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REVIEW ARTICLE

GLP-1 RA-SEMAGLUTIDE A GAME CHANGER DRUG FOR MANAGEMENT OF OBESITY WITH AND WITHOUT DIABETES -A NARRATIVE REVIEW

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Abstract:

Obesity is a chronic and relapsing disease marked by excessive fat accumulation that poses serious health risks, with an increasing global prevalence including in low- and middle-income countries. Obesity-related complications, including cardiovascular diseases, diabetes, and cancer, also contribute to significant healthcare costs. Management strategies involve lifestyle modifications, pharmacological interventions, and, in severe cases, surgical procedures. Semaglutide, a GLP-1 receptor agonist, has emerged as an effective treatment for both obesity and type 2 diabetes, showing significant weight loss outcomes and improvements in metabolic health across various patient groups. However, careful monitoring of adverse effects and drug interactions is crucial for optimizing therapeutic outcomes.Several novel agents are under development, with multi-hormone receptor agonists and oral formulations likely to become available in the coming years. As effective treatment options expand, cost and availability will need to be addressed to enable equitable access to treatment.

Key words: *Obesity, Anti-obesity medications (AOMs), Glucagon-like peptide 1 receptor agonists, Semaglutide, Weight loss, Type 2 diabetes, Cardiometabolic health*

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Introduction:

Obesity is a chronic and complex disease defined by excessive fat deposits that can impair health. Recent estimates suggest that 1 in 8 people worldwide live with obesity, and the overall number of adult obese individuals has more than doubled since 1990, with cases among adolescents quadrupling. Similarly, the number of overweight individuals has also increased significantly. There is a clear disparity in the prevalence of overweight by region, ranging from 31% in the World Health Organization (WHO) South-East Asia Region and the African Region to 67% in the Region of the Americas. Once considered a high-income country problem, the rise in obesity and overweight is now evident in low- and middle-income countries[1].

Obesity has several clinical and public health implications, and more recently, the concern has been emphasized by the World Healthorganization[2].A high body mass index (BMI) (BMI >25 kg/m^2) is associated with an increased risk of developing a broad set of comorbidities, termed obesity-related complications (ORCs), which can affect all organ systems. These complications include cardiovascular disease (CVD), metabolic conditions such as type 2 diabetes (T2D), respiratory issues including asthma and obstructive sleep apnoea, and disorders affecting mobility such as osteoarthritis and pain. Additionally, obesity is linked to an increased risk of cerebrovascular accidents like stroke[2,3].Certain cancers, including endometrial, breast, and colon cancer, are also associated with

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obesity[4].Furthermore, it limits daily activities and lowers health-related quality of life[5,6].The healthcare costs related to treating these conditions are significant; on average, EU28 member states will spend more than 8% of national healthcare budgets on overweight, obesity, and related conditions between 2020 and 2050[7]. According to WHO 2024 projections, the global costs of overweight and obesity are predicted to reach US$ 3 trillion per year by 2030 and more than US$ 18 trillion by 2060[8].Another concern is the rising number of overweight and obese individuals in low- and middle-income countries like Bangladesh, particularly given their limited resources to respond to this epidemic.

Management options of obesity and overweight:

Measuring weight, assessing lifestyle, and taking a thorough medical history are crucial for evaluating risks associated with overweight or obesity and determining therapeutic options. Patients with normal (healthy) weight (BMI 18.5 to &<25 kg/m²) should be counseled on the health benefits of avoiding weight gain. Patients at high risk for overweight or obesity due to genetics, biomarkers, family history, ethnicity, cultural practices, or individual behaviors should be educated on healthy meal planning and physical activity[9]. Several interventions include lifestyle changes, anti-obesity medications (AOMs), endoscopic procedures, and surgery are also available for treatment ofobesity[10].

Non-pharmacological:

A structured and comprehensive lifestyle intervention program designed for weight loss (lifestyle therapy) is recommended for all patients with overweight or obesity seeking to lose weight. This should include a healthy meal plan, physical activity, and behavioral interventions tailored to each patient[9,11]. Recommended dietary practices include consuming a variety of foods such as vegetables, fruits, low-fat dairy products, lean meats, other protein sources, and whole grains while limiting foods high in calories and low in nutrients. Drinking plenty of water can help individuals feel full and avoid overeating. General recommendations for physical activity include 30 minutes of walking five days a week (150 minutes weekly). Gradually increasing exercise intensity is recommended to build strength and endurance. Low-impact exercises such as walking, swimming, or yoga are advised initially. Individual counseling sessions every four weeks can help patients adhere to a reduced-calorie diet based on suggestions from a qualified dietitian[12].

