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REVIEW ARTICLE

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New insights into the treatment of obesity

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Abstract

Obesity is a chronic, progressive and relapsing disease with a rising global prevalence associated with increased morbidity and mortality and reduced quality of life. Treatment of obesity requires a comprehensive medical approach that includes behavioural interventions, pharmacotherapy and bariatric surgery. The degree of weight loss with all approaches is highly heterogeneous, and long-term weight maintenance remains challenging. For years, antiobesity medications have been limited in number, often delivering meagre efficacy and raising numerous safety concerns. Therefore, there is a need for the development of highly efficacious and safe new agents. Recent insights into the complex pathophysiology of obesity have increased our understanding of intervenable targets for pharmacotherapies to treat obesity and improve weight-related cardiometabolic complications, namely, type 2 diabetes, hyperlipidaemia and hypertension. As a result, novel potent therapies have emerged, such as semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA) recently approved for the treatment of obesity. Semaglutide 2.4 mg once weekly significantly reduces body weight by approximately 15%, with simultaneous improvement in cardiometabolic risk factors and physical functioning in people with obesity. Tirzepatide, the first dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1RA, has recently demonstrated that body weight reduction exceeding 20% in people with obesity and

coupled with improved cardiometabolic measures is feasible. Thus, these novel agents promise to narrow the gap between the weight-loss effects of behaviour interventions, previous pharmacotherapies, and bariatric surgery. In this narrative review, we highlight established and emerging therapeutic treatments for long-term obesity management and position them in a framework according to their weight loss effects.

KEYWORDS

antiobesity drug, drug development, GIP, GLP-1 analogue, incretin therapy, obesity therapy

1 | INTRODUCTION

Obesity is a chronic, relapsing, multifactorial disease.[1,2] Its prevalence has reached pandemic proportions in the last few decades, with a nearly threefold increase between 1975 and 2016.[3,4] The World Health Organization estimates that over 650 million adult individuals, approximately 13% of the world population, were living with this chronic disease in 2016.[3] By 2035, nearly two billion adults, children and adolescents, or 24% of the world's population, are projected to be living with obesity.[1] This rise in prevalence of obesity contributes to increased morbidity and mortality—adults living with obesity in their 20s have a reduced life expectancy by 5.6 to 10.3 years.[5] In 2019, premature deaths attributed to high body mass index (BMI) were estimated at five million per year.[1] The leading cause of death associated with obesity is cardiovascular (CV) disease, followed by chronic kidney disease, type 2 diabetes (T2D), and various types of cancer,[6] which are the most common complications of obesity.[1,3] Moreover, obesity impacts mental health, quality of life, and physical and sexual function.[1,7] In view of recent global developments, such as the COVID-19 pandemic[8] and increased food insecurity, global obesity rates are expected to continue to rise.

Common polygenic obesity arises from overconsumption of highly palatable, energy-dense foods, and increased sedentary behaviour.[9] The interaction of these two environmental components appreciably contribute to positive energy balance and the accumulation of excessive energy in body fat stores. Crucially, a strong genetic component determines the individual's response to this "obesogenic" environment.[10] In some individuals, the excess body fat accumulates predominantly in the intra-abdominal adipose tissue and can also infiltrate other visceral organs, fostering cardiometabolic risk. Adipose tissue is more than a storage depot of excess energy, it is an active endocrine and paracrine organ that secretes a myriad of hormones, adipokines, and inflammatory cytokines that have key roles in regulating energy homeostasis, immune response and inflammation. In obesity, adipose tissue becomes dysregulated, triggering a proinflammatory cascade, leading to systemic insulin resistance and thereby eventually causing glucose and fatty acid dysregulation. This dysregulation produces damage to organs such as the arteries, heart, liver, skeletal muscle, and pancreas, further contributing to systemic hormonal, metabolic and target-organ alterations. The presence of such obesity-related adverse effects correlates to the magnitude of excess body weight and its distribution.[2,11]

Most of obesity's detrimental effects can be mitigated, reversed, or prevented by reducing body weight. However, this proves challenging since weight loss activates numerous central and peripheral compensatory mechanisms, including complex and persistent hormonal and metabolic adaptations in hunger and satiety signals, which oppose weight reduction and favour weight regain.[9,12,13] Furthermore, small increases in body weight become permanent over relatively short periods of time.[14] Its complex pathophysiology and significant impact on health make obesity more appropriately a chronic disease rather than a risk factor. Nevertheless, obesity is not yet universally recognized as the chronic, and progressive illness that it is.[2] Unfortunately, people with obesity are persistently stigmatized as obesity is regarded as an individual's lifestyle choice by the public and even by some healthcare professionals.[15] As a result, it is significantly undertreated.[16] Similar to other chronic conditions, obesity requires therapeutic interventions and appropriate treatment strategies on a long-term basis. Thus, in this narrative review, we will discuss currently available and emerging treatments for chronic weight management.

2 | OBESITY MANAGEMENT

2.1 | Current therapeutic options

According to the recommendations of most obesity guidelines in Europe and North America, screening and diagnosing obesity in routine care should be mainly based on BMI.[17,18] BMI interrelates the height and weight of individuals and provides an indirect estimate of body fat mass (Table 1).[19] The relationship between the percentage and distribution of body fat and the BMI is different for many Asian populations when compared to White populations, resulting in lower BMI thresholds.[20] Since BMI is a simplistic measurement as it does not account for body composition, racial and gender differences, anthropometric assessments beyond BMI are required for accurate diagnosis of obesity, particularly for individuals in the intermediate BMI ranges.[21]

Apart from its use for diagnosis of obesity, BMI cut-offs guide obesity treatment recommendations in most obesity guidelines in Europe and North America.[17,18] These can be divided into three groups—the pillars of obesity management. Firstly, lifestyle modifications comprising nutrition, physical activity and behavioural interventions are the basis

TABLE 1 Adult weight classification based on body mass index[19,20]

