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SEMAGLUTIDE FOR WEIGHT MANAGEMENT: A COMPREHENSIVE NARRATIVE REVIEW OF MECHANISMS, EFFICACY, SAFETY, AND CLINICAL APPLICATIONS

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Abstract

Background: Obesity is a global chronic disease affecting over 650 million adults and is associated with numerous comorbidities, including type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease. Traditional weight management strategies often yield limited and unsustainable results, and while bariatric surgery is effective, it is inaccessible to most. Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist initially developed for type 2 diabetes, has demonstrated substantial efficacy for chronic weight management and is now approved for this indication.

Aim: This narrative review aims to (i) elucidate the pharmacological mechanisms of semaglutide-induced weight loss; (ii) synthesize clinical evidence on its efficacy across diverse populations; (iii) evaluate its safety and tolerability profile; (iv) discuss practical implementation considerations; (v) examine cardiometabolic and other health outcomes; (vi) assess weight maintenance after discontinuation; (vii) analyze cost-effectiveness and accessibility; and (viii) identify key research gaps and future directions.

Methods: A comprehensive narrative review was conducted, drawing on data from pivotal clinical trials (notably the STEP program), cardiovascular and renal outcome studies (e.g., SELECT, FLOW), regulatory documents, and peer-reviewed

literature. The review integrates findings on pharmacology, efficacy, safety, special populations (including adolescents), real-world implementation challenges, and health equity issues.

Results: Semaglutide promotes weight loss primarily through central appetite suppression, delayed gastric emptying, enhanced satiety signaling, and modulation of food reward pathways. In clinical trials, once-weekly subcutaneous semaglutide 2.4 mg produced mean weight losses of 14–17% over 68–104 weeks, surpassing placebo and other anti-obesity medications. Significant improvements were also observed in glycemic control, blood pressure, lipids, liver fat, and inflammatory markers. The SELECT trial confirmed a reduction in major adverse cardiovascular events in patients with obesity and established cardiovascular disease. Common adverse effects were gastrointestinal (nausea, vomiting, constipation, diarrhea), typically transient and manageable with dose titration. Serious but rare risks include pancreatitis, gallbladder disease, and contraindications in patients with personal or family history of medullary thyroid carcinoma. Discontinuation leads to substantial weight regain, supporting the need for long-term treatment. High costs, insurance barriers, and supply shortages limit equitable access.

Conclusion: Semaglutide represents a major advance in obesity pharmacotherapy, offering clinically meaningful weight loss and improvements in cardiometabolic health. Its efficacy is well-established, and its safety profile is generally favorable with appropriate patient selection and dose titration. However, long-term safety beyond two years, strategies for post-discontinuation weight maintenance, optimal patient stratification, comparative effectiveness against surgery, and equitable access remain critical challenges. Semaglutide should be integrated into comprehensive, multidisciplinary obesity care that includes lifestyle modification, behavioral support, and ongoing monitoring. Future research must address existing knowledge gaps to optimize its use in diverse clinical settings.

Keywords: adiposity, anti-obesity pharmacotherapy, bariatric medicine, body weight regulation, GLP-1 receptor agonist, health equity, metabolic syndrome, obesity, treatment adherence, chronic weight loss, appetite suppression

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1. INTRODUCTION

Obesity represents a global health crisis affecting over 650 million adults worldwide **[1]**. The condition associates with increased morbidity and mortality from cardiovascular disease, type 2 diabetes mellitus, certain cancers, osteoarthritis, and numerous other chronic conditions **[2]**. Traditional weight management approaches emphasizing dietary modification and physical activity produce modest weight loss that proves difficult to maintain long-term **[3]**. Bariatric surgery achieves substantial weight reduction but carries surgical risks, requires lifelong dietary modifications, and remains inaccessible to most patients due to cost and contraindications **[4]**.

Pharmacological interventions for obesity have historically demonstrated limited efficacy or unacceptable safety profiles leading to market withdrawal **[5]**. Earlier anti-obesity medications including fenfluramine-phentermine combinations, sibutramine, and rimonabant were discontinued due to cardiovascular or psychiatric adverse effects **[6]**. Orlistat, the only obesity medication approved for long-term use for many years, produces modest weight loss with gastrointestinal side effects that limit adherence **[7]**.

The development of glucagon-like peptide-1 (GLP-1) receptor agonists has transformed obesity pharmacotherapy **[8]**. GLP-1 represents an incretin hormone secreted by intestinal L-cells in response to nutrient ingestion. The hormone regulates glucose homeostasis through multiple mechanisms including glucose-dependent insulin secretion, suppression of glucagon release, and delayed gastric emptying **[9]**. Early GLP-1 receptor agonists developed for type 2 diabetes mellitus demonstrated weight loss as a secondary effect, prompting investigation of higher doses specifically for obesity treatment **[10]**. Semaglutide, a GLP-1 receptor agonist with extended half-life enabling once-weekly administration, received initial approval for type 2 diabetes mellitus management **[11]**. Subsequent clinical trials investigating higher doses for weight management demonstrated substantial weight reduction exceeding that achieved with other pharmacological interventions **[12]**. Regulatory agencies approved semaglutide specifically for chronic weight management in adults with obesity or overweight with weight-related comorbidities **[13]**.

The medication has garnered substantial attention in both medical and popular media, leading to widespread off-label use, supply shortages, and concerns about appropriate patient selection **[14]**. Questions persist regarding long-term efficacy, safety with extended use, weight regain after discontinuation, cardiovascular outcomes, effects on body composition, psychological impacts, cost-effectiveness, and equitable access **[15]**.

Despite growing clinical use, several critical gaps in knowledge remain. First, long-term safety data beyond two years remain limited. Second, optimal patient selection criteria require refinement beyond body mass index thresholds. Third, strategies for maintaining weight loss after discontinuation need development. Fourth, comparative effectiveness against

bariatric surgery and other interventions remains incompletely characterized. Fifth, effects on body composition, particularly lean mass preservation, require clarification. Sixth, cardiovascular and metabolic outcomes beyond weight reduction need comprehensive evaluation. Seventh, psychosocial impacts including effects on eating behaviors, body image, and quality of life warrant investigation. Eighth, cost-effectiveness analyses across diverse healthcare systems remain limited. Ninth, strategies for addressing supply shortages and ensuring equitable access require development. Tenth, potential for misuse in individuals without clinical indications necessitates monitoring.