Pharmacological:

The treatment of obesity is challenging; therefore, a one-size-fits-all approach does not apply. The choice of anti-obesity medication needs to consider the patient's clinical profile, co-morbidities, drug contraindications, expected weight loss, and improvements in cardio-renal and metabolic risks. In the last decade, two drugs have been approved for syndromic obesity; one treats leptin deficiency in patients with generalized lipodystrophy. Six drugs have been approved for non-syndromic obesity management: Metreleptin, Setmelanotide, Orlistat, Phentermine/Topiramate, Naltrexone/Bupropion, Liraglutide, Semaglutide, and Tirzepatide. Most of these compounds act centrally to reduce appetite and increase satiety while also affecting the gastrointestinal tract by slowing gastric emptying[13]. Summary of the approved drugsused for obesity are summarize in the Table 1.

Surgical Procedures and Devices:Bariatric surgery is a category of operations intended to help individuals with obesity lose weight when other methods have failed. Procedures include gastric bypass, sleeve gastrectomy, gastric banding, and duodenal switch. These surgeries modify the digestive system to regulate calorie intake and absorption while also reducing hunger signals traveling from the digestive system to the brain. These operations have proven results in treating class III obesity or morbid obesity (BMI >40 kg//m^2)[14].

The FDA has also approved several weight loss devices that expand treatment options for obesity. These include gastric band devices, gastric space-occupying devices, and gastric emptying devices for weight loss. These devices offer less invasive and reversible alternatives to bariatric surgery for patients who haven't responded to conservative treatments[15].

Such procedures should be considered for patients with a BMI of at least 40 kg/m² or those with a BMI of at least 35 kg/m² who have severe weight-related conditions when therapeutic goals cannot be attained using structured lifestyle change and pharmacotherapy alone[16].It is essential to evaluate patients thoroughly before recommending bariatric procedures while considering risks, patient preferences, individualized therapy goals, and available procedural expertise. Importantly, surgery is not a cure for obesity, but rather a tool to help patients achieve sustained weight loss and improve their overall health[17].

Newer agents:

Many new agents are under development for treating obesity. Most of these agents replicate or inhibit the action of gut-derived hormones such as GLP-1, GIP, amylin, and glucagon. Glucagon-like peptide-1 receptor

Table-I

Summary of the approved drugs used for obesity

Date of FDA approval	Name of the drug	Target	Pharmacological group	Mechanism of action	Major adverse events	Long/short term
2006	Orlistat OTC 120mg	Intestine	Tetrahydrolipstatin: lipase inhibior	Lipase inhibitor: Decreased absorption of fat	Oily rectal leakage, abdominal distress, abdominal pain, flatulence with discharge, fecal urgency, steatorrhea, fecal incontinence, increased defecation	Short term
2012	Lorcaserin 10mg	CNS	Serotonin 2C receptor agonist	Selective serotonergic 5-HT receptor agonist - causes appetite suppression - causes appetite suppression	High blood pressure, bad headache or dizziness, passing out, or change in eyesight, mood changes likedepression, hallucinations (seeing or hearing things that are not there)	Long tern
2012–present (USA)	Phentermine/topiramate ER (with titration) (15 mg/92 mg, OD, oral)	CNS	Sympathomimetic amine	NE agonist/GABA agonist, glutamate antagonist	Elevation in heart rate, mood and sleep disorders, cognitive impairment, metabolic acidosis, paresthesia, dry mouth	Long term
2014	Metreleptin (2.5mg)	Body fat	Analog of the human hormone leptin	activating the human leptin receptor (ObR): regulate satiety	Headache, hypoglycemia, decreased weight, abdominal pain	Short term
2014	Naltrexone (360mg)	CNS	Opioid antagonist	Norepinephrine-dopamine reuptake inhibitor antidepressant/opioid antagonist - causes appetite suppression	Seizures, palpitations, transient blood pressure elevations	Short term
2014	Bupropion (32mg)	CNS	Anti-depressant	Norepinephrine-dopamine reuptake inhibitor antidepressant/opioid antagonist - causes appetite suppression	Dry mouth	Long tern
2014	Liraglutide (3.0mg)	CNS	GLP-1RA	Glucagonlike peptide-1 (GLP-1) agonist - reduce hunger, increase satiety	Nausea/vomiting, diarrhoea, constipation, pancreatitis, gallstones	Long term
2017	Semaglutide (2.4mg)	CNS	GLP-1RA	Glucagonlike peptide-1 (GLP-1) agonist - reduce hunger, increase satiety	Nausea/vomiting, diarrhoea, constipation	Long term
2020	Setmelanotide (3mg)	CNS	Melanocotin agonist	Decreases activity at the melanocortin 3 (MC3) and melanocortin 1 (MC1) receptors	Skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection	Long term
2022	Tirzepatide (15mg)	CNS	GIP and GLP-1 receptor agonist	Activates both the GIP and GLP-1 receptors-reduce hunger, increase satiety	Nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain	Long term

agonists (GLP-1 RAs), including semaglutide, liraglutide, and the recently approved dual GLP-1/GIP RAs agonist tirzepatide, have emerged as effective medications for managing obesity with significant weight loss outcomes. The new generation of medications like semaglutide and tirzepatide shows greater efficacy in terms of mean weight loss and reductions in cardiometabolic risk factors compared with older agents (though there are few head-to-head comparisons). These agents promote weight reduction while also improving metabolic parameters such as lipid profiles and glucose levels[18].However, efficacy is not the only consideration; other factors influencing medication choice include contraindications, adverse effect profiles, expected benefits for each patient (e.g., GLP-1RAs may be preferred for individuals at high risk

of T2D), mode of delivery (injectable vs. oral), and frequency of administration[19].

