Drugs for Treating Obesity

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Abstract

Older medications approved for chronic weight management (orlistat, naltrexone/bupropion, liraglutide 3 mg and, in the USA, phentermine/topiramate) have not been widely adopted by health care providers. Those medications produce only modest additional weight loss when used to augment lifestyle intervention. However, semaglutide 2.4 mg weekly has recently emerged and produces much more weight loss – on average 15% weight loss at 1 year. Semaglutide's

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enhanced efficacy and that its class (GLP-1 receptor analogs) is well-known may result in more clinicians adopting pharmacotherapy. Furthermore, the first dedicated cardiovascular outcome trial powered for superiority testing an anti-obesity medication (SELECT) is underway with semaglutide 2.4 mg. A positive outcome will further promote the concept that weight management should be a primary target for cardiometabolic disease control. In phase 3, tirzepatide and cagrilintide/semaglutide combination are showing promise for even greater weight loss efficacy. Another recently approved medication takes a personalized medicine approach; setmelanotide is approved as a therapy for those with some of the ultra-rare genetic diseases characterized by severe, early onset obesity. This chapter reviews the currently available and anticipated medications for chronic weight management as well as those approved for the genetic and syndromic obesities.

Keywords

Anti-obesity medication · Bimagrumab · Cagrilintide · Chronic weight management · Liraglutide · Naltrexone/bupropion · Obesity drugs · Obesity pharmacotherapy · Orlistat · Phentermine/topiramate · Semaglutide · Setmelanotide · Tirzepatide

1 Introduction and Rationale for Anti-obesity Medications

Obesity is increasingly being recognized as the root cause of the growing global burden of non-communicable diseases (NCDs), such as diabetes, cardiovascular diseases, and cancers. The NCDs stress societies' health systems, both economically and logistically. Thus, reducing excess abnormal fat has become a target for chronic disease prevention and remediation. In March 2021, the European Commission issued a brief in which it defined obesity as a "chronic relapsing disease, which in turn acts as a gateway to a range of other non-communicable diseases.". To effectively achieve and sustain weight loss in persons with obesity, it must be recognized as a disease, a chronic disease.

To address obesity as a disease, development of safe and effective pharmacologic agents is an imperative. When medications for weight management are used to augment lifestyle intervention targeting diet and physical activity, they offer potential as a rational pathway to cardiometabolic disease treatment and prevention, because they will provide more weight loss than can be achieved with lifestyle intervention alone.

Rationale for Anti-obesity Medications and for Long-Term Use Medications work through biology to promote greater adherence to consumption of fewer calories. In the case of orlistat, the mechanism is through blocking absorption of dietary fat and promoting adherence to low-fat meals and snacks (Guerciolini 1997). In the case of naltrexone/bupropion, liraglutide, phentermine/topiramate, and semaglutide, the mechanism is through appetite – reducing hunger, increasing

satiation, and making the patient less susceptible to highly hedonic foods (Pilitsi et al. 2019). As will be demonstrated in the discussions below, patients who take medications approved for chronic weight management will lose more weight than those taking placebo and as long as the medication is continued weight regain will be avoided. When the medications are stopped, weight is then regained. This is because obesity is like other chronic diseases. In the case of obesity, the body's defense of its highest fat mass drives weight regain through biologic effects on appetite regulation and energy expenditure regulation (Laughlin et al. 2021).

Indications for Anti-obesity Medications Regulatory authorities in the United States of America (USA) and European Union (EU) currently provide labeling that indicates anti-obesity medications are indicated for adults with BMI >30 kg/m^2 or >27 kg/m^2 and at least one comorbidity as an adjunct to reduced calorie diet and increased physical activity when the patients are unsuccessful in losing weight with lifestyle changes alone, or need to lose 10% or more body weight to achieve health benefits, or need to maintain weight loss (regardless of the methods used to achieve initial weight loss). As genetic defects and endocrine syndromes are discovered, indications are being granted for specific therapies. We now have treatment for defects in leptin, the leptin receptor, POMC, and PCSK1.

How Much Weight Loss Is Needed? For years, obesity medicine specialists have promoted the benefits of modest weight loss (5–10%), in part because that is all that can be achieved in most patients using older therapeutic approaches, excepting bariatric surgery. Modest weight loss (5–10%) is associated with improvement in glycemia, cardiovascular risk factors like blood pressure and lipids, and improvements in how patients feel and function (Ryan and Yockey 2017). However, greater amounts of weight loss (>10%) produce continued improvement in these outcomes. Further, 10% or more weight loss is needed for improvement in symptoms of obstructive sleep apnea (OSA) and for improvements in NASH Activity Scores in patients with Non-Alcoholic Steatotic Hepatitis (NASH) (Ryan and Yockey 2017). For diabetes remission, 15 kg weight loss is needed; (Lean et al. 2018, 2019) and for reduction in cardiovascular events, 15% or more weight loss is probably needed (Ryan and Yockey 2017). Different amounts of weight loss produce different effects on different tissues (Magkos et al. 2016). Visceral and ectopic fat stores are mobilized preferentially (Magkos et al. 2016), and this may account for the metabolic improvements with more modest weight loss, while greater weight loss is required for other conditions.

Variation in Weight Loss Response An important observation in weight management is that no matter what treatment we are initiating, there is enormous individual variation in weight loss response (MacLean et al. 2018). This is true for all our treatments, including surgery and medications. The implications of this for prescribers is that for all medications, early response is predictive of long-term outcomes.

2 Anti-obesity Medications Recently Brought to Market: Semaglutide 2.4 mg and Setmelanotide

2.1 Semaglutide 2.4 mg

Semaglutide is an analog of native GLP-1 (glucagon-like peptide-1) and has 94% homology with the native peptide sequence. In semaglutide, arginine replaces lysine at position 28, aminoisobutyric acid replaces glycine at position 2 (to resist degradation) and a C-18 fatty acid and lengthy spacer is attached to Lysine (to promote albumen binding) (Pearson et al. 2019). While native GLP-1 has a half-life of 1–2 min, the half-life of semaglutide is 165 h, allowing it to be dosed subcutaneously once weekly (Pearson et al. 2019). Thus, semaglutide 2.4 mg is given weekly by subcutaneous injection. The dose escalation schedule is to increase every 4 weeks from 0.25 mg to 0.5 mg, to 1.0 mg, to 1.7 mg, to 2.4 mg (Wegovy™ Product Label, FDA).

GLP-1 receptor analogs have pleiotropic effects (Ryan and Acosta 2015). There are multiple agents in this class approved for type 2 diabetes, but liraglutide (discussed below) is the only GLP-1 analog approved for weight management. Semaglutide is approved for management of diabetes at doses of 0.5 and 1.0 mg weekly and oral semaglutide in doses up to 14 mg is also approved for diabetes. Semaglutide 0.5 and 1.0 mg have been shown to reduce cardiovascular events in persons with type 2 diabetes (Marso et al. 2016).

Semaglutide is approved in the USA and is under review by the European Medicines Agency (EMA). Five phase 3 studies, all called STEP (Semaglutide Treatment Effect in People with obesity) are now completed; (Kushner et al. 2020) four have been published (Wilding et al. 2021; Davies et al. 2021; Wadden et al. 2021; Rubino et al. 2021). In these studies, a "treatment policy estimand" was used for the primary analysis. This is like an intention-to-treat analysis where all assigned participants are considered, and missing data are accounted for with statistical measures of multiple imputation. Another "trial product estimand" was calculated which considered observations on treatment. This review will report the more conservative "treatment policy estimand" for the discussion of results across trials, except where noted.

The characteristics of the four STEP trials are shown in Table 1. In STEP 1, more than 70% patients had a comorbidity and while none had diabetes, almost 44% had prediabetes. Both placebo and semaglutide 2.4 mg groups received a lifestyle intervention with a 500 kcal/day deficit diet and recommendations to increase physical activity to 150 min per week. The trajectory of mean weight loss in this study was such that the mean weight loss did not reach a plateau until 60 weeks see Fig. 1a. In STEP 1, when the semaglutide-treated group is compared to the placebo-treated group, there were greater improvements in cardiometabolic risk factors and a greater increase in participant-reported physical functioning.

