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Advancements in the management of obesity: a review of current evidence and emerging therapies

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Abstract

Introduction: Obesity is the modern world's current epidemic, with substantial health and economic impact. This study aimed to provide a narrative overview of the past, currently available, and future treatment options that offer therapeutic and preventive advantages for obesity management.

Topic covered: Historically, rimonabant, and lorcaserin, were approved and used for managing non-syndromic obesity. Currently, orlistat, naltrexone/ bupropion, glucagon-like peptide-1 receptor agonist (GLP-1 RA), and a few promising therapeutic agents are under investigation, including retatrutide, cagrilintide and orforglipron, which show promising weight reduction effects. We have developed a search string of the Medical Subject Headings (MeSH), including the terms GLP-1 RAs, obesity, and weight loss. This string was then used to perform a systematic literature search in the database including PubMed, EMBASE, MEDLINE and Scopus up to January 31st, 2024.

Expert opinion: Managing obesity often requires medical interventions, particularly in cases of severe obesity or obesity-related comorbidities. Thus, it is important to approach obesity management holistically, considering individual needs and circumstances. In our opinion, consulting with healthcare professionals is crucial to developing a personalised plan that addresses both weight loss and overall health improvement.

1 Introduction

Obesity is a major global health risk with increasing prevalence at an alarming rate, putting a financial burden on the world's economy[1]. Traditionally, obesity is defined as an increased body weight that is greater than 20%. However, in today's world, the definition of obesity is merely based on measuring the body mass index (BMI) which is calculated by dividing height in meter square (m^2) and body weight in kilograms (Kg). Thus, normal body weight is when the BMI ranges between 18.5 - 24.9 Kg/m^2, while a BMI ranging from 25-29.9 Kg/m^2 is overweight and a BMI more than 30 Kg/m^2 is considered obese. Therefore, based on these parameters and according to the latest evidence from the World Health Organisation (WHO), in 2016, more than 1.9 billion adults aged 18 years and older were overweight, and of those, over 650 million were obese. The prevalence of obesity has nearly tripled since 1975, making it a major global health issue[2]. The prevalence of obesity varies by region and country. The highest prevalence of obesity is seen in the Americas, with over 60% of the population in some countries being classified as obese. In Europe, the prevalence of obesity ranges from 20% to 30%, with higher rates seen in Eastern Europe[3]. In Asia, the prevalence of obesity is generally lower than in the Americas and Europe, but it is increasing rapidly. The prevalence of obesity in the United Kingdom (UK) has been steadily increasing over the past few decades. In 2022, 26% of adults in England were obese. The prevalence of obesity among women was 27% while that for men was 29%. Obesity rates are highest in adults aged 45-74, with over 45% of this age group classified as overweight or obese[4].

Several factors contribute to excess body weight in many patients with obesity. These factors include diet, physical inactivity, medications, abnormal sleep patterns as well as genetic and environmental factors[5]. The interaction of these different factors in an individual contributes

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to the complexity of obesity and makes obesity treatment more challenging. Although efforts to develop and implement policies and interventions to prevent obesity are essential, it is equally important to find effective treatments for people who are already obese or overweight, because obesity is associated with an increased risk of cardiovascular disorders, metabolic disease and risk of cancer[6]. These comorbidities have an impact on the quality of life as well as the level of mortality. According to the data from the global burden of disease (GBD), in 2017, nearly over 4 million deaths globally were linked to a high BMI (> 25 kg/m^2), and most of these deaths were attributed to cardiovascular disease and diabetes[7, 8]. In addition, there is also a psychosocial burden associated with obesity including low mood, body image issues and low self-esteem[9, 10].

Managing obesity is a multidisciplinary task including lifestyle interventions, behavioural therapy, pharmacotherapy, and bariatric/metabolic surgery. The first line treatment of for obesity is lifestyle modifications which include dietary adjustment and an increase in physical activity [11-13]. Additionally, some patients may require cognitive behavioural therapy as an adjunct to the lifestyle intervention[14]. However, these interventions are associated with modest weight loss and most patients tend to regain weight soon after withdrawing from treatment [15-17]. For patients who fail to achieve their treatment goals on lifestyle modifications alone, pharmacotherapy can be effective alone or as an adjunct if patients meet certain criteria[10, 14]. These criteria include but are not the least BMI ≥ 30 kg/m2 or lower (in some ethnic groups) and a BMI of ≥ 27 kg/m2 in the presence of one or more comorbidities such as diabetes and hypertension[14]. The combination of lifestyle modifications and pharmacotherapy is a safe and effective way to treat obesity[18]. However, their effectiveness has been surpassed by bariatric/metabolic surgery which is only indicated if certain criteria were fulfilled. Therefore, in this review, we have aimed to provide a narrative overview of the past, currently available, and future treatment options that offer therapeutic and preventive advantages for obesity management.

2 Method

A systematic and comprehensive search for literature was conducted between June 2023 and 31st of January 2024. All search terms were developed and searched in a combination of title, abstract and Medical Subject Headings (MeSH) for the best possible retrieval of evidence. All publication types and year were included in the search to ensure the best possible literature

were located and no language restriction applied. The search was performed using the electronic databases: PubMed, EMBASE, MEDLINE, Scopus, Cochrane Library (CENTRAL) and Web of Science for all published studies. Moreover, we also searched for grey and unpublished literature using both the Open Grey Repository and Open Thesis Repository databases. Even further, we searched the clinical trial register at European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) and ClinicalTrial.gov for the currently running and future trials.

3 Results

3.1 Current treatment options for obesity management

3.1.1 Orlistat

Orlistat is a derivative of lipstatin which is a potent suppressor to the pancreatic and gastric lipase the enzyme that breaks triglycerides into fatty acids[19]. **Table 1**. It is an effective and well-tolerated obesity treatment which is usually used as adjunct to lifestyle interventions. Several studies have confirmed the efficacy of orlistat as weight loss medication. In a randomised study of 80 patients with obesity who were randomised in two equal groups to receive orlistat 120 mg/TDS or placebo, treatment with orlistat showed significant reduction in body weight compared to placebo (4.65 kgs vs 2.5 kgs, respectively)[20]. Another randomised study of eighty-nine patients with eating disorders who were randomised in a double-blinded fashion to receive either orlistat or placebo for 24-weeks, treatment with orlistat showed significant weight loss compared with placebo (7.4% vs 2.3%, respectively)[21]. Several trials assessed orlistat as an adjunct to diet, exercise and behavioural modification, treatment with orlistat showed statistically significant reduction in the body weight compared with placebo[22]. However, despite its efficacy orlistat has several side effects including nausea, loss of appetite, pale/oily stool, flatulence, and fat-soluble vitamin deficiencies [23, 24].

3.1.2 Cetilistat

Cetilistat is a selective pancreatic lipase inhibitor which was approved in Japan in 2013 for treatment of obesity. It reduces the absorption of fat with same efficiency as the orlistat but with fewer side effects[25]. In phase 2 (dose finding) randomised double blind controlled trial of 371 obese individuals randomised to receive different doses of Cetilistat 60 mg, 120 mg and 240 mg three times a day or placebo for duration of 12 weeks. Cetilistat showed significant

dose dependent weight loss of 3.3 kgs, 3.5 kgs and 4.1 kgs, respectively compared with placebo[26].

3.1.3 Semaglutide

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that stimulates insulin secretion from the pancreas and inhibits glucagon secretion in a glucose-dependent fashion[27, 28]. **Figure 1.** GLP-1 is secreted by the L-cells of the small bowel[29]. The effects of GLP-1 include a reduction of energy intake and hunger as well as the promotion of satiety[30, 31]. Studies in patients with overweight or obesity with or without diabetes have shown that glucagon-like peptide-1 receptor agonists (GLP-1RA) can reduce body weight as well as improve glucose control[32, 33].

Semaglutide is a GLP-1RA that is currently being used in obesity and diabetes treatment. It is a GLP-1 analogue that underwent 3 modifications to give it an extended half-life, making it suitable for once-weekly administration[34]. The first modification was the substitution of an amino acid at position 8. This reduced the susceptibility of Semaglutide to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4)[27]. There is the further substitution of the amino acid at position 34 which is derivatized at Lysine 26[34].