Discovery and approval history of semaglutide:

Bayliss and Starling first described the connection between the pancreas, the gut, and incretin hormones in the early twentieth century. The incretin hormone glucagon-like peptide-1 (GLP-1) was identified as having potential therapeutic effects in type 2 diabetes (T2D). However, GLP-1's short half-life limited its therapeutic use[20]. Various approaches have since been used to extend the half-life of native GLP-1, which has led to the development of safe and effective entero-pancreatic hormone-based treatments for obesity such as glucagon-like peptide-1 (GLP-1) receptor agonists (RA). Semaglutide 2.4 mg once weekly, a subcutaneously administered GLP-1 RA approved for obesity treatment in 2021, results in 15–17% mean weight loss with evidence of cardio-protection[21].Oral semaglutidewas also developed for the management of type 2 DM and obesity.

In December 2017, the US FDA approved subcutaneous once weekly semaglutide injection to improve glycaemic control as an adjunct to diet and exercise. It was launched under the Ozempic Pen brand name—it's the latest generation of Novo Nordisk prefilled devices[22]. The approval of semaglutide was based on results from the SUSTAIN clinical trial programme[23].In 2021, the FDA also approved semaglutide medication Wegovy developed by Novo Nordisk for weight management in adults with obesity or overweight conditions related to weight. This approval was based on STEP (Semaglutide Treatment Effect in People with Obesity) trials[24].Several trials were conducted about the role of Semaglutide (wegovy)and each trial has its own direction. Such as STEP 1 (large pivotal study) examined the efficacy of semaglutide for weight loss[25]; STEP 2, investigate weight loss in type 2 diabetes[26]; STEP 3 trial focusing weight loss in combination with intensive behavioural therapy[27];STEP 4 assessed effects of continuing versus withdrawing semaglutide on weight-loss maintenance[28]; STEP 5 emphasized weight maintenance over2 years[29]; and STEP 8 trial compared efficacy and safety of semaglutide versus liraglutide[30]. In addition to these STEP trials, a regional phase IIIa trial, STEP6, assessed the effect of semaglutide versus placebo for weight managementin 401 adults from east Asia (Japan and South Korea) with obesity,with or without type 2 diabetes[31].

Over various clinical trials, once-weekly subcutaneous semaglutide 2.4 mg led to a mean weight loss of 14.9% compared to 2.4% with placebo over 68 weeks[25–29]. This weight loss was observed across various baseline characteristics with slightly greater effects noted in females and individuals with lower initial body weight. The STEP program demonstrated consistent weight loss results ranging from 14.9% to 17.4% in non-diabetic individuals over 68 weeks.Semaglutide led to significant reductions in body weight, waist circumference, and body mass index compared to placebo[25–29]. Additionally, semaglutide improved cardiometabolic risk factors including blood pressure, glycated hemoglobin levels, and lipid profiles. The medication was generally well tolerated; gastrointestinal events were the most common adverse effects but were typically mild-to-moderate and transient.Notably, the intensity of behavioral interventions in the STEP trials did not significantly impact weight loss outcomes, suggesting that semaglutide's effect may be independent of lifestyle modifications. These findings led to the FDA approval of semaglutide 2.4 mg (Wegovy) for chronic weight management in 2021[32].

Semaglutide:

In 2021, semaglutide was first launched in Bangladesh by Novo Nordisk and this once weekly semaglutide injections were marketed for the treatment of type 2 diabetes and obesity management. Recently, several pharmaceuticals also marketing in different brand names[33].

Chemical Structure:

Semaglutide is a long-acting GLP-1 analog with 94% sequence homology to human GLP-1 that selectively binds to the GLP-1 receptors. Semaglutide consists of amino acids 7–37 of native GLP-1, with two amino acid substitutions at positions 8 (Aib8) and 34 (Arg34) and a C18 fatty diacid attached to lysine 26 via a long hydrophilic spacer. These structural modifications enable semaglutide to reversibly bind to albumin and prevent degradation by DPP-4, thereby reducing renal clearance. This formulation provides semaglutide with a longer half-life (range, 155– 184 h, ~7 days) than both liraglutide (range, 11–15 h) and native GLP-1 (range, 1–2 min), allowing for once-weekly subcutaneous dosing without compromising weight-loss efficacy[23,34].Thus, the modified semaglutide can bind tightly to albumin, cover up the DPP-4 enzymatic hydrolysis site, and reduce renal excretion, prolong the biological half-life, and achieve the effect of long circulation[35].