STEP 2 (Davies et al. 2021) enrolled 1,210 persons with type 2 diabetes and randomized them 1:1:1 to semaglutide 2.4 mg weekly, semaglutide 1.0 mg weekly, or placebo. The weight loss trajectory for semaglutide 2.4 and 1.0 mg was like that in

Table 1 Characteristics of four recently published phase 3 studies of semaglutide 2.4 mg weekly for obesity

	STEP 1 (Wilding et al. 2021)	STEP 2 (Davies et al. 2021)	STEP 3 (Wadden et al. 2021)	STEP 4 (Rubino et al. 2021)
Population	1,961 adults with BMI ≥30 or BMI ≥27 kg/m^2 with ≥1 weight-related comorbidity, without diabetes enrolled at 129 sites in 16 countries	1,210 adults with BMI ≥27 kg/m^2 with type 2 diabetes enrolled at 149 clinics in 12 countries	611 adults with BMI ≥30 or BMI ≥27 kg/m^2 with ≥1 weight-related comorbidity, without diabetes enrolled at 41 sites in the United States	902 adults with BMI >30 or BMI >27 kg/m^2 with >1 weight-related comorbidity entered 20-week run-in; 806 reached 2.4 mg dose semaglutide and entered randomization; 73 sites in 10 countries
Randomization scheme	Randomized 2:1 to 2.4 mg semaglutide vs. placebo	Randomized 1:1:1 to 2.4 mg semaglutide vs. 1.0 mg semaglutide[a] vs. placebo	Randomized 2:1 to 2.4 mg semaglutide vs. placebo	At week 20, those who achieved 2.4 mg dose semaglutide randomized 2:1 to continued 2.4 mg semaglutide vs. placebo
Drug treatment scheme	Prefilled pens; initial semaglutide dose 0.25 mg subcutaneous Once weekly for first 4 weeks; semaglutide dose increased every 4 weeks to reach 2.4 mg; treatment duration 68 weeks	Prefilled pens for 2 injections once a week; initial semaglutide dose 0.25 mg subcutaneous Once weekly for first 4 weeks; semaglutide dose increased every 4 weeks to reach 2.4 mg; treatment duration 68 weeks	Prefilled pens; initial semaglutide dose 0.25 mg subcutaneous Once weekly for first 4 weeks; semaglutide dose increased every 4 weeks to reach 2.4 mg; treatment duration 68 weeks	First 20 weeks, open-label treatment with once-weekly subcutaneous Semaglutide, 0.25 mg, increased every 4 weeks to the maintenance dose of 2.4 mg by week 16, and Continued to week 20. Then, randomized to pre-filled pens with placebo or semaglutide 2.4 mg weekly for double-blind therapy
Background treatment	Both groups received lifestyle intervention: 500 kcal/day deficit diet and increased physical activity to 150 min/ week	All groups received lifestyle intervention: 500 kcal/day deficit diet and increased physical activity to 150 min/ week	Both groups received low-calorie diet for 8 weeks followed by intensive behavioral therapy (i.e., 30 counseling visits)	Both groups received lifestyle intervention: 500 kcal/day deficit diet and increased physical activity to 150 min/ week

(continued)

Table 1 (continued)

	STEP 1 (Wilding et al. 2021)	STEP 2 (Davies et al. 2021)	STEP 3 (Wadden et al. 2021)	STEP 4 (Rubino et al. 2021)
Primary end point(s)	Percentage change in body weight and weight reduction of at least 5% at week 68	Percentage change in body weight and weight reduction of at least 5% at week 68	Percentage change in body weight and weight reduction of at least 5% at week 68	Percentage change in body weight from week 20 to week 68
Trial completion rate	93.4%	96%	92.8%	98.0% of randomized
Treatment adherence rate	81.1%	87%	82.7%	92.3% of randomized
Baseline characteristics	74.1% female 75.1% white Mean age 46 years Mean weight 105.3 kg Mean BMI 37.9 43.7% had prediabetes 70.5% had one or more coexisting conditions	50.9% female 62.1% white Mean age 55 years Mean weight 99.8 kg Mean BMI 35.7 Mean HbA_{1c} 8.1% Biguanide drug use in 91.8%	81.0% female 76.3% white Mean age 46 years Mean weight 105.8 kg Mean BMI 38.0 74.1% had one or more comorbidity at screening	79% female 83.7% white Mean age 46 years Mean weight 107.2 kg Mean BMI 38.4 64.8% had 1–3 comorbidities
Mean change in body weight at week 68				
Semaglutide 2.4 m	−14.9%	−9.6%[a]	−16.0%	−7.9% from week 20 −17.4% from week 0
Placebo	−2.4%	−3.4%	−5.7%	+6.9% from week 20 −5.9% from week 0
Proportion achieving >5% weight loss at week 68				
Semaglutide 2.4 mg	86.4%	68.8%	86.6%	88.7% from week 0
Placebo	31.5%	28.5%	47.6%	46.6% from week 0
Proportion reporting serious adverse events				
Semaglutide 2.4 mg	9.8%	9.9%	9.1%	7.7%
Placebo	6.4%	9.2%	2.9%	5.6%

Proportion discontinuing because of adverse events				
Semaglutide	7.0%	6.2%	5.9%	2.4%
Placebo	3.1%	3.5%	2.9%	2.2%

[a]Body weight change at week 68 was −6.99% for semaglutide 1.0 mg weekly

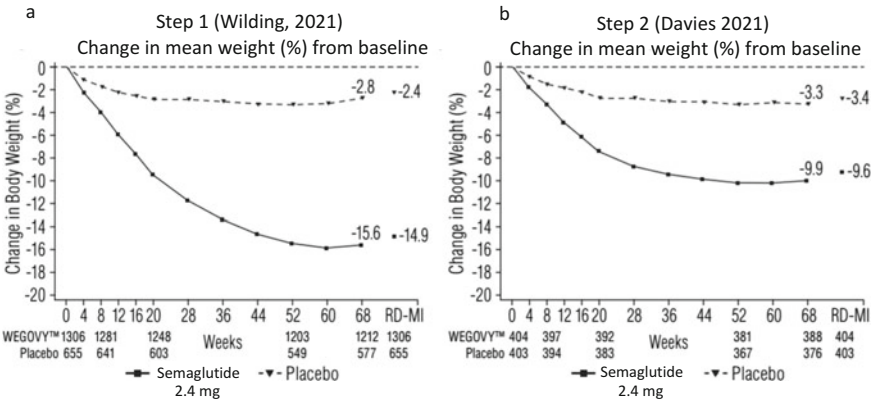


Fig. 1 (**a**, **b**) Step 1 and Step 2 Trials. In these studies, all individuals are given the same lifestyle intervention and randomized to placebo or semaglutide 2.4 mg subcutaneous weekly. Trajectories represent observed data (trial product estimand). Also shown are the intention to treat endpoint (treatment policy estimand. The visual data are publicly available in the US product label at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215256s000lbl.pdf

STEP 1, except the mean weight losses for semaglutide 2.4 mg in STEP 2 were lesser than those in STEP 1 at the same dose, albeit greater than semaglutide 1.0 mg or placebo see Fig. 1b. One of the coprimary endpoints was percent weight loss at 68 weeks for semaglutide 2.4 mg vs. placebo. Mean change in body weight was −9.6% at week 68 for semaglutide 2.4 mg and −3.4% for placebo, with an estimated treatment difference of 6.21% [CI 7.28 to 5.15]; $P < 0.0001$. For the semaglutide 1.0 mg treatment group mean weight loss at week 68 was −7.0% at week 68.

The mean weight loss in STEP 2 is less than that in STEP 1. The background lifestyle intervention follows the same protocol in both studies, but the populations differ; STEP 2 consists of persons with type 2 diabetes and there were none in STEP 1 and the mean weight loss observed in persons with diabetes is always less than those without diabetes. There was biguanide use in 91.8% of enrolled persons in STEP 2 and the protocol called for a 50% dose reduction of biguanide medication at study start. In Look AHEAD, a lifestyle intervention that produced 9.6% weight loss at 52 weeks, there was a personalized protocol for stopping or reducing diabetes medications, whereby persons with acceptable diabetes control at baseline had medications stopped at the start of the dietary intervention (Look AHEAD Research Group 2006).