Body mass index		Weight classification
White populations	Asian populations	
<18.5 kg/m^2	<18.5 kg/m^2	Underweight
18.5–24.9 kg/m^2	18.5–22.9 kg/m^2	Normal weight
25.0–29.9 kg/m^2	23.0–24.9 kg/m^2	Overweight
30.0–34.9 kg/m^2	25.0–29.9 kg/m^2	Class I obesity
35.0–39.9 kg/m^2	≥30.0	Class II obesity
≥40.0 kg/m^2	–	Class III obesity (severe obesity)

of weight management and should be considered for all individuals with overweight or obesity (BMI ≥25 kg/m^2 in White people and ≥ 23 kg/m^2 in Asian people; Table 1).[18] Secondly, pharmacotherapies approved for long-term weight management are recommended as an adjunct to lifestyle interventions in White adults with Class I obesity or higher (BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 and at least one weight-related complication).[18,22] The respective cut-offs for use of pharmacotherapy in the Asian Indian population are BMI ≥27 kg/m^2 and ≥ 25 kg/m^2,[23] while the cut-off values for the Asia-Pacific are even lower—≥25 kg/m^2, and ≥ 23 kg/m^2, respectively.[24] Lastly, metabolic and bariatric surgery should be considered in all patients with Class II obesity. In their recently updated guideline, the American Society for Metabolic and Bariatric Surgery and the International Federation for the Surgery of Obesity and Metabolic Disorders recommend metabolic and bariatric surgery for White people with BMI ≥35 kg/m^2 or Asian people with BMI ≥27.5 kg/m^2, regardless of presence, absence or severity of obesity-related complications.[25] Surgery should be considered in individuals with Class I obesity and metabolic disease as well (BMI 30-34.9 kg/m^2 in White people and ≥ 25 kg/m^2 in Asian people).[25] These three pillars of obesity management will be discussed in further detail in this review.

The primary aim of obesity treatment is often defined as the reversal of excess body weight. Professional guidelines recommend a therapeutic goal of 5% to 10% weight loss from baseline weight for all adults over the course of 6 to 12 months[18] because, at this weight reduction, there is an improvement in health and a reduction in the risk of weight-related complications. A more appropriate approach is to define the main therapeutic objective as health risk reduction and health improvement with weight loss, and not weight reduction per se.[26] In addition, patients should be made aware that obesity is a chronic disease and therapy is prescribed with the intention of lifelong use.[17,27] This further emphasizes the need for long-term weight-loss maintenance, also highlighted in current guidelines.[18]

2.1.1 | Diet, physical activity and behavioural intervention

Lifestyle modification has been established as a first-line treatment of obesity.[18,28] A multifactorial, comprehensive lifestyle programme that includes a high-quality hypocaloric diet should also involve a minimum of 150 minutes of moderate-intensity activity per week[28] as well as behaviour-changing strategies to foster adherence to dietary and physical activity for at least 6 to 12 months.[18] These lifestyle modifications are recommended for weight loss and weight loss maintenance.[18] Importantly, when creating the personalized lifestyle programme, the weight loss targets should be chosen realistically, revisited frequently, and aimed at the long term. Patient motivation, personal weight loss goals, nutritional habits, cultural and ethnic dietary preferences, weight-related complications, and previous lifestyle change attempts should be taken into account.[27]

Nutrition

To achieve clinically significant weight loss, most international guidelines recommend a daily energy deficit of at least 500 kcal.[18] In contrast, the recently published Canadian Adult Obesity Clinical Practice Guideline on nutrition emphasized that caloric restriction achieves short-term weight reduction (up to 12 months) with no proven sustainable long-term weight loss effect (exceeding 12 months).[29] In addition to structured meal plans, portion control, and meal replacements,[18] an individualized dietary plan should be used based on the patient's personal and cultural preferences and modifying the unhealthy components.[17,18,29] According to the obesity guidelines of the American Heart Association, the Academy of Nutrition and Dietetics, and the German Obesity Society, the macronutrient composition of a diet is insignificant, as long as it is balanced and healthy.[18] However, the scientific evidence for the weight loss effect of dietary programmes in general is often inconsistent and partly contradictory. For instance, one meta-analysis suggested that clinically significant weight loss can be expected with any low-carbohydrate or low-fat diet.[30] A more recent meta-analysis found that a modest weight reduction is feasible at 6 months with low-carbohydrate diets and low-fat diets compared to control diets, but these effects prove temporary after a year.[31] While both studies conveyed a similar message, the extent of weight reduction differed considerably. Higher weight loss was reported with low-carbohydrate diets (8.73 kg at 6-month follow-up and 7.25 kg at 12-month follow-up) and low-fat diets (7.99 kg at 6-month follow-up and 7.27 kg at 12-month follow-up) in the first study compared to the second meta-analysis (4.63 kg and 4.40 kg, respectively at 6-month follow-up).

Physical activity

Foundational to any weight loss effort should be a weekly exercise target of minimum 150 minutes of accumulated moderate-intensity endurance exercise, in combination with strength training.[18] Lifestyle modification for long-term weight maintenance after successful weight reduction includes increasing exercise to 300 minutes of moderate-intensity activity every week, which is not sustainable for many people with obesity. Further recommendations include tailoring the exercise objectives to the individual's physical capabilities and preferences, as well as reducing sedentary behaviour (eg, television viewing, computer use) and increasing daily activities (eg, walking, cycling, climbing stairs and gardening).[18]

A meta-analysis has reported an additive benefit of physical activity alongside dietary intervention on weight loss.[32] At 12 months, combined programmes demonstrated a mean difference of −1.72 kg and −6.29 kg, compared to diet-only or exercise-only interventions, respectively. Thus, exercise should be considered in conjunction with caloric restriction. These results underline the importance of exercise as an essential component of weight reduction programmes. In addition to weight loss, physical activity is known to have other health benefits, such as reducing the risk of CV events, as well as improving physical functioning, mobility, and quality of life.[28,33] Weight loss achieved through diet, exercise or their combination also significantly reduced the incidence of T2D among individuals with impaired glucose tolerance, as demonstrated in a study in Da Qing, China.[34] Over a 6-year follow-up, 67.7% in the control group compared with 43.8% in the diet group, 41.1% in the exercise group, and 46.0% in the diet-plus-exercise group were diagnosed with T2D. Similarly, the Diabetes Prevention Program clinical trial[35] demonstrated a reduction in the incidence of diabetes among individuals with prediabetes in the United States. Over a mean follow-up of 2.8 years, a 58% reduction in incident diabetes was reported with the lifestyle intervention, as compared with placebo,[35] which was reduced to 34% at the 10-year follow-up.[36] Moreover, a placebo-subtracted weight loss of 5.5 kg[35] was largely regained after 10 years,[36] which was a comparable result to that obtained in the Da Qing trial.[34] The long-term outcomes of these two trials highlight the fact that modest weight reduction, even if not sustained, may have long-term benefits, in particular in reducing the risk of diabetes. They also illustrated the transient effect of weight loss achieved by lifestyle modification and emphasize the importance of long-term weight loss maintenance.