Studies done under the Semaglutide Treatment Effect in People with Obesity (STEP)clinical trial development program, evaluated the effect of 2.4mg once weekly Semaglutide in overweight and obese people. The data from these STEP trials provided the evidence that led to the approval of 2.4mg weekly Semaglutide for use in adults who are obese, or overweight (with weight-related comorbidities)[17]. This approval applies to Europe, the USA, Canada, and the UK[35-37]. STEP trials 1, 3, 4 and 8 reported a mean weight loss of 14.9%-17.4% from baseline to week 68 associated with the use of weekly Semaglutide 2.4mg in patients with overweight or obesity without diabetes[38-41]. In addition, 69%-79% of participants in these 4 trials achieved a weight loss of greater or equal to 10%[17]. Furthermore, the STEP trials demonstrated improvement in waist circumference, and lipid profiles, as well as reduction in blood pressure and C-reactive protein, which are all cardiometabolic risk factors[38-42].

In the UK, the National Institute for Health, and Care Excellence (NICE) released the guidelines for the use of Semaglutide in the management of obesity and overweight. These guidelines, released in March 2023 recommend the use of Semaglutide for a maximum of 2 years for

obesity/overweight. Patients should have one weight-related comorbidity and a body mass index (BMI) of at least 35kg/m^2. Patients with a BMI between 30 and 34.9 kg/m^2, should meet the criteria for referral to a specialist weight management service. It is expected that Semaglutide will be given with a multidisciplinary team weight management service[43].

The OASIS 1 study was a double-blind randomised placebo-controlled trial evaluated the efficacy of the daily oral semaglutide 50 mg for weight loss in overweight and adults with obesity without diabetes. A total of 667 participants were recruited to receive either semaglutide 50 mg/day (n=334) or placebo (n=333) for a total duration of 68 weeks. Treatment with semaglutide showed a significant weight reduction from baseline (-15.1%) compared to placebo (-2.4%). Moreover, a vast majority of the participants on semaglutide (85%) reached 5% weight reduction compared to placebo (26%)[44].

3.1.4 Liraglutide

The Satiety and Clinical Adiposity—Liraglutide Evidence (SCALE) trial is where liraglutide, a glucagon-like peptide-1 analogue was used in a 3 mg subcutaneous weekly dose for a duration of 56 weeks. The trial included a total of 3731 non-diabetic and patients with obesity who were randomised to receive either placebo (n=1244) or liraglutide (n= 2487) in addition to lifestyle intervention. The trial showed that 63.2% of patients who received liraglutide lost around 5% of their body weight compared with 27.1% in the placebo group. Moreover, 33.1% of patients on liraglutide lost around 10% of their initial body weight compared to 10.6% of those on placebo[33]. **Figure 1**.

3.1.5 Tirzepatide

Tirzepatide is a novel dual GLP-1 receptor agonist (RA) and glucose-dependent insulinotropic polypeptide (GIP) with 39 amino acids that act on GLP-1 and GIP receptors. Its half-life is around 5 days which allows it to be used once a week for subcutaneous injection. Recent basic research has shown that GIP receptor agonists induce leptin secretion, activate arcuate nucleus nerves and POMC nerves through a cooperative action with leptin, and suppress feeding[45]. In SURPASS 1-5 trials, the various dosages of Tirzepatide (5 mg, 10 mg and 15 mg) showed significant weight reduction in patients with obesity with type 2 diabetes mellitus (T2DM) particularly when compared with placebo (SURPASS 1), semaglutide 1 mg (SURPASS 2), insulin degludec (SURPASS 3), insulin glargine (SURPASS 4), and with placebo+

insulin glargine (SURPASS 5)[46-50]. The overall weight loss ranged from 7.6 kg, 10.7 kg to 12.9 kg with Tirzepatide 5 mg, 10 mg, and 15 mg, respectively. **Table 1.**

SURMOUNT 1-4 trials were designed to evaluate the effectiveness and the safety of Tirzepatide as an adjunct to lifestyle interventions compared to a placebo in patients with obesity with or without T2DM. In all trials (SURMOUNT 1-4), treatment with Tirzepatide at various dosages was associated with significant body weight reduction ranging between 12-20% compared with placebo (3%) [51-53]. SURMOUNT 5 which is expected to be finished in January 2025 is designed to compare Tirzepatide with Semaglutide 2.4 mg in overweight and adults with obesity with weight-related comorbidities. Tirzepatide is currently approved by the FDA for obesity management.

3.1.6 Phentermine/ topiramate

In 2012 the FDA approved the combination of phentermine/topiramate as an adjunct to dietary intervention and physical activity as a treatment for weight management in overweight and adult with obesity patients. In a clinical trial, a high dose of phentermine/topiramate (15/92 mg) has achieved 9.8-11% of weight loss after 1 year compared to 7.5% with the lower dose (7.5/ 46 mg). In the Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and adults with obesity (CONQUER) trial where low dose (7.5 mg/ 46 mg) phentermine/topiramate was used in 2487 adult with obesity (994 placebo vs 498 phentermine/ topiramate) for 56-weeks. Thus, the results showed significant weight reduction with the combination compared to placebo[54]. Similar results were also observed in the controlled-release phentermine/ topiramate in severely adults with obesity (EQUIP) where adults with obesity were randomised in three arms to receive either placebo (n=514), phentermine/topiramate 3.75 mg/23 mg (n=241) and phentermine/topiramate 15 mg/ 92 mg (n= 512) in conjunction with the standard lifestyle modifications. As a result, after 56 weeks the weight loss was 1.6%, 5.1% and 10.9% in placebo and phentermine/topiramate (3.75/23 mg and 15/92 mg), respectively[55]. However, increased heart rate, mood changes, sleep disorders and gastrointestinal symptoms were amongst the most common adverse events reported with the phentermine/topiramate use[1]. Thus, few countries have denied marketing authorisation for this combination based on their adverse effects. **Figure 1.**

3.1.7 Naltrexone/ Bupropion

Naltrexone is an opioid antagonist which is approved by the FDA for manging alcohol and opioid dependency. On the other hand, bupropion is an antidepressant works centrally and approved by the FDA for manging major depressive disorders and to support smoking cessation[56]. The combination of naltrexone/bupropion is approved by the FDA for obesity management. Their exact mechanism of action leading to weight loss is yet to be fully understood; however, data form preclinical studies hypothesised that the combined therapy work centrally in the hypothalamus to promote satiety and subsequently reduce food intake[57]. They are effective when they used as add-on to lifestyle modification in overweight or obese subjects. Their efficacy has been examined in several clinical studies. The Contrave Obesity Research-I (COR-I) study, the Contrave Obesity Research-II (COR-II) study, the Contrave Obesity Research-Diabetes study (COR-Diabetes), and the Contrave Obesity Research-Intensive Behaviour Modification (COR-BMOD) study were multi-centre randomised, double-blind, placebo-controlled phase-3 clinical trials included over 4000 overweight and obese participants with and without diabetes for 56 weeks[58-61]. All trials showed statistically significant weight loss ranging between 5.4 – 8.1 kgs in patients treated with the combination compared with 1.3 kg in placebo group. **Figure 1.**

3.2 Current treatment options for syndromic obesity

3.2.1 Setmelanotide

Setmelanotide is an anorexigenic drug that acts as a melanocortin-4 receptor (MC4R) agonist approved by the FDA in 2020 for the management of genetic obesity. It helps restore appetite control but did not treat those hereditary defects that lead to obesity[1]. Setmelanotide is indicated in patients with obesity due to the deficiency in the pro-opiomelanocortin (POMC), Leptin receptors (LEPR) and proprotein convertase subtilisin/kexin type 1 (PCSK1). Thus, it was approved for patients over 6 years of age with approved genetic defects. Appetite is controlled by the satiety centre in the brain which is itself regulated by the regulatory hormone leptin. Leptin acts centrally in the hypothalamus by binding to its receptors on the POMC expression neurons and regulates satiety, appetite, and energy expenditure; therefore, defect in activating the MC4R due to POMC, PCSK1 and LEPR is a leading cause of hyperphagia and subsequent obesity. Thus, setmelanotide can restore the defect in these pathways and thereby reduce appetite, enhance satiety and induce energy expenditure[62]. **Table 1.**