Based on these identified gaps, this narrative review aimed to: (i) elucidate the pharmacological mechanisms through which semaglutide produces weight loss; (ii) synthesize clinical trial evidence regarding efficacy across diverse populations and comparisons with alternative interventions; (iii) comprehensively evaluate the safety profile including common and serious adverse events; (iv) analyze practical implementation considerations including dosing protocols, patient selection, and contraindications; (v) examine effects on cardiometabolic outcomes beyond weight reduction; (vi) assess weight maintenance and outcomes after discontinuation; (vii) evaluate cost-effectiveness and accessibility considerations; (viii) critically appraise methodological limitations in existing research; and (ix) identify priority areas for future investigation.

2. PHARMACOLOGY AND MECHANISMS OF ACTION

2.1. GLP-1 Physiology and Receptor Signaling

Glucagon-like peptide-1 represents an incretin hormone derived from post-translational processing of proglucagon in intestinal L-cells **[9]**. The hormone secretes in response to nutrient ingestion, particularly carbohydrates and fats. Native GLP-1 has a short half-life of approximately two minutes due to rapid degradation by dipeptidyl peptidase-4 (DPP-4) enzyme **[16]**.

GLP-1 binds to GLP-1 receptors expressed in multiple tissues including pancreatic beta cells, gastrointestinal tract, cardiovascular system, kidneys, and specific brain regions **[17]**. In pancreatic beta cells, GLP-1 receptor activation stimulates glucose-dependent insulin secretion. This glucose-dependency reduces hypoglycemia risk compared to insulin secretagogues that function independently of glucose levels **[18]**. GLP-1 also suppresses glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production **[19]**. In the gastrointestinal tract, GLP-1 delays gastric emptying, prolonging nutrient absorption and enhancing satiety **[20]**.

Central nervous system effects prove particularly relevant for weight management. GLP-1 receptors localize in hypothalamic nuclei regulating appetite and energy homeostasis, including the arcuate nucleus, paraventricular nucleus, and dorsomedial hypothalamus **[21]**. GLP-1 receptor activation in these regions reduces food intake and increases energy expenditure. The brainstem also expresses GLP-1 receptors in areas processing satiety signals from the periphery **[22]**. Additionally, GLP-1 modulates reward pathways in the mesolimbic system, potentially reducing hedonic eating and food cravings **[23]**.

2.2. Semaglutide: Structural Modifications and Pharmacokinetics

Semaglutide represents a GLP-1 receptor agonist with structural modifications that extend its half-life and enable once-weekly subcutaneous administration **[11]**. The molecule contains 94% sequence homology with native human GLP-1 but includes three key modifications. First, an amino acid substitution at position 8 provides resistance to DPP-4 degradation. Second, attachment of a C18 fatty diacid side chain via a spacer enables binding to albumin, prolonging circulation time. Third, an amino acid substitution at position 34 reduces albumin binding affinity, allowing tissue distribution **[24]**.

These modifications result in a half-life of approximately one week, enabling once-weekly dosing **[11]**. Steady-state concentrations achieve after four to five weeks of administration. The medication demonstrates high selectivity for GLP-1 receptors with minimal cross-reactivity to other receptors **[25]**. Absorption following subcutaneous injection occurs slowly, with maximum concentration reached within one to three days. Metabolism occurs via proteolytic cleavage and beta-oxidation of the fatty acid side chain. Renal clearance remains minimal **[26]**.

2.3. Mechanisms of Weight Loss

Semaglutide produces weight loss through multiple complementary mechanisms **[27]**. The predominant effect involves appetite suppression and enhanced satiety through central and peripheral pathways. GLP-1 receptor activation in hypothalamic appetite-regulating centers reduces hunger and food-seeking behavior **[21]**. Peripheral effects include delayed gastric emptying, which prolongs the sensation of fullness after meals **[20]**. Vagal afferent signaling from gastrointestinal GLP-1 receptors communicates satiety information to brainstem nuclei **[22]**.

Table 1. Mechanisms of Semaglutide-Induced Weight Loss

Mechanism	Anatomical Site	Effect	Clinical Manifestation	Key References
Appetite suppression	Hypothalamic nuclei (arcuate, paraventricular)	Activation of POMC/CART neurons;	Reduced hunger; earlier satiety; decreased food intake	[21, 28]

Mechanism	Anatomical Site	Effect	Clinical Manifestation	Key References
		inhibition of NPY/AgRP neurons		
Delayed gastric emptying	Gastric smooth muscle; vagal afferents	Reduced gastric motility; prolonged nutrient presence in stomach	Extended fullness after meals; reduced meal frequency	[20, 29]
Enhanced satiety signaling	Brainstem (nucleus tractus solitarius, area postrema)	Integration of peripheral satiety signals	Increased meal-terminating signals; reduced portion sizes	[22, 30]
Reward pathway modulation	Mesolimbic dopamine system (ventral tegmental area, nucleus accumbens)	Reduced reward value of palatable foods	Decreased hedonic eating; reduced food cravings	[23, 31]
Energy expenditure	Brown adipose tissue; skeletal muscle	Potential increase in thermogenesis (evidence mixed)	Modest increase in resting energy expenditure	[32, 33]
Food preference alteration	Prefrontal cortex; insula	Modified neural responses to food cues	Preference for lower-calorie foods; reduced appeal of high-fat foods	[34, 35]

Modulation of reward pathways represents another important mechanism. Functional neuroimaging studies demonstrate that semaglutide reduces neural activation in reward-related brain regions in response to food cues **[34]**. This effect potentially reduces hedonic eating driven by food palatability rather than physiological hunger. Patients report decreased food cravings and reduced preoccupation with food **[36]**. Some evidence suggests semaglutide may increase energy expenditure, though this effect appears modest compared to effects on energy intake **[32]**. Potential mechanisms include increased thermogenesis in brown adipose tissue and enhanced postprandial energy expenditure. However, the contribution of increased energy expenditure to overall weight loss remains uncertain and likely small relative to reduced caloric intake **[33]**. Semaglutide may also alter food preferences, with some patients reporting reduced preference for high-fat, high-sugar foods **[35]**. Whether this represents a direct pharmacological effect or secondary consequence of altered reward processing remains unclear. Additionally, the medication may reduce alcohol consumption in some individuals, potentially through similar reward pathway modulation **[37]**.