Behavioural intervention

International guidelines recommend that behavioural intervention in the form of individual or group sessions be considered for all adults enrolled in a weight management programme.[18] Moreover, self-monitoring is recommended as essential in behavioural therapy[18] and involves tracking dietary intake and physical activity levels. Other commonly employed behavioural strategies include regular weighing, stimulus control, modifying existing dietary and fitness habits, and setting reasonable and individualized weight loss targets. All of these strategies aim to support weight loss management and enhance patient's adherence to their lifestyle modification programme.

Multicomponent lifestyle modification is recommended as the cornerstone of obesity management.[18,28] However, some patients do not respond to even the highest-quality programmes. Others manage to achieve initial clinically meaningful weight loss of 5% to 10%, but experience a tendency of weight regain towards pre-treatment level.[37] Both could be explained by the patient's difficulty to adhere to long-term lifestyle interventions or by adaptive biological mechanisms of the body in response to weight loss.[38] If behavioural interventions are not sufficiently effective in achieving individual weight loss or health-related goals after 6 months, or if the patient has a higher BMI along with an obesity-related complication, antiobesity pharmacotherapy in conjunction with lifestyle modification is recommended.[18]

2.1.2 | Weight loss medications

Five agents are currently available for chronic weight management in adults in the United States and/or the European Union.[22,39] Among them are orlistat, phentermine/topiramate extended-release (ER), naltrexone (ER)/bupropion (ER), and the glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) liraglutide and semaglutide (Table 2). For the treatment of rare monogenic obesities, the melanocortin-4 receptor (MC4R) agonist setmelanotide is indicated in adults and children aged 6 years and over. All of these agents result in clinically meaningful weight reduction.[40] The continuous use of orlistat, semaglutide, and the combination products phentermine/topiramate ER, and bupropion ER/naltrexone ER is recommended only with weight loss of at least 5% in the first 3 months of treatment[18] (or at least 4% at 16 weeks for liraglutide[41]) and can be continued as long as treatment provides benefit and no serious adverse events occur.[38] Evidently, the combination of exercise and pharmacotherapy reduces risk factors in people with obesity and thus increases their general health and quality of life.[42,43] Moreover, combining physical activity and antiobesity drug therapy effectively prevents weight regain.[44] Physical activity is considered a prerequisite for prescribing antiobesity medication. This is reflected in the regulatory approvals of the agents highlighted in this chapter. These specify that they should be used as adjuncts to lifestyle interventions.[18]

Orlistat

Orlistat is licensed in Europe and the United States for chronic weight management in adults, and in the United States in children aged 12 years and older. It is a selective gastric and pancreatic lipase inhibitor. It acts locally in the intestinal lumen and reduces absorption of ingested fat by approximately 30%, thereby decreasing caloric intake. Orlistat is associated with modest weight loss. At 1 year, the mean placebo-subtracted weight loss with orlistat was 3.4 kg (3.1% of initial body weight) in addition to a low-fat diet. Clinically meaningful (≥5%) body weight loss varied from 35% to 73%.[45] In the 4-year XENDOS study, orlistat treatment led to 2.8-kg (2.4%) placebo-subtracted weight loss. However, this modest weight reduction translated into a 37.3% reduction in the risk of diabetes.[46] Orlistat is associated with a good safety profile. Adverse effects are mainly gastrointestinal and include flatulence, oily stool, faecal urgency, and small decrease in fat-soluble vitamins.[27,47]

Phentermine/topiramate

Phentermine is approved in the United States for short-term obesity management (up to 12 weeks). It is a sympathomimetic amphetamine analogue, which suppresses appetite by serotonin, norepinephrine, and dopamine agonism in the central nervous system. The synergistic combination with topiramate, an anticonvulsant used to treat seizures and migraine headaches, enhances phentermine's anorectic effect. In

TABLE 2 Currently available medications for long-term weight management in adults

Medication name	Pharmacological class	Typical adult maintenance dose, administration	Approval	Mean placebo-subtracted body weight loss from baseline, %[a]
Orlistat	Gastric and pancreatic lipase inhibitor	60 mg (OTC), 120 mg (Rx) three times daily, oral	United States, EU	3.1[45] (120 mg three times daily)
Phentermine/topiramate ER	Sympathomimetic amine anorectic/antiepileptic	7.5 mg/46 mg[b] once daily, oral	United States	8.6[48] – 9.3[49] (15 mg/92 mg daily dose)
Bupropion ER/naltrexone ER	Antidepressant/opioid antagonist	16 mg/180 mg[c] twice daily, oral	United States, EU	4.8[50] – 5.2[51] (32 mg/360 mg daily dose)
Liraglutide	GLP-1RA	3 mg once daily, SC	United States, EU	5.4 (1 year)[52] 4.4 (3 year)[53]
Semaglutide	GLP-1RA	2.4 mg weekly, SC	United States, EU	12.4[54]
Setmelanotide	Melanocortin agonist	3 mg[d] once daily, SC	United States, EU	–[e,55]

Abbreviations: ER, extended release; EU, European Union; GLP-1RA, glucagon-like peptide-1 receptor agonist; OTC, over the counter; Rx, prescription; SC, subcutaneous.
[a]Results in the context of concomitant lifestyle modifications.
[b]Recommended dose; maximum dose 15/92 mg.
[c]Usual dosage, may be increased to 32 mg naltrexone/360 mg bupropion once daily.
[d]Recommended dose for adults and paediatric patients aged ≥6 years; starting dose for adults and paediatric patients aged ≥12 years, and for paediatric patients between 6 and 12 years of age is 2 mg and 1 mg, respectively, once daily for 2 weeks.[56]
[e]Two single-arm studies without a comparator. At approximately 1 year, 80% of participants with proopiomelanocortin deficiency and 45% of these with leptin receptor deficiency achieved at least 10% weight loss.

the two large trials CONQUER[48] and EQUIP[49] with a duration of up to 1 year, the mean placebo-subtracted weight reduction attributable to the combination ranged from 8.6% to 9.3% at the 15/92 mg dose when added to a low-intensity lifestyle programme. In these studies, 67%[49] to 70%[48] of 15/92 mg participants, lost at least 5% of baseline body weight relative to 17.3% and 21%, respectively, in the placebo group ($P < 0.0001$ for both). SEQUEL,[57] an extension study to CONQUER, confirmed the sustained efficacy of the combination by showing a placebo-subtracted weight loss of 8.7% at a total of 108 weeks. Moreover, a significantly lower incidence of diabetes progression in the 15/92 mg group (0.9%) versus placebo (3.7%) as well as a lower rate of adverse events compared to the CONQUER trial was observed.[57]