3.2.2 Metreleptin

Leptin is a hormone produced by the adipose tissues and its primary role is to regulate energy balance by influencing appetite, and satiety and managing behavioural feeding. Metreleptin is a leptin analogue, and it was approved by the FDA back in 2014 as a substitute for deficient leptin in patients with lipodystrophy, its route of administration is subcutaneously daily at starting dose of 0.03 mg/kg[1]. In a non-randomised crossover trial of 25 patients with lipodystrophy, treatment with Metreleptin for six months was associated with a significant reduction in resting and total energy expenditure six. Also, it improved the metabolic parameters and increased the bioactive thyroid hormone (FreeT3)[63]. Moreover, the beneficial effect was also observed in improving insulin resistance, liver steatosis and hypogonadism[64]. However, leptin has a recently noticeable adverse effect including the development of leptin antibodies which has a nullified effect on leptin administration. There were also three reported cases of T-cell lymphoma which indicate further future studies to understand its possible causal effect[65]. **Table 1.**

3.3 Therapeutic agents currently under investigation

3.3.1 Bimagrumab

Bimagrumab is a monoclonal antibody that targets activin receptor type II (ActRII). It binds to ActRII receptors and this blocks the natural ligands that are known to negatively impact skeletal muscle growth[66]. The role of activin signalling and its blockade by Bimagrumab has previously been studied as a potential treatment for sporadic myositis. In a pilot trial, inhibition of ActRII increased muscle mass and function[67]. In a study looking at cast-inducing disuse atrophy in healthy young men, Bimagrumab led to fast recovery of thigh muscle volume and reversal of inter-muscular adipose tissue following a single intravenous dose[68]. A study done in mice showed that inhibition of ActRIIB increased the amount of brown adipose tissue independent of white adipose tissue. As a result, ActRIIB blockade in the brown adipose tissue increases mitochondrial function and uncoupled respiration. This ultimately increases energy expenditure[69]. Another study in mice involving chemical disruption of ActRIIB signalling showed reduced fat content, increased skeletal muscle mass, and enhanced insulin sensitivity, thereby signalling its potential role in the treatment of obesity and insulin resistance[70]. A ten-week trial of obese participants with insulin resistance showed a reduction in fat mass (7.9%), and glycated haemoglobin (HbA1c) by 0.21% at week 18 and improved insulin sensitivity[71]. Relatedly, Bimagrumab has been shown to cause a 20.5%

reduction in fat mass when compared to placebo in patients with obesity with type 2 diabetes. In addition, this 48-week phase II trial reported a significant gain in lean mass and improvements in metabolic components (HbA1C, waist circumference) over the same period[72]. The most reported side effects of Bimagrumab are mild diarrhoea and muscle spasms[10]. In addition, in older participants, one study reported a 19% occurrence of respiratory tract infections following the administration of Bimagrumab[73]. Cases of raised pancreas and liver enzymes have also been reported[72]. Although safety and tolerability in this trial were comparable to prior Bimagrumab trials, safety will need to be evaluated further in subsequent trials[66]. **Figure 1.**

3.3.2 Retatrutide

Retatrutide is a triple hormone agonist of GLP-1, GIP, and glucagon receptors currently in phase 2 clinical trials showing a promising significant weight loss with 4 mg, 8 mg and 12 mg dosages and the. In phase 2 double-blind randomised placebo-controlled trial of 338 adults with obesity with an average BMI > 30 kg/m^2 or with BMI < 30 kg/m^2 and at least one obesity-related condition. Patients were randomised to receive retatrutide or a placebo once weekly for 48 weeks. By the end of the trial patients who received retatrutide had lost significant weight ranging from 7.2% to 17.5% compared to 1.6% in the placebo group. A gastrointestinal adverse event was higher with retatrutide; however, it has a great potential for weight loss[74]. **Table 1.**

3.3.3 Cagrilintide

Cagrilintide is an amylin analogue that acts centrally to reduce appetite and peripherally to slow gastric emptying. Amylin is a 37-amino acid peptide that is co-secreted with insulin from the pancreatic β-cells. It is currently being investigated in phase 2 and phase 3 (CagriSema) clinical trials for the management of obesity compared with liraglutide and Semaglutide, respectively. However, in a previous multi-centre double-blind randomised placebo-controlled clinical trial 706 participants were assigned to receive cagrilintide, 99 received liraglutide and 101 received a placebo for 26 weeks. Treatment with cagrilintide showed greater weight reduction (11.5 kg) compared to liraglutide (9.6 kg) and placebo (3.3 kg) and the common side effects of amylin analogue are nausea, vomiting, and headache [75, 76]. **Table 1.**

3.3.4 Orforglipron

Orforglipron is an investigational product, and it is a nonpeptide oral GLP-1 agonist being currently studied as a potential medication for weight management in overweight and patients with obesity as well as diabetes medication. Currently, Orforglipron is in phase 2 clinical trial and showed promising results[77]. In this phase 2 randomised double-blind clinical trial a total of 272 overweight and obese participants were enrolled to receive either orforglipron 12, 24, 36 or 48 mg or placebo for 36 weeks. By the end of the study, the mean changes in body weight from baseline ranged from -8.6% to 12.6% across orforglipron doses compared to only -2% in the placebo group[78].

3.4 Potential therapeutic agents currently on the horizon

3.4.1 Methylphenidate

Methylphenidate is a central nervous system stimulant that is used in the management of attention deficit hyperactivity disorder (ADHD), it inhibits the reuptake of dopamine and subsequently reduces food intake. **Figure 2**. In a study where nine obese men ingested methylphenidate in lower and higher dosages (0.5 mg/kg and 1.0 mg/kg, respectively) or placebo. There was a significant reduction in the food intake (23%) with methylphenidate compared to placebo[79]. A prospective study of 78 adults with ADHD and severe obesity who received methylphenidate with other psychiatric stimulants showed significant weight loss (12%) after 466 days from the intervention[80]. Currently, in a phase 3 randomised placebo-controlled trial comparing methylphenidate in obese adolescents and young adults, their primary outcome was the effect of energy expenditure and the effect on weight was a secondary outcome. However, even though the expected date of completion was passed no data was released yet[1].

3.4.2 Tesofensine

Tesofensine is a noradrenaline, dopamine and serotonin reuptake inhibitor used to suppress appetite. In phase 2 randomised, double-blind placebo-controlled trial where 203 patients with obesity were randomised to receive either tesofensine 0.25 mg, 0.5 mg, or 1.0 mg once daily for 24 weeks. By the end of the study tesofensine at the various dosage showed significant weight loss (4.5%, 9.2% and 10.6%, respectively) compared to placebo (2%)[81]. The Viking study is a phase 3 randomised, double-blind, placebo-controlled clinical trial of tesofensine in 372 patients with obesity where they were randomised to receive tesofensine 0.25 mg or 0.5 mg and placebo for 24 weeks. The preliminary results showed significant

weight loss at around 10% with tesofensine. However, the data from this study have not been made publicly available[1]. **Figure 2.**

3.4.3 Diazoxide Choline

Diazoxide is a potent adenosine triphosphate-sensitive potassium (K_{ATP}) channel activator that can cross the brain-blood barrier. It acts centrally by activating the K_{ATP} channel in neuropeptide Y (NPY) resulting in reduced NPY secretion. NYP is a potent appetite stimulatory neuropeptide in the hypothalamus and inhibiting NPY is potentially contributing to the reduction in food intake. Activating the K_{ATP} channel has also been shown to improve insulin and leptin resistance[82]. Prader-Willi Syndrome (PWS) is a rare neurobehavioral metabolic disorder caused by the lack of the paternally expressed chromosome 15q11-q13 and characterised by hyperphagia and excess body weight[83]. Phase 3 randomised, double-blind, placebo-controlled clinical trial where 127 participants aged 4 years and above were randomised to receive either Diazoxide or a placebo for 13 weeks. By the end of the study patients on the diazoxide arm showed significant improvement of the hyperphagia compared to placebo which could potentially leads to weight loss[84]. **Figure 2.**