2.4. Dose-Response Relationships

Weight loss demonstrates dose-dependent relationships with semaglutide **[38]**. Lower doses approved for type 2 diabetes mellitus produce modest weight reduction. Higher doses specifically approved for obesity treatment produce substantially greater weight loss. The dose-response relationship appears relatively steep, with meaningful differences between doses **[39]**.

However, higher doses also associate with increased adverse event frequency, necessitating careful dose titration **[40]**. The medication requires gradual dose escalation to minimize gastrointestinal adverse effects **[41]**. Standard protocols initiate treatment at low doses with incremental increases every four weeks until reaching the target maintenance dose. This titration strategy substantially reduces treatment discontinuation due to adverse effects compared to immediate initiation at higher doses **[42]**.

3. CLINICAL EFFICACY

3.1. Pivotal Clinical Trials

Multiple large-scale randomized controlled trials have evaluated semaglutide for weight management (Table 2). The STEP (Semaglutide Treatment Effect in People with obesity) program comprises the primary evidence base for regulatory approvals **[43]**.

Table 2. Major Clinical Trials of Semaglutide for Weight Management

Trial	Population	Intervention	Duration	Primary Findings	Reference
STEP 1	Adults with obesity or overweight with comorbidity (without diabetes)	Semaglutide 2.4 mg weekly vs placebo; both with lifestyle intervention	68 weeks	Semaglutide group achieved significantly greater weight loss than placebo; improvements in cardiometabolic parameters	[12]

Trial	Population	Intervention	Duration	Primary Findings	Reference
STEP 2	Adults with obesity or overweight and type 2 diabetes	Semaglutide 2.4 mg vs 1.0 mg vs placebo; all with lifestyle intervention	68 weeks	Both semaglutide doses superior to placebo; higher dose achieved greater weight loss; improvements in glycemic control	[41]
STEP 3	Adults with obesity or overweight	Semaglutide 2.4 mg vs placebo; both with intensive behavioral therapy	68 weeks	Semaglutide plus intensive behavioral therapy achieved substantial weight loss; combination superior to either intervention alone	[44]
STEP 4	Adults with obesity or overweight	Continued semaglutide 2.4 mg vs switch to placebo after 20-week run-in	68 weeks total	Continued treatment maintained weight loss; placebo group experienced weight regain	[39]
STEP 5	Adults with obesity or overweight	Semaglutide 2.4 mg vs placebo; both with lifestyle intervention	104 weeks	Sustained weight loss maintained at two years; continued improvements in cardiometabolic markers	[45]

The STEP 1 trial enrolled adults with obesity or overweight plus at least one weight-related comorbidity, excluding those with diabetes **[12]**. Participants received once-weekly subcutaneous semaglutide or placebo, both combined with lifestyle counselling on diet and physical activity. The trial demonstrated substantial weight reduction in the semaglutide group compared to placebo. A meaningful proportion of participants achieved clinically significant weight loss thresholds. Improvements in cardiometabolic risk factors including blood pressure, lipid profiles, and inflammatory markers accompanied weight reduction.

The STEP 2 trial specifically enrolled participants with type 2 diabetes mellitus and obesity or overweight **[41]**. The study compared two semaglutide doses against placebo, all with lifestyle intervention. Both semaglutide doses produced greater weight loss than placebo, with the higher dose achieving superior results. Glycemic control improved substantially in semaglutide groups, with many participants achieving target HbA1c levels and reducing or discontinuing other diabetes medications.

The STEP 3 trial combined semaglutide with intensive behavioral therapy including frequent counselling sessions, meal replacements, and structured physical activity programs **[44]**. The combination produced substantial weight loss, demonstrating that semaglutide enhances rather than replaces behavioral interventions. Participants receiving combination treatment achieved greater weight loss than historical controls receiving intensive behavioral therapy alone.

The STEP 4 trial employed a withdrawal design to assess weight maintenance **[39]**. All participants received semaglutide for 20 weeks, after which responders were randomized to continued treatment or switch to placebo. Participants continuing semaglutide maintained weight loss and achieved additional modest reductions. Those switched to placebo experienced substantial weight regain, though not returning fully to baseline weights. This trial demonstrates that continued treatment remains necessary for weight loss maintenance.

The STEP 5 trial extended treatment duration to two years, addressing questions about long-term efficacy and safety **[45]**. Weight loss continued progressively through the first year before plateauing. Participants maintained weight reduction at two years with continued treatment. Cardiometabolic improvements persisted or enhanced over time. Adverse event profiles remained consistent with shorter-duration trials, with no new safety signals emerging.

3.2. Comparisons with Other Interventions

Head-to-head trials comparing semaglutide to other anti-obesity medications demonstrate superior efficacy. Comparisons with liraglutide, an earlier GLP-1 receptor agonist approved for weight management at lower receptor activation levels, show greater weight loss with semaglutide **[46]**. Indirect comparisons suggest semaglutide produces weight loss exceeding that achieved with other approved pharmacotherapies including phentermine-topiramate, naltrexone-bupropion, and orlistat **[47]**.

Comparisons with bariatric surgery remain limited. Retrospective analyses and indirect comparisons suggest that semaglutide produces weight loss approaching but not exceeding that achieved with sleeve gastrectomy and substantially less than Roux-en-Y gastric bypass **[48]**. However, direct randomized comparisons are lacking. Combination approaches using semaglutide to enhance post-surgical weight loss or prevent weight regain after surgery warrant investigation **[49]**.

3.3. Special Populations

Clinical trials have evaluated semaglutide efficacy across diverse subgroups. Age does not appear to substantially modify treatment response, with older adults achieving meaningful weight loss comparable to younger participants **[50]**. Sex differences in weight loss magnitude remain inconsistent across trials, with most showing similar efficacy in men and women **[51]**.

Racial and ethnic diversity in trials remains limited, constraining conclusions about efficacy across populations **[52]**. Available data suggest comparable efficacy across racial groups, though sample sizes for some populations remain small. Cultural factors affecting diet, physical activity, and body weight perceptions may influence treatment response and require consideration **[53]**.

