Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *The Year in Diabetes and Obesity*
REVIEW

Updates on obesity pharmacotherapy

Amanda Velazquez[1] and Caroline M. Apovian[2]

[1]Bariatric Medicine and Internal Medicine, Kaiser Permanente Medical Center, Los Angeles, California. [2]Section of Endocrinology, Diabetes, Nutrition and Weight Management, Boston Medical Center, Boston University School of Medicine, Boston, Massachusetts

Address for correspondence: Caroline M. Apovian, M.D., Section of Endocrinology, Diabetes, Nutrition and Weight Management, Boston Medical Center, Boston University School of Medicine, 88 East Newton Street, Robinson 4400, Boston, MA 02118. caroline.apovian@bmc.org

Obesity is a chronic, relapsing disease that necessitates a multidisciplinary approach to management. Behavioral changes are the foundation to management, but adjunctive therapy is often warranted, including pharmacologic therapies and/or bariatric surgery. Until recently, treatment options included only short-term therapy (≤12 weeks), and paths beyond that schedule were challenging, as knowledge of the biology of obesity was lacking. With increased recognition of obesity as a chronic, complex medical disease, newer agents have been approved as long-term therapy, and the cornerstone of treatment is chronic behavior and lifestyle change. In the last decade, the Food and Drug Administration (FDA) has approved several new weight loss medications for the chronic management of obesity. In this review paper, we provide the latest updates on obesity pharmacotherapy. The main areas we will cover include (1) pharmacological management of obesity, (2) a review of FDA-approved weight loss medications, (3) comanagement of obesity and its metabolic sequelae (type 2 diabetes mellitus, hypertension, and dyslipidemia), and (4) obesity-centric prescribing for mental illness, neurological disorders, and contraceptive planning.

Keywords: obesity; weight loss; overweight; pharmacotherapy

Background

Obesity is a chronic, relapsing disease that affects over 78 million adults in the United States.[1,2] As a result, prevention and management of this disease is essential. While behavioral modification is the foundation of management, additional adjuncts are often necessary, including pharmacological interventions and/or bariatric surgery. The panoply of available medications for weight loss has evolved significantly in the last half century. The Food and Drug Administration (FDA) has approved weight loss medications dating back to 1959 for short-term (≤12 weeks) use; however, algorithms for obesity management, including prescriptions for weight loss medications, did not gain traction until the mid-1990s. This change was in response to the dramatic rise and prevalence of obesity during that time period, with rates nearly doubling between 1980 and 2004.[3] The most commonly prescribed medications in 1994–1997 were phentermine, fenfluramine and dexfenfluramine.[4] The use of the combination of phentermine and fenfluramine (phen-fen) increased after Weintraub *et al.* published a series of papers documenting weight loss using this combination in patients with obesity in a trial funded by the National Heart Lung and Blood Institute.[5] Unfortunately, in July 1997, the Mayo Clinic reported findings of 24 patients developing valvular heart disease following use of the phentermine–fenfluramine combination. More reports of valvular heart complications were soon found with patients taking fenfluramine alone and dexflenfluramine alone, but none reported with phentermine monotherapy.[6] As a result, fenfluramine and dexfenfluramine were removed from the market, and, in turn, this caused a lull in the number of weight loss medicine prescriptions in the early 2000s, most likely due to the potential catastrophe with the phen-fen combination and its aftermath.

In recent years, the FDA has approved newer pharmacological options that were even more carefully investigated for safety and efficacy.

doi: 10.1111/nyas.13542

Importantly, these weight loss medications are approved for long-term management, which helps to provide a better appreciation of obesity as a chronic, complex, and relapsing disease.[7] Also, the availability and variety of medications gives healthcare providers more options to better tailor patient treatment plans.

Despite the greater availability, obesity drug therapies are still underused by healthcare providers.[8] Only 2% of American adults who are eligible for obesity pharmacotherapy actually receive them from a provider, even though nearly half of Americans meet the medical obesity pharmacotherapy criteria.[9,10]

Numerous barriers preclude healthcare providers from adequately prescribing weight loss medications. First, inadequate training in medical schools and residency programs leads to a lack of confidence in prescribing such medications. Next, since obesity is a highly stigmatized disease, misconceptions still exist that excess body weight is due to a lack of willpower and that obesity is not a disease that deserves to be treated with medications and surgery, even when indicated.[11–13] Additionally, healthcare provider reimbursement for management of obesity is challenging.

Fortunately, it is becoming more widely accepted that obesity is a chronic disease with deeper, complex roots that has numerous contributors, such as genetics, epigenetics, biology and economical, psychosocial, and behavioral determinants.[3] Weight loss is extremely challenging to achieve and sustain, especially when adaptive biological responses occur that counteract a patient's desire to restrict food and energy intake in response to weight loss.[7] Therefore, it is fundamental that providers, especially primary care physicians, properly manage obesity. By treating obesity, providers are addressing the root issue of numerous common chronic medical conditions cared for on a daily basis, including but not limited to type 2 diabetes mellitus (T2DM), hypertension (HTN), dyslipidemia (DLD), obstructive sleep apnea (OSA), and nonalcoholic fatty liver disease (NAFLD). Successful management of obesity often requires adjunctive pharmacological interventions to reinforce behavior strategies that lead to a negative energy balance.

In this review paper, we provide the latest updates on obesity pharmacotherapy. The main areas we will cover include (1) pharmacological management of obesity, (2) a review of FDA-approved weight loss medications, (3) comanagement of obesity and its metabolic sequelae (T2DM, HTN, and DLD), and (4) obesity-centric prescribing for mental illness, neurologic disorders, and contraceptive planning.