Side effects accompanying the use of phentermine/topiramate include paresthesia, dry mouth, constipation, as well as effects on the central nervous system such as headache, dizziness, insomnia, taste alterations, disturbances in attention and memory, anxiety, and depression.[48,49] While all antiobesity agents are contraindicated during pregnancy, the phentermine/topiramate combination therapy requires additional counselling for women of childbearing age on the teratogenicity of topiramate. Moreover, a mitigation strategy for these women is in place in the United States.[38]

Bupropion/naltrexone

The combination treatment with bupropion and naltrexone is based on the principle of a synergistic combination of two centrally acting agents, which had already been approved and which, taken separately, lead to modest weight loss. Bupropion is approved for unipolar depression, seasonal affective disorder, and smoking cessation since it affects the central perception of reward.[58] It is a nonselective inhibitor of the dopamine and norepinephrine transporters. Naltrexone, on the other hand, is an opioid receptor antagonist widely used to treat addiction syndromes including alcohol and opioid use disorder. Based on animal studies, the anorectic effect of the bupropion/naltrexone combination is attributable to stimulation of proopiomelanocortin (POMC) secretion in the arcuate hypothalamic nucleus, resulting in reduced food craving, increased satiety, and indirectly enhanced energy expenditure.[58]

The Contrave Obesity Research (COR) clinical trial programme assessed the efficacy and safety of the drug combination.[50,51,59,60] In the COR-I[50] and COR-II[51] trial, participants received a 32/360 mg daily dose of the combination adjunct to mild hypocaloric diet and exercise or lifestyle modification advice, respectively. At 1 year, bupropion/naltrexone produced an average placebo-subtracted weight reduction of 4.8%[50] to 5.2%.[51] A total of 48% to 50% of study participants treated with the combination lost ≥5% of initial body weight compared with approximately 17% in the respective placebo-treated group.[50,51] The addition of bupropion/naltrexone in the same daily dose to an intensive behavioural modification programme was studied in the COR Behavioural Modification (COR-BMOD) trial.[59] It demonstrated a placebo-subtracted body weight reduction of 4.2% with the drug combination. The most frequently reported adverse effects were nausea, dizziness, dry mouth, insomnia and constipation. In addition, there is a need to monitor patients for psychiatric adverse effects (ie, suicidal ideation), elevated heart rate and/or blood pressure.[47]

Liraglutide

The GLP-1RAs are established glucose-lowering agents with cardioprotective effect in individuals with T2D.[61,62] Meanwhile, liraglutide and semaglutide have been shown to promote weight loss in people

with overweight and obesity also in the absence of T2D.[52,54] The weight loss effect of this class of drugs is achieved by mimicking the incretin hormone GLP-1, which regulates appetite and food intake in the brain and delays gastric emptying.[61,63] Both medications have been approved in the United States and Europe for obesity management in adults as an adjunct to calorie reduction and increased physical activity. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have also approved liraglutide for the treatment of children aged 12 years and older with obesity. Treatment with liraglutide has been shown to benefit patients with obesity caused by MC4R mutations.[64,65] However, liraglutide has not been approved for this indication.

The SCALE clinical trial programme formed the foundation for the approval of liraglutide 3.0 mg for weight management. It demonstrated a significant placebo-subtracted weight loss of 5.4% at 1 year[52] and 4.4% at 3 years[53] with liraglutide 3.0 mg when added to lifestyle modifications (counselling or calorie reduction and increased physical activity, respectively). In the first year of treatment, liraglutide led to a body weight reduction of ≥5% in 63.2% in the active treatment group as compared with 27.1% in the placebo group.[52] From this study cohort, approximately 60% of participants had prediabetes.[52] The treatment of these patients was extended for an additional 2 years to determine the effect of liraglutide on reducing the risk of progression to overt T2D.[53] Indeed, fewer cases of T2D progression were diagnosed in the liraglutide group (1.8%) than in the placebo-treated group (6.2%) during the trial.[53] Liraglutide's effect on weight loss was less pronounced in two further trials of the SCALE programme with a 1-year follow-up—in the SCALE Diabetes trial, the placebo-subtracted weight loss was 3.9% in individuals with T2D[66] and in the SCALE IBT trial, liraglutide 3.0 mg as an adjunct to intensive behavioural therapy resulted in 3.4% placebo-subtracted weight loss.[67] Finally, sustained weight loss with liraglutide 3.0 mg was evaluated in the SCALE Maintenance trial.[68] Prior to randomization, participants successfully lost ≥5% of initial body weight through caloric restriction. This weight loss effect was not only maintained but further enhanced by liraglutide 3.0 mg, resulting in a mean overall weight loss of 12.2% (estimated placebo-subtracted difference of 6.1%) over a year. In addition, the participants in the active treatment group were more likely to both maintain their initial ≥5% weight loss (81%) and to lose additional ≥5% of randomization weight (51%) compared to the placebo-treated group (49% and 22%, respectively).[68] Generally, liraglutide is well tolerated with the most common, usually transient, adverse effects being gastrointestinal, predominantly nausea, vomiting, diarrhoea or constipation.[38,69] The incidence of acute pancreatitis and gallbladder-related adverse events was greater in individuals treated with liraglutide 3.0 mg than in placebo-treated patients.[41] Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid cancer as it has been demonstrated to cause thyroid C-cell tumours in rats and mice, although no increased risk has been determined in humans.[41]

Semaglutide

Similar to liraglutide, semaglutide is a GLP-1 receptor analogue approved as treatment for T2D with potential for CV protection in this patient population.[62,70] Modifications in the semaglutide molecule prolong its half-life and protect against dipeptidyl peptidase-4 degradation.[71] At the higher dose of 2.4 mg, semaglutide has been granted approval both in Europe and the United States as the first weekly injectable therapy for chronic weight management in adults. Recently, the FDA has approved semaglutide 2.4 mg for the indication of treating obesity in adolescents aged 12 years and older. Among the currently approved antiobesity agents (Table 2), semaglutide 2.4 mg is the most potent,[40] associated with a mean placebo-subtracted 1-year body weight loss of 12.4%.[54] Its efficacy has been tested as an adjunct to lifestyle intervention within the comprehensive STEP clinical trial programme, spanning a total of 18 trials. The core of the STEP programme includes eight international (STEP 1-5,[54,72-75] STEP 8,[76] STEP 9, 10) and three regional (STEP 6,[77] 7,[78] STEP 11) studies. Additional trials focus on weight management in adolescents (STEP TEENS,[79]) and/or in children (STEP Young); in patients with heart failure with preserved ejection fraction (STEP-HFpEF in obesity,[80] and STEP HFpEF DM in obesity plus T2D[81]); in obesity (STEP UP)[82] and in obesity plus T2D (STEP UP T2) with very high semaglutide dosage of 7.2 mg weekly, as well as in a CV outcome trial (SELECT).[83] The results of the trials with previously published findings are summarized in Table 3.