Baseline body mass index does not strongly predict treatment response within the studied range **[54]**. Individuals with higher baseline BMI achieve greater absolute weight loss but similar percentage reductions. Those with lower baseline BMI still achieve clinically meaningful weight loss. Whether efficacy extends to individuals below currently approved BMI thresholds remains unknown.

The presence of type 2 diabetes mellitus does not substantially reduce weight loss efficacy, though some trials show modestly attenuated responses compared to individuals without diabetes **[41]**. Importantly, semaglutide produces dual benefits of weight reduction and glycemic control in this population, often enabling reduction or discontinuation of other diabetes medications **[55]**.

Limited data exist for populations with specific medical conditions that commonly coexist with obesity. Preliminary evidence suggests efficacy in individuals with polycystic ovary syndrome, non-alcoholic fatty liver disease, obstructive sleep apnea, and osteoarthritis, though dedicated trials in these populations remain limited **[56]**. Effects on condition-specific outcomes beyond weight loss require investigation.

3.4. Adolescents and Pediatric Use

Semaglutide received approval for adolescents aged 12 years and older with obesity **[57]**. A dedicated trial in this age group demonstrated substantial weight reduction with acceptable tolerability **[58]**. However, long-term safety data in developing adolescents remain limited. Questions persist regarding effects on growth, bone development, psychological wellbeing, and long-term metabolic health **[59]**. The appropriateness of pharmacological obesity treatment in adolescents requires careful consideration of benefits, risks, and alternatives including family-based behavioral interventions and bariatric surgery in severe cases **[60]**.

4. SAFETY AND ADVERSE EVENTS

4.1. Common Adverse Effects

Gastrointestinal symptoms represent the most frequent adverse effects associated with semaglutide (Table 3) **[61]**. Nausea occurs most commonly, typically emerging shortly after dose initiation or escalation. The symptom usually diminishes over several weeks as tolerance develops **[62]**. Vomiting, diarrhea, constipation, and abdominal pain also occur frequently. These adverse effects contribute to treatment discontinuation in some patients **[63]**.

Table 3. Common and Serious Adverse Effects of Semaglutide

Category	Adverse Effect	Frequency	Clinical Management	Key References
Gastrointestinal (common)	Nausea	Very common	Dose titration; dietary modifications; antiemetics if severe	[61, 62]
Gastrointestinal (common)	Vomiting	Common	Hydration; electrolyte monitoring; dose reduction if persistent	[63]
Gastrointestinal (common)	Diarrhea	Common	Hydration; dietary modifications; antimotility agents if needed	[61]
Gastrointestinal (common)	Constipation	Common	Increased fluid and fiber intake; stool softeners; physical activity	[61]
Gastrointestinal (serious)	Pancreatitis	Rare	Discontinue medication; hospital evaluation; lipase monitoring	[64]
Hepatobiliary (serious)	Gallbladder disease; cholelithiasis	Uncommon	Ultrasound evaluation; surgical consultation if symptomatic	[65]
Endocrine (preclinical)	Thyroid C-cell tumors	Not observed in humans (rodent finding)	Contraindicated with personal/family history of MTC or MEN 2	[66]
Metabolic	Hypoglycemia	Rare (unless combined with insulin/sulfonylureas)	Reduce concomitant glucose-lowering medications	[67]

Category	Adverse Effect	Frequency	Clinical Management	Key References
Injection site	Injection site reactions	Uncommon	Rotate injection sites; proper technique education	[68]
Psychiatric	Suicidal ideation (debated)	Unclear if causal	Monitor mental health; careful history before initiation	[69]

Several strategies reduce gastrointestinal adverse effects. Gradual dose escalation represents the most effective approach, allowing tolerance development at each dose level before advancing **[41]**. Dietary modifications including smaller, more frequent meals, avoidance of high-fat foods, and adequate hydration may help **[70]**. For patients with persistent nausea despite dose titration, temporary dose reduction or addition of antiemetic medications may provide relief. In severe cases requiring treatment discontinuation, rechallenge at lower doses after symptom resolution sometimes succeeds **[71]**. Injection site reactions occur less frequently but include erythema, pruritus, and induration **[68]**. Proper injection technique education and site rotation minimize these reactions. Rarely, allergic reactions including urticaria and angioedema occur, necessitating treatment discontinuation **[72]**.

4.2. Serious Adverse Events

Pancreatitis represents a serious adverse event associated with GLP-1 receptor agonists, though causality remains debated **[64]**. Clinical trial data show low absolute rates of pancreatitis in both semaglutide and placebo groups, with some meta-analyses suggesting slightly elevated risk **[73]**. Obesity itself increases pancreatitis risk, complicating attribution. Patients should receive counselling about pancreatitis symptoms (severe abdominal pain radiating to the back, nausea, vomiting) with instructions to discontinue medication and seek immediate evaluation if these occur. Those with prior pancreatitis history require careful risk-benefit assessment before initiation **[74]**.

Gallbladder disease including cholelithiasis and cholecystitis occurs more frequently with semaglutide than placebo **[65]**. Rapid weight loss independent of method increases gallstone formation risk. Whether semaglutide carries risk beyond that attributable to weight loss remains unclear. Symptomatic gallbladder disease requires standard management including potential cholecystectomy. Some clinicians consider ursodeoxycholic acid prophylaxis in high-risk patients, though evidence supporting this practice remains limited **[75]**.

Thyroid safety concerns originated from preclinical studies showing thyroid C-cell tumors in rodents exposed to GLP-1 receptor agonists **[66]**. These findings resulted in contraindications for patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. However, extensive postmarketing surveillance and clinical trial data show no evidence of increased thyroid cancer risk in humans **[76]**. The relevance of rodent findings to human risk remains controversial, with most experts considering human risk very low **[77]**. Nevertheless, the contraindication remains in regulatory labeling.

Hypoglycemia risk remains low with semaglutide monotherapy due to glucose-dependent mechanisms of action **[67]**. However, when combined with insulin or insulin secretagogues like sulfonylureas, hypoglycemia risk increases. Patients taking these medications require dose reductions of concomitant agents when initiating semaglutide **[78]**. Those with type 1 diabetes should not receive semaglutide, as safety and efficacy remain unestablished in this population **[79]**.

Cardiovascular safety receives particular attention given historical concerns with some obesity medications. Cardiovascular outcome trials demonstrate cardiovascular safety with no increased risk of major adverse cardiovascular events **[80]**. Some evidence suggests potential cardiovascular benefits including reduced events in high-risk populations, though dedicated outcome trials for weight management indications are ongoing **[81]**.

