not meet the first 2007 FDA draft guidance criteria for ≥5% mean percent weight loss between drug and placebo. However, the second criterion was satisfied, e.g., the proportion of subjects who lose ≥5% weight is at least 35%, and approximately double the proportion in the placebo group.[40] Echocardiography was performed at the screening visit and at scheduled time points over the course of the studies. There was no difference in the development of FDA-defined valvulopathy between drug-treated subjects versus placebo at 1 or 2 years. Modest statistical improvements were seen in selected cardiovascular and metabolic outcome measurements that were consistent with the weight loss. The most frequent adverse events experienced by the drug group were headache, dizziness, and nausea.

Phentermine–topiramate extended release

Phentermine and topiramate (PHEN/TPM) is combination drug that contains a catecholamine releaser (phentermine) and an anticonvulsant (topiramate). Topiramate is currently approved by the FDA as an anticonvulsant for the treatment of epilepsy and for the prophylaxis of migraine headaches under the trade name Topamax (Janssen Pharmaceuticals, Inc., Titusville, NJ). Weight loss was seen as an unintended side effect of this drug during clinical trials for epilepsy. The mechanism responsible for weight loss is uncertain but thought to be mediated through its modulation of gamma-aminobutyric acid receptors, inhibition of carbonic anhydrase, and antagonism of glutamate to reduce food intake. Topiramate has been demonstrated to produce significant weight loss in double-blind, placebo-controlled trials among obese subjects.[45] Although effective, further drug development as an anti-obesity agent was terminated due to unacceptable side effects of cognitive impairment and paresthesias. PHEN/TPM is developed to reduce adverse events of both agents by incorporating lower doses in a fixed combination formulation.

PHEN/TPM has undergone two 1-year pivotal randomized, placebo-controlled, double-blind trials to assess efficacy and safety called EQUIP[46] and CONQUER.[47] In a third study, SEQUEL, 78% of CONQUER participants continued to receive their blinded treatment for an additional year.[48] Similar to the lorcaserin trial design, all subjects received diet and exercise counseling. Subject number, eligibility, characteristics, and weight loss outcomes are displayed in Table 1. Intention-to-treat 1-year placebo-subtracted weight loss for the PHEN/TPM 15-mg/92-mg dose was 9.4% and 8.8%, respectively, for the EQUIP and CONQUER trials. Superior 5% categorical weight loss was also demonstrated. Clinical and statistical dose-dependent improvements were seen in selected CV and metabolic outcome measurements that were related to the weight loss. The most frequent adverse events experienced by the drug group were paresthesias, dry mouth, constipation, dysgeusia, and insomnia. Due to an increased risk of congenital fetal oral cleft formation from topiramate, PHEN/TPM was approved by the FDA with a Risk Evaluation and Mitigation Strategies requirement to education prescribers about the need for active birth control among child-bearing women and contraindication of use during pregnancy.

In approving both lorcaserin and PHEN/TPM, the FDA introduced a new provision with important clinical relevance—a prescription trial period to assess effectiveness. According to the package insert, response to lorcaserin therapy should be evaluated by week 12. If a patient has not lost at least 5% of baseline body weight, it is recommended to discontinue the drug, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment. Similar guidance is provided for PHEN/TPM. According to this package insert, prescribers should evaluate weight loss after 12 weeks of treatment with PHEN/TPM 7.5 mg/46 mg (mid dose). If a patient has not lost at least 3% of baseline body weight on this dose, discontinue the medication or escalate the dose with titration to PHEN/TPM 15 mg/92 mg (top dose). Weight loss is then evaluated following dose escalation after an additional 12 weeks of treatment. If a patient has not lost at least 5% of baseline body weight on the top dose, PHEN/TPM should be discontinued as directed, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment. These recommendations are sensible and ensure that only responders will continue taking the medication, thus maximizing the benefit to risk ratio.

Bariatric surgery

According to the 1991 NIH Consensus Development Conference Panel on bariatric surgery,[49] patients with a BMI ≥40 kg/m^2 or those with a BMI ≥35 kg/m^2 who have associated high-risk comorbid conditions such as cardiopulmonary disease or type 2 diabetes could be considered surgical candidates. Although the FDA approved the indication for Laparoscopic Adjustable Gastric Banding (LAGB) for a BMI of ≥30 with a comorbidity, Medicare and other third-party insurance payers have generally not followed this more liberal criteria for reimbursement qualifications.

Weight loss surgeries have traditionally been classified into three categories based on anatomical changes —restrictive, restrictive malabsorptive and malabsorptive. However, more recently the clinical benefits of bariatric surgery in achieving weight loss and improving metabolic comorbidities have largely been attributed to changes in the physiological responses of gut hormones and adipose tissue metabolism.[50,51] Metabolic effects resulting from bypassing the foregut include altered responses of ghrelin, glucagon-like peptide-1 and peptide $YY_{3–36}$, and oxyntomodulin. Additional effects on food intake and body weight control may be attributed to changes in vagal signaling. The loss of fat mass, particularly visceral fat, is associated with multiple metabolic, adipokine, and inflammatory changes that include improved insulin sensitivity and glucose disposal, reduced free fatty acid flux, increased adiponectin levels, and decreased interleukin-6, tumor necrosis factor-α, and high-sensitivity C-reactive protein levels.