In STEP 3, (Wadden et al. 2021) enrolled participants were randomized to semaglutide 2.4 mg or placebo. Both groups received an intensive behavioral intervention which consisted of an initial 8-week low-calorie diet (1,000–1,200 kcal/day) provided as meal replacements. Then, this highly structured diet was transitioned to a 1,200–1,800 kcal/day of conventional food for the remainder of the 68 weeks. Physical activity began with 100 min of physical activity per week and increased by 25 min every 4 weeks to ultimately 200 min per week. The

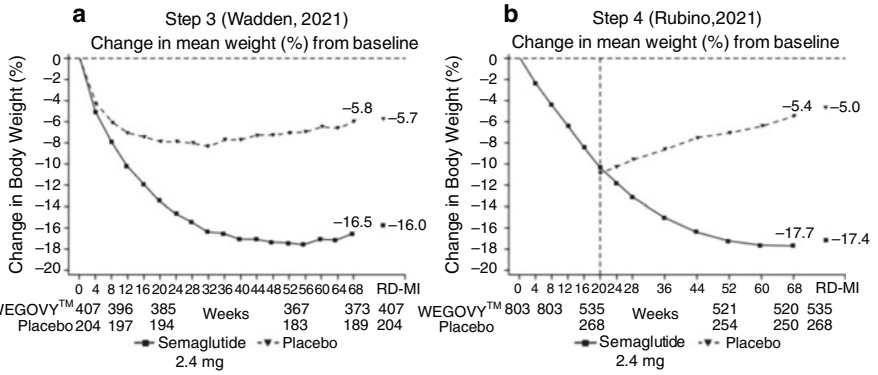


Fig. 2 (**a**) STEP 3. Participants were randomized to semaglutide 2.4 mg or placebo. Both groups received an intensive lifestyle intervention (see text). The weight loss in the placebo group illustrates the effect of the more intensive intervention. (**b**) STEP 4. During the first 16 weeks, all patients receive semaglutide dose escalation to 2.4 mg. Those achieving this dose (92%) were randomized to placebo or semaglutide 2.4 mg. For both studies, trajectories represent observed data (trial product estimand). Also shown are the intention to treat endpoint (treatment policy estimand. The visual data are publicly available in the US product label at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215256s000lbl.pdf

mean weight loss in this study with placebo reflects the greater intensity of the lifestyle intervention; placebo-treated participants lost on average −5.7% at week 68 see Fig. 2a. Although not head-to-head comparisons, this is greater than the mean weight loss of −2.4% in a similar population in STEP 1 (See Fig. 1a.) who received a similar intervention. However, the mean weight loss in the semaglutide 2.4 mg treatment group was −16.0% (see Fig. 6); this is slightly greater than STEP 1 (−14.9%). The estimated treatment differences in mean weight loss at 68 weeks between placebo and semaglutide 2.4 mg were −12.4% in STEP 1 and −10.3% in STEP 3.

STEP 4 (Rubino et al. 2021) was designed to show the long-term impact over 48 weeks of continuing semaglutide after reaching the 2.4 mg dose at 20 weeks see Fig. 2b. All participants received semaglutide open label during a dose escalation period over 16 weeks and then the dose was continued for 4 weeks. Of the 902 individuals who enrolled, 806 (92%) reached the 2.4 mg dose and were randomized to placebo or continued semaglutide 2.4 mg. Those who continued semaglutide after randomization continued to lose weight reaching a plateau at week 60 to week 68 and ultimately achieving −17.4% weight loss from entry. In comparison, those on placebo gradually regained weight see Fig. 2b. The weight loss with semaglutide 2.4 mg was associated with improvements in cardiometabolic risk factors in this study.

The safety and tolerability across STEP 1, 2, 3, and 4 (Wilding et al. 2021; Davies et al. 2021; Wadden et al. 2021; Rubino et al. 2021) demonstrated the predicted findings with this drug and class. In all studies, gastrointestinal disorders (typically nausea, diarrhea, vomiting, and constipation) were the most frequently reported

events and occurred in more participants receiving semaglutide than those receiving placebo. Most gastrointestinal events were mild to moderate in severity, were transient, and resolved without permanent discontinuation of the regimen. Gallbladder-related disorders (mostly cholelithiasis) were reported more often in STEP 1 and STEP 3. In STEP 1, gallbladder disorders occurred in 2.6% and 1.2% of participants in the semaglutide and placebo groups, respectively (Wilding et al. 2021). In STEP 3, gallbladder-related disorders (mainly cholelithiasis) were reported in 4.9% of semaglutide-treated participants and 1.5% of those on placebo (Wadden et al. 2021). Acute pancreatitis also occurred in small numbers in semaglutide-treated patients (3 in STEP 1, 1 in STEP 2, 0 in STEP 3, and 1 in STEP 4) (Wilding et al. 2021; Davies et al. 2021; Wadden et al. 2021; Rubino et al. 2021). Overall, there were no unexpected safety findings in the reports of the four trials.

The chief safety issues with drugs of this class are the rare occurrence of pancreatitis and a prohibition of use in patients with a personal or family history of Multiple Endocrine Neoplasia Type 2 or medullary thyroid carcinoma. Semaglutide 1.0 mg weekly has been shown to reduce cardiovascular events in persons with diabetes and other GLP-1 receptor agonists have also demonstrated cardioprotection (Marso et al. 2016). Prescribers' confidence in semaglutide for obesity will likely increase if the ongoing SELECT study (Ryan et al. 2020) demonstrates that semaglutide 2.4 mg weekly is associated with reduction of cardiovascular events in persons with overweight and obesity and who have pre-existing cardiovascular disease.

The aim of weight management should be normalization of body composition, not just reducing weight. In STEP 1, Dual Emission X-ray Absorptiometry data were reported on a subset of participants ($N = 140$) (Wilding et al. 2021). In that substudy, there was mean loss of −8.36 kg of total body fat mass and −5.26 kg of total body lean mass in the semaglutide-treated participants. In the placebo group the mean loss was −1.37 kg fat mass and −1.83 kg lean mass. The usual proportion lean loss in total weight loss is 25% (Heymsfield et al. 2014). It is important to reduce excess abnormal fat mass, without adversely affecting muscle and bone. Look AHEAD, a study comparing intensive lifestyle intervention (ILI) to diabetes support and education (DSE) in persons with type 2 diabetes is informative in showing that not all persons experience only health benefits from weight loss; there are some negative outcomes (Wing and Look AHEAD Research Group 2021). As expected with weight loss, ILI led to greater reductions in fat mass than DSE, but also greater loss of lean body mass during active weight loss and when ILI participants regained weight, they regained mainly fat mass (Pownall et al. 2015). In addition, there were greater decreases in bone density for both total hip (−1.4% vs. −0.4%, $P < 0.001$) and femoral neck (−1.5% vs. −0.8%; $P < 0.009$) in ILI vs. DSE at 1 year (Schwartz et al. 2012). The relationship to hip fracture in Look AHEAD is uncertain. The risk for hip fracture was elevated in ILI compared to DSE (HR = 1.78 [95% CI 0.98, 3.25] $P = 0.06$), but this finding was not statistically significant (Johnson et al. 2017). It cannot be determined with accuracy from DEXA what the loss of muscle mass or bone mass might be. But this issue deserves further study with more advanced techniques to measure body composition changes. Meanwhile, we will

need to reinforce the importance of weight bearing exercise and strength training in patients who are losing weight with semaglutide and use caution in patients with sarcopenic obesity.

2.2 Setmelanotide

Setmelanotide Setmelanotide is a cyclized octapeptide that binds and activates multiple melanocortin receptors – MC4R, MC3R, and MC1R selectively over MC5R and MC2R (Sharma et al. 2019). Setmelanotide is one of Multiple MC4R agonists that have been studied as potential anti-obesity medications (Sharma et al. 2019). Some of these activate the sympathetic nervous system with blood pressure elevation and increased heart rate making them unacceptable in clinical care, while setmelanotide has not been shown to have this characteristic (Sharma et al. 2019). In a diet-induced obese nonhuman primate model, setmelanotide produced persistent weight loss (−13.5%) over 8 weeks (Kievit et al. 2013). Importantly, it did not increase heart rate or blood pressure. In a phase 1b study in humans, individuals with obesity and heterozygous for complete or partial loss of function mutations in MC4R were treated with setmelanotide by infusion or placebo over 28 days (Collet et al. 2017). Interestingly, both groups lost weight similarly, in comparison with placebo. There were no increases in heart rate or blood pressure in this study, but the most frequent side effect was skin darkening, or "tanning" associated with setmelanotide (Collet et al. 2017). This early study demonstrated that there would probably be limited advantage for setmelanotide in heterozygous individuals, although depending on functional variants, different responses might be obtained. The clinical development of the drug then focused on identifying homozygous individuals with genetic defects that might respond to setmelanotide.