Renal safety data show no concerning signals in clinical trials **[82]**. Some evidence suggests potential renal protective effects, possibly mediated through weight loss, blood pressure reduction, and direct renal GLP-1 receptor effects. Patients with severe renal impairment were excluded from most trials, limiting safety data in this population **[83]**.

4.3. Psychiatric and Psychological Effects

Reports of suicidal ideation in patients taking semaglutide prompted regulatory reviews **[69]**. Analyses of clinical trial data show no clear signal of increased suicidal ideation or behavior compared to placebo **[84]**. However, rapid weight loss from any method can affect mood and psychological wellbeing. Additionally, individuals with obesity have elevated baseline rates of depression and anxiety **[85]**. Careful psychiatric assessment before treatment initiation and monitoring during treatment remain prudent, particularly in patients with psychiatric history **[86]**.

Body image changes resulting from rapid weight loss may produce psychological distress in some individuals. Loose skin, changed appearance, and altered self-perception require psychological adjustment **[87]**. Some patients report changes in appetite and relationship with food that feel distressing despite being therapeutic targets. Mental health support should be readily available for patients experiencing psychological difficulties during treatment **[88]**.

4.4. Long-Term Safety

Long-term safety data beyond two years remain limited **[45]**. Extended follow-up studies are ongoing but have not yet reported results. Potential concerns requiring long-term monitoring include bone health effects, as rapid weight loss can

reduce bone mineral density **[89]**. Nutritional deficiencies may develop if inadequate dietary intake accompanies appetite suppression **[90]**. Cardiac structural changes related to weight loss warrant attention in longitudinal studies **[91]**. Potential effects on reproductive function and fertility require investigation **[92]**. Unknown effects of chronic GLP-1 receptor activation over decades represent a theoretical concern given limited human experience with lifelong treatment **[93]**.

Postmarketing surveillance programs continue monitoring for rare adverse events not detected in clinical trials **[94]**. Healthcare providers should report unexpected serious adverse events to regulatory agencies **[95]**. Long-term registries tracking patients treated with semaglutide will provide valuable safety data as clinical experience accumulates over time.

4.5. Contraindications and Precautions

Absolute contraindications for semaglutide include personal or family history of medullary thyroid carcinoma **[66]**, multiple endocrine neoplasia syndrome type 2 **[66]**, previous severe hypersensitivity reaction to semaglutide or excipients **[72]**, and pregnancy (medication should be discontinued at least 2 months before planned conception) **[96]**. Relative contraindications and situations requiring caution include history of pancreatitis **[74]**, severe gastrointestinal disease **[97]**, diabetic retinopathy (due to rapid glycemic improvement potentially worsening retinopathy) **[55]**, severe renal impairment **[83]**, and psychiatric conditions including suicidal ideation **[86]**. Each of these situations requires individualized risk-benefit assessment considering patient-specific factors, disease severity, alternative treatment options, and monitoring capabilities.

5. PRACTICAL IMPLEMENTATION

5.1. Patient Selection Criteria

Regulatory approvals specify semaglutide for adults with body mass index equal to or greater than 30 kg/m² (obesity), or body mass index equal to or greater than 27 kg/m² (overweight) with at least one weight-related comorbidity **[13]**. Weight-related comorbidities include hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea, cardiovascular disease, and others **[98]**. The relatively broad approval criteria allow treatment of many patients with obesity or overweight-related health consequences.

However, appropriate patient selection extends beyond regulatory criteria. Ideal candidates demonstrate previous unsuccessful attempts at weight loss through lifestyle modification **[99]**, understanding that medication represents one component of comprehensive weight management **[100]**, willingness and ability to implement dietary and physical activity changes **[101]**, acceptance of ongoing treatment requirement for weight loss maintenance **[102]**, financial means or insurance coverage to afford medication long-term **[103]**, absence of contraindications and acceptable risk profile **[104]**, and realistic expectations about weight loss magnitude and timeline **[105]**.

Shared decision-making should incorporate discussion of treatment goals, expected outcomes, adverse effects, costs, duration of therapy, and alternatives **[106]**. Patients should understand that discontinuation typically results in weight regain, necessitating indefinite treatment for most individuals **[39]**. The conversation should address individual values, preferences, and priorities regarding weight management approaches.

5.2. Dosing and Administration

Standard dosing protocols for weight management initiate semaglutide at 0.25 mg once weekly for four weeks **[41]**. The dose then escalates to 0.5 mg weekly for four weeks, followed by increases to 1.0 mg, 1.7 mg, and finally 2.4 mg at four-week intervals. The 2.4 mg dose represents the target maintenance dose for weight management. Some patients may require slower escalation if gastrointestinal symptoms prove limiting **[42]**. Clinicians should individualize escalation schedules based on tolerability, emphasizing that slower advancement often improves long-term adherence compared to forcing rapid escalation despite symptoms.

Patients receive training on subcutaneous injection technique. The medication comes in prefilled, single-use pens requiring refrigeration until first use **[107]**. Injection sites include abdomen, thigh, or upper arm, with site rotation recommended to minimize injection site reactions **[68]**. Administration timing can be any day of the week, though consistency improves adherence **[108]**. Patients should select a day that fits their schedule and supports consistent weekly administration.

Missed doses create challenges given the weekly schedule. If a dose is missed and remembered within five days, patients should administer immediately. If more than five days have passed, the missed dose should be skipped **[109]**. Prolonged interruptions may necessitate dose re-titration to minimize gastrointestinal symptoms upon resumption **[110]**. Clear instructions about managing missed doses should be provided at treatment initiation to prevent confusion and inappropriate dosing.

5.3. Monitoring and Follow-Up

Regular monitoring during semaglutide treatment should include weight and body mass index assessment at each visit **[111]**, blood pressure monitoring **[112]**, heart rate assessment (GLP-1 receptor agonists may increase heart rate modestly) **[113]**, gastrointestinal symptom evaluation **[114]**, assessment of diet quality and nutritional adequacy **[115]**, physical activity level evaluation **[116]**, screening for mood changes or suicidal ideation **[86]**, and medication adherence assessment **[117]**. Initial visits may occur monthly during dose escalation, with subsequent visits every three months once stable on maintenance dose.