Pharmacological management of obesity

As indicated in the 2015 Endocrine Society Clinical Practice Guidelines on Pharmacologic Management of Obesity,[7] all patients with a body mass index (BMI) $\geq$ 25 kg/m^2 warrant intervention with diet, exercise, and behavior modification. Weight loss medications should be introduced as adjuncts to diet, exercise, and behavioral modification for patients with a BMI $\geq$ 30 kg/m^2 or patients with a BMI $\geq$ 27 kg/m^2 if they have at least one obesity-related comorbid condition, such as T2DM, DLD, and/or HTN.[7] While practical recommendations for healthcare providers were necessary, the current BMI limits are based on a measure (BMI) that only estimates body fat and risk of disease.[7]

Patients who meet label indications are candidates for obesity pharmacotherapy. The objective for using pharmacotherapy to manage obesity is to amplify patient adherence to lifestyle changes and to overcome the biological adaptations that occur with weight loss.[7] Notably, the American Association of Clinical Endocrinologists, the American College of Endocrinology, and the American Society of Bariatric Physicians agree that patients failing lifestyle changes should be offered adjuncts, such as medications, if the BMI $\geq$30 or $\geq$27 kg/m^2 with a comorbidity.[14]

Pharmacological therapy may be necessary to help patients achieve weight loss for various reasons, most importantly to help improve obesity-related health complications, but also preoperative weight loss if indicated before bariatric surgery or other procedures, such as orthopedic hip and knee replacements. Additionally, weight regain is a common occurrence following bariatric surgery after nadir weight is achieved, typically around 18 months postoperation. Research demonstrates that the failure rate based on weight regain following Roux-en-Y gastric bypass ranges anywhere from 5% to 30%, with greater weight regain over time.[15] For this reason, weight loss medications play an important role at various stages of the weight loss journey for patients. Table 1 summarizes the various approaches to weight loss for patients, along with

Table 1. Overview of approaches to weight loss, including BMI criteria and weight loss achieved

Modality	Description	Criteria BMI (kg/m^2)	Weight loss of TBW at 1 year
Lifestyle changes	• Diet, exercise, behavior	≥25	3–10%
Drugs	• Phentermine HCl • Orlistat • Phentermine/topiramate ER • Lorcaserin • Naltrexone SR/Bupropion SR • Liraglutide 3.0 mg	≥27 with comorbidity or ≥30	3–12%
Devices[66]	FDA approved[a] • LAGB (laparoscopic adjustable gastric band)[*] • Vagal-blocking therapy[67,**] • Intragastric balloons[**] • Aspiration device[**] Under investigation • Hydrogel therapeutic[68,**] • DJBS (EndoBarrier duodenal–jejunal bypass sleeve)[**]	Criteria varies	10–20%[*] or 6–12%[b,**]
Surgery	• Gastric sleeve • Roux-en-Y gastric bypass • Biliopancreatic diversion (with and without duodenal switch)	≥35 with comorbidity or ≥40	20–40%

Note: Asterisks show what percent weight loss (10–20% or 6–12%) is associated with each device.
[a]www.fda.gov/MedicalDevices.
[b]At 6 months only.
Abbreviations: BMI, body mass index; TBW, total body weight; FDA, Food and Drug Administration.

their respective BMI criteria and expected weight loss outcomes.

Ultimately, the initial weight loss goal with behavioral changes and adjunctive pharmacotherapy is 5% or more of initial total body weight. This amount of weight loss is sufficient to reduce significant health risks, such as impaired glucose tolerance, HTN, and NALFD.[16] Typically, monotherapy leads to no more than 6–8% total body weight loss from baseline; however, combination therapy can sometimes result in greater loss.[16] In 2015, the Endocrine Society Guidelines strongly recommended monitoring the effectiveness of weight loss medications. A pharmacological intervention that leads to a weight loss of ≥5% of total body weight after 3 months is considered effective and should be continued for the long term if approved. If the medication is found to be ineffective, intolerable due to side effects, or unsafe for the patient, it should be discontinued, and alternative dosing and/or therapies should be considered.[7]

Below, we discuss medication options in obesity management. We review these drugs in order of their FDA year of approval, starting from oldest. This order will also reflect the transition of medications that have been approved for short-term use to long-term use. Since the last "Update on obesity pharmacotherapy" review,[17] new therapies have been made available, including naltrexone sustained release (SR)/buproprion SR (Contrave^{TM}), liraglutide (Saxenda^{TM}), and a low-dose phentermine (Lomaira^{TM}) in the form of a 8 mg tablet. Individualization and a careful review of options are needed when initiating a new weight loss medication for a patient. Healthcare providers should keep in mind the drug's contraindications, expected weight loss, tolerability, feasibility of dosing, side effects, and cost. It is critical that shared decision making between the provider and patient is used in determining which weight loss medication may be most appropriate to start. A summary of these medications can be found in Table 2.

Table 2. FDA-approved pharmacotherapy for obesity[23]

Generic name	Trade names	Year approved	DEA schedule	Mechanism of appetite suppression	Dosing	Estimated mean % weight loss (medications compared with placebo, ITT data) at 1 year	DEA schedule
Phentermine HCl[a]	Adipex, Lomaira	1973	IV	Noradrenergic	15 or 37.5 mg PO QD[b] OR 8 mg PO TID[c]	Not available	IV
Orlistat	Xenical, Alli	1999	None	Lipase inhibitor	60 or 120 mg PO TID with fat-containing meals	For 60 mg TID: 2.5% For 120 mg TID: 3.4%	None
Phentermine/ topiramate ER	Qysmia	2012	IV	Noradrenergic/ neurostablizer	Dose-escalation PO as follows: 3.75/ 23 mg QD with gradual dose escalation (7.5/ 46 mg daily, then 11.25/69 mg daily, then 15/92 mg daily)	For 7.5/46 mg QD: 6.7% For 15/92 mg QD: 8.9%	IV
Lorcaserin	Belviq	2012	IV	5-HT_{2c} receptor agonist	10 mg PO BID	For 10 mg BID: 3.2%	IV
Naltrexone SR/ buproprion SR	Contrave	2014	None	Opioid receptor antagonist/ dopamine and nor-epinephrine reuptake inhibitor	Dose-escalation PO as follows: Week 1: 8/90 mg daily in AM Week 2: 8/90 mg BID Week 3: 16/180 mg in AM and 8/90 mg in PM Week 4: 16/180 mg BID	For 16/180 mg BID 4.8%	None
Liraglutide	Saxenda	2014	None	GLP-1 analog	Dose-escalation subq as follows: Week 1: 0.6 mg QD Week 2: 1.2 mg QD Week 3: 1.8 mg QD Week 4: 2.4 mg QD Week 5: 3.0 mg QD	For 3.0 mg QD: 5.4%	None