3.4.4 Glabridin analogues

Glabridin is a natural compound found in liquorice root[85]. It is a prenylated polyphenolic isoflavone which has anti-inflammatory and anti-oxidative properties[86, 87]. In addition, because the mechanism of formation of atheroma involves oxidation, this anti-oxidative effect of glabridin may be beneficial in the prevention of atherosclerosis[85]. The role of glabridin in obesity management comes from its potential to enhance energy expenditure[86]. A study done in diabetic; obese mice showed that glabridin (as the main flavonoid in liquorice) lowered abdominal fat in addition to hypoglycaemic effects. These effects are thought to be medicated through peroxisome proliferator-activated receptor gamma[88]. Another pre-clinical trial in obese mice showed that glabridin decreased food intake which resulted in approximately 25% weight loss[86, 89]. In addition, this study demonstrated an increase in body temperature which may imply that glabridin plays a role in stimulating energy expenditure in these obese mice. Other metabolic benefits demonstrated in this study included improvement in fatty liver as well as relief in hepatic dysfunction in mice fed on a high fat diet[89]. Relatedly, liquorice flavonoid oil (LFO) given to high-fat diet-induced obese mice prevented and improved obesity in these animals. These effects were thought to be

through regulation of gene expression in the liver, related to lipid metabolism[90]. Glabridin is unstable and has a low bioavailability and this has hindered its development as a therapeutic drug [91, 92]. Derivatives and analogues of glabridin are currently being investigated since their anti-obesity properties remain unknown. One synthetic glabridin analogue called HSG4112 has shown preclinical efficacy in obesity. It demonstrated potent effects in enhancing energy expenditure as well as controlling appetite[86]. HSG4112 is currently in phase 1 clinical trial. Further studies on its effects in humans will provide more insight into its role in treating metabolic diseases. **Figure 2**.

3.4.5 Survodutide (BI 456906)

The endogenous gut peptide hormone, oxyntomodulin, weakly activates the glucagon receptor as well as glucagon-like peptide-1 receptor (GLP-1R) simultaneously[93]. **Figure 2.** When used in overweight and obese volunteers, oxyntomodulin was shown to reduce energy intake while at the same time increasing energy expenditure[94]. This leads to a negative energy balance. This concept may provide a solution to the problem of continued adaptation during weight loss, where reduced intake causes a reduction in energy expenditure, that favours weight gain[93]. In a double-blind randomised, controlled trial, oxyntomodulin showed a 2.3kg reduction in body weight compared to the control group, when administered for 4 weeks[95].

Survodutide (BI 456906) is a potent and selective synthetic Glucagon receptor (GCGR)/ Glucagon-like peptide-1 (GLP-1) duo agonist. It is currently in a phase II clinical trial for non-alcoholic steatohepatitis, type 2 diabetes, and obesity. It is administered as a weekly injection. Preclinical data in obese mice shows that survodutide causes a reduction in body weight through various mechanisms including reduced food intake, inhibition of gastric emptying, as well as an increase in energy expenditure thus creating a negative energy balance. Interestingly, the balanced duo agonism maintains normal glycaemia in these animals[93]. A phase II, randomised, double-blind, placebo-controlled trial of BI 456906 (survodutide) involved 387adults with a body mass index of 27 or more, randomised to different weekly doses (0.6,2.4,3.6,4.8mg) of BI 456906 or placebo for 46weeks. The results showed that the mean body weight lost was dose dependent. There was -6.2%, -12.5%, -13.2% and -14.9% reduction in mean body weight achieved by 0.6, 2.4,3.6 and 4.8 mg doses respectively,

compared to -2.8% reduction in the placebo arm[96]. Further results and analysis from these trials are awaited. **Table 1.**

3.4.6 Taste receptor activators.

Identifying nutritional or potentially toxic substances is a key function of taste perception and has a role in the choice of food intake and behaviour. Thus, taste receptors have been considered potential targets for obesity therapy[97]. Type 2 taste receptors (T2R) are G protein-coupled receptors and are responsible for bitter taste perception and there are 25 different subtypes in humans, with receptor activation in the mouth, gastrointestinal tract and enteroendocrine cells[98]. Their function is still not wholly understood but they appear to play a role in energy homeostasis and innate immunity; alongside bronchodilation and mucus clearance, inhibition of thyroid stimulating hormone, muscle relaxation, ghrelin, and GLP-1 release[99]. ARD-101 is a first-in-class TAS2R agonist developed by Aardvark Therapeutics, it is taken orally and acts and remains in the gut with systemic effects of GLP-1, GLP-2 and CCK activation[100]. ARD-101 has undergone phase 2 trials focused on obesity, outcomes following bariatric/metabolic surgery and Prader-Willi Syndrome. Unpublished data from the open-label obesity trial showed that those on ARD-101 had a hunger rating score 2.5 times less than the control when measured by the Control of Eating Questionnaire (COEQ) (P 0.015), with a reduction in hunger scores and cravings for both sweet and savoury foods in 11 individuals who gained weight after bariatric/metabolic surgery. In an open-label trial looking at the effects of ARD-101 in Prader-Willi Syndrome, unpublished data showed that 11 of the 12 participants experienced reduced hyperphagia at 28 days, as measured by the HQ-CT (Hyperphagia Questionnaire for Clinical Trials)[100]. ARD-101 was not associated with significant gastrointestinal side effects, such as nausea and diarrhoea, and has anti-inflammatory properties, unlike GLP-1 agonists[98]. Further research is currently being undertaken to look at T2R's role in other clinical areas, such as respiratory and neurological disease, and if it could be used in conjunction with genetics for future personalised medicine[99, 101]. There is also great interest in utilising this compound to make commonly utilised drugs more palatable[99].

Lingual CD36 and GPR120 are fat taste receptors on the tongue and play a role in adipogenesis, appetite homeostasis and the preferential intake of lipids in the diet[102]. GPR120 is a long-chain fatty acid receptor and is thought to have a role in GLP-1 secretion, sensitivity to insulin

and inflammatory processes[103]. CD36 is a glycoprotein that has a role in fat storage alongside lingual fat perception[102]. Murine studies have shown reduced food intake and weight loss when compared to control with CD36 and GPR120 agonists[102, 104]. Reduced expression of GPR120 in mice leads to glucose intolerance, obesity, and organ adiposity with increased levels of expression seen in humans with obesity[105]. However, there are currently no human trials utilising the role of CD36 or GPR120 as there is currently a lack of suitable receptor modulators[103]. **Figure 2.**

3.4.7 Leptin sensitizers

Leptin is a satiety hormone released from fat cells and is key for energy homeostasis[106]. Previous mice and human models have shown that exogenous application of leptin does not increase satiety or lead to weight loss[107]. The general obese population have high levels of leptin, suggesting it is not leptin deficiency but leptin resistance that is associated with obesity[106]. ERX pharmaceuticals have developed ERX-1000, a first-in-class leptin sensitizer, which has just completed its first human phase 1 double-blinded, placebo-controlled, single, and multiple oral dose trial in participants with and without obesity. Unpublished murine models have shown ERX-1000 to result in a marked appetite reduction of 80 per cent and weight loss of 45 per cent with no reduction in muscle mass. Murine models showed improved glucose homeostasis, insulin sensitivity, hepatic steatosis, and liver enzymes[108]. Unpublished preliminary clinical data have shown a dose-dependent weight loss over four weeks suggesting ERX-1000 is an efficacious treatment for obesity in humans alongside potential beneficial effects on insulin and glucose homeostasis[108]. EXR-2000 is an analogue of ERX-1000 and has shown promising anti-diabetic and anti-obesity properties in animal models.

Multiple other leptin sensitizers have shown efficacy in mice studies but have not yet been tested on humans. Withaferin-A is a leptin sensitizer that was identified using gene expression profiling. Diet-induced obese leptin-resistant mice treated with withaferin A had a 23 per cent body weight loss and 62 reduced food intake after 21 days, this was alongside a 35 per cent reduction in fat mass and reduced hepatic steatosis compared to control. This effect diminished as leptin levels normalised and was absent in those with leptin deficiency or absent leptin receptors, signifying withaferin A as a leptin sensitizer. Withaferin A was also found to

have beneficial effects on glucose homeostasis regardless of leptin status[107]. No human trials have been undertaken with withaferin A.