Setmelanotide was developed with a personalized medicine approach, targeting the drug for individuals with defects in the melanocortin pathway. Setmelanotide showed excellent outcomes in two patients with POMC deficiency, reversing hyperphagia and producing dramatic weight loss in both patients (Kühnen et al. 2016). When given to three patients with LEPR deficiency, setmelanotide produced clinically significant reduction in both body weight and hyperphagia (Clément et al. 2018). The drug has also been studied in 7 patients with Bardet-Biedl syndrome, showing hunger reduction and mean weight loss at 1 year of −16.3% (90% CI, −19.9% to−12.8%; $n = 7$) (Haws et al. 2020). Bardet-Biedl continues to be studied as potential indication for setmelanotide.

The regulatory approval of setmelanotide rests on a study (Clément et al. 2020) in 21 participants (Imcivree™ Product Label, FDA 2021; Imcivree™ product label, EMA 2021), where the genetic defects were biallelic variations in either the prohormone, pro-opioid melanocortin (POMC) ($n = 9$), PCSK1 (proprotein convertase subtilisin and kexin type 1) ($n = 1$), an important enzyme in activating the melanocortin 4 receptor pathway, or the leptin receptor (LEPR) ($n = 11$), which is essential for POMC function. The study was designed with a variable period of dose-finding where the drug was administered daily, and dose adjusted to manage

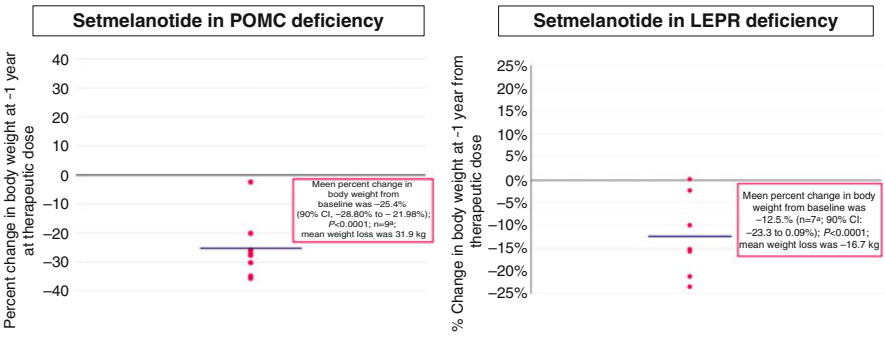


Fig. 3 In this study, the drug was administered daily, starting at 1 mg to patients with homozygous genetic deficiency in POMC, PCSK1, and Leptin Receptor. There was maximum 32 weeks of open-label therapy for responsive patients. Note: Y axis scales are not identical. Visual data publicly available at https://rhythmpharmaceuticals.gcs-web.com/static-files/bc6550a7-a5df-4d9a-9a81-fcf41ba95066

hyperphagia. Then a 10-week open-label period occurred, and participants were required to lose 5 kg or 5% if the body weight was less than 100 kg to continue the study. Successful patients entered an 8-week placebo-controlled phase inclusive of a 4-week placebo period and then continued for 32 weeks of open-label therapy.

The study (Clément et al. 2020) showed that for the 10 patients with POMC or PCSK1 deficiency, 8 of 10 met the primary outcome of 10% or more weight loss at 1 year; among all enrollees, mean weight loss was −25.6%. These results are shown in Fig. 3, *below*. For the 11 patients with LEPR deficiency, the response was more variable. Of those 11, four failed to achieve the required 5% weight loss by week 12 and only five (45%) achieved the primary outcome of 10% or more weight loss at 1 year (Clément et al. 2020). Still, all five achieved 15% or more weight loss and two achieved 20% or more weight loss (Clément et al. 2020). These results are also shown in Fig. 3. For both LEPR and POMC deficiency patients, tolerability and safety seemed acceptable. The most common adverse events were injection site reactions, skin darkening and nausea, vomiting, and diarrhea (Clément et al. 2020). Other side effects included spontaneous penile erections and spontaneous female arousal, depression and suicidal thoughts and darkening of moles. Compared to those with LEPR deficiency, the results with setmelanotide were best for patients with POMC deficiency. We cannot be sure of the response in the one patient with PCSK1 deficiency since that patient had to drop out of study because the patient developed depression after hyperphagia recurred during a required blinded placebo phase (Clément et al. 2020). While the results were not as encouraging for all patients with LEPR deficiency as those with POMC deficiency in terms of amount of weight loss, this should be interpreted in the face of no alternative treatments for this severe disease.

Setmelanotide was approved by the US FDA (Imcivree™ Product Label, FDA 2021) with an indication for "chronic weight management (weight loss and weight maintenance for at least one year) in patients six years and older with obesity due to

three rare genetic conditions: pro-opiomelanocortin (POMC) deficiency, proprotein subtilisin/kexin type 1 (PCSK1) deficiency, and leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes considered pathogenic (causing disease), likely pathogenic, or of uncertain significance." The drug is priced at $330 per mg, making annual costs very high for this drug which requires daily subcutaneous injection and where doses begin at 1 mg (Imcivree™ Price 2021).

What does setmelanotide mean for the practice of obesity medicine? Regulatory approval has come only for patients with proven genetic defects in the leptin-melanocortin pathway. Having a drug that is effective would then drive clinicians to increase genetic testing for patients with a history of severe early onset obesity. Thus, the impact of setmelanotide in the obesity clinic is likely to mean a renewed appreciation for the biologic underpinnings of obesity and an increase in genetic screening to identify a subset of patients. Still, the three genetic conditions for which setmelanotide has been approved are ultrarare. They are associated with severe childhood obesity and hyperphagia and may be associated with various other endocrinopathies, e.g., adrenocorticotropic hormone deficiency, hypothyroidism, hypogonadism, hypopigmentation, hypoglycemia, and others. The number of individuals in the USA proposed to have genetic mutations in the melanocortin pathway if we tested widely is estimated to be 12,800, a miniscule fraction of the population with obesity (Ayers et al. 2018). While they may occur only rarely, these conditions present enormous challenges for health care providers, parents, and patients. Thus, the primary users of setmelanotide are likely to be clinics where children with severe obesity are referred for evaluation. Practitioners must await guidance on adults – when and whom to test. Certainly, a history of early onset severe obesity would be the clinical presentation might stimulate genetic testing.

There will be efforts to identify other patients with other genetic obesity syndromes that might respond to setmelanotide. Setmelanotide is being tested in Bardet-Biedl syndrome and Alström syndrome in a Phase 3 trial (NCT03746522), as well as SRC1, SH2B1, and MC4R deficiency, and Smith-Magenis syndrome in a basket Phase 2 trial (NCT03013543). Still, this is unlikely to expand the user base for setmelanotide significantly. Given the global prevalence of obesity, the obvious question is, "Could setmelanotide have a broader indication for weight management?"

The data in nonhuman primates (Kievit et al. 2013) and in humans with obesity used as controls (Collet et al. 2017) demonstrate that there is some weight loss efficacy with setmelanotide in those without genetic melanocortin pathway defects. But the chief side effect, tanning, must be considered. That side effect might make the drug undesirable from a patient perspective. Will patients accept tanning if weight loss is robust? This question and other safety considerations could only be answered through the expensive and time-consuming drug development process requiring large patient numbers to establish safety and efficacy. That is not likely to happen and for now, setmelanotide is likely to remain solely in the realm of treatment for those with proven genetic defects in the melanocortin pathway. The

search for other indications will continue, however, with attempts to identify genotypes that would be highly responsive to this drug.

3 Older Anti-obesity Medications

3.1 Orlistat

Orlistat reversibly blocks the action of pancreatic and gastric lipases (Guerciolini 1997). Inactivation of these lipases prevents the hydrolysis of triglycerides, and thus free fatty acids are not absorbed. Orlistat is usually prescribed at 120 mg taken before meals three times daily and at this dose, 30% of dietary fat is not absorbed. Thus, orlistat has the effect of enforcing a low-fat diet, since foods or snacks high in fat will result in steatorrhea.