For patients with diabetes, glucose monitoring intensity depends on concomitant medications and hypoglycemia risk **[118]**. Hemoglobin A1c should be assessed every three to six months **[119]**. Adjustment of other glucose-lowering

medications, particularly insulin and sulfonylureas, requires careful attention to prevent hypoglycemia **[78]**. Frequent communication during the initial months allows timely medication adjustments as weight loss and improved insulin sensitivity alter glucose dynamics.

Lipid panels and liver function tests should be monitored periodically, though no specific monitoring schedule is mandated **[120]**. Patients with rapid or extensive weight loss may benefit from bone density assessment given potential effects on bone mineral density **[89]**. Nutritional assessment including vitamin and mineral status may be warranted in patients with very restricted intake **[90]**. Individualized monitoring plans should consider patient-specific risk factors, comorbidities, and rate of weight loss.

5.4. Combination with Lifestyle Interventions

Semaglutide should always accompany lifestyle modifications including dietary changes and increased physical activity **[101]**. The medication enhances effectiveness of behavioral interventions rather than replacing them **[44]**. Reduced caloric intake facilitated by appetite suppression should focus on nutrient-dense foods to prevent nutritional deficiencies **[121]**. Patients benefit from understanding that medication addresses physiological drivers of obesity while behavioral changes address environmental, psychological, and habitual factors.

Dietary counselling should address portion control and mindful eating practices **[122]**, emphasis on vegetables, fruits, whole grains, lean proteins, and healthy fats **[123]**, strategies for managing gastrointestinal symptoms through food choices **[70]**, adequate protein intake to preserve lean body mass during weight loss **[124]**, and hydration maintenance **[125]**. Working with registered dietitians can help patients develop sustainable eating patterns that support both weight loss during treatment and maintenance if treatment discontinues.

Physical activity recommendations include gradual increase to at least 150 minutes of moderate-intensity activity weekly **[126]**, incorporation of resistance training to preserve muscle mass **[127]**, activities appropriate for individual fitness level and joint health **[128]**, and strategies for overcoming barriers to physical activity **[129]**. As weight loss progresses, many patients find physical activity becomes easier and more enjoyable, creating positive reinforcement loops that support continued engagement.

Behavioral interventions addressing eating behaviors, stress management, sleep quality, and environmental factors that influence weight should complement pharmacotherapy **[130]**. Referral to registered dietitians, exercise physiologists, or behavioral health specialists may enhance outcomes **[131]**. Multidisciplinary care teams provide comprehensive support addressing the biological, psychological, and social dimensions of obesity.

6. CARDIOMETABOLIC OUTCOMES

6.1. Effects on Glycemic Control

In patients with type 2 diabetes, semaglutide substantially improves glycemic control beyond effects attributable to weight loss alone **[41]**. Hemoglobin A1c reductions occur through multiple mechanisms including enhanced glucose-dependent insulin secretion, suppressed glucagon release, and delayed gastric emptying **[132]**. Many patients achieve glycemic targets, allowing reduction or discontinuation of other diabetes medications **[55]**. The glucose-dependent mechanism of action results in low hypoglycemia risk when used as monotherapy **[67]**.

Fasting plasma glucose decreases with semaglutide treatment **[133]**. Postprandial glucose excursions improve due to delayed gastric emptying and enhanced insulin response **[134]**. These glycemic improvements translate to reduced diabetes-related complications risk over time **[135]**.

For patients with prediabetes, semaglutide reduces progression to type 2 diabetes, though dedicated prevention trials are limited **[136]**. The glycemic benefits of semaglutide persist with continued treatment **[45]**. Some patients with relatively recent diabetes onset achieve remission defined as maintaining normal glucose levels without glucose-lowering medications **[137]**. However, cessation of semaglutide typically results in glycemic deterioration, requiring resumption of treatment or alternative medications **[138]**.

6.2. Blood Pressure and Lipid Effects

Semaglutide produces modest reductions in systolic and diastolic blood pressure **[112]**. The blood pressure lowering effects occur partially through weight loss but may involve additional mechanisms including natriuresis and improved endothelial function **[139]**. Patients taking antihypertensive medications may require dose adjustments to prevent excessive blood pressure reduction **[140]**. Improvements in blood pressure contribute to overall cardiovascular risk reduction.

Lipid profile changes include reductions in total cholesterol, LDL cholesterol, and triglycerides **[141]**. HDL cholesterol may increase modestly **[142]**. These lipid improvements result primarily from weight loss and dietary changes rather than direct medication effects **[143]**. Patients taking lipid-lowering medications may achieve better lipid control, potentially allowing medication dose reductions in some cases **[144]**.

Inflammatory markers including C-reactive protein decrease with semaglutide treatment **[145]**. Adiponectin, an anti-inflammatory adipokine, increases **[146]**. These changes reflect improved metabolic health and reduced systemic inflammation associated with obesity **[147]**. The anti-inflammatory effects may contribute to cardiovascular benefits beyond traditional risk factor improvements.

6.3. Cardiovascular Outcomes

Cardiovascular outcome trials of semaglutide demonstrate cardiovascular safety with no increased risk of major adverse cardiovascular events **[80]**. The SELECT trial specifically evaluated cardiovascular outcomes in patients with established cardiovascular disease and overweight or obesity without

diabetes **[148]**. The trial demonstrated reduced risk of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke with semaglutide compared to placebo **[148]**. These findings establish semaglutide as the first obesity medication proven to reduce cardiovascular events.

The mechanisms underlying cardiovascular benefits likely involve multiple pathways. Weight reduction itself improves cardiovascular risk factors **[149]**. Blood pressure and lipid improvements contribute to reduced atherosclerotic progression **[150]**. Anti-inflammatory effects may stabilize atherosclerotic plaques **[151]**. Direct effects on vascular endothelium, cardiac muscle, and atherosclerotic plaque composition represent additional potential mechanisms **[152]**.

Heart rate increases modestly with GLP-1 receptor agonists including semaglutide **[113]**. The clinical significance of this heart rate increase remains uncertain **[153]**. Most studies show no association with adverse cardiovascular outcomes despite elevated heart rate **[74]**. Patients with resting tachycardia or those on heart rate-limiting medications require monitoring.