[a]Only medication listed that was approved by the FDA for short-term therapy of ≤12 weeks; all other listed medications are approved for long-term therapy.
[b]Tablet formulations of phentermine can be halved or quartered with a pill cutter. Gradual dose escalation is advised before prescribing full-strength formulations of phentermine 37.5 mg once daily.
[c]Note that 8 mg PO TID dosing applies to Lomaira™. Tablets are scored to facilitate individualized dosing accordingly.
Abbreviations: FDA, Food and Drug Administration; DEA, Drug Enforcement Administration; PO, per os (by mouth); ER, extended release; SR, sustained release; subq, subcutaneous; HCl: hydrochloride; BID: twice daily; TID: three times daily; QD: daily; ITT: intention-to-treat; GLP-1: glucagon-like peptide-1; 5-HT_{2C}: selective 5-hydroxytryptamine 2C.

FDA-approved medications for obesity

Diethylproprion, phendimetrazine, and benzphetamine

There is limited use of diethylproprion (Tenuate™; Tenuate dospan™), phendimetrazine (Bontril™ or Prelu-2™), and benzphetamine (Didrex™) in the United States, despite FDA approval in the late 1950s and early 1960s.[18] The studies investigating these noradrenergic drugs provided data with significant limitations, including small sample sizes, poor retention rates, and short study duration (i.e., <1 year).[16] A meta-analysis of nine small studies ranging from 5 weeks to 1 year in duration found that diethylproprion 75 mg daily resulted in 3.0 kg of weight loss versus placebo. Phendimetrazine led to similar results, as demonstrated in two small,

short-term trials lasting 3 months.[19,20] The least well-studied medication in terms of its safety and efficacy is benzphetamine, and hence it is the least commonly prescribed noradrenergic drug in the United States.[21,22]

The number of U.S. prescriptions dispensed from 2008 to 2011 for diethylproprion and phendimetrazine were one and three million, respectively. In contrast, 25.3 million prescriptions for phentermine were dispensed in 2008–2011 in the United States.[21] Hence, phentermine, also a noradrenergic drug, has produced more data and is the most commonly prescribed medication of this group of short-term anti-obesity agents, which we review in more detail below.

Phentermine HCl

Phentermine HCl is the most commonly prescribed weight loss medication in the United States. It was approved by the FDA in 1959 for short-term use (<12 weeks)[23] and is a noradrenergic drug that acts on the sympathetic nervous system, causing an increase in norepinephrine release. This neurotransmitter release leads to appetite suppression in addition to increased resting energy expenditure.[24] Phentermine HCl is a Drug Enforcement Agency (DEA) schedule IV controlled substance because it is an amphetamine analog.[25] Common prescription of this drug involves doses between 15.0 and 37.5 mg oral (PO) once daily in the morning. Dosing should be tailored to the needs of the patient, because some patients may respond to partial doses, such as one quarter tablet (9.375 mg) or one half tablet (18.75 mg). Phentermine HCl is one of the more cost-effective antiobesity medications available and is therefore a very favorable agent for patients who are financially strained. The most commonly reported side effects of phentermine include dry mouth, insomnia, dizziness, palpitations, constipation, and agitation, as well as irritability and mood changes.[7]

Perhaps most importantly, the 2015 Endocrine Society Guidelines strongly recommend against prescribing phentermine HCl to patients with uncontrolled HTN and/or a history of cardiovascular disease. Numerous short-term, placebo-controlled studies assessing phentermine's cardiovascular effects have found mixed results, but case reports have included complications such as new onset atrial fibrillation and elevations in blood pressure and heart rate.[26,27] However, long-term studies are lacking on monotherapy effects of phentermine HCl on cardiovascular risk factors.[18] A dilemma exists over whether phentermine should be prescribed for the long term. The drug has been widely prescribed for over two decades in the United States without evidence of serious side effects, and recent literature has also suggested that the addiction potential of phentermine HCl is low. Hence, a long-term randomized controlled study is needed.[7]

Phentermine HCl has been available on the market for over half a century, but few trials have been performed that lasted longer than 6 months. A 2002 meta-analysis of six studies assessing patients using phentermine HCl 15–30 mg daily versus placebo for anywhere between 2 weeks to 6 months demonstrated a mean total weight loss of 6.3 kg.[22] The longest study assessing phentermine HCl was performed in 1968 as a 36-week, double-blind, placebo-controlled trial of 108 women who were overweight or obese prescribed phentermine HCl 30 mg continuously versus phentermine HCl 30 mg intermittently (i.e., 4 weeks of phentermine HCl 30 mg alternated with 4 weeks of placebo) versus placebo. All participants were given a one-time instruction on diet at the start of the study to follow a low-carbohydrate diet in which patients would eat on average 1000 kcal/day. Among these groups, the weight loss achieved was comparable to the continuous versus intermittent users of phentermine HCl 30 mg (12.2 versus 13.0 kg, respectively) and was significantly greater than that of placebo (4.8 kg).[28]

More recently, the 2013 randomized, placebo-controlled trial EQUATE assessed the effectiveness of the monotherapies that make up a combination pill—phentermine/topiramate ER—a weight loss medication approved for long-term management of obesity. The dosages of phentermine HCl assessed included 7.5 mg daily versus 15 mg daily, which led to weight loss of 5.3 and 6.0 kg, respectively, at the end of the 28-week trial. This was significantly less absolute weight loss than what was produced from combination therapy of phentermine/topiramate ER 7.5/46 mg and phentermine/topiramate ER 15/92 mg groups (8.3 versus 9.0 kg).[29]