In a meta-analysis of 23 trials of patients with and without diabetes, orlistat plus intensive behaviorally based intervention produced weight loss of "5 to 10 kg (11 to 22 pounds), average, 8% of baseline weight, compared with 3 to 6 kg in the placebo groups" (Leblanc et al. 2011). The best study to demonstrate orlistat's efficacy is the 4-year double-blind, randomized, placebo-controlled trial (XENDOS Study) of lifestyle intervention with or without orlistat 120 mg three times daily in 3,304 patients with overweight or obesity (Torgerson et al. 2004) see Fig. 4. In that study, mean weight loss at 1 year was 11% with orlistat, but the orlistat-treated patients remained 6.9% below baseline at 3 years, compared with 4.1% for those receiving placebo. For those with impaired glucose tolerance (21% of the population), there was a reduction of 37% in the progression to type 2 diabetes with lifestyle

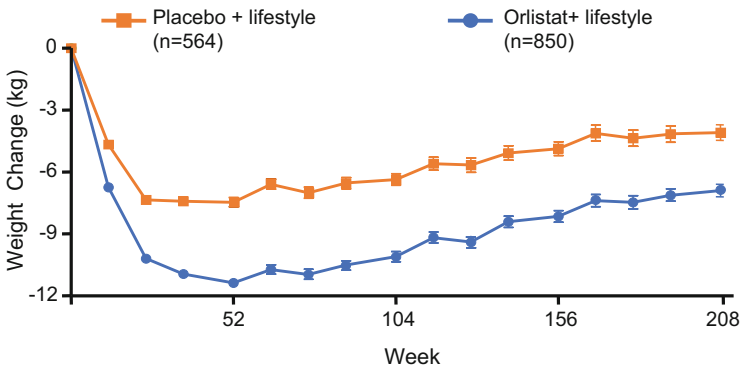


Fig. 4 Xendos Study Change in body weight (kg) are depicted as mean and SEM over 4 years (208 weeks) for patients receiving lifestyle intervention and randomly assigned to placebo or orlistat. Statistical analysis is by last observation carried forward (LOCF). Weight loss and maintenance is superior with orlistat when added to lifestyle intervention (image redrawn from Torgerson et al. 2004). $P < 0.001$. Baseline placebo + lifestyle = n 1637. Baseline orlistat + lifestyle = n 1640

intervention plus orlistat compared to lifestyle intervention plus placebo (Torgerson et al. 2004).

Orlistat is approved for weight management for adolescents in some countries. In 539 adolescents who received 120 mg three times per day of orlistat, on average, BMI decreased by 0.55 kg/m^2 in the drug-treated group compared to an increase of +0.31 kg/m^2 in the placebo-treated group (Chanoine et al. 2005).

Adherence to orlistat use falls off rapidly after initial prescription. In a Canadian study, the use of orlistat among 16,968 people initially started on this drug had fallen to 6% by 1 year and to only 2% by 2 years (Padwal et al. 2007). This may relate to the drug's tolerability profile, discussed below.

Orlistat is not absorbed from the GI tract to any significant degree, and its side effects relate to blockade of triglyceride digestion in the intestine (Guerciolini 1997). If orlistat is taken with a high fat meal or snack, then the effects of unabsorbed fat – steatorrhea –are likely to occur. Counseling patients about gastrointestinal side effects is important, so that patients can adhere to lower fat foods. It may also be helpful to take blond psyllium along with orlistat to minimize gastrointestinal side effects (Cavaliere et al. 2001). Because orlistat can cause small but significant decreases in fat-soluble vitamins some patients may need vitamin supplementation given at bedtime, particularly if it is continued long-term (McDuffie et al. 2002). Orlistat can reduce the absorption of some medications, notably cyclosporine, amiodarone, levothyroxine, anti-retroviral medications, and the lipophilic antiepileptics (Filippatos et al. 2008). It can also interfere with warfarin because of its action on Vitamin K (Filippatos et al. 2008). Orlistat has also been associated with calcium oxalate renal stones (Humayun et al. 2016).

3.2 Naltrexone SR/Bupropion SR

Bupropion has been used as a single agent for depression and for smoking cessation and is known to produce weight loss at 300 or 400 mg daily (Anderson et al. 2002). Naltrexone is an opioid receptor antagonist that is used for addiction to opioids or alcohol. It has minimal effect on weight loss on its own. Bupropion stimulates the POMC neuron which releases α-MSH and β-endorphin in the hypothalamus which stimulates feeding (Greenway et al. 2009). This effect on β-endorphin is blocked by naltrexone thus allowing the inhibitory effects of α-melanocyte stimulating hormone (α-MSH) to reduce food intake by acting on the melanocortin-4 receptor system (Greenway et al. 2009).

Efficacy of Naltrexone/Bupropion Three phase 3 studies with this combination provided the basis for its approval. In the COR I study (Contrave Obesity Research I) there were three treatment arms: placebo, NB 32/360 (32 mg of naltrexone and 360 mg of sustained release bupropion), and NB 16/360 (16 mg of naltrexone and 360 mg of sustained release bupropion). Using the primary analysis population in COR-I, the Least Squares (LS) mean percentage weight loss (SE) at 56 weeks was −1.3% (0.3) for the Placebo, −5.0% (0.3) for Naltrexone/Bupropion-16/360

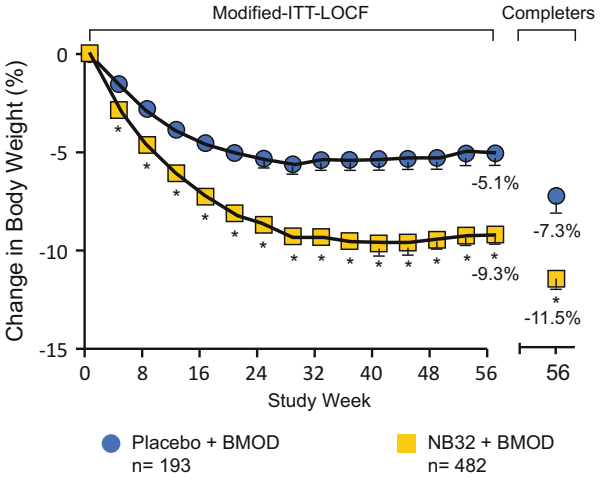


Fig. 5 COR/BMOD Study: Percent change in body weight over 56 weeks with intensive behavioral modification lifestyle intervention (BMOD) and randomized assignment to placebo or naltrexone 32 mg/bupropion 360 mg (NB32) (image redrawn from Wadden et al. 2011). The mean body weight for each study group is shown for the Modified-ITT-LOCF population across 56 weeks. The mean weight loss of completers is shown at week 56. $^{*}P < 0.001$, for NB32 + BMOD vs. placebo + BMOD. COR/BMOD = Contrave Obesity Research/Behavioral Modification; ITT = intent to treat; LOCF = last observation carried forward

(NB 16/360) ($P < 0.0001$ vs. placebo) and −6.1% (0.3) for NB 32/360 ($P < 0.0001$ vs. placebo) (Greenway et al. 2010). The NB16/360 and NB32/360 treatment arms had improvements in waist circumference, fasting glucose, fasting insulin, homeostasis assessment model of insulin resistance (HOMA-IR), HDL cholesterol, CRP, and Impact of Weight on Quality of Life – Lite (IWQOL-Lite) (Kolotkin et al. 2001) scores, when compared to placebo (Greenway et al. 2010).

As shown above in Fig. 5, below, COR-BMOD (Contrave Obesity Research-Behavior Modification) randomly assigned participants in a 1:3 ratio to either placebo (P) given with a behavior modification program (BMOD), or naltrexone sustained release 32 mg plus bupropion sustained release 360 mg (NB32/360) plus BMOD. The behavior modification program consisted of 28 group sessions, each of 90 min duration. The weight loss in COR BMOD was excellent for both the placebo and active treatment groups. At 56 weeks, mean weight loss in the P + BMOD group was 5.1 + 0.6% and for the NB 32/360 + BMOD group it was 9.3 + 0.4% ($P < 0.001$ vs. placebo +BMOD) (Wadden et al. 2011). There were significantly greater improvements in waist circumference, insulin, HOMA IR, HDL cholesterol, and triglycerides as for quality-of-life measurement, the scores on the IWQOL-Lite questionnaire improved significantly more in the group on active drug treatment than placebo (Wadden et al. 2011).