The available data on weight loss from the STEP clinical trial programme can be summarized into the following key learnings. Substantial weight loss is feasible with semaglutide 2.4 mg in adults (STEP 1)[54] and adolescents (STEP TEENS)[79] with obesity, independent of racial background (STEP 6).[77] The vast majority of adult participants in the programme (between 77% and 89%) achieved a clinically meaningful weight reduction of at least 5%. Crucially, weight loss of above 20%, a target feasible so far only with bariatric surgery, was reached by almost one-third of the semaglutide-treated participants compared to just over 1% with placebo.[54] Weight reduction plateaued after approximately 60 weeks of therapy (consistently throughout the programme) and was sustained over 2 years on-treatment (STEP 5).[75] However, if discontinued, the lost weight was gradually regained (STEP 4,[74] STEP 1 extension study[84]), underlining the necessity of continued antiobesity pharmacotherapy for sustained benefit. The inclusion of intensive behavioural therapy (reduced-calorie diet, physical activity, and individual intensive counselling) to high-dose semaglutide failed to contribute significant additional weight loss (STEP 3)[73] beyond that achieved by semaglutide and less-intensive lifestyle intervention (STEP 1).[54] In T2D, increasing the semaglutide dose to 2.4 mg compared with the approved dose of 1.0 mg in this patient population yielded significantly greater weight loss and, importantly, only a small incremental improvement in glycaemic variables (STEP 2).[72] Finally, the superiority in terms of body weight loss of high-dose semaglutide over daily liraglutide, the other GLP-1RA approved for obesity management, was confirmed in a head-to-head trial (STEP 8).[76]

Because improved CV risk factors and better glycaemic control were evident in semaglutide diabetes trials, these findings were expected and indeed were confirmed in the STEP clinical

TABLE 3 STEP clinical trial programme with efficacy results

Trial	Trial objective	*N*	EOT, weeks	Comparator	Mean body weight change from baseline, % (semaglutide 2.4 mg vs. comparator)	Study participants with ≥5% weight loss from baseline, % (semaglutide 2.4 mg vs. comparator)
STEP 1[54]	WM	1961	68	Placebo	−14.9 vs. −2.4	86.4 vs. 31.5
STEP 2[72]	WM in T2D	1210	68	Semaglutide 1.0 mg or placebo	−9.6 vs. −7.0 vs −3.4	68·8 vs. 57.1 vs. 28.5
STEP 3[73]	WM with IBT	611	68	Placebo	−16.0 vs. −5.7	86.6 vs. 47.6
STEP 4[74]	Sustained WM	803	68	Placebo for 48 weeks after 20 weeks of semaglutide 2.4 mg	−7.9 vs. + 6.9[a]	88.7 vs. 47.6[b]
STEP 5[75]	Long-term WM	304	104	Placebo	−15.2 vs. −2.6	77.1 vs. 34.4
STEP 6[77]	East Asia	401	68	Semaglutide 1.7 mg or placebo	−13.2 vs. −9.6 vs. −2.1	82.9 vs. 72.4 vs. 21.0
STEP 8[76]	H2H vs. liraglutide	338	68	Liraglutide 3.0 mg or placebo	−15.8 vs. −6.4 vs. −1.9	87.2 vs. 58.1 vs. 29.5
STEP TEENS[79]	WM in adolescents[c]	201	68	Placebo	−16.1 vs. +0.6[d]	73 vs. 18

Abbreviations: EOT, end of treatment; H2H, head-to-head; IBT, intensive behavioural therapy; T2D, type 2 diabetes; WM, weight management.
[a]% change in body weight from Week 20 to Week 68 (after the run-in phase with semaglutide 2.4 mg); total weight loss of 17.4% (semaglutide 2.4 mg) versus 5.0% (placebo).
[b]Proportions of participants achieving ≥5% body weight loss from Week 0 to Week 68 with continued semaglutide versus placebo.
[c]12 to <18 years of age with a body mass index (BMI) in the 95th percentile or higher, or BMI in the 85th percentile or higher and least one weight-related coexisting condition.
[d]Change in baseline BMI.

trial programme. However, improvement in most CV risk factors diminishes after a year following treatment withdrawal.[84] SELECT, the dedicated CV outcome trial with high-dose semaglutide,[83] will provide detailed insight if this agent reduces the risk for CV events in patients with obesity at high CV risk. In line with other GLP-1RAs, adverse events with semaglutide were predominantly gastrointestinal with mild to moderate severity. To avoid or reduce these side effects, gradual uptitration over multiple weeks is generally recommended. Similar to liraglutide, semaglutide is associated with an increased risk of acute pancreatitis and acute gallbladder disease, and is contraindicated in patients with a personal or family history of medullary thyroid cancer despite the lack of evidence for causal relationship between this disease and GLP-1RA use in humans.[85]

Setmelanotide

The orphan drug setmelanotide is another recent addition to the list of approved medications for chronic weight management in adults and children aged 6 years or older. It is a highly selective MC4R agonist for the treatment of obesity, arising from deficiency disorders of the MC4R pathway. These include POMC, proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency.[86] People with these genetic defects develop severe early-onset obesity due to inadequate energy homeostasis. Setmelanotide addresses the underlying hyperphagia and specific molecular mechanism of these rare genetic diseases, by activating the MC4R resulting in suppressed hunger, increased satiety, and stimulated energy expenditure.[87] Given the rarity of these three syndromes, setmelanotide was approved without long-term placebo-controlled studies, but with evidence of significant body weight reduction. The regulatory approval rests on two 1-year studies in 21 patients with severe obesity caused by either POMC/PCSK1 or LEPR deficiency.[55] At approximately 1 year, 80% of participants with POMC/PCSK1 deficiency, and 45% of those with LEPR deficiency, achieved at least 10% weight loss. Hunger scores were assessed in patients 12 years and older and were significantly reduced by 27.1% in the POMC trial and by 43.7% in the LEPR trial, with high variability among participants. The most common side effects were injection site reactions in all participants, hyperpigmentation, as well as nausea and vomiting with no serious treatment-related adverse events. Importantly, setmelanotide is approved for the treatment of obesity and the control of hunger only in patients with proven pathogenic variation in *POMC*, *PCSK1* or *LEPR* genes confirmed by genetic testing. Moreover, long-term treatment with the agent is required because it treats the symptoms but not the genetic cause underlying the disease. Although setmelanotide is restricted to the treatment of a minority of patients with monogenic obesity, it is an important addition to the arsenal of agents for weight management.