The three most common bariatric surgical procedures performed are LAGB, laparoscopic sleeve gastrectomy (LSG), and Roux-en-Y gastric bypass (RYGB). Two banding devices are commercially available in the United States, the LAP-BAND™ (Allergan, Inc., Irvine CA) and the REALIZE™ band (Ethicon Endo-Surgery, Inc). The diameter of these bands is adjustable by way of its connection to a reservoir that is implanted under the skin. Injection or removal of saline into the reservoir tightens or loosens the band's internal diameter, respectively, thus changing the size of the gastric opening. Mean percent weight loss at 5 years is estimated to be 20% to 25% of total weight.[52] In performing the LSG, the stomach is restricted by stapling and dividing it vertically and removing approximately 80% of the greater curvature, leaving a slim "banana shaped" remnant stomach along the lesser curvature. Weight loss offered by the LSG is superior to that of LAGB.[53] The third procedure, RYGB, is the most commonly performed operation and generally results in greater weight loss than LAGB or LSG. It involves formation of a 10- to 30-ml proximal gastric pouch by surgically separating the stomach across the fundus. Outflow from the pouch is created by performing a narrow (10 mm) gastrojejunostomy. The distal end of jejunum is then anastomosed 50 to 150 cm below the gastrojejunostomy. "Roux-en-Y" refers to the Y-shaped section of small intestine created by the surgery; the Y is created at the point where the pancreo-biliary conduit (afferent limb) and the Roux (efferent) limb are connected. "Bypass" refers to the exclusion or bypassing of the distal stomach, duodenum, and proximal jejunum. Weight loss averages 25% to 30% of initial body weight at 5 years.[54]

Significant improvement in multiple obesity-related comorbid conditions have been reported including type 2 diabetes (T2D), hypertension, dyslipidemia, obstructive sleep apnea and quality of life[54,55] and long-term CV events.[56] A meta-analysis of controlled clinical trials comparing bariatric surgery versus no-surgery showed that surgery was associated with a reduced odds ratio (OD) risk of global mortality (OR = 0.55), CV mortality (OR = 0.58) and all-cause mortality (OR = 0.70).[57] Among the observed improvements in comorbidities, the role of bariatric surgery in the prevention and treatment of T2D has garnered the most attention.[58] Fifteen-year data from the Swedish Obese Subjects (SOS) study demonstrated that bariatric surgery markedly reduced the incidence of developing T2D by 78% in obese patients who underwent bariatric surgery.[59] Two recent randomized controlled trials comparing bariatric surgery (RYGB, LGS and biliopancreatic diversion) to conventional medical therapy demonstrated superior weight loss and glycemic control at 12 months[60] and 24 months.[61,62] A third study, the Diabetes Surgery Study Randomized Clinical Trial, compared intensive medical management to surgical treatment with RYGB among patients with a BMI of 30 to 39.9.[62] After 12 months, 49% of surgical patients established diabetes management goals compared with 19% of medically managed patients. A retrospective cohort study among 4434 adults with diabetes found that overall, 68.2% of patients experienced an initial complete T2D remission within 5 years after surgery.[63] However, among these patients, one-third redeveloped T2D within 5 years.

The decision to recommend bariatric surgery must be based on risk–benefit ratio along with other factors including psychosocial health, adherence, expectations and cost. There is not enough predictive information available to differentially select one procedure over another for an individual patient. However, the RYGB appears to result in greater weight loss and improvement in comorbid conditions than the LAGB and LSG.[60] Contraindications include an extremely high operative risk, active substance abuse or a major unstable or uncontrolled psychopathological condition such as major depressive disorder, schizophrenia or bulimia.

All patients who are considering weight loss surgery should undergo a comprehensive assessment by a multidisciplinary team of health care providers that includes a physician, registered dietitian and mental health care professional.[64] During the preoperative process, patients are typically instructed on healthy eating and physical activity patterns, behavioral strategies to implement the lifestyle changes, and the importance of stress reduction and social support for long-term success. Nutritional complications resulting from the altered anatomy and dietary changes have been well described and must be proactively managed. Evidence-based recommendations for "Best Practice" patient care have been recently been published.[64,65]

Conclusion

Obesity is a serious and highly prevalent disease associated with increased morbidity and mortality. Although weight management is largely patient centered regarding selection of

treatment options, health care providers should take an active role in identification, evaluation and treatment of high-risk individuals. All patients should be provided lifestyle therapy with consideration for pharmacotherapy and bariatric surgery when indicated. Utilization of evidence-based community and commercial resources is a reasonable approach to support lifestyle change. Two new medications, phentermine–topiramate and lorcaserin, provide additional options for patients who do not respond to lifestyle counseling alone. Bariatric surgery is an effective treatment for patients with moderate or severe obesity that is complicated by comorbidities such as T2D.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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