In summary, phentermine is a very affordable medication that has been on the market for over a half-century with widespread use in the United States. It leads to clinically significant weight loss

of typically 3–5% in 12 weeks.[22,29] However, one disadvantage of this medication is the lack of long-term safety data.[7]

Low-dose phentermine

Lomaira™ is the lower dose form of phentermine HCl, available in 8 mg tablets. The medication can be prescribed up to 8 mg PO three times daily. The tablet is scored, allowing for half-tablet dosing for prescriptions to be customized according to a patient's tolerability, preferences, and schedule.[30] This lower dose form of phentermine can potentially help patients with later afternoon and evening appetite control issues.[31] Typically, patients are advised to take the last tablet of the day no later than early evening (i.e., 4–5 pm) to avoid the side effect of insomnia; however, this recommendation should vary depending on the patient profile. It is important to note that there are no existing studies comparing efficacy and safety of Lomaira to standard doses of phentermine or any other antiobesity drugs.[32]

Orlistat

Orlistat was made available on the market as Xenical™ in 1999 when it was first approved by the FDA in a 120 mg dose form. In 2007, it became commercially available as Alli™ in a lower dose (60 mg) over-the-counter form. Orlistat 12 0 mg is actually FDA approved for adults and adolescents $\geq$12 years of age.[18] Orlistat inhibits pancreatic and gastric lipases, which leads to about a 30% reduction in intestinal fat absorption. Common side effects include fecal urgency, flatus with discharge, fatty/oily stools, and increased defecation.[23] However, prescribing a fiber-containing supplement, such as psyllium, with orlistat can help reduce these gastrointestinal side effects.[18]

With regard to weight loss effects, orlistat (versus placebo) led to 2.4% total body weight loss compared with baseline weight after 4 years in the XENDOS trial. This trial was a large, randomized, prospective, and placebo-controlled trial that examined 3305 patients. The trial found that orlistat not only decreased weight but also significantly reduced the risk of T2DM compared with placebo (6.2% versus 9.0%) over 4 years.[33] Additionally, orlistat has demonstrated improvement in insulin sensitivity, glucose levels, blood pressure, and cholesterol profiles owing to its mechanism of action of decreasing fat absorption.[33,34]

It has been shown to be challenging in practice to convince patients to enroll in trials of orlistat because of its undesirable side effects. Nonetheless, it leads to modest weight loss and may positively affect weight related comorbidities.[7]

Phentermine/topiramate extended release

Phentermine/topiramate extended release (ER; Qysmia™) was approved by the FDA in 2012 as the first combination medication approved for chronic management of obesity. It is a controlled DEA schedule IV substance owing to the phentermine component. Phentermine is a noradrenergic agonist, and topiramate ER acts on GABA receptors, leading to appetite suppression. The medication is prescribed as once-daily (QD) dosing that is advisable to take in the morning to prevent exacerbating the known side effect of insomnia. The dose should gradually be escalated according to the package insert. This involves a starting dose of 3.75/23 mg QD for 2 weeks followed by 7.5/46 mg thereafter, which was best tolerated by participants in research studies and is considered the recommended dose. The dose should be tried for a minimum of 3 months before further escalation to the top dose of 15/92 milligrams. Increasing the dose is only advised if the patient does not achieve 3% total body weight loss after 3 months. If the medication is poorly tolerated, slowly titrating down or off the medication is warranted (i.e., over 3–5 days ideally) to reduce the risk of precipitating a seizure. This effect was seen in clinical research where patients with a history of seizures who were taking topiramate abruptly stopped the medication.[7] Common side effects of phentermine/topiramate ER include dizziness, paresthesia, insomnia, dry mouth, constipation, and dysgeusia.[23] An imperative fetal safety concern with this medication arises in that topiramate is known to increase the risk of oral clefts. Therefore, contraceptive planning is key before prescribing it to female patients of childbearing age.

Phentermine/topiramate ER has been well assessed for its weight loss efficacy in several long-term investigation studies. EQUIP and CONQUER were each 1-year, large cohort, randomized, double-blind, placebo-controlled studies and included 1267 and 2487 participants, respectively. The EQUIP trial included patients with a BMI $\geq$ 35 kg/m^2 who were at lower risk in that they lacked T2DM, in contrast to the CONQUER study, which included patients

with a BMI ranging from 27–45 kg/m^2 who had at least two obesity-related comorbid conditions. The findings from these two studies provided support for the FDA approval of phentermine/topiramate ER. In the EQUIP study, the mean weight loss at 1 year for participants on phentermine/topiramate ER 15/92 mg was 10.9% compared with 1.6% on placebo. Similarly, participants on the same dose of phentermine/topiramate ER for 1 year in the CONQUER trial lost 9.8% of weight from baseline compared with 1.2% in the placebo group. The CONQUER trial also found 7.8% total body weight loss for patients taking phentermine/topiramate ER 7.5/46 mg for 1 year. Notably, all of these studies demonstrated an improvement in cardiovascular risk factors.[35,36] A 2-year extension trial, SEQUEL was performed to assess the continued weight loss of patients following completion of the CONQUER trial.[37] The SEQUEL study reinforced previous findings that phentermine/topiramate ER can lead to significant weight loss and improvement in cardiovascular risk factors, including blood pressure, lipid profiles, fasting glucose, fasting insulin, and waist circumference.[37]

Phentermine/topiramate ER leads to meaningful weight loss compared with placebo and has been well studied in long-term trials. Notably, its teratogenic effects limit its usefulness for women of childbearing age who are planning to have children.[7]