Pharmacotherapy currently holds a limited arsenal of five safe and effective drugs for general obesity. Historically, these were considered as promoters of adherence to lifestyle interventions and enhancers of weight loss.[18] Conventional pharmaceutical agents result in clinically meaningful, albeit modest, effects on weight reduction and/or obesity-related complications.[88] These benefits increase with progressively greater weight reduction.[89] With a mean weight

loss of 15% in combination with the associated cardiometabolic improvements, high-dose semaglutide is a game changer in chronic obesity management.[54] Nevertheless, bariatric surgery remains the single most effective treatment in the context of weight loss and long-term weight maintenance.

2.1.3 | Bariatric surgery

Bariatric surgery is considered the "gold standard" treatment for severe obesity due to its high efficacy in terms of weight loss, duration of effectiveness and improvement of obesity-related complications.[28,38] Common surgical procedures include gastric banding, sleeve gastrectomy, and Roux-en-Y gastric bypass, all of which yield substantial and significant weight loss of 15.9%,[90] 29.5% and 31.9%.[91] The achieved weight reduction is largely conserved beyond 10 years.[92] Crucially, since the approval of semaglutide 2.4 mg for the treatment of obesity, gastric banding has fallen out of favour as, in contrast to the pharmacotherapeutic option, it does not treat the underlying hormonal dysregulation of obesity and is associated with significant complications, including band slippage and erosion, while yielding a similar degree of weight loss.

The sustained weight loss as a result of bariatric surgery is associated with a wide range of benefits, largely in the context of cardiometabolic diseases.[93-95] In pooled analysis of four studies, bariatric surgery led to a significant risk reduction of composite CV adverse events (odds ratio 0.54), myocardial infarction (odds ratio 0.46) and stroke (odds ratio 0.49) compared to nonsurgical controls.[96] According to a recent meta-analysis, bariatric surgery also leads to a substantially lower all-cause mortality rate (49.2%) and longer life expectancy (6.1 years) compared with usual care, with a particularly pronounced survival benefit in individuals with baseline diabetes.[97] People living with diabetes benefit from bariatric surgery in other ways as well—a study in the 1990s showed normalized glycaemia, insulin function and glycated haemoglobin (HbA1c) levels in 83% of people with diabetes after bariatric surgery.[98] Since then, a robust body of evidence supports the implementation of bariatric surgery in T2D therapy due to its significant, consistent, and durable glucose control in addition to weight loss.[95] Diabetes remission is also feasible for the majority of patients with T2D undertaking bariatric surgery, especially in younger patients.[99] Almost 70% of patients experience complete T2D remission within 5 years following surgery, with a median remission duration of 8.3 years.[100] Depending on the surgical procedure, between 25% and 50% of patients remained in remission over 10-year follow-up.[101] Meanwhile, surgical management has been endorsed as an effective intervention for T2D by leading diabetes guidelines including the American Diabetes Association, which recommends bariatric surgery for patients with a BMI of 35.0 to 39.9 kg/m^2 and inadequately controlled hyperglycaemia despite optimal medical therapy.[102]

Contemporary bariatric operations exhibit a good safety profile with low peri-operative morbidity and mortality, with the less invasive procedures associated with lower short- and long-term risks.[103] Nevertheless, important limitations of this therapeutic approach persist, including the risk of surgical complications, nutritional deficiencies, and the need for lifelong nutritional monitoring and supplementation.[93] Hence, a comprehensive benefit-to-risk assessment by the patient and their care team should guide treatment decisions.[18,27] After the surgical intervention, multidisciplinary follow-up for at least 2 years is recommended.[18]

2.2 | Therapeutic options of the (near) future

Up until the approval of semaglutide for obesity management, conventional pharmaco-therapies provided a modest and transient weight loss of up to 10.9% from baseline body weight.[45] Semaglutide achieves a mean weight reduction of 14.9% yielding significant benefits when it comes to weight-related complications.[54] However, dose-related gastrointestinal adverse events limit GLP-1RA efficacy and prevent further dose escalation potentially resulting in additional weight loss.[104] On the other hand, contemporary surgical approaches result in substantial and sustained weight loss of approximately 30% at 1 year,[91] revealing a gap between the weight loss achieved by currently available pharmacotherapies and surgical management. Closing this gap and reducing body weight by more than 20% represents an informal benchmark for emerging antiobesity treatments in late-stage development (Figure 1). Among these, tirzepatide is the agent which promises to further diversify obesity management in the not-too-distant future.

2.2.1 | Tirzepatide

Tirzepatide is a synthetic linear peptide based on the native glucose-dependent insulinotropic polypeptide (GIP) sequence with dual agonist activity at GIP and GLP-1.[107] Both GIP and GLP-1 are gut-produced incretin hormones, which orchestrate postprandial glucose and lipid metabolism. Hence, tirzepatide was developed to determine whether GIP could enhance the established glucose-lowering effect of GLP-1RAs in diabetes. This was extensively studied in the SURPASS clinical trial programme in adult patients with T2D.[61] The five trials evaluated once-weekly tirzepatide doses of 5, 10 and 15 mg as either a monotherapy or as an add-on to other diabetes drugs, and compared its efficacy to placebo, semaglutide 1.0 mg, and two long-acting insulin analogues. Across all trials, the highest tirzepatide dose lowered HbA1c by up to 1.6% more than placebo. As a result of these clinically relevant findings, in 2022, the FDA and EMA both granted approval to tirzepatide as a glucose-lowering agent with once-weekly subcutaneous administration for adults with T2D, as an adjunct to diet and exercise.