Mechanism of action:

Semaglutide activates GLP-1 receptors located in the hindbrain and hypothalamus while exerting direct and indirect effects on neural pathways. By binding to GLP-1R receptors semaglutide activates cAMP signaling

cascades via PKA pathways resulting in increased insulin secretion from pancreatic â-cells along with suppression of glucagon release. Additionally these pathways have been associated with appetite regulation modulation gastric emptying as well as cardiovascular effects[36,37]. Mechanism of action of semaglutide is illustrated in Fiure-1.

How to use of semaglutide

Semaglutide is available in both subcutaneous and oral forms in various doses. Treatment is administered as a once-weekly subcutaneous injection and should be administered on the same day each week with or without meals. The injection time and injection site can be changed without any dose adjustment. In the USA, subcutaneous semaglutide for weight management is delivered as 0.25, 0.5, 1.0, 1.7, or 2.4 mg doses. Treatment should be initiated at 0.25 mg once weekly for 4 weeks, and the dose should be escalated at 4-week intervals until the maintenance dose of 2.4 mg is reached. If patients do not tolerate a dose during the dose titration, further escalation can be delayed for 4 weeks[39].Oral forms are still under investigation with FDA approved dose of 14mg once daily on 2019[40]. However, Filip K Knop et al demonstrated significant weight loss among those using oral semaglutide compared against placebo through OASIS trial data(NCT05035095) where findings indicated patients receiving oral dosage (50mg once daily) experienced clinically meaningful decreases compared with placebo[41]. In another study, oral semaglutide was compared among 1600 participants in 14 mg, 25 mg, or 50 mg daily doses and after 52weeks, changes were significantly higher in participants who take 50mg daily doses respectively[42]. Hence, doses of oral semaglutide higher than those currently approved appear to be tolerated reasonably well and to be increasingly effective for short-term management of both diabetes and obesity as dosages increase. Also, weight loss was substantially greater in patients without diabetes than in those with diabetes[41,42].The dosage schedule of the injectable semaglutide is illustrated in Figure 2.