In COR II (Contrave Obesity Research II), participants were randomized 2:1 to combined naltrexone sustained release (SR) (32 mg/day) plus bupropion SR

(360 mg/day) (NB32) or placebo for up to 56 weeks. Significantly greater weight loss was observed with NB32 vs. placebo at week 56 (−6.4% vs. −1.2%) ($P < 0.001$) (Apovian et al. 2013). The weight loss was accompanied by improvements in cardiometabolic risk markers, weight-related quality of life, and a measure of control of eating (Apovian et al. 2013).

Finally, in patients with type 2 diabetes, use of the combination resulted in significantly greater weight reduction compared to placebo (5.0% vs. 1.8%; $P < 0.001$) and significantly greater reduction in HbA1c (−0.6 vs. −0.1%; $P < 0.001$) (Hollander et al. 2013). There was also improvement in triglycerides and HDL -cholesterol compared with placebo (Hollander et al. 2013).

Safety and Tolerability Profile of Naltrexone/Bupropion The chief tolerability issue with this medication is nausea, associated with the naltrexone component, which occurs on initiating the drug or escalating its dose (Contrave Product Label 2021; Mysimba Product Label 2021). While relatively common (about 30% of participants in the phase III studies) it accounted for <7% of dropouts (Contrave Product Label 2021). A dose escalation period of 4 weeks is used to minimize this side effect (Contrave Product Label 2021; Mysimba Product Label 2021). The drug should not be prescribed with concomitant use of SSRIs or MAOIs because of risk of serotonin syndrome with bupropion (Contrave Product Label 2021; Mysimba Product Label 2021).

The decline in blood pressure is not as great as one would expect from the weight loss in the Phase III trials of naltrexone/bupropion (Greenway 2010; Wadden et al. 2011). Bupropion is associated with an increase in pulse and both bupropion and naltrexone increase blood pressure. A required pre-marketing study of the combination drug with assessment of cardiovascular outcomes was subjected to an interim analysis (Nissen et al. 2016). This resulted in early study termination at the 50% interim analysis. Termination was due to inclusion of the 25% interim analyses on the patent publication, resulting in the potential for unblinding.

3.3 Liraglutide 3.0 mg

Liraglutide is a GLP-1 agonist that has a 97% homology to native GLP-1. The molecule has been modified to extend the circulating half-life from native GLP-1's 1–2 min to 13 h (Saxenda™ Product Label (FDA) 2021; Saxenda™ Product Label (EMA) 2021). Liraglutide reduces body weight through reduction of food intake (Holst 2007). Liraglutide is indicated for treatment of type 2 diabetes at a dose of up to 1.8 mg. The indication for chronic weight management is for liraglutide dosed at 3.0 mg, given once daily by injection. A dose escalation is required to minimize side effects, beginning at 0.6 mg and increasing by 0.6 mg weekly to the recommended dose of 3.0 mg daily (Saxenda™ Product Label (FDA) 2021; Saxenda™ Product Label (EMA) 2021).

Efficacy of Liraglutide Three 56-week studies with liraglutide 3.0 mg form the basis for regulatory approval (Pi-Sunyer et al. 2015; Wadden et al. 2013; Davies et al. 2015). One of those studies had an extended follow-up to determine the effect on emergence of type 2 diabetes in at-risk persons (Le Roux et al. 2016). In a large multi-center phase III trial called SCALE Obesity and Prediabetes, 3,731 patients without diabetes were instructed in a 500 kcal/day deficit diet and lifestyle recommendations and were treated in a ratio of 2:1 with liraglutide 3.0 mg/day (after dose titration) or with placebo (Pi-Sunyer et al. 2015). Liraglutide reduced body weight in those who completed 56 weeks by an average of 8.4 kg compared to 2.8 kg on average in the placebo-treated group. Weight loss of >5% was achieved by 62.3% of those receiving liraglutide but only 34.4% in those with placebo. The corresponding numbers losing >10% were 33.9% for those on liraglutide 3.0 mg and 15.4% for those assigned to placebo (Pi-Sunyer et al. 2015). The patients with prediabetes in the trial were followed out to 3 years to determine the effect on diabetes prevention (Le Roux et al. 2016). At 160 weeks, 26 of 1,472 individuals in the liraglutide 3.0 mg/day treatment group (2%) and 46 of 738 (6%) taking placebo were diagnosed with diabetes while on treatment. The time to onset of diabetes diagnosis with liraglutide 3.0 mg/day was 2.7 times longer than with placebo ($P < 0.0001$) (Le Roux et al. 2016).

Another trial, called SCALE Maintenance, had a unique design where weight loss of at least 5% was induced with a low-energy diet before patients were randomized to lifestyle counseling and either placebo or 3.0 mg/day (after titration) liraglutide (Wadden et al. 2013). This study is illustrated in Fig. 6, below. Weight loss on the highly structured low-calorie diet given for up to 12 weeks was 6% on average. After randomization, those receiving liraglutide 3.0 mg had additional loss of mean 6.2% (SD 7.3) and for placebo only 0.2% (SD 7.0). The percentage losing 5% and 10% of body weight was more than twice as high in the liraglutide treated patients (Wadden et al. 2013).

SCALE Diabetes trial (Davies 2015) illustrates not only the weight loss effect of liraglutide 3.0 mg, but also delineates the drug's effect on glycemia. In this study, patients with type 2 diabetes received a lifestyle intervention and were randomized to liraglutide 3.0 mg, liraglutide 1.8 mg, or placebo. At week 56, mean weight losses from baseline were, respectively, 6.0%, 4.7% and 2.0%. Exploratory comparisons of liraglutide 3.0 mg vs. 1.8 mg in this study showed that while weight loss differences were clinically and statistically superior for liraglutide 3.0 mg, the effect on glycemia, while statistically significant was small (−0.19%) (Davies et al. 2015).

Liraglutide has also been studied in patients with obstructive sleep apnea who could not tolerate conventional treatment with continuous positive airway pressure. In that study, (Blackman et al. 2016) the primary endpoint was reduction in apnea-hypopnea events per hour. There was a significant reduction in mean events when a lifestyle intervention was given with liraglutide 3.0 mg vs. placebo (−12.2 vs. −6.1 events per hour). In these patients, there were also improvements in body weight, systolic blood pressure, and Hemoglobin A_{1c} (Blackman et al. 2016).

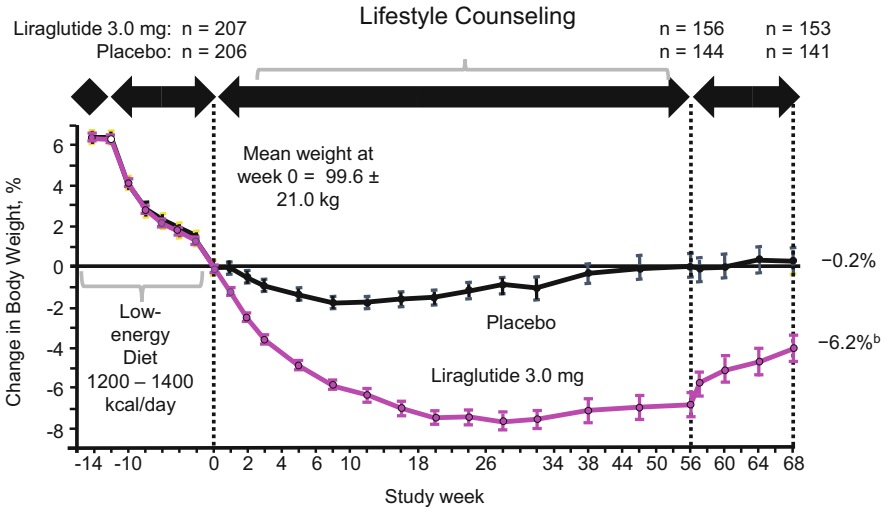


Fig. 6 SCALE Maintenance Study: Percent change in body weight over an initial period of highly structured low-calorie diet (1,200–1,400 kcal per day) is depicted from week 0 to −14. Participants who lost at least 5% received continued lifestyle counseling and were randomized to placebo or Liraglutide 3.0 mg. Percent change in body weight is depicted over 56 weeks for each treatment. After treatment stopped at week 56, participants returned for 4 follow-up visits through week 68. Note that after initial weight loss on diet alone, participants receiving lifestyle counseling and placebo maintained weight loss. Those on liraglutide 3.0 mg lost additional weight. After medication was stopped at week 56, weight regain is observed (image redrawn from Wadden et al. 2013). $P < 0.0001$ at week 56 for liraglutide vs. placebo