Celastrol is a phytochemical found in the thunder god vine. It has been shown to reduce food intake and body weight in diet-induced obese mice with no effect on lean mice with disrupted leptin signalling, suggesting its role as a leptin sensitizer[108]. More recently it has been shown that celastrol reduces food intake and improves glucose control with no associated effect on energy expenditure when given to aged obese mice. However, it was seen that administration of celastrol just before the 'dark period' resulted in disrupted circadian rhythm and lean muscle loss. Further research is needed to determine celastrol's possible clinical relevance due to its restricted bioavailability, insolubility, and narrow therapeutic index[109]. Other leptin sensitizers which are currently being investigated in mice include sulforaphane betulinic acid, Rutundic acid R, 1,3-butanediol, and meta-chlorophenylpiperazine [110-114].

3.5 Historical therapeutic agents for obesity management

3.5.1 Sibutramine

Sibutramine is a medication that works as an appetite suppressant and is often used alongside diet and exercise to manage obesity. It functions as a serotonin-norepinephrine reuptake inhibitor, reducing the reuptake of neurotransmitters like serotonin, noradrenaline and dopamine[115]. This leads to a reduction in appetite and subsequently, food consumption[116]. However, despite its effectiveness, sibutramine has been associated with significant cardiovascular events and strokes, which led to its withdrawal from the market in 2010 due to safety concerns[117]. **Figure 1.**

3.5.2 Fenfluramine

Fenfluramine is a serotonergic medication which has gained popularity as an appetite suppressant. It was used in France as an antidepressant then later as a weight loss medication. By early 1970 it was approved in the United State for obesity management, but it has never gained popularity due to its severe side effects. To lessen its side effect and to increase its potency it was combined with phentermine which was become known as fen-phen during the 1990[118]. In a double-blind controlled trial using fenfluramine alone and in combination with phentermine in 80 patients with obesity for a duration of 24 weeks and compared with placebo. There was a significant weight loss in the fenfluramine and phentermine group than in placebo group (8.4 kgs vs 4.4 kgs)[119]. **Figure 1.**

3.5.3 Rimonabant

Rimonabant is a medication used to treat obesity via selectively blocking the cannabinoid receptor 1 (CB1), thus reducing appetite[120]. Figure 1. A recent study found that rimonabant could significantly reduce alanine aminotransferase (ALT) and weight in obese women with polycystic ovary syndrome (PCOS) who did not have non-alcoholic fatty liver disease (NAFLD) [121]. Another trial compared rimonabant to metformin for treating obese women with PCOS and found that rimonabant increased glucose-dependent insulinotropic polypeptide (GIP) after three months of treatment, while metformin did not[122]. Rimonabant also helped women lose weight and improved their metabolic health when combined with metformin treatment[123]. In comparison, rimonabant was found to be more effective than metformin in reducing weight, improving insulin resistance, and lowering androgen levels in women with PCOS[124]. However, it is important to note that rimonabant has been associated with severe psychiatric problems, such as depressive disorders, mood changes, and suicidal ideation[125]. Due to these side effects, rimonabant has been withdrawn from the market.

3.5.4 Lorcaserin

Lorcaserin, a weight loss medication, was approved by the Food and Drug Administration (FDA) for obesity management in patients with BMI > 30 kg/m2 or with BMI < 27 kg/m2 and diabetes, dyslipidaemia, or hypertension. It activated the serotonin receptor (5-HT_{2c}) in the hypothalamus to suppress appetite and was associated with significant weight loss ranging from 3-5% when used alone or added to diet and exercise interventions[126, 127]. However, due to serious concerns about cancer, the FDA requested its withdrawal from the market in 2020[128]. **Figure 1.**

3.5.5 Mazindol

Mazindol is a noradrenergic or sympathomimetic agent that acts by releasing and blocking the reuptake of dopamine and noradrenaline. This mechanism makes it an effective anorectic drug, suppressing appetite. While Mazindol is effective in treating cataplexy and narcolepsy, its significant side effects have limited its popularity[129]. In a double-blind randomized trial involving 46 patients with obesity with T2DM, participants were randomized to receive either mazindol 2 mg/day or placebo for 12 weeks. The study found a significant weight loss of approximately 13.5 kg in the mazindol-treated group compared to 4.2 kg in the placebo group [130].

3.6 Conclusion

There is a wide range of therapeutic options with potential advantages available for the management of obesity. However, we must appreciate each agent's efficacy and safety profile while prescribing them to the patient. Acknowledging that no single agent can be completely effective without considering other factors such as affordability, adherence, and the patient's willpower is imperative. Generally, the combination of medical intervention in addition to lifestyle modification was more successful than medical therapy alone. For instance, GLP-1 RAs and the newer dual GLP-1/ GIP agonist were very promising therapeutic agents with greater potential advantages in reducing weight and improving other metabolic parameters. Several therapeutic agents are emerging with even greater potential for weight reduction; however, more clinical trials are needed to evaluate their cardiovascular safety profiles.

3.7 Expert opinion

Recent advances in obesity management research can have a significant impact on real-world outcomes by providing more effective and personalized treatment strategies. New research may lead to updated diagnosis criteria and treatment guidelines, potentially reducing the economic burden of obesity-related healthcare costs. For instance, the newer dual GLP-1 RA/GIP agonist which has shown a remarkable weight loss efficacy and other several medications are currently in the pipeline will drastically change our perspective on the management of obesity. However, implementation into clinical practice may be hindered by factors like resistance to change, resource limitations, and healthcare policy constraints. On the other hand, key areas for improvement in obesity management include developing more effective and sustainable interventions, addressing the complexity of obesity as a multifactorial condition, and reducing disparities in access to care. Moreover, challenges such as limited long-term success in weight loss, psychological factors, and the need for individualized approaches remain. However, advancements in technology, genetics, and a deeper understanding of metabolic processes may help overcome some of these limitations. Further research in obesity management holds the potential to continually refine our understanding and approaches to this complex condition. While there may never be a definitive endpoint, ongoing research can lead to more tailored and successful treatments, improved prevention strategies, and a better grasp of obesity's long-term health effects. Obesity management remains a promising area for future study, given its global impact on public health. However, it's essential to continue exploring other areas within the field of

health and wellness as well, such as preventive health, mental health, and emerging health technologies. In the next five to ten years, the field of obesity management is likely to become more personalized, incorporating genetic and metabolic data into treatment plans. Telehealth and digital health tools may play a more prominent role in monitoring and support. There may be a shift towards a greater focus on long-term health outcomes and addressing obesity-related comorbidities. Some current norms, such as one-size-fits-all approaches, could be challenged, and a greater emphasis on holistic, patient-centered care may emerge. However, it's challenging to predict specific changes with certainty due to the dynamic nature of healthcare.

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3.9 Conflict of interest

None.

3.10 References

1. Chakhtoura, M., et al., *Pharmacotherapy of obesity: an update on the available medications and drugs under investigation.* EClinicalMedicine, 2023. **58**: p. 101882.
2. Fruh, S.M., *Obesity: Risk factors, complications, and strategies for sustainable long-term weight management.* J Am Assoc Nurse Pract, 2017. **29**(S1): p. S3-S14.
3. Collaboration, N.C.D.R.F., *Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults.* Lancet, 2017. **390**(10113): p. 2627-2642.
4. Public Health England. *Patterns and trends in adult obesity*. [cited 2023 29 March 2023]; Available from: https://fingertips.phe.org.uk/profile/national-child-measurement-programme/data#page/13/.
5. Ahmad, N.N., W.S. Butsch, and S. Aidarous, *Clinical Management of Obesity in Women: Addressing a Lifecycle of Risk.* Obstet Gynecol Clin North Am, 2016. **43**(2): p. 201-30.
6. Guh, D.P., et al., *The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis.* BMC Public Health, 2009. **9**: p. 88.
7. Collaborators, G.B.D.O., et al., *Health Effects of Overweight and Obesity in 195 Countries over 25 Years.* N Engl J Med, 2017. **377**(1): p. 13-27.
8. Dai, H., et al., *The global burden of disease attributable to high body mass index in 195 countries and territories, 1990-2017: An analysis of the Global Burden of Disease Study.* PLoS Med, 2020. **17**(7): p. e1003198.
9. Sarwer, D.B. and H.M. Polonsky, *The Psychosocial Burden of Obesity.* Endocrinol Metab Clin North Am, 2016. **45**(3): p. 677-88.
10. Angelidi, A.M., et al., *Novel Noninvasive Approaches to the Treatment of Obesity: From Pharmacotherapy to Gene Therapy.* Endocr Rev, 2022. **43**(3): p. 507-557.
11. Garvey, W.T., et al., *American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity.* Endocr Pract, 2016. **22 Suppl 3**: p. 1-203.
12. Durrer Schutz, D., et al., *European Practical and Patient-Centred Guidelines for Adult Obesity Management in Primary Care.* Obes Facts, 2019. **12**(1): p. 40-66.
13. Jensen, M.D., et al., *2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society.* J Am Coll Cardiol, 2014. **63**(25 Pt B): p. 2985-3023.
14. Yumuk, V., et al., *European Guidelines for Obesity Management in Adults.* Obes Facts, 2015. **8**(6): p. 402-24.
15. Wadden, T.A., J.S. Tronieri, and M.L. Butryn, *Lifestyle modification approaches for the treatment of obesity in adults.* Am Psychol, 2020. **75**(2): p. 235-251.
16. Sumithran, P., et al., *Long-term persistence of hormonal adaptations to weight loss.* N Engl J Med, 2011. **365**(17): p. 1597-604.
17. Bergmann, N.C., et al., *Semaglutide for the treatment of overweight and obesity: A review.* Diabetes Obes Metab, 2023. **25**(1): p. 18-35.