Lorcaserin

Lorcaserin (Belviq^{TM} and Belviq XR^{TM}) was approved by the FDA in 2012 for chronic management of obesity. It acts centrally as a selective 5-hydroxytryptamine (5-HT) 2C receptor agonist and is a DEA schedule IV controlled medication.[7,25] Weight loss is achieved by decreasing food intake caused by increased satiety through activation of anorexigenic pro-opiomelanocortin neurons in the hypothalamus.[23] In 2016, a once-daily ER form of Belviq^{TM} was approved in the form of 20 mg daily.[25] Typical side effects reported with lorcaserin include headache, nausea, dizziness, dry mouth, constipation, fatigue, hypoglycemia, back pain, and cough.[23]

The effects of lorcaserin on weight were studied in two randomized, double-blind, placebo-controlled phase III trials known as BLOOM and BLOSSOM. These studies included 3182 and 4004 nondiabetic patients, respectively, who were given low-intensity counseling on nutrition and exercise.[38–40] Lorcaserin led to a weight loss of approximately 3.3% from baseline total body weight.[39,40] Fasting glucose, fasting insulin, and hemoglobin A1c improved as well.[40] An additional, smaller cohort of 603 patients with T2DM and HbA1c 7.0–10.0%, who were overweight or obese, were studied in the BLOOM-DM trial.[38] The results of this study showed a mean reduction of A1c in the treated group compared with placebo (0.9% versus 0.4%).[38] Since lorcaserin acts on 5-HT2C receptors selectively, there was concern for the possibility that it could exert some effect on other 5-HT receptors that could, in turn, affect valvular competency, as was seen with patients who took fenfluramine–phentermine as well as those who took dexfenfluramine in the 1990s.[41] Patients were monitored with serial echocardiograms during all of these phase III trials, with a pooled risk of 1.15 (95% CI: 0.81–1.67) for FDA-defined valvulopathy, suggesting no unacceptably increased risk of valvulopathy with use of lorcaserin.[42]

Several long-term trials have assessed lorcaserin for efficacy and safety, and safety is a major positive attribute for this medication. Additionally, it has shown to be beneficial for improvement in T2DM parameters, but, unfortunately, its weight loss efficacy is modest.[7]

Naltrexone SR/buproprion SR

Naltrexone SR/buproprion SR (Contrave^{TM}) is a combination drug for weight loss approved by the FDA in 2014. The individual components of this medication are drugs that have been in use since the 1980s for other medical conditions.[7] The mechanism of action for buproprion SR is inhibition of dopamine and norepinephrine reuptake. Naltrexone acts to antagonize the feedback loop that limits buproprion's anorexic effects; hence, this drug combination works synergistically.[43] The recommended prescription for naltrexone SR/bupropropion SR is a slow dose escalation to minimize the side effect of nausea. The medication is available in 8/90 mg combination tablets and initially should be taken as one pill daily for 1 week. Subsequently, at week 2, the prescription is one tablet PO twice daily (BID), then week 3 includes two tablets PO in the morning and one tablet PO in the evening before dinner. Finally, the fourth week is when maximum dosing is achieved (32/360 mg) with two tablets PO

BID.[7] Typical side effects are dizziness, headache, dry mouth, and gastrointestinal upset (i.e., nausea, vomiting, constipation, and/or diarrhea).[23]

Naltrexone SR/buproprion SR was evaluated in four phase III multicenter, long-term, double-blind placebo-controlled trials. The names of these trials are Contrave Obesity Research I (COR-I), Contrave Obesity Research II (COR-II), Contrave Obesity Research Behavior Modification (COR-BMOD), and Contrave Obesity Research Diabetes (COR-DM). COR-I ($n = 1742$), COR-II ($n = 1496$), and COR-BMOD ($n = 793$) assessed patients with obesity or with at least one weight-related comorbid condition (i.e., HTN) in addition to a BMI $\geq$ 27.[44–47] The percent weight loss seen in COR-I, COR-II, and COR-BMOD for patients taking naltrexone SR/buproprion SR 32/360 mg for 56 weeks versus placebo was 6.1% versus 1.3%, 6.4% versus 1.2%, and 9.3% versus 5.1%, respectively.[48] As shown with the weight loss percentage results, the total weight loss after approximately 1 year was greatly increased with the addition of behavior counseling in the COR-BMOD trial. The final study, COR-DM ($n = 505$), assessed weight loss in patients with T2DM and overweight or obesity.[44] This study found that patients treated with naltrexone SR/buproprion SR 32/360 mg for 56 weeks versus placebo lost 5.0% versus 1.8% ($P < 0.001$) and improved their HbA1c compared to baseline 0.6% versus 0.1% ($P < 0.001$).[49] These trials demonstrated improvement in high-density lipoprotein and triglycerides for those treated with naltrexone SR/buproprion SR compared with placebo. However, waist circumference, fasting insulin, and insulin resistance index (HOMA-IR) improvement was shown only in participants in the COR-I, COR-II, and COR-BMOD studies.[23]

Naltrexone SR/buproprion SR leads to impactful weight loss, with long-term evidence supporting its efficacy.[7] There is no abuse potential with this medication, and it is therefore not a controlled substance. Buproprion alone is indicated for depression and smoking cessation and, notably, has a black box warning for suicidal ideation.[25] However, the combination medication of naltrexone/bupropion is not approved for these conditions. Importantly, the side effects of increased blood pressure and heart rate can make it challenging to prescribe this medication to patients with significant cardiovascular disease.