Apart from its robust glycaemic control, stand-alone treatment with tirzepatide exhibited profound and clinically meaningful impact on body weight in a dose-dependent manner (mean placebo-subtracted weight loss of 7.0%, 8.6% and 10.9% with tirzepatide 5, 10 and 15 mg, respectively).[108] This weight loss effect stems from the synergistic physiological activity of GLP-1 and GIP. As discussed

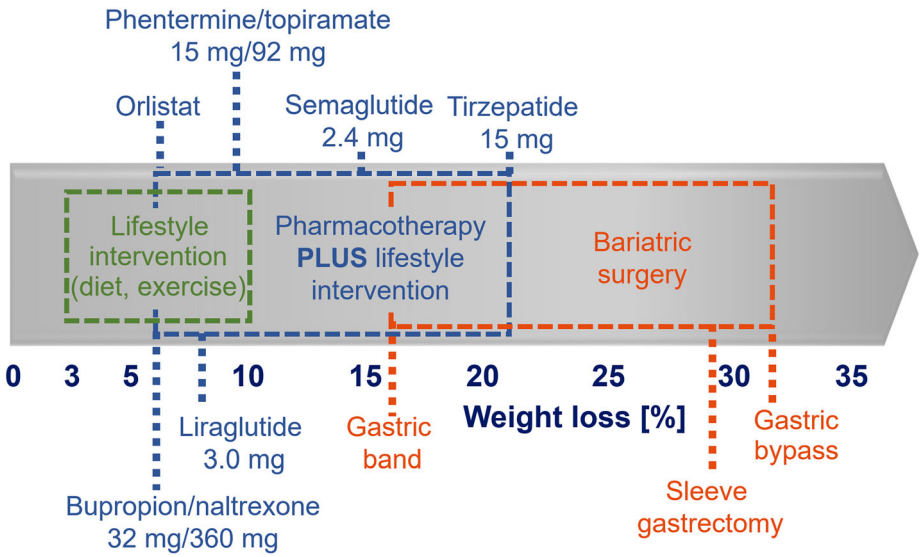

FIGURE 1 Effect sizes for different obesity therapies at 1 year. Data refer to bupropion extended release (ER)/naltrexone ER (6.1%),[50] orlistat (6.3%),[105] liraglutide (8.0%),[52] phentermine/topiramate ER (9.8%),[48] semaglutide 2.4 mg (14.9%),[54] gastric band (15.9%),[90] tirzepatide 15 mg (20.9%),[106] sleeve gastrectomy (29.5%)[91] and Roux-en-Y gastric bypass (31.9%)[91]

above, GLP-1 reduces body weight via central (lowering food intake, increasing satiety),[63] and peripheral action (slowing gastric emptying).[61] These effects are complemented by GIP, whose receptors are expressed both in the brain (partially overlapping expression patterns with GLP-1 receptors[109]) and in the subcutaneous white adipose tissue.[110] Hence, GIP receptor activation results in reduced energy consumption centrally, and improves white adipose tissue health and function.[104] In addition, GIP may further enhance the anorexigenic effects of GLP-1 by lowering the incidence of GLP-1RA-induced nausea, thereby increasing tolerance and expanding the GLP-1RA efficacy.[104,111]

The efficacy and safety of tirzepatide in adults with obesity in the absence of diabetes is currently being assessed in the SURMOUNT clinical trial programme, consisting of six international[106,112-116] and two regional trials[117,118] (Table 4). Although the study designs of the STEP and SURMOUNT trial programmes resemble one another, they differ in three major ways (Tables 3 and 4). First, none of the SURMOUNT trials compares tirzepatide to an active comparator, which is standard given that tirzepatide is first-in-class dual GIP/GLP-1RA. Next, the duration of SURMOUNT-1, -2 and -3 is extended by 4 weeks compared to the STEP trials due to its longer dose-escalation period. Finally, no long-term weight management trial with a follow-up of approximately 2 years is currently planned for tirzepatide in obesity, excluding the two CV trials. However, in SURMOUNT-4, data from the patient group receiving tirzepatide throughout the trial (88 weeks in sum) should provide an insight into when a body weight plateau is reached. Notably, tirzepatide was not associated with an increased CV risk in participants with T2D versus controls, as assessed by a recent prespecified meta-analysis based on seven SURPASS clinical trials.[119] While this study was underpowered for significance, ongoing outcome trials in individuals with (SURPASS-CVOT) and without diabetes (SURMOUNT-MMO[115]) will shed more light on the CV safety of tirzepatide.

To date, the findings of a single study, SURMOUNT-1, have been published.[106] In this trial, tirzepatide's efficacy and safety were tested against placebo in over 2500 adults with obesity or those with overweight plus at least one weight-related complication, excluding diabetes. At 72 weeks, once-weekly tirzepatide 5 mg, 10 mg or 15 mg resulted in a significant mean weight loss of 15.0%, 19.5% and 20.9%, respectively, compared to 3.1% with placebo in addition to lifestyle intervention. Clinically meaningful weight loss of ≥5% was achieved by 85%, 89% and 91% of participants on each of the three tirzepatide doses, a result superior to placebo (35%). These findings represent the average treatment effect of tirzepatide for all individuals who had undergone randomization, regardless of treatment discontinuation, also referred to as the treatment estimand. In participants for whom the treatment was administered as intended (efficacy estimand), the mean weight reduction at Week 72 in response to tirzepatide 5 mg, 10 mg or 15 mg was unsurprisingly further increased to 16.0%, 21.4% and 22.5%, respectively, compared to 2.4% in placebo. With the use of the efficacy estimand, the respective percentage of participants achieving ≥5% body weight reduction was 89%, 96%, 96% and 28% in the 5 mg, 10 mg and 15 mg tirzepatide and placebo groups. This is an unusually substantial degree of weight loss as a result of pharmacotherapy. Although direct comparison between clinical trials should be avoided due to differences in study population and design, the mean placebo-adjusted weight reduction of semaglutide 2.4 mg (12.4%) and the percentage of study participants having a weight reduction of ≥20% (nearly one-third) roughly corresponded to the results observed with the lowest maintenance dose of tirzepatide (5 mg)—11.9% and 30%, respectively.