18. Kushner, R.F., *Weight Loss Strategies for Treatment of Obesity: Lifestyle Management and Pharmacotherapy.* Prog Cardiovasc Dis, 2018. **61**(2): p. 246-252.
19. Johnson, S. and S.M. Schwartz, *Pharmacologic and Pharmacodynamic Equivalence of 2 Formulations of Orlistat.* Clin Pharmacol Drug Dev, 2018. **7**(7): p. 773-780.
20. Jain, S.S., et al., *Evaluation of efficacy and safety of orlistat in obese patients.* Indian J Endocrinol Metab, 2011. **15**(2): p. 99-104.
21. Golay, A., et al., *Effect of orlistat in obese patients with binge eating disorder.* Obes Res, 2005. **13**(10): p. 1701-8.
22. Chanoine, J.P., et al., *Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial.* JAMA, 2005. **293**(23): p. 2873-83.
23. Kujawska-Luczak, M., et al., *The influence of orlistat, metformin and diet on serum levels of insulin-like growth factor-1 in obeses women with and without insulin resistance.* J Physiol Pharmacol, 2018. **69**(5).
24. McDuffie, J.R., et al., *Effects of orlistat on fat-soluble vitamins in obese adolescents.* Pharmacotherapy, 2002. **22**(7): p. 814-22.
25. Padwal, R., *Cetilistat, a new lipase inhibitor for the treatment of obesity.* Curr Opin Investig Drugs, 2008. **9**(4): p. 414-21.
26. Kopelman, P., et al., *Cetilistat (ATL-962), a novel lipase inhibitor: a 12-week randomized, placebo-controlled study of weight reduction in obese patients.* Int J Obes (Lond), 2007. **31**(3): p. 494-9.
27. Blundell, J., et al., *Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity.* Diabetes Obes Metab, 2017. **19**(9): p. 1242-1251.
28. Donath, M.Y. and R. Burcelin, *GLP-1 effects on islets: hormonal, neuronal, or paracrine?* Diabetes Care, 2013. **36 Suppl 2**(Suppl 2): p. S145-8.
29. Hjerpsted, J.B., et al., *Semaglutide improves postprandial glucose and lipid metabolism, and delays first-hour gastric emptying in subjects with obesity.* Diabetes Obes Metab, 2018. **20**(3): p. 610-619.
30. Flint, A., et al., *Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans.* J Clin Invest, 1998. **101**(3): p. 515-20.
31. Gutzwiller, J.P., et al., *Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2.* Am J Physiol, 1999. **276**(5): p. R1541-4.
32. Nauck, M., et al., *Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study.* Diabetes Care, 2009. **32**(1): p. 84-90.
33. Pi-Sunyer, X., et al., *A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management.* N Engl J Med, 2015. **373**(1): p. 11-22.
34. Lau, J., et al., *Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide.* J Med Chem, 2015. **58**(18): p. 7370-80.
35. European Medicines Agency. *Wegovy – summary of product characteristics*. [cited 2023 20 April 2023]; Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/wegovy.
36. Health Canada. *Wegovy – product monograph.* [cited 2023 20 April 2023]; Available from: https://health-products.canada.ca/dpd-bdpp/info?lang=eng&code=101167.
37. Medicines & Healthcare Products Regulatory Agency. *Wegovy 2.4 mg, solution for injection in pre-filled pen – summary of product characteristics*. [cited 2023 20 April 2023]; Available from: https://mhraproducts4853.blob.core.windows.net/docs/04bd114b87aac3b439436d9317d836ef2b400ea9.
38. Wilding, J.P.H., et al., *Once-Weekly Semaglutide in Adults with Overweight or Obesity.* N Engl J Med, 2021. **384**(11): p. 989-1002.

39. Wadden, T.A., et al., *Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial.* JAMA, 2021. **325**(14): p. 1403-1413.
40. Rubino, D., et al., *Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial.* JAMA, 2021. **325**(14): p. 1414-1425.
41. Rubino, D.M., et al., *Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial.* JAMA, 2022. **327**(2): p. 138-150.
42. Davies, M., et al., *Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial.* Lancet, 2021. **397**(10278): p. 971-984.
43. National Institute for Health and Care Excellence. *Semaglutide for managing overweight and obesity*. [cited 2023 28 April 2023]; Available from: https://www.nice.org.uk/guidance/ta875/resources/semaglutide-for-managing-overweight-and-obesity-pdf-82613674831813.
44. Knop, F.K., et al., *Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet, 2023. **402**(10403): p. 705-719.
45. Han, W., et al., *Glucose-dependent insulinotropic polypeptide counteracts diet-induced obesity along with reduced feeding, elevated plasma leptin and activation of leptin-responsive and proopiomelanocortin neurons in the arcuate nucleus.* Diabetes Obes Metab, 2023. **25**(6): p. 1534-1546.
46. Rosenstock, J., et al., *Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial.* Lancet, 2021. **398**(10295): p. 143-155.
47. Frias, J.P., et al., *Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes.* N Engl J Med, 2021. **385**(6): p. 503-515.
48. Ludvik, B., et al., *Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial.* Lancet, 2021. **398**(10300): p. 583-598.
49. Del Prato, S., et al., *Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial.* Lancet, 2021. **398**(10313): p. 1811-1824.
50. Dahl, D., et al., *Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial.* JAMA, 2022. **327**(6): p. 534-545.
51. Jastreboff, A.M., et al., *Tirzepatide Once Weekly for the Treatment of Obesity.* N Engl J Med, 2022. **387**(3): p. 205-216.
52. Garvey, W.T., et al., *Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial.* Lancet, 2023.
53. le Roux, C.W., et al., *Tirzepatide for the treatment of obesity: Rationale and design of the SURMOUNT clinical development program.* Obesity (Silver Spring), 2023. **31**(1): p. 96-110.
54. Kelly, A.S., et al., *Phentermine/Topiramate for the Treatment of Adolescent Obesity.* NEJM Evid, 2022. **1**(6).
55. Allison, D.B., et al., *Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP).* Obesity (Silver Spring), 2012. **20**(2): p. 330-42.
56. Sherman, M.M., S. Ungureanu, and J.A. Rey, *Naltrexone/Bupropion ER (Contrave): Newly Approved Treatment Option for Chronic Weight Management in Obese Adults.* P T, 2016. **41**(3): p. 164-72.