Liraglutide

The newest weight loss medication on the market for chronic management of obesity is liraglutide 3.0 mg subcutaneous (SC) injection daily (brand name Saxenda™). Liraglutide was approved by the FDA in 2014 at a dose of 3.0 mg; a lower dose form, 1.8 mg daily, with the brand name Victoza™ was approved in 2010 for management of T2DM. Dose-dependent weight loss was associated with liraglutide 1.8 mg SC daily, and, hence, the drug was further studied as a potential pharmacological agent in the management of obesity. Liraglutide is an analog of human glucagon-like peptide-1 (GLP-1) with a much longer half-life of 13 h compared with the human endogenous GLP-1 that lasts just a few minutes. This drug mimics the actions of endogenous GLP-1, a hormone released from the small intestines that plays a role in in the peripheral regulation of appetite through anorexigenic effects in addition to effects of increasing release of insulin from the pancreas in the presence of glucose.[50] Liraglutide should be titrated over the course of 4 weeks to achieve the recommended daily dose of 3.0 mg SC. The initial dose is 0.6 mg SC daily for 1 week, and the dose is increased by increments of 0.6 mg every week until the maximum dose is reached. This slow escalation helps to mitigate the side effect of nausea. If patients encounter this problem, they can delay increasing the dose for additional time until a stronger tolerance level is reached.[7] Common side effects of liraglutide include nausea, abdominal pain, dyspepsia, diarrhea, constipation, hypoglycemia, and headache.[23]

Three trials played a critical role in assessing the efficacy and safety of liraglutide at a dose of 3.0 mg SC daily. The SCALE Obesity and Prediabetes study was a randomized, double-blind, placebo-controlled 56-week investigation that assessed 3731 patients without T2DM who had a BMI $\geq$ 30 or BMI $\geq$ 27 with weight-related comorbidity, such as HTN or DLD. A total of 2487 patients met inclusion criteria, and 61.2% suffered from prediabetes. All participants received lifestyle intervention (i.e., reduced-calorie diet and exercise counseling) and were randomized to liraglutide 3.0 mg SC daily versus placebo, in which weight loss achieved after 56 weeks was 8.0% versus 2.6%, respectively. Cardiovascular parameters, including blood pressure and lipid profiles, improved more in the treatment group. Importantly, HbA1c (–0.30% $\pm$ 0.28) and

fasting glucose levels (–7.1 mg/dL ± 0.8) decreased significantly for those taking liraglutide 3.0 mg compared with placebo.[51]

The next study, SCALE Diabetes, is another randomized, 56-week, placebo-controlled study but with a parallel-trial component (126 sites and nine countries) and an additional 12-week observational off-drug follow-up period. Patients met inclusion criteria if they had a BMI ≥ 27 and T2DM with HgA1c 7.0–10.0% treated with lifestyle management only or with one of three oral hypoglycemic medications (i.e., sulfonylurea, metformin, or thiazolidinedione). A total of 846 patients received lifestyle intervention (i.e., 500 kcal/day diet deficit and increased physical activity to ≥150 min/week) and were randomized to one of three medication arms: liraglutide 3.0 mg SC daily, liraglutide 1.8 mg SC daily, or placebo. The change in baseline weight for patients significantly decreased (6.0%, 4.7%, and 2.0%, respectively) in each of the three arms. The liraglutide 3.0 mg SC daily group had significantly greater improvements in T2DM measures, such as HbA1c, fasting plasma glucose level, HOMA-IR, fasting proinsulin level, proinsulin-to-insulin ratio, and number of hypoglycemic agents used to manage T2DM, compared with the 1.8 mg SC daily group. It is important to point out that the SCALE Diabetes trial also assessed drug safety, and no cases of pancreatitis were reported.[52]

Finally, the third study, titled SCALE Maintenance, was a 56-week, randomized, placebo-controlled, double-blind clinical trial evaluating weight maintenance in nondiabetic patients. Patients included in this study were similar to those in the SCALE Obesity and Pre-Diabetes study in that they did not have T2DM and required a BMI ≥ 30 or BMI ≥2 7 with weight related comorbidity, such as HTN or DLD. These patients underwent a ≥4-week run-in with a low-calorie diet, and those who lost ≥5% of their body weight ($n = 422$) were randomized to liraglutide 3.0 mg SC daily versus placebo for 56 weeks. The liraglutide 3.0 mg SC daily group achieved an additional mean weight loss of 6.2% ± 7.3 compared with placebo (0.2% ± 7.0, $P < 0.0001$).[53]

In July 2016, 1.8 mg SC daily liraglutide, approved for T2DM and give the brand name Victoza, was evaluated in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) study. This was a long-term, multicenter, international, randomized, double-blind, placebo-controlled trial to determine the effects of liraglutide on cardiovascular events, including major cardiovascular events (MACEs): cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction. The results of this study showed noninferiority of liraglutide compared with placebo in time to first MACE.[54]

If a patient can afford liraglutide 3.0 mg and is agreeable to administering a daily injection, then this is an excellent medication to consider. Liraglutide has supportive long-term data for its meaningful weight loss effects and is typically well tolerated if carefully and slowly titrated up to the goal dose.[7]

Pharmacological comanagement of obesity and its metabolic sequelae

Obesity is a public health crisis that is finally gaining attention as such in the medical community. As a result, now is the time to shift current practice management for chronic diseases to prioritize obesity treatment to improve these diseases, especially in the primary care setting. Previously, chronic diseases, such as T2DM, HTN, and DLD, were managed in a very fixed approach that involved monitoring each condition individually with diet and drugs. Even though obesity is known to be the root cause for these conditions, weight loss has not been a priority in the management of these diseases. However, it is well established that obesity can cause disease through changes in hormone expression and increased inflammation.[55,56] Thus, a shift from the old treatment paradigm is needed. The old and new treatment paradigms are compared in Figure 1.