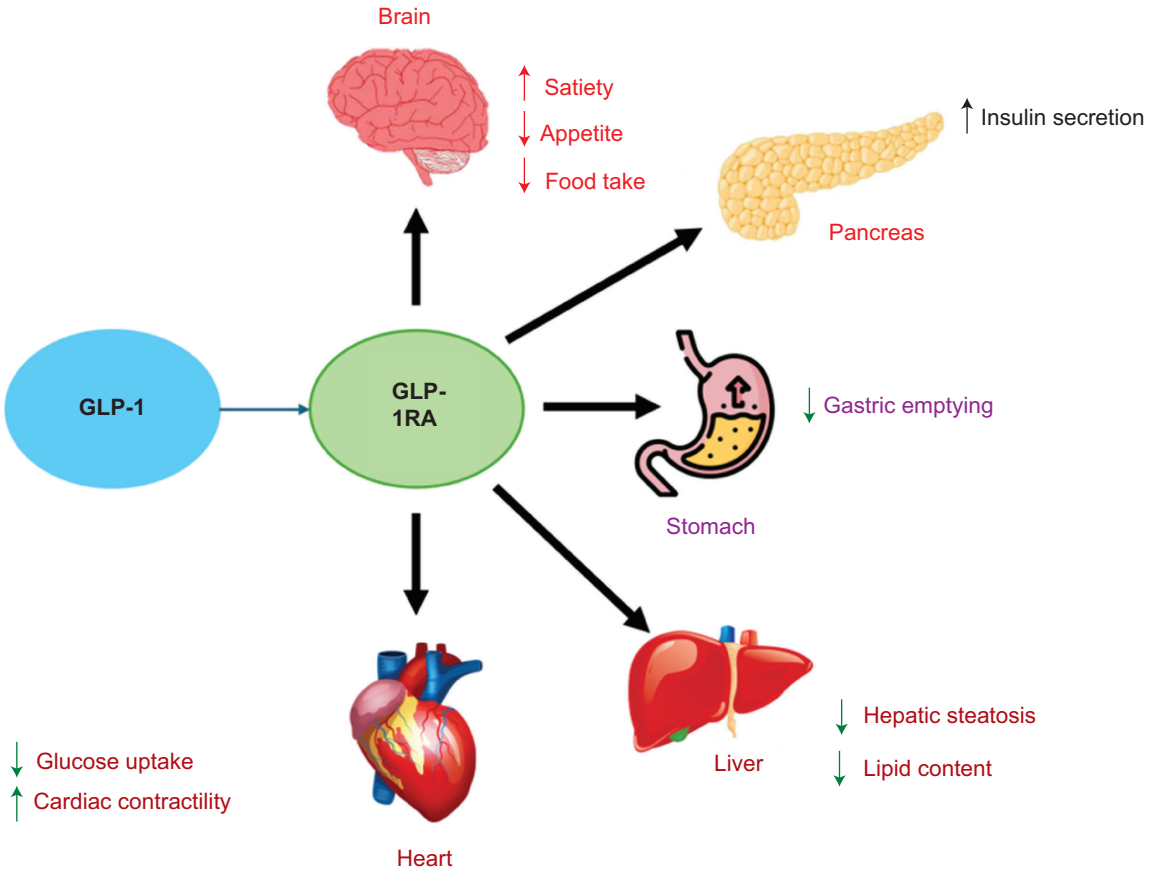

Figure-1: *Mechanism of action of semaglutide[38].*

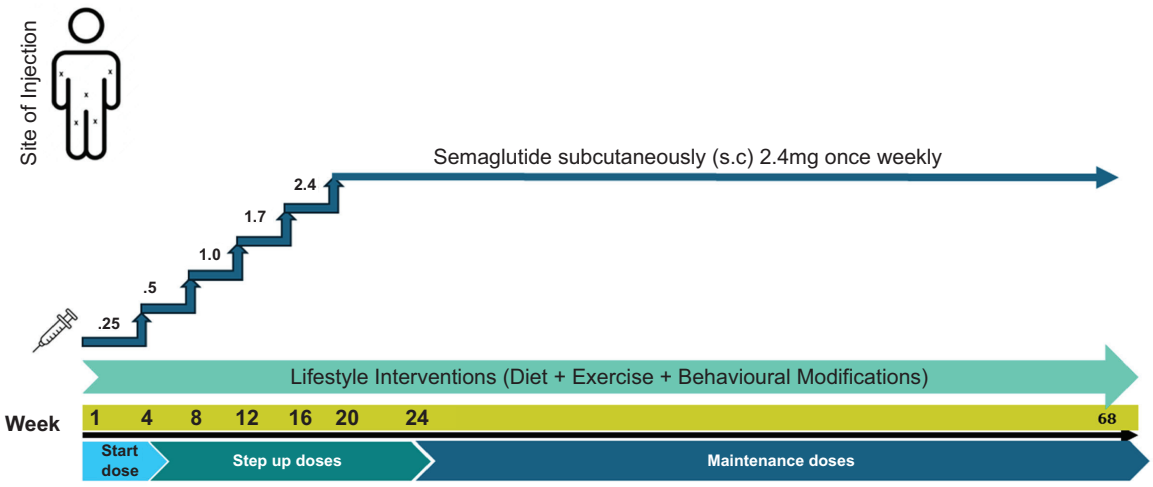

Figure-2: *Injectable dose schedule of semaglutide*

Role of semaglutide in weight reduction in adults: Semaglutide (wegovy) is effective in weight management as evidenced by STEP 1-5[25–29].Compared against other GLP-RAs such as Liraglutide findings from STEP trial eight indicated that Semaglutide was significantly more effective overall when assessing changes from baseline weights comparing either placebo groups or those receiving lower dosages[30].The efficacy table summarizing results can be found below Table 2.

Effect of semaglutide on obesity other age group:

- In children and adolescent:Childhood obesity is associated with significant comorbidities including type 2 diabetes, metabolic-associated fatty liver disease, obstructive sleep apnoea, and hypertension. Treatment remains challenging as dietary/lifestyle interventions have limited sustained effects; however according FDA regulations only children aged twelve years or older can receive semaglutide treatment[43].As a first-line treatment, guidelines recommend multimodal behaviour-changing interventions, focusing on improving diet and increasing physical activity, for children and adolescents living with obesity; however, the impact of these interventions on body weight status is limited[43].According to STEP TEENS study results showed that among adolescents treated weekly using a dose equivalent at two point four milligrams seventy-three percent achieved five percent reductions compared against only eighteen percent who received lifestyle intervention alone[44].
- In elderly: The incidence of type 2 diabetes (T2D) increases with age, reaching a peak at 65-69 years for men and 75-79 years for women.When considering diabetes treatment for older patients, frailty and common comorbidities including cardiovascular (CV) disease, renal impairment and cognitive dysfunction should be taken into consideration. Certain drugs must be used with caution because of their associated risks[45].The SUSTAIN 1-5 trials evaluated the efficacy and safety of semaglutide compared to other treatments in both non-elderly (<65 years) and elderly (e”65 years) patients with type 2 diabetes (T2D), demonstrating that semaglutide is an effective treatment option for elderly patients with T2D[46–51]
- In pregnant women: Potentially beneficial effects exist wherein some research suggests using semaglutides may alleviate subfertility related complications stemming from diabetes/overweight/PCOS conditions[52].However, data surrounding human pregnancy outcomes remains scarce particularly concerning long-term fetal exposure potential after cessation due prolonged washout periods. Although not contraindicated, it has been suggested to discontinue semaglutide in women at least 2 months before a planned pregnancy due to the long washout period[53].
- In lactating women: As semaglutide are new drugs for type 2 diabetes and obesity, their safety during pregnancy and lactation is unclear. Animal studies linked GLP-1 agonists to reduced fetal weight and skeletal issues, while human studies showed minimal placental transfer. Though studies found GLP-1 drug types in animal breast milk, human data was lacking as well as data regarding semaglutide was also rare[54].