57. Billes, S.K. and F.L. Greenway, *Combination therapy with naltrexone and bupropion for obesity.* Expert Opin Pharmacother, 2011. **12**(11): p. 1813-26.
58. Greenway, F.L., et al., *Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet, 2010. **376**(9741): p. 595-605.
59. Apovian, C.M., et al., *A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II).* Obesity (Silver Spring), 2013. **21**(5): p. 935-43.
60. Hollander, P., et al., *Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes.* Diabetes Care, 2013. **36**(12): p. 4022-9.
61. Wadden, T.A., et al., *Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial.* Obesity (Silver Spring), 2011. **19**(1): p. 110-20.
62. Jeong, D. and R. Priefer, *Anti-obesity weight loss medications: Short-term and long-term use.* Life Sci, 2022. **306**: p. 120825.
63. Grover, A., et al., *Leptin Decreases Energy Expenditure Despite Increased Thyroid Hormone in Patients With Lipodystrophy.* J Clin Endocrinol Metab, 2021. **106**(10): p. e4163-e4178.
64. Hinney, A., A. Korner, and P. Fischer-Posovszky, *The promise of new anti-obesity therapies arising from knowledge of genetic obesity traits.* Nat Rev Endocrinol, 2022. **18**(10): p. 623-637.
65. Tsoukas, M.A., O.M. Farr, and C.S. Mantzoros, *Leptin in congenital and HIV-associated lipodystrophy.* Metabolism, 2015. **64**(1): p. 47-59.
66. Ryan, D.H., *Next Generation Antiobesity Medications: Setmelanotide, Semaglutide, Tirzepatide and Bimagrumab: What do They Mean for Clinical Practice?* J Obes Metab Syndr, 2021. **30**(3): p. 196-208.
67. Amato, A.A., et al., *Treatment of sporadic inclusion body myositis with bimagrumab.* Neurology, 2014. **83**(24): p. 2239-46.
68. Rooks, D.S., et al., *Effect of bimagrumab on thigh muscle volume and composition in men with casting-induced atrophy.* J Cachexia Sarcopenia Muscle, 2017. **8**(5): p. 727-734.
69. Fournier, B., et al., *Blockade of the activin receptor IIb activates functional brown adipogenesis and thermogenesis by inducing mitochondrial oxidative metabolism.* Mol Cell Biol, 2012. **32**(14): p. 2871-9.
70. Akpan, I., et al., *The effects of a soluble activin type IIB receptor on obesity and insulin sensitivity.* Int J Obes (Lond), 2009. **33**(11): p. 1265-73.
71. Garito, T., et al., *Bimagrumab improves body composition and insulin sensitivity in insulin-resistant individuals.* Diabetes Obes Metab, 2018. **20**(1): p. 94-102.
72. Heymsfield, S.B., et al., *Effect of Bimagrumab vs Placebo on Body Fat Mass Among Adults With Type 2 Diabetes and Obesity: A Phase 2 Randomized Clinical Trial.* JAMA Netw Open, 2021. **4**(1): p. e2033457.
73. Rooks, D., et al., *Safety and pharmacokinetics of bimagrumab in healthy older and obese adults with body composition changes in the older cohort.* J Cachexia Sarcopenia Muscle, 2020. **11**(6): p. 1525-1534.
74. Jastreboff, A.M., et al., *Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial.* N Engl J Med, 2023.
75. Lau, D.C.W., et al., *Once-weekly cagrilintide for weight management in people with overweight and obesity: a multicentre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial.* Lancet, 2021. **398**(10317): p. 2160-2172.
76. Adeghate, E. and H. Kalasz, *Amylin analogues in the treatment of diabetes mellitus: medicinal chemistry and structural basis of its function.* Open Med Chem J, 2011. **5**(Suppl 2): p. 78-81.
77. Sidik, S., *Beyond Ozempic: brand-new obesity drugs will be cheaper and more effective.* Nature, 2023.

78. Wharton, S., et al., *Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity.* N Engl J Med, 2023.
79. Leddy, J.J., et al., *Influence of methylphenidate on eating in obese men.* Obes Res, 2004. **12**(2): p. 224-32.
80. Levy, L.D., J.P. Fleming, and D. Klar, *Treatment of refractory obesity in severely obese adults following management of newly diagnosed attention deficit hyperactivity disorder.* Int J Obes (Lond), 2009. **33**(3): p. 326-34.
81. Astrup, A., et al., *Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients: a randomised, double-blind, placebo-controlled trial.* Lancet, 2008. **372**(9653): p. 1906-1913.
82. Cowen, N. and A. Bhatnagar, *The Potential Role of Activating the ATP-Sensitive Potassium Channel in the Treatment of Hyperphagic Obesity.* Genes (Basel), 2020. **11**(4).
83. Castellano, J.M., A.B. Ariza-Jimenez, and M. Tena-Sempere, *New avenues for pharmacological management of hyperphagia and associated behavioral disorders in Prader-Willi Syndrome.* J Clin Endocrinol Metab, 2023.
84. Miller, J.L., et al., *Diazoxide Choline Extended-Release Tablet in People With Prader-Willi Syndrome: A Double-Blind, Placebo-Controlled Trial.* J Clin Endocrinol Metab, 2023. **108**(7): p. 1676-1685.
85. Vaya, J., P.A. Belinky, and M. Aviram, *Antioxidant constituents from licorice roots: isolation, structure elucidation and antioxidative capacity toward LDL oxidation.* Free Radic Biol Med, 1997. **23**(2): p. 302-13.
86. Choi, L.S., et al., *Discovery and preclinical efficacy of HSG4112, a synthetic structural analog of glabridin, for the treatment of obesity.* Int J Obes (Lond), 2021. **45**(1): p. 130-142.
87. Simmler, C., G.F. Pauli, and S.N. Chen, *Phytochemistry and biological properties of glabridin.* Fitoterapia, 2013. **90**: p. 160-84.
88. Nakagawa, K., et al., *Licorice flavonoids suppress abdominal fat accumulation and increase in blood glucose level in obese diabetic KK-A(y) mice.* Biol Pharm Bull, 2004. **27**(11): p. 1775-8.
89. Lee, J.W., et al., *AMPK activation with glabridin ameliorates adiposity and lipid dysregulation in obesity.* J Lipid Res, 2012. **53**(7): p. 1277-86.
90. Aoki, F., et al., *Suppression by licorice flavonoids of abdominal fat accumulation and body weight gain in high-fat diet-induced obese C57BL/6J mice.* Biosci Biotechnol Biochem, 2007. **71**(1): p. 206-14.
91. Ao, M., et al., *Factors influencing glabridin stability.* Nat Prod Commun, 2010. **5**(12): p. 1907-12.
92. Ito, C., et al., *Absorption of dietary licorice isoflavan glabridin to blood circulation in rats.* J Nutr Sci Vitaminol (Tokyo), 2007. **53**(4): p. 358-65.
93. Zimmermann, T., et al., *BI 456906: Discovery and preclinical pharmacology of a novel GCGR/GLP-1R dual agonist with robust anti-obesity efficacy.* Mol Metab, 2022. **66**: p. 101633.
94. Wynne, K., et al., *Oxyntomodulin increases energy expenditure in addition to decreasing energy intake in overweight and obese humans: a randomised controlled trial.* Int J Obes (Lond), 2006. **30**(12): p. 1729-36.
95. Wynne, K., et al., *Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects: a double-blind, randomized, controlled trial.* Diabetes, 2005. **54**(8): p. 2390-5.
96. LE ROUX, C., et al., *51-OR: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study of BI 456906 in People with Overweight/Obesity.* Diabetes, 2023. **72**(Supplement_1).
97. Turner, A., et al., *Interactions between Bitter Taste, Diet and Dysbiosis: Consequences for Appetite and Obesity.* Nutrients, 2018. **10**(10).
98. Niethammer, A.G., et al., *First-in-Human Evaluation of Oral Denatonium Acetate (ARD-101), a Potential Bitter Taste Receptor Agonist: A Randomized, Double-Blind, Placebo-Controlled Phase 1 Trial in Healthy Adults.* Clin Pharmacol Drug Dev, 2022. **11**(8): p. 997-1006.