Furthermore, T2DM was the seventh leading cause of death in the United States in 2013, and there is a clear, established link between excess body weight and insulin resistance.[57] Hence, it is important that pharmacotherapy directed at glycemic control is also weight favorable. If patients have a BMI ≥ 35 kg/m^2 with T2DM, bariatric surgery is an option to consider as well. Per the 2015 Endocrine Society Guidelines,[7] patients with T2DM who are overweight or obese should receive antidiabetic medications that also promote weight loss in adjunct to lifestyle modifications. As illustrated in Figure 1, metformin is the first-line agent recommended in this population.[7] The mechanism of action of metformin is to inhibit gluconeogenesis and hepatic glucose production

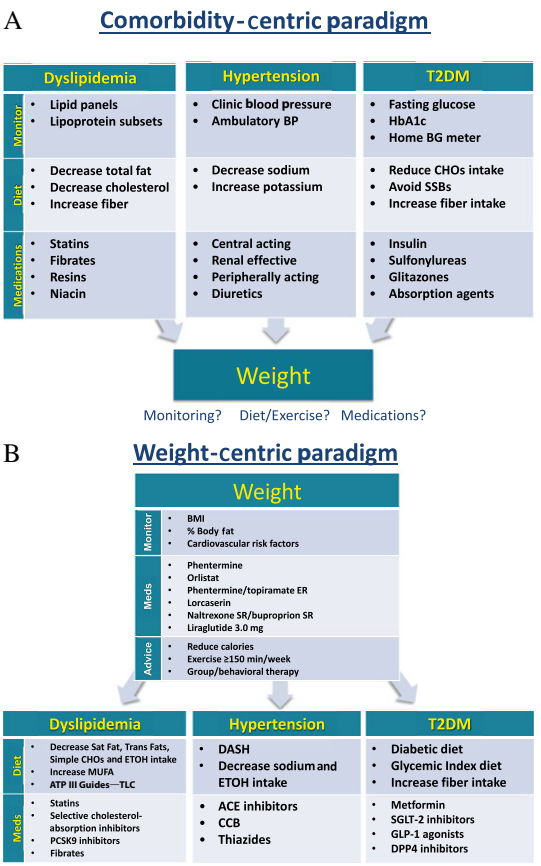

Figure 1. Old treatment paradigm (A) versus new treatment paradigm (B). T2DM, type 2 diabetes mellitus; BP, blood pressure; HbA1c, hemoglobin A1c; BG, blood glucose; carb, carbohydrate; CHO, carbohydrates; SSBs, sugar-sweetened beverages; sat fat, saturated fat; MUFA, monounsaturated fatty acids; ATP, Adult Treatment Panel III; TLC, therapeutic lifestyle changes; PCSK9, proprotein convertase subtilisin-kexin type 9; DASH, dietary approaches to stop hypertension; ACE, angiotensin-converting enzyme; CCB, calcium-channel blocker; SGLT-2, sodium–glucose cotransporter-2; GLP-1, glucagon-like peptide-1; DPP4, dipeptidyl peptidase-4. The authors acknowledge Susan Morreale for her assistance in creating this figure.

while also improving tissue sensitivity to insulin.[57] Additionally, weight loss may be another advantage, as a recent meta-analysis demonstrated statistically significant weight loss benefits with metformin therapy compared with placebo (mean weight loss of 1.1 kg).[58] Second-line therapy varies depending on the clinical and medical history of the patient, for example, age and renal function. Options for second-line therapy include GLP-1 agonists or sodium–glucose-linked transporter-2 (SGLT-2) inhibitors.[7] Drugs in this medication class of GLP-1 agonists include liraglutide, exenatide, dulaglutide, and albiglutide. A recent meta-analysis found a 1.7 kg weight loss associated with liraglutide, which is the most commonly prescribed medication among the GLP-1 agonists.[58] In addition to weight loss, GLP-1 agonists typically lead to reduction of HbA1c by 1.0% (95% CI: 0.5–1.5), as well as improvement in numerous other weight-related comorbidities, such as DLD and NAFLD.[57] SGLT-2 inhibitors include medications such as empagliflozin, canaglifozin, and dapagliflozin. Typical weight loss with these medications is 1.8 kg (95% CI: 0.11–3.50 kg) and improvement in HbA1c is 0.66% (95% CI: 0.73–0.58). Notably, a recent 2016 meta-analysis assessed eight randomized, placebo-controlled trials and demonstrated an association between empagliflozin and a reduction in cardiovascular morbidity and mortality in patients with T2DM, including those with low/medium or high cardiovascular risk.[59] Finally, another class of medications to consider is dipeptidyl peptides IV (DPP-4) inhibitors, which are weight neutral and lead to a HbA1c reduction of 0.5–1.0%.[57] In general, healthcare providers should consider the weight effects of glucose-lowering medications and make every effort to choose weight-lowering and weight-neutral agents as first- and second-line therapy in patients with obesity and T2DM.

A key point in comanagement of T2DM and obesity is consideration of the status of patients' T2DM. For those with uncontrolled T2DM (i.e., HbA1c ≥ 9%) and excess body weight, the first priority is to achieve immediate glycemic control to prevent glucose toxicity. In these clinical situations, the first-line therapy indicated is basal insulin.[57] Basal insulin is preferable to sulfonylureas or using other forms of insulin, such as premixed insulin or combination insulin therapy.[7] Initial therapy for these patients should ideally include insulin in combination with metformin. Data from a large placebo-controlled clinical trial indicated that patients with obesity and uncontrolled T2DM treated with insulin plus metformin versus insulin plus placebo required significantly less insulin therapy and gained less weight.[60] If metformin is not tolerated and/or is contraindicated in the particular patient, another option is to use basal insulin therapy plus a GLP-1 agonist or SGLT-2 inhibitor to help offset insulin-induced weight gain.[7]

With regard to comanagement of obesity and HTN, the general first-line therapies recommended for adults by the JNC-8 guidelines are all weight favorable.[61] For non-African American patients, initiation of thiazide, angiotensin-converting enzyme inhibitors, or calcium channel blockers (CCBs) is recommended. For African American patients, a thiazide or CCB should be considered as first-line therapy for HTN. These agents are weight neutral and recommended by the 2015 Endocrine Society Guidelines as first-line therapy for HTN in patients with obesity.[7] The goal is to avoid the use of beta-blockers (BBs) unless indicated for heart failure, cardiovascular disease, or other medical conditions warranting such. In the case that BBs are indicated, it is preferential to choose carvedilol or nebivolol because studies have shown these to cause less weight gain or negative effects on glucose and lipid metabolism.[7] The mechanism of action of BBs produces a reduced heart rate, a side effect of which is commonly fatigue.[61] This constellation of symptoms makes it very challenging for patients to have the desire to exercise or even be able to exercise, owing to the inability to increase heart rate upon exertion. Additionally, a meta-analysis that looked at randomized, controlled HTN trials (minimum of 6 months duration), found body weight to be 1.2 kg higher in the BB group compared with the placebo group.[62] Hence, the importance of following evidence-based guidelines for the treatment of HTN cannot be sufficiently stressed, as this will also facilitate prescribing weight-neutral medications the majority of the time.