Safety Profile of Liraglutide As with other drugs in the GLP-1 receptor agonist class, Liraglutide is contraindicated in people with a family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN2) (Saxenda™ Product Label (EMA) 2021; Saxenda™ Product Label (FDA) 2021). As with all medications for weight management, it is contraindicated in pregnancy. Liraglutide should not be studied in patients with a history of pancreatitis and should be discontinued if acute pancreatitis develops (Saxenda™ Product Label (EMA) 2021; Saxenda™ Product Label (FDA) 2021). Its safety when combined with other drugs for weight management has not been established. This drug is given by injection, and nausea was one of its most troublesome side effects, occurring in 39.3% of those on liraglutide compared to 13.8% in the placebo-treated group (Saxenda™ Product Label (EMA) 2021; Saxenda™ Product Label (FDA) 2021). Diarrhea, constipation, vomiting, dyspepsia, and abdominal pain also occurred in more than 5% of those treated with liraglutide (Saxenda™ Product Label (EMA) 2021; Saxenda™ Product Label (FDA) 2021). Mean serum calcitonin was statistically significantly higher in the liraglutide group but did not require further follow-up and calcitonin monitoring is not required (Saxenda™ Product Label (EMA) 2021; Saxenda™ Product Label (FDA) 2021). Hypoglycemia was only a problem in patients also taking sulfonylureas (Saxenda™ Product Label (EMA) 2021;

Saxenda™ Product Label (FDA) 2021). Blood pressure was significantly reduced, but pulse rate increased by an average of 2.5 beats/min. An increase of >10 beats/min was seen in 34% of the liraglutide treated group compared with 19% in the placebo-treated group (Saxenda™ Product Label (EMA) 2021; Saxenda™ Product Label (FDA) 2021). There were no changes in serum lipids. Liraglutide should be used with caution in patients with renal impairment (Saxenda™ Product Label (EMA) 2021; Saxenda™ Product Label (FDA) 2021). If weight loss does not exceed 4% by 16 weeks, the drug should be discontinued (Saxenda™ Product Label (EMA) 2021; Saxenda™ Product Label (FDA) 2021).

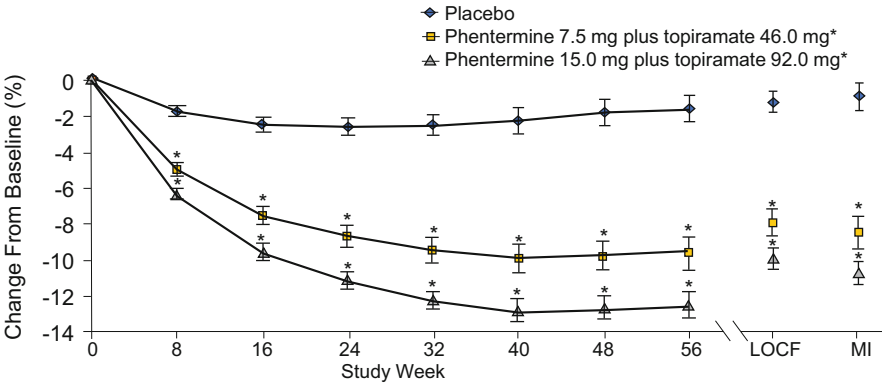
Liraglutide has been approved at a lower dose of 1.8 mg/day for the treatment of diabetes and is marketed under a different name. The indications for these two doses are distinct – if patients with and without diabetes are undertaking a weight loss effort, liraglutide 3.0 mg may be indicated but if the primary goal is management of glycemia in patients with diabetes, then liraglutide 1.8 mg is indicated. A cardiovascular outcome trial with liraglutide 1.8 mg/day has been completed (Marso et al. 2016). The endpoint was a combined index of major cardiovascular events which was reduced significantly in the patients receiving liraglutide, indicating clinical superiority for reduced CVD incidence over the placebo-treated group (Marso et al. 2016).

3.4 Phentermine/Topiramate Extended Release (ER) (Available in the USA, But Not Available in the EU)

The combination of phentermine and topiramate as an extended release (ER) form (PHEN/TPM ER) is approved for chronic weight management in the USA. It is not approved in the EU due to unresolved concerns on cardiovascular and psychiatric safety (Qsivia Assessment Report 2013). Phentermine acts to reduce appetite through increasing norepinephrine in the hypothalamus; topiramate may reduce appetite through its effect on GABA receptors (Qsymia™ Product Label, FDA 2021). The combination contains lower doses of phentermine (3.75–15 mg) than are usually prescribed when phentermine is used as a single agent. The dose of topiramate in the combination is between 23 and 92 mg, (Qsymia™ Product Label, FDA 2021) and is also lower than when topiramate is typically used for migraine prophylaxis or to control seizures.

Two clinical studies (Allison et al. 2012; Gadde et al. 2011) provided efficacy and safety data for approval of this medication (FDA 2021). The first trial, called EQUIP (Allison et al. 2012), enrolled subjects ≤70 years of age with BMI ≥35 kg/m^2 with controlled blood pressure (≤140/90 mmHg using 0–2 antihypertensive medications), fasting blood glucose ≤110 mg/dL, and triglycerides ≤200 mg/dL using 0 or 1 lipid lowering medication. EQUIP randomized participants to placebo or PHEN/TPM doses of 3.75/23, and 15/92 mg and achieved mean weight loss of 1.6%, 5.1%, and 10.9% of baseline body weight (Allison et al. 2012).

The other study, called CONQUER (Gadde et al. 2011), enrolled adults ≤70 years of age with BMI between 27 and ≤45 kg/m^2, except that patients with



Patients	Placebo	Mid	Full
Completers (% of randomized)	557 (57%)	338 (69%)	625 (64%)

Fig. 7 CONQUER study: percent change in body weight over 56 weeks with lifestyle intervention and randomization to placebo or phentermine 7.5 mg/topiramate 46 mg or phentermine 15 mg/topiramate 92 mg. The mean weight loss of last observation carried forward (LOCF) and multiple imputation(MI) data analysis is shown at week 56. Bars indicate standard errors. Figure redrawn from Gadde et al. (2011). *Weight change for either dose vs. placebo, $P < 0.0001$

type 2 diabetes had no lower BMI limit. The patients in the CONQUER study had 2 or more of the following comorbidities: hypertension, hypertriglyceridemia, dysglycemia (impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes) or an elevated waist circumference (≥40 in. for men or ≥35 in. for women). At 56 weeks, body weight loss was least-squares mean 1.2% (95% CI 1.8 to 0.7) for placebo, 7.8% (CI 8.5 to 7.1; $P < 0{\cdot}0001$) for those on PHEN/TPM at the 7.5/43 mg dose and 10.2 kg (95% CI 10.4 to 9.3; $P < 0{\cdot}0001$) for PHEN/TPM at the 15/92 mg dose (Gadde et al. 2011). The CONQUER study results are depicted in Fig. 7.

The patient population in the EQUIP and CONQUER studies represents those with higher risk profiles from the consequences of excess weight. A titration period of 2 weeks is required for PHEN/TPM ER, starting at 3.75/23 mg dosage. This combination medication produces mean weight losses approaching 10% more than placebo which is larger than observed in clinical trials with single drugs (Colman et al. 2012).

The SEQUEL study (Garvey et al. 2012) was a second-year extension of the CONQUER study keeping those patients who participated in their initial treatment assignment (SEQUEL). Patients completing 2 years at the dose of 7.5 mg/46 mg maintained a mean weight loss of 9.3% below baseline and those on the top dose maintained a mean 10.7% weight loss from baseline (Garvey et al. 2012).

Improvements in blood pressure, glycemic measures, HDL cholesterol, and triglycerides occurred with both the recommended and the top doses of the medication in these trials (Qsymia product label, FDA). Improvements in risk factors were related to the amount of weight loss (Allison et al. 2012; Gadde et al. 2011). In

patients with sleep apnea this combination reduced the severity of symptoms (Garvey et al. 2012).