Table-II

Efficacy of semaglutide in weight management along with diet and exercise

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 8
	Weightmanagement	**Weight management in type 2 diabetes**	**Weight management with intensive behavioural therapy**	**Sustained weight management**	**Two-year weight management**	**Semaglutide vs. liraglutide**
N	1961	1210	611	803	304	338
Participants	Adults with BMI ≥30, or BMI ≥27 with ≥1 comorbidity, and without diabetes	Adults with BMI ≥27 and type 2 diabetes, with HbA1c 7.0%-10.0%	Adults with BMI ≥30, or BMI ≥27 with ≥1 comorbidity, and without diabetes	Adults with BMI ≥30, or BMI ≥27 with ≥1 comorbidity, and without diabetes	Adults with BMI ≥30, or BMI ≥27 with ≥1 comorbidity, and without diabetes	Adults with BMI ≥30, or BMI ≥27 with ≥1 comorbidity, and without diabetes
Treatment arms	Semaglutide 2.4 mg vs. placebo	Semaglutide 2.4 mg Semaglutide 1.0 mg Placebo	Semaglutide 2.4 mg vs. placebo	All receive semaglutide for 20 weeks (dose escalation) Then semaglutide 2.4 mg vs. placebo	Semaglutide 2.4 mg vs. placebo	Semaglutide 2.4 mg vs. placebo vs. liraglutide 3.0 mg vs. placebo
Duration of study	68 weeks of treatment	68 weeks	68 weeks	68 weeks	104 weeks	68 weeks
Outcome assessment	% change in body weight ≥5% weight loss ≥10% weight loss ≥15% weight loss	% change in body weight ≥5% weight loss ≥10% weight loss ≥15% weight loss	% change in body weight ≥5% weight loss ≥10% weight loss ≥15% weight loss	% change in body weight	% change in body weight ≥5% weight loss ≥10% weight loss ≥15% weight loss	% change in body weight ≥10% weight loss ≥15% weight loss ≥20% weight loss
% weight change	Semaglutide (-14.9%) vs Placebo (-2.4%)	Semaglutide 2.4 mg (-9.6%) vs Semaglutide 1.0 mg (-7%) vs Placebo (-3.4%)	Semaglutide (-16%) vs Placebo (-5.7%)	Semaglutide (-17.4%) vs Placebo (-5.0%)	Semaglutide (-15.2%) vs Placebo (-2.6%)	Semaglutide (-15.2%) vs Placebo (-2.6%)
≥5%	86.4 vs 31.5	68.8 vs 57.1 vs 28.5	86.6 vs 47.6	88.7 vs 47.6	77.1 vs 34.4	87.2 vs 58.1 vs 29.5
≥10%	69.1 vs 12.0	45.6 vs 28.7 vs 8.2	75.3 vs 27.0	79.0 vs 20.4	61.8 vs 13.3	70.9 vs 25.6 vs 15.4
≥15%	50.5 vs 4.9	25.8 vs 13.7 vs 3.2	55.8 vs 13.2	63.7 vs 9.2	52.1 vs 7.0	55.6 vs 12.0 vs 6.4
≥20%	32.0 vs 1.7	13.1 vs 4.7 vs 1.6	35.7 vs 3.7	39.6 vs 4.8	36.1 vs 2.3	38.5 vs 6.0 vs 2.6

Role of semaglutide in other indications:

- On glucose control, lipid panel and blood pressure

  Currently recognized among effective classes alongside insulin improving glycated hemoglobin levels notably greater effectiveness perceived through long-acting formulations(SUSTAIN-11 study revealed once-weekly administration yielding improved glycemic control relative thrice-daily insulin regimens alongside numerically greater respective losses)[55].

  Moreover potential impacts extend toward cholesterol levels where scientific studies indicate varying individual responses exist although collectively demonstrated reductions concerning LDL alongside increases across HDLs hence comprehensive approaches should continue incorporating diet/exercise strategies alongside lipid-lowering medications[56,57].