99. D'Urso, O. and F. Drago, *Pharmacological significance of extra-oral taste receptors.* Eur J Pharmacol, 2021. **910**: p. 174480.
100. Senior, M., *After GLP-1, what's next for weight loss?* Nat Biotechnol, 2023. **41**(6): p. 740-743.
101. Liszt, K.I., et al., *Human intestinal bitter taste receptors regulate innate immune responses and metabolic regulators in obesity.* J Clin Invest, 2022. **132**(3).
102. Khan, A.S., et al., *Novel Fat Taste Receptor Agonists Curtail Progressive Weight Gain in Obese Male Mice.* Cell Mol Gastroenterol Hepatol, 2023. **15**(3): p. 633-663.
103. Shimpukade, B., et al., *Discovery of a potent and selective GPR120 agonist.* J Med Chem, 2012. **55**(9): p. 4511-5.
104. Douglas Braymer, H., et al., *Lingual CD36 and nutritional status differentially regulate fat preference in obesity-prone and obesity-resistant rats.* Physiol Behav, 2017. **174**: p. 120-127.
105. Ichimura, A., et al., *Dysfunction of lipid sensor GPR120 leads to obesity in both mouse and human.* Nature, 2012. **483**(7389): p. 350-4.
106. Crunkhorn, S., *Metabolic disease: Leptin sensitizer reverses obesity.* Nat Rev Drug Discov, 2016. **15**(9): p. 601.
107. Lee, J., et al., *Withaferin A is a leptin sensitizer with strong antidiabetic properties in mice.* Nat Med, 2016. **22**(9): p. 1023-32.
108. Liu, J., et al., *Treatment of obesity with celastrol.* Cell, 2015. **161**(5): p. 999-1011.
109. Chellappa, K., et al., *The leptin sensitizer celastrol reduces age-associated obesity and modulates behavioral rhythms.* Aging Cell, 2019. **18**(3): p. e12874.
110. Cakir, I., et al., *Sulforaphane reduces obesity by reversing leptin resistance.* Elife, 2022. **11**.
111. Ahangarpour, A., R. Shabani, and Y. Farbood, *The effect of betulinic acid on leptin, adiponectin, hepatic enzyme levels and lipid profiles in streptozotocin-nicotinamide-induced diabetic mice.* Res Pharm Sci, 2018. **13**(2): p. 142-148.
112. Zhao, S., et al., *Partial Leptin Reduction as an Insulin Sensitization and Weight Loss Strategy.* Cell Metab, 2019. **30**(4): p. 706-719 e6.
113. Isoda, M., et al., *Leptin sensitizing effect of 1,3-butanediol and its potential mechanism.* Sci Rep, 2021. **11**(1): p. 17691.
114. Yan, C., et al., *Meta-chlorophenylpiperazine enhances leptin sensitivity in diet-induced obese mice.* Br J Pharmacol, 2015. **172**(14): p. 3510-21.
115. Elfhag, K., et al., *Sibutramine treatment in obesity: predictors of weight loss including rorschach personality data.* Obes Res, 2003. **11**(11): p. 1391-9.
116. Rolls, B.J., et al., *Sibutramine reduces food intake in non-dieting women with obesity.* Obes Res, 1998. **6**(1): p. 1-11.
117. James, W.P., et al., *Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects.* N Engl J Med, 2010. **363**(10): p. 905-17.
118. Samanta, D., *Fenfluramine: A Review of Pharmacology, Clinical Efficacy, and Safety in Epilepsy.* Children (Basel), 2022. **9**(8).
119. Weintraub, M., et al., *A double-blind clinical trial in weight control. Use of fenfluramine and phentermine alone and in combination.* Arch Intern Med, 1984. **144**(6): p. 1143-8.
120. Robson, P.J., *Therapeutic potential of cannabinoid medicines.* Drug Test Anal, 2014. **6**(1-2): p. 24-30.
121. Dawson, A.J., et al., *Endocannabinoid receptor blockade reduces alanine aminotransferase in polycystic ovary syndrome independent of weight loss.* BMC Endocr Disord, 2017. **17**(1): p. 41.
122. Sathyapalan, T., et al., *Effect of rimonabant and metformin on glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 in obese women with polycystic ovary syndrome.* Clin Endocrinol (Oxf), 2010. **72**(3): p. 423-5.
123. Sathyapalan, T., et al., *Metformin maintains the weight loss and metabolic benefits following rimonabant treatment in obese women with polycystic ovary syndrome (PCOS).* Clin Endocrinol (Oxf), 2009. **70**(1): p. 124-8.

124. Sathyapalan, T., et al., *A comparison between rimonabant and metformin in reducing biochemical hyperandrogenaemia and insulin resistance in patients with polycystic ovary syndrome (PCOS): a randomized open-label parallel study.* Clin Endocrinol (Oxf), 2008. **69**(6): p. 931-5.
125. Moreira, F.A. and J.A. Crippa, *The psychiatric side-effects of rimonabant.* Braz J Psychiatry, 2009. **31**(2): p. 145-53.
126. Shukla, A.P., R.B. Kumar, and L.J. Aronne, *Lorcaserin Hcl for the treatment of obesity.* Expert Opin Pharmacother, 2015. **16**(16): p. 2531-8.
127. Bray, G.A., et al., *Management of obesity.* Lancet, 2016. **387**(10031): p. 1947-56.
128. Higgins, G.A., P.J. Fletcher, and W.R. Shanahan, *Lorcaserin: A review of its preclinical and clinical pharmacology and therapeutic potential.* Pharmacol Ther, 2020. **205**: p. 107417.
129. Inoue, S., et al., *Clinical and basic aspects of an anorexiant, mazindol, as an antiobesity agent in Japan.* Am J Clin Nutr, 1992. **55**(1 Suppl): p. 199S-202S.
130. Slama, G., et al., *Double blind clinical trial of mazindol on weight loss blood glucose, plasma insulin and serum lipids in overweight diabetic patients.* Diabete Metab, 1978. **4**(3): p. 193-9.

Table 1: Class and mechanism of action for the currently available and novel therapeutic agents for obesity management

Class of the drug	Example of the drug	Mechanism of action	References
Orlistat Cetilistat	Xenical Oblean	↓ cholesterol synthesis	[19-21, 23, 24].
GLP-1 RA	Liraglutide Semaglutide	↓ gastric motility ↓ appetite	[33, 38-41]
GLP-1/GIP (dual) agonist	Tirzepatide	↓ appetite ↓ gastric motility	[46-50]
GLP-1/GIP/ glucagon (triple) RA	Retatrutide	↓ appetite ↓ gastric motility	[74]
Oral GLP-1 RA	Orforglipron	↓ appetite ↓ gastric motility	[77, 78]
MC4R agonist	Setmelanotide	↓ appetite	[62]
Monoclonal Antibody	Bimagrumab	↓ fat mass ↑ Skeletal muscle mass	[68, 69]
Amylin analogue	Cagrilintide	↓ appetite ↑ satiety	[75, 76]
Leptin analogue	Metreleptin	↓ appetite ↑ satiety	[63]
Sympathomimetic	Phentermine/topiramate	↓ appetite ↑ satiety	[1]

GLP-1 RA: Glucagon-like-peptide receptor agonist, **GIP:** gastric inhibitory polypeptide, **MC4R:** melanocortin 4 receptor.

Figure 1: Historic, current, and future therapies for obesity

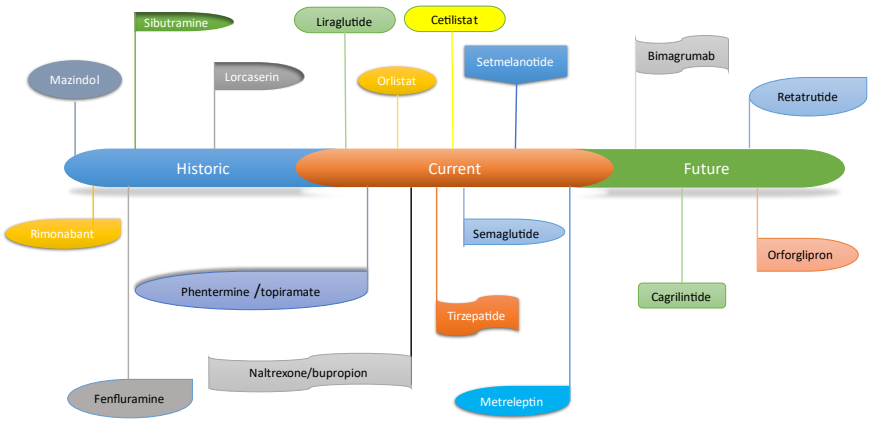

Figure 2: Potential therapeutic agents currently on the horizon