Crucially, weight loss efficacy within the surgical range is achievable with the two higher doses of tirzepatide. Over half of participants in these treatment arms achieved a weight reduction of 20% or more as compared to 3% in the placebo-treated group, while 32% and 36% of individuals on 10 and 15 mg tirzepatide treatment (35% and 40% in the efficacy-regimen estimand) met the explorative weight-reduction target of ≥25% compared with 1.5% of participants in the placebo group (0.3% in the efficacy estimand analysis). The staggering number of responders to tirzepatide is also worth mentioning—body weight

TABLE 4 SURMOUNT clinical trial programme

Trial	Trial objective	N	EOT	Comparator
SURMOUNT-1[106]	WM	2539	72 weeks	Placebo
SURMOUNT-2[112]	WM in T2D	900	72 weeks	Placebo
SURMOUNT-3[113]	WM with IBT	800	72 weeks	Placebo
SURMOUNT-4[114]	Sustained WM	750	88 weeks	Placebo for 52 weeks after 36 weeks of tirzepatide
SURMOUNT-J[117]	Japan	261	72 weeks	Placebo
SURMOUNT-CN[118]	China	210	52 weeks	Placebo
SURMOUNT-MMO[115]	CVOT	15 000	5 years	Placebo
SUMMIT[116]	HFpEF	700	120 weeks	Placebo

Abbreviations: CVOT, cardiovascular outcome trial; EOT, end of treatment; HFpEF, heart failure with preserved ejection fraction; IBT, intensive behavioural therapy; T2D, type 2 diabetes; WM, weight management.

reduction was observed in 96.6%, 96.7% and 97.7% of participants in the tirzepatide 5 mg, 10 mg and 15 mg groups, respectively, compared to 66.9% of participants in the placebo group. In addition, tirzepatide improved cardiometabolic risk factors and physical function, including waist circumference, systolic and diastolic blood pressure, lipids, fasting insulin, and SF-36v2 physical functioning domain score. Notably, prediabetes at baseline was resolved at Week 72 in almost all participants (95.3%) in the tirzepatide-treated arms.

The safety and tolerability profile of tirzepatide was consistent with the findings from the SURPASS clinical trials in T2D and similar to that of GLP-1RAs. Transient gastrointestinal adverse events (eg, nausea, diarrhoea, constipation) with mostly mild-to-moderate severity were reported most frequently, occurring primarily during the titration phase. Despite the higher incidence of adverse events in tirzepatide-treated participants versus placebo, tolerability was similar in the 10-mg and 15-mg groups, indicating that the highest tirzepatide dose may provide greater efficacy and increased benefit in some patients, without added safety concerns.

2.2.2 | Other treatments in development

Tirzepatide is the first of multiple next-generation therapies for obesity management currently in development,[47] many of which are based on GLP-1 receptor agonism. For instance, the oral formulation of semaglutide, which has been approved to improve glycaemic control in T2D as an adjunct to diet and exercise, is currently being tested in the Phase III trial OASIS in adults with obesity in the absence of T2D.[120]

An alternative strategy is the creation of peptide combinations with complementary modes of action such as dual and triple co-agonists, with GLP-1 again emerging as an ideal partner.[121] Tirzepatide and mazdutide fall into this category. Mazdutide is a dual GLP-1 receptor and glucagon receptor agonist which utilizes the catabolic and thermogenic actions of glucagon.[122] It achieved mean body weight loss of 11.57% at Week 24 during a Phase II trial and is currently being tested in a Phase III clinical trial (GLORY-1) in the same population of Chinese adults with overweight or obesity.[123] Moreover, a triple agonist peptide at the glucagon, GIP, and GLP-1 receptors is also in early development.[124]

Co-agonism mimicking several endogenous hormones is not the only possible strategy for a unimolecular agent. AMG 133 is a bispecific GIP receptor antagonist and GLP-1RA molecule.[125] Interestingly, up to 14.5% reduction in body weight and a good safety profile were observed at 12 weeks. This high extent of weight loss provokes questions regarding the drug's mode of action and the role of GIP and GLP-1 in physiological weight regulation.

Finally, combining agents possessing GLP-1 pharmacology with molecules targeting alternative pathways may further expand the therapeutic options. As an example, concomitant treatment with semaglutide 2.4 mg and the human amylin analogue cagrilintide (CagriSema) resulted in an average weight reduction of 17.1% from baseline body weight after 20 weeks of treatment.[126]

3 | CONCLUSIONS

Social and environmental challenges, including stigma regarding the disease, sedentary jobs, barriers to physical activity, and ubiquity of affordable energy-dense foods, persist and dash hopes for the elimination of the global obesity epidemic. The key to effectively addressing the disease is substantial and durable weight loss and long-term weight loss maintenance. Successful weight reduction exceeding 15% has significant implications such as prevention of T2D, T2D remission as well as improvement in cardiometabolic risk factors and in already developed obesity-related complications, including T2D, CV disease, hyperlipidaemia, hypertension, obstructive sleep apnoea, nonalcoholic fatty liver disease, and cancer. For years, such degree of weight loss could be achieved only by bariatric surgery. With a better understanding of the pathophysiology of obesity, new treatment approaches with an improved weight reduction effect have emerged. Among them is the recently approved semaglutide 2.4 mg, which results in mean weight loss close to 15% of body weight. Meanwhile, evidence of weight reduction exceeding 20% has been achieved with the dual GIP/GLP-1RA

tirzepatide in people living with obesity. Other emerging antiobesity agents hold promise to further diversify the available treatment options and could be at our disposal in the near future. By utilizing a polymodal approach of combination therapy with two or more antiobesity medications, patients may be capable of achieving weight loss of 25%, or even 30%, that was previously possible only with bariatric surgery in a personalized manner depending on the patient's disease phenotype. Thus, by treating obesity, we will eventually be able to tackle the root cause of a whole spectrum of "obesity diseases" and achieve the ultimate goal of effective weight management and health improvement.

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CONFLICT OF INTEREST STATEMENT

Dr. Matthias Blüher declares receiving honoraria for lectures and/or as a consultant from the following companies – Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Lilly, Novo Nordisk, Novartis, Pfizer, Sanofi.

Dr. Mohini Aras declares no conflicts of interest.

Dr. Louis J. Aronne reports receiving consulting fees from/and serving on advisory boards for Allurion, Altimmune, Atria, Gelesis, Jamieson Wellness, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Novo Nordisk, Pfizer, Optum, Eli Lilly, Senda Biosciences and Versanis; receiving research funding from Allurion, AstraZeneca, Gelesis, Janssen Pharmaceuticals, Novo Nordisk and Eli Lilly; having equity interests in Allurion, ERX Pharmaceuticals, Gelesis, Intellihealth, Jamieson Wellness and Myos Corp; and serving on a board of directors for ERX Pharmaceuticals, Intellihealth and Jamieson Wellness.

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