  As dietary intervention has been associated with decreased blood pressure, semaglutide also has an effect on decreasing blood pressure. According to a meta-analysis, a clinically significant reduction in BP was evident following semaglutide treatment in normotensive populations without diabetes. However, the effect of semaglutide in those with obesity and hypertension is as yet undetermine[58].

- On metabolic liver diseases

  Metabolic dysfunction-associated fatty liver disease (MAFLD) and metabolic dysfunction-associated steatohepatitis (MASH) are common in individuals with type 2 diabetes (T2D) and/or obesity. These conditions share pathogenic mechanisms, including adipose tissue dysfunction, insulin resistance, hyperglycemia, gut microbiome impairment, and cytokine profile changes, leading to liver injury, fibrosis, and cirrhosis. Semaglutide improve metabolic parameters and promote weight loss, suggesting their potential role in managing these liver diseases[59]. Recent trials demonstrated daily subcutaneous usage significantly improved metabolic parameters promoting respective reductions among treated subjects showing MASH resolution rates at fifty-nine percent compared against seventeen percent seen within placebo cohorts although fibrosis differences remained negligible[60].

- On cardiovascular and renal diseases

  Semaglutide has already shown promising cardiovascular benefits in patients with type 2 diabetes and obesity through SUSTAIN-6 trial and in patient without diabetes in SELECT trial[59,61]. While semaglutide appears to be a promising treatment for obesity-associated cardiovascular disease prevention, it may increase the risk of other complications. Further research is needed to fully understand semaglutide's cardiovascular and renal benefits and potential risks.

- On diet and exercise

  Adding supervised exercise regimens alongside pharmacotherapy appears beneficial toward maintaining healthy weights post-treatment termination compared solely relying upon pharmacotherapies alone resulting positive outcomes regarding body composition sustained over one-year timeframes exhibited contrasted against observed quick regain rates following cessation methods noted previously[62].

- In others disease

  A major concern with weight loss is concomitant bone loss. The randomized clinical trial found that the combination of exercise and GLP-1RA (liraglutide) was the most effective weight loss strategy while preserving bone health[63]. However, direct results with semaglutide are yet to be discussed.

  Obstructive sleep apnoea (OSA) and associated hypopnoea syndromes are chronic conditions of sleep-disordered breathing with significant sequelae if poorly managed, including hypertension, cardiovascular disease, metabolic syndrome and increased mortality. Semaglutide or other GLP-1RAs may improve OSA as defined by reduction in apnoea-hypopnoea index (AHI)[64].

  Semaglutide was linked to a reduced risk of needing health care for smoking-related issues, including efforts to quit smoking. It also lowered the chances of having medical visits for tobacco use disorder, especially compared to other diabetes medications, with the most significant difference being compared to insulin[65].

Adverse effects:

Semaglutide and other GLP-1RAs demonstrate a generally favorable risk-benefit profile, though several adverse effects have been reported. The most common side effects are mild to moderate gastrointestinal disturbances, such as nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, flatulence, gastroenteritis, gastroesophageal reflux disease, and nasopharyngitis(ure-3). Nausea affects up to 25% of patients, while vomiting or diarrhea occurs in up to 10%[44]. These symptoms are usually transient and resolve on their own, even with continued use. However, there is an increased risk of biliary diseases, like gallstones, and rare cases of hepatobiliary disorders, such as acute pancreatitis, requiring careful monitoring and individualized risk. Initial concerns arose about potential risks of pancreatitis, pancreatic cancer, and thyroid cancer due to the presence of GLP-1 receptors in thyroid cells. As a result, these treatments are not recommended for individuals with a family history of rare thyroid cancers, such as medullary thyroid cancer, based on genetic testing recommendations[66–68].Semaglutide has also characterized skin findings in patients on this medication.Injection site reactions,dysesthesia, hyperesthesia, neuralgia, pain of the skin, paresthesia, sensitive skin, and a skin burning sensation are some of the effects of semaglutide. Higher rates of alopecia and altered skin sensations were also seen in individuals on oral semaglutide[69].

Drug–Drug Interactions:

Semaglutide, a medication that causes delayed gastric emptying, has the potential to affect the way other drugs are processed in the body. However, several crossover trials have demonstrated that semaglutide does not interfere with the bioavailability of various co-administered drugs such as oral contraceptives, lisinopril, metformin, warfarin, furosemide, digoxin, atorvastatin, rosuvastatin, and omeprazole. One exception is levothyroxine, where co-administration with oral semaglutide leads to a 33% increase in levothyroxine exposure. To avoid unnecessary interactions with semaglutide, it is recommended that patients take levothyroxine three hours after their last meal[70].