6.4. Effects on Non-Alcoholic Fatty Liver Disease

Obesity associates strongly with non-alcoholic fatty liver disease (NAFLD) and its progressive form, non-alcoholic steatohepatitis (NASH) **[154]**. Semaglutide reduces hepatic steatosis assessed by imaging or biopsy **[155]**. Liver enzyme elevations improve with treatment **[156]**. Histological improvements in NASH including reductions in steatosis, inflammation, and fibrosis have been demonstrated in dedicated trials **[157]**.

The hepatic benefits of semaglutide result primarily from weight loss and improved insulin sensitivity **[158]**. Direct hepatic effects through GLP-1 receptors may also contribute, though hepatocyte GLP-1 receptor expression remains controversial **[159]**. For patients with NAFLD or NASH, semaglutide represents a promising treatment option that addresses both obesity and liver disease **[160]**.

6.5. Renal Outcomes

Semaglutide demonstrates renal protective effects in patients with type 2 diabetes **[82]**. Albuminuria decreases with treatment **[161]**. Estimated glomerular filtration rate remains stable or improves in most patients **[162]**. The FLOW trial specifically evaluated renal outcomes in patients with type 2 diabetes and chronic kidney disease, demonstrating reduced risk of kidney disease progression, end-stage renal disease, cardiovascular death, and renal death **[162]**.

Renal benefits likely result from multiple mechanisms. Blood pressure reduction decreases intraglomerular pressure **[163]**. Improved glycemic control reduces diabetic kidney disease progression **[164]**. Weight loss and metabolic improvements contribute to renal protection **[165]**. Direct effects on renal GLP-1 receptors may modulate sodium reabsorption and glomerular hemodynamics **[166]**.

7. WEIGHT MAINTENANCE AND POST-DISCONTINUATION OUTCOMES

7.1. Weight Regain After Discontinuation

The STEP 4 withdrawal trial demonstrated that discontinuation of semaglutide results in substantial weight regain **[39]**. Participants switched to placebo after 20 weeks of treatment regained approximately two-thirds of lost weight over the subsequent year. Cardiometabolic improvements including glycemic control, blood pressure, and lipid profiles deteriorated with weight regain **[39]**. These findings indicate that semaglutide addresses underlying biological drivers of obesity that reassert when treatment stops rather than permanently resetting body weight regulation.

The biological mechanisms driving weight regain involve multiple compensatory responses to weight loss. Reductions in energy expenditure below predicted levels based on new body weight occur with weight loss through any method **[167]**. Increased hunger and food preoccupation emerge as body weight falls below defended set point **[168]**. Neurohormonal changes including decreased leptin and increased ghrelin promote weight regain **[168]**. Semaglutide counteracts these compensatory mechanisms during treatment, but they reassert after discontinuation.

Individual variability exists in weight regain trajectories. Some patients maintain greater proportions of weight loss after discontinuation, particularly those who successfully modified diet and physical activity patterns **[101]**. However, most patients require continued pharmacotherapy for sustained weight loss **[169]**. This pattern parallels other chronic diseases like hypertension or diabetes where ongoing treatment remains necessary for disease control.

7.2. Strategies for Sustained Weight Loss

Given high rates of weight regain after semaglutide discontinuation, most patients require indefinite treatment for weight loss maintenance **[170]**. This approach treats obesity as a chronic disease requiring ongoing management rather than an acute condition curable with temporary intervention **[98]**. Patients should understand treatment duration expectations before initiating therapy to make informed decisions about starting medication **[171]**.

For patients who discontinue semaglutide due to cost, side effects, or personal preference, intensive behavioral interventions may help minimize weight regain **[172]**. Structured programs including frequent counseling, meal replacements, and activity monitoring provide external support replacing pharmacological appetite regulation **[173]**. However, behavioral interventions alone rarely maintain pharmacologically-achieved weight loss **[174]**.

Transitioning to alternative weight management medications represents another strategy. Patients intolerant of semaglutide might tolerate other GLP-1 receptor agonists or different

medication classes **[175]**. Combination pharmacotherapy using multiple mechanisms may provide alternatives for some patients **[176]**. However, medication access and cost often limit these options.

Bariatric surgery after semaglutide discontinuation could provide more durable weight loss for appropriate candidates **[177]**. Whether prior semaglutide use affects surgical outcomes remains unclear **[178]**. Some patients may view medications as bridging therapy while pursuing surgical options or preparing for surgery **[179]**.

7.3. Long-Term Efficacy Data

The longest randomized controlled trial data extend to two years from the STEP 5 trial **[45]**. Weight loss was maintained at this timepoint with continued treatment. Participants achieved substantial reductions from baseline with continued improvements in cardiometabolic parameters. These findings demonstrate maintained efficacy through two years without evidence of tolerance development.

However, data beyond two years remain limited to extension studies and observational cohorts **[138]**. Whether weight loss plateaus, continues gradually, or begins reversing with very long-term treatment remains uncertain **[180]**. The STEP 5 data suggest plateau rather than continued loss after the first year **[45]**. Long-term registry studies will provide valuable data about outcomes with extended treatment duration.

Durability of cardiometabolic benefits with sustained treatment requires investigation. The SELECT cardiovascular outcomes trial provides data through several years, demonstrating maintained cardiovascular benefits **[148]**. Whether benefits plateau, increase progressively, or diminish over time needs clarification **[181]**. The time course of benefits for specific outcomes like diabetes prevention, sleep apnea improvement, or joint health enhancement warrants study.

8. COST-EFFECTIVENESS AND ACCESSIBILITY

8.1. Economic Considerations

Semaglutide represents a high-cost obesity treatment **[182]**. The medication costs substantially more than older anti-obesity medications and lifestyle interventions **[183]**. For most patients, lifelong treatment is required, resulting in cumulative costs over decades **[184]**. These costs create access barriers for many individuals who might benefit clinically.

Insurance coverage for obesity medications varies widely. Some insurers cover semaglutide for weight management while others restrict coverage to diabetes indications **[185]**. Prior authorization requirements, step therapy protocols, and coverage limitations constrain access **[186]**. Medicare coverage for obesity medications has been restricted historically, though policy discussions about expanding coverage are ongoing **[187]**.