The most observed side effects in these clinical trials were paresthesia, dizziness, dysgeusia (altered taste), insomnia, constipation, and dry mouth (Qsymia™ Product Label, FDA 2021). These side effects are related to the constituents of PHEN/TPM ER or, in the case of constipation, to weight loss per se. Phentermine causes insomnia and dry mouth, usually early in treatment, which then resolves. Topiramate is a carbonic anhydrase inhibitor that is associated with altered taste for carbonated beverages and tingling in fingers, toes, and perioral areas and may lead to mild metabolic acidosis.

Safety concerns are seen in several areas. This drug is contraindicated in pregnancy, as are all weight loss medications, but the topiramate constituent requires special precautions in women of childbearing potential (Qsymia™ Product Label, FDA 2021). If a patient becomes pregnant while taking PHEN/TPM ER, treatment should be stopped immediately (Qsymia™ Product Label, FDA 2021). Topiramate is associated with oral clefts if used during early pregnancy and PHEN/TPM ER is thus US pregnancy Category X (Qsymia™ Product Label, FDA 2021). Because of the risk of oral clefts, a negative pregnancy test before treatment and monthly thereafter and use of effective contraception are required (Qsymia™ Product Label, FDA 2021). Glaucoma is a rare side effect of topiramate, and the drug is contraindicated in glaucoma (Qsymia™ Product Label, FDA 2021). PHEN/TPM ER is also contraindicated in hyperthyroidism and within 14 days of treatment with monoamine oxidase inhibitors (MAOIs) and in patients with hypersensitivity to any of the ingredients in the medication (Qsymia™ Product Label, FDA 2021). Other potential issues include risk of kidney stones (associated with topiramate) and increased heart rate in patients susceptible to phentermine (Qsymia™ Product Label, FDA 2021).

4 Obesity Pharmacotherapy for the Next Decade

Semaglutide has shown clinicians how to significantly affect energy balance by affecting appetite (Friedrichsen et al. 2021). And setmelanotide is a great example of personalizing obesity therapy, albeit with a challenge of identifying a broader population that might benefit from the drug, beyond the ultra-rare genetic and syndromic obesities. Tirzepatide, now in phase 3, and bimagrumab, in phase 2, are illustrative of two different approaches that might make an impact on clinical practice in the next decade.

4.1 Tirzepatide

Tirzepatide, a single-molecule with a dual-action, given as once-weekly injection, targets both the glucagon-like peptide-1 (GLP-1) receptor and the glucose-insulin peptide (GIP) receptor. In a phase 2 trial it produced mean weight loss in the range of

~12% at 26 weeks at a dose of 15 mg/day and had potent effects on glycemia (Frias 2008). Tirzepatide is being evaluated for obesity in SURMOUNT-1, a phase 3 randomized double-blind, placebo-controlled trial with 2,400 participants who have obesity and comorbidity, but not diabetes (ClinicalTrial.gov). The drug is also being evaluated for an indication for type 2 diabetes in a series of studies, SURPASS (Min and Bain 2021). The results of one of the phase 3 studies has been released publicly, but not yet published in a peer-reviewed format. In that study, the highest dose (15 mg) of tirzepatide produced 13.1% weight loss over 40 weeks in persons with type 2 diabetes (Lilly News Release 2021). The safety and efficacy of tirzepatide in persons with obesity will be watched closely. The combined targeting of GLP-1 and GIP is interesting, and it will be important to understand the mechanistic pathway by which tirzepatide produces weight loss – appetite, lipolysis, and energy expenditure effects should all be investigated.

4.2 Bimagrumab

Bimagrumab is a human monoclonal antibody that binds to the activin type II receptor (ActRII) to block natural ligands that negatively regulate skeletal muscle growth (Rooks et al. 2017; Heymsfield et al. 2021). Bimagrumab was tested in a double-blind, placebo-controlled, 48-week, phase 2 randomized clinical trial (Heymsfield et al. 2021) in adults with type 2 diabetes and body mass index $28 \leq 40$ kg/m^2. Bimagrumab or placebo was dosed at 10 mg/kg up to 1,200 mg in 5% dextrose solution every 4 weeks for 48 weeks; both groups received diet and with both DEXA and MRI being used for body composition. At week 48, the changes for bimagrumab vs. placebo were as follows: fat mass (FM), −20.5% (−7.5 kg [80% CI, −8.3 to −6.6 kg]) vs. −0.5% (−0.18 kg [80% CI, −0.99 to 0.63 kg]) ($P < 0.001$); lean mass (LM), 3.6% (1.70 kg [80% CI, 1.1 to 2.3 kg]) vs. −0.8% (−0.4 kg [80% CI, −1.0 to 0.1 kg]) ($P < 0.001$) (Heymsfield et al. 2021). Thus rather than loss of both lean and fat with weight loss with the typical ratio of 25:75 (Heymsfield et al. 2014), bimagrumab was associated with loss of fat mass and gain in lean mass (Heymsfield et al. 2021). Safety will need to be evaluated further; there were cases of elevations of pancreas and liver enzymes with bimagrumab compared to placebo in this small study (Heymsfield et al. 2021).

4.3 Cagrilintide + Semaglutide

Cagrilintide is a long-acting amylin analog. It is being developed as a combination approach with semaglutide. It was evaluated in a phase 1b study and semaglutide 2.4 mg + 2.4 mg or 4.5 mg cagrilintide produced weight loss at 20 weeks that was −17.1% and 15.1% in those two doses (Enebo et al. 2021). The molecule has been studied in phase 2 for obesity treatment (Fletcher et al. 2021). The combination's robust early weight loss shows promise for even greater long-term weight loss (Becerril and Frühbeck 2021). A study found on ClinicalTrials.gov documents a

study comparing the two drugs injected separately or as two injections. The combination is not yet in phase 3, however.

5 The Way Forward in Obesity Pharmacotherapy

There are other drugs in the pipeline that show various degrees of promise and the reader is referred to recent reviews for addition information on individual drugs (Srivastava and Apovian 2018; Rebello and Greenway 2020). Rather than singling out individual agents, a few comments on the path forward are in order. We need more drugs that work through appetite, like semaglutide does in targeting the GLP-1 receptors in the areas of the brain that affect appetite. Not all patients respond to semaglutide with enough weight loss; not all patients can tolerate semaglutide; additional medications are needed. We need more medications that take a personalized approach, like setmelanotide. With better phenotyping and better genotyping, we should be better able to develop targeted therapies for individuals based on the personal profile of the patient with obesity. We need to consider mechanisms of promoting negative energy balance other than reducing food intake through appetite effects. One positive aspect of setmelanotide is that it increases energy expenditure, an important quality in the face of the metabolic adaptation found with the weight reduced state. Setmelanotide appears to do this without cardiovascular effects of increased blood pressure and pulse. Tirzepatide offers the intriguing possibility that its effectiveness in weight loss may be more than just food intake. Increasing lipolysis is a viable hypothetical mechanism for one of this drug's mechanism of action. Bimagrumab gives the first evidence that we might succeed in targeting improved quality of weight loss for our patients. We might be able to preserve or even increase lean mass, especially muscle and bone, in our patients as they lose weight.

The goal of weight loss is health improvement. Obesity medicine specialists want to reduce the excess abnormal adipose tissue that is driving ill health. At the same time, we want to achieve healthy weight reduction with preservation of muscle and bone. Can we achieve these goals pharmacologically? Of course, it would be better to live in a world where healthy eating and active living were the default behaviors and where those behaviors were reinforced in a world without undue emotional and financial stress. Those social determinants drive risk for obesity. All of us need to work toward creating that world, but we also need to explore better pharmacologic options for weight management for those who need to lose weight as a pathway to better health. The next generation of anti-obesity medications is emerging, bringing the possibility of weight loss sufficient to produce meaningful health improvement in many patients with obesity. But we need to continue the efforts to identify other medications and to shift our focus to more than just weight loss. We need to start thinking about improved quality of weight loss.

The clinical practice of obesity medicine has until now been a struggle for patients and providers. At last, we are getting some powerful tools to help our patients. The focus can finally shift from treating all the complications of obesity

with antihypertensives, with lipid lowering drugs, with glycemia management drugs. We can finally focus on the root cause of these comorbidities – obesity – because we can finally do something about it.

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Author Contribution: I conceived and created this document in its entirety.

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