Figure-3: *Common adverse effects of semaglutide*

Cost benefits:

Because healthcare resources are limited and healthcare budgets are faced with growing strain, the common goal of healthcare systems worldwide is to maximize the health across populations with limited healthcare resources.Thus, choosing therapies that are both effective and cost-saving are paramount for optimizing treatment for obesity as well as type 2 diabetes. Cost of a 14 mg dose of orally administered semaglutide came out the least at USD 15,430 and USD 17,383 for patients achieving glycaemic targets of <7% and d"6.5%, respectively[71]. In another cost-effectiveness analysis done for the UK market, orally administered semaglutide 14 mg was found to be cost effective relative to sitagliptin 100 mg and empagliflozin 25 mg and dominant in comparison to liraglutide 1.8 mg daily dose for the treatment of T2DM. The cost-effectiveness ratio per quality-adjusted life year (QUALY) was reported as GBP 11,006 versus empagliflozin and GBP 4930 versus sitagliptin[72]. On the other hand, under a willingness-to-pay threshold of $150,000, semaglutide 2.4 mg was estimated to be cost-effective compared with no treatment, diet and exercise, and anti-obesity medications over a 30-year horizon. This finding may support coverage and reimbursement decisions for patients with obesity or overweight and weight-related comorbidities.Having obesity can be expensive given the high risk of many related health conditions[73].

Cautions and contraindications:

Semaglutide is contraindicated for individuals with a personal or family history of medullary thyroid carcinoma, Multiple Endocrine Neoplasia Syndrome Type 2 (MEN 2) or known hypersensitivity to the drug or its excipients. It should also be avoided in patients with increased pancreatic lipase, pancreatitis, metastatic pancreatic carcinoma, retinopathy, gallbladder issues, and heart rate increase. WEGOVY, a form of semaglutide, may also cause hypoglycemia, kidney injury, hypersensitivity reactions, and suicidal thoughts, necessitating careful monitoring and potential discontinuation[39].

Future Indications and Trials:

Semaglutide, a notable GLP-1 RA, is highly effective in achieving these goals including improving glycaemic control, promoting weight loss, and reducing cardiovascular risk. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) highlight weight control as a crucial element of T2DM treatment, acknowledging semaglutide's high efficacy for both glucose lowering and weight loss[74].Future trials of semaglutide could explore its long-term efficacy, safety, and impact on diverse populations, comparing it with other diabetes and weight loss medications. Research may focus on its role in smoking cessation, combination therapies, and quality of life. Additionally, studies could investigate semaglutide's effects on cardiovascular diseases, metabolic dysfunction-associated fatty liver disease (MAFLD), and cognitive function, potentially broadening its therapeutic applications beyond diabetes and obesity. Evaluating its cost-effectiveness, outcomes in pregnancy and elderly populations, as well as its effects on renal, cerebrovascular, and other systems, may further contribute to understanding the full spectrum of semaglutide's benefits and risks. A summary of some future trials has been accumulated in Table-2[21].

Table-II

Summary for future obesity medications

Name	Dose	Administration	Mechanism of action	Expected completion date	Indication other than obesity
Phase 3 trials					
Orforglipron	NA	PO, OD	GLP-1 RA	September-2027	Phase 3 - T2D, CV outcomes in T2D
Semaglutide	7.2 mg	SC, OW	GLP-1 RA	NA	NA
CagriSema	2.4 mg/2.4 mg	SC, OW	GLP-1 RA + Amylin RA	October-2026	Phase 3 - T2D, CV outcomes
Mazdutide	9 mg	SC, OW	GLP-1 RA + GCG RA	September 2025	NA
Retatrutide	4–12 mg	SC, OW	GLP-1 RA + GIP RA + GCG RA	May-2026	Phase 3 - T2D, OA Phase 2 - CKD
Phase 2 trials					
AMG 133	NA	SC, once monthly	GLP-1 RA + GIP receptor antagonist	January-2025	NA
Bimagrumab + Semaglutide	30 mg/kg + 1–2.4 mg	IV, every 4 weeks (Bimagrumab) + SC, OW	Activin receptor II inhibition + GLP-1 RA	September-2025	NA
Phase 1 trials					
Amycretin (NNC0487-0111)	1–100 mg	PO, OD	GLP-1 RA + Amylin RA	November-2024	NA
Preclinical trials					
ZP6590	NA	NA	GIP RA	NA	NA

Conclusion:

Semaglutide, a GLP-1 receptor agonist, has become a key treatment for obesity and type 2 diabetes. It effectively lowers blood sugar and body weight and is available in both injectable and oral forms, making it more accessible for patients. Its ability to promote weight loss, similar to bariatric surgery, highlights its potential as a major breakthrough in obesity treatment. Additionally, semaglutide may offer benefits for heart, kidney, and liver diseases. However, the high cost of semaglutide can make it unaffordable for many patients as this medication is supposed to be used for long-term weight management. A cost-effective ness analysis of semaglutide will help clinicians decide if it should be preferred compared with other weight loss drugs. Future research will help us to better understand its role in other systematic disease management along with cost-effectiveness.

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