Weight-centric prescribing

Weight-centric prescribing involves treating medical conditions with weight-neutral and/or weight-lowering medications as first-line therapy when possible. Drug-induced weight gain is definitely a preventable cause of obesity. Careful review of medication lists to assess for drugs that may be contributing to a patient's current weight status is indispensable. Below, we discuss common medical conditions, including mental illness and neurological disorders, as well as contraceptive planning, where weight-centric prescribing can be very impactful.

Mental illness

The 2015 Endocrine Society Guidelines recommend a shared decision-making process between providers and patients regarding the expected weight side effects of medications for mental illness.[7] There are several different classes of drugs to choose from when treating patients for depression and obesity. Bupropion is an excellent option, since it is associated with a weight loss of 1.3 kg.[7,58] Other options to consider are selective serotonin reuptake inhibitors; specifically, fluoxetine is associated with a 1.3 kg weight loss.[58] Anti-depressants that are associated with weight gain, specifically tricyclic antidepressants, such as amitriptyline and mirtazapine, have been shown to cause a weight gain of 1.8 and 1.5 kg, respectively, in a recent meta-analysis.[58]

Antipsychotics, another class of medication, are commonly associated with weight gain. These drugs are prescribed to treat mood disorders, bipolar disorder, and schizophrenia. A meta-analysis of 257 randomized, controlled trials, including both parallel and crossover study design, found that the antipsychotic drugs that are most commonly associated with weight gain were olanzapine (2.4 kg), quetiapine (1.1 kg), and risperidone (0.8 kg). None of the drugs in this class were associated with weight loss; however, aripiprazole and ziprasidone are generally weight neutral.[58]

Neurological disorders

Neurological disorders, such as migraines and epilepsy, are cumbersome illnesses that can severely affect the quality of life of patients. Weight-centric prescribing is indicated for patients with obesity who have one or both of these illnesses. In the case of migraines, topiramate is a desirable option because it promotes weight loss. Two randomized, controlled meta-analyses conducted in 2015 and 2016 found that topiramate led to a similar amount of weight loss of 3.8 and 3.14 kg, respectively.[63] With regard to epilepsy treatment, favorable treatment options in patients with obesity are weight-neutral agents, such as lamotrigine, or weight-lowering agents, such as zonisamide, and again topiramate may work in certain cases with recommended discussion with neurologists. Valproic acid, carbamazepine, and gabapentin are weight-promoting medications.[7]

Contraceptive planning

Women with obesity who are of childbearing age merit thorough discussions with their providers about contraceptive options and the weight-related side effects of those options. Topiramate is a

component of the weight loss medication phentermine/topiramate ER approved for the chronic management of obesity, and is a known teratogen.[25] Hence, a contraceptive plan needs to be agreed upon and arranged before prescribing this medication.[7] The 2015 Endocrine Society Guidelines recommend oral contraceptive pills rather than injectable medications. This is because most studies demonstrate an association between depot medroxyprogesterone acetate and weight gain compared with other forms of hormonal contraception.[64] However, more research is needed, since the majority of the investigations only assessed normal-weight individuals.[7]

Conclusions

Obesity rates are predicted to rise in the upcoming years, with the subgroup of severe obesity (BMI >40) rapidly increasing.[25,65] Nevertheless, obesity is undertreated in clinical practice.[11] Healthcare providers need to recognize obesity as a disease and manage it appropriately, prescribing weight loss medication as adjunctive therapy to diet and exercise when indicated. In the last few decades, more pharmacological options for the management of obesity have been made available. There are now five agents approved for long-term weight management, as well as the class of noradrenergic drugs that are approved for short-term management.[14] Successful use of obesity pharmacotherapy requires thoughtful, patient-centered discussions between providers and patients centered on topics such as the patient's eating and social behaviors, medical history, financial preferences, and the expectations as well as known side effects of the weight loss medications. These medications have the potential to augment lifestyle modification and significantly affect the quality of life of countless individuals who suffer from chronic disease stemming from excess body weight.[23] Additionally, patients with obesity being treated for other conditions, whether related to weight or not, should receive medications that do not dramatically affect weight. In summary, obesity is a complex disease that is multifactorial in origin and should be treated accordingly.

Competing interests

C.M.A. discloses the following relationships—Advisory Board: Amylin, Arena, EnteroMedics, Gelesis, GI Dynamics, Johnson and Johnson, Merck, Novo Nordisk, Nutrisystem, Orexigen, Sanofi-Aventis, Scientific Intake, Zafgen; other: Science-Smart LLC (stock ownership), Takeda (Contrave Speaker's Bureau). Research funding came from Amylin, Aspire Bariatrics, Coherence Lab, the Dr. Robert C. and Veronica Atkins Foundation, Eli Lilly, Energesis, Gelesis, GI Dynamics, MetaProteomics, MYOS Corporation, Orexigen, PCORI, Pfizer, Sanofi-Aventis, Takeda, and the Vela Foundation. C.M.A. receives royalties from the Philip Lief Group (author, *The Overnight Diet* and *The Age-Defying Diet*) and is a site coinvestigator for NPS Pharmaceutical.

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