Cost-effectiveness analyses compare treatment costs to health benefits measured as quality-adjusted life years **[188]**. Modeling studies suggest semaglutide may be cost-effective compared to usual care when accounting for reduced obesity-related complications **[189]**. However, cost-effectiveness depends critically on assumptions about medication duration, adherence, complication rates, and medication pricing **[190]**. Results vary across healthcare systems with different cost structures.

The cardiovascular benefits demonstrated in SELECT may improve cost-effectiveness by preventing expensive cardiovascular events **[148]**. Reduced diabetes incidence and progression in treated patients could generate healthcare savings **[191]**. However, these benefits must offset high medication costs over many years **[192]**. Whether semaglutide ultimately proves cost-effective at current pricing remains debated.

8.2. Supply Chain and Access Issues

Widespread demand for semaglutide has created supply shortages affecting access for both obesity and diabetes indications **[193]**. Manufacturing capacity has not kept pace with demand growth **[194]**. These shortages have led to treatment interruptions for established patients and delays initiating new patients **[195]**.

The supply constraints have prompted some clinicians to prioritize patients based on clinical need. Patients with diabetes may receive priority over those seeking weight management **[196]**. Those with severe obesity and multiple complications may receive priority over those with lower BMI **[197]**. Such prioritization raises ethical questions about equitable access to effective treatments.

Compounding pharmacies have filled some supply gaps by producing semaglutide formulations **[198]**. However, quality control concerns exist regarding compounded products **[199]**. Regulatory agencies have issued warnings about compounded GLP-1 receptor agonists that may lack appropriate oversight **[200]**. Patients using compounded formulations should understand potential differences from approved products.

8.3. Health Equity Considerations

High costs and variable insurance coverage create disparities in semaglutide access across socioeconomic groups **[201]**. Individuals with comprehensive insurance or financial resources can access treatment while those lacking coverage or unable to afford out-of-pocket costs cannot **[202]**. These disparities may worsen obesity-related health inequities if effective treatments remain available only to advantaged populations.

Clinical trial populations have limited racial and ethnic diversity, constraining understanding of efficacy and safety across populations **[52]**. Underrepresented groups may have different responses to treatment or different adverse event profiles **[203]**. Cultural factors affecting diet, physical activity,

and perceptions of obesity treatment may influence outcomes **[53]**.

Language barriers, health literacy limitations, and lack of culturally concordant care may further limit access for some populations **[204]**. Injectable medication requirements and need for refrigeration could present practical barriers for patients with unstable housing or limited resources **[205]**. Addressing these equity concerns requires policy interventions, community-based care delivery models, and efforts to reduce medication costs.

9. RESEARCH GAPS AND FUTURE DIRECTIONS

Despite substantial research on semaglutide for weight management, critical knowledge gaps remain.

First, long-term safety data beyond two years are limited. Extended follow-up studies tracking patients for five years, ten years, and longer are needed to identify late adverse effects not apparent in shorter trials. Particular attention should focus on bone health, nutritional status, cardiovascular structure, cancer incidence, and potential effects of chronic GLP-1 receptor activation over decades.

Second, strategies for maintaining weight loss after semaglutide discontinuation require development and testing. Most patients regain weight when treatment stops, creating a need for maintenance approaches. Research should evaluate intensive behavioral interventions, transitioning to alternative medications, intermittent treatment strategies, and factors predicting successful maintenance to identify patients who might sustain weight loss after discontinuation.

Third, optimal patient selection criteria need refinement beyond current BMI-based thresholds. Biomarkers, genetic factors, behavioral characteristics, or clinical features that predict treatment response could enable personalized medicine approaches. Understanding which patients benefit most helps target treatment to those likely to achieve meaningful outcomes.

Fourth, comparative effectiveness research directly comparing semaglutide to bariatric surgery is lacking. Randomized trials comparing medications to surgical interventions would inform treatment selection. Studies examining combination approaches using semaglutide to enhance surgical outcomes or prevent post-surgical weight regain could identify synergistic strategies.

Fifth, effects on body composition require clarification. Weight loss includes both fat mass and lean mass reduction. Whether semaglutide preferentially reduces adipose tissue while preserving muscle compared to other interventions remains uncertain. Strategies combining semaglutide with resistance training and adequate protein intake to optimize body composition warrant investigation.

Sixth, mechanisms of weight loss beyond appetite suppression deserve further investigation. The relative contributions of delayed gastric emptying, altered food preferences, modified reward processing, and potential effects on energy expenditure need quantification. Understanding mechanisms could identify combination approaches targeting multiple pathways.

Seventh, psychosocial impacts including effects on eating behaviors, body image, quality of life, and mental health require comprehensive evaluation. Rapid weight loss affects psychological wellbeing and social functioning in complex ways. Research should examine both benefits and potential harms across psychological domains.

Eighth, pediatric long-term safety data are critically needed. Effects on growth, development, bone health, and long-term metabolic health in adolescents treated during development require investigation. Studies should examine whether early intervention prevents adult obesity and associated complications or produces unexpected long-term consequences.

Ninth, cardiovascular and metabolic outcomes in diverse populations need examination. Most trial participants have been from Western countries with limited representation of global populations. Whether cardiovascular and metabolic benefits extend across ethnic, racial, and geographic populations requires confirmation.

Tenth, strategies for ensuring equitable access to effective obesity treatments deserve attention. Research on implementation approaches, policy interventions, and care delivery models that reduce disparities would support broader benefit from advances in obesity pharmacotherapy. Studies examining barriers to access and testing interventions to overcome them could improve health equity.

10. CONCLUSION

Semaglutide represents a major advancement in obesity pharmacotherapy, offering substantial weight reduction through multiple biological mechanisms. The medication functions primarily by suppressing appetite and enhancing satiety through effects on hypothalamic appetite centers, delayed gastric emptying, and modulation of reward pathways. Clinical trials demonstrate superior efficacy compared to placebo and other approved anti-obesity medications across diverse populations. Meaningful proportions of patients achieve clinically significant weight loss thresholds with accompanied improvements in cardiometabolic risk factors including blood pressure, lipid profiles, glycemic control, and systemic inflammation.

The safety profile of semaglutide includes primarily gastrointestinal adverse effects that typically diminish with dose titration and time. Serious adverse events remain relatively rare but include pancreatitis and gallbladder disease. Long-term safety beyond two years requires further investigation. Cardiovascular outcome trials demonstrate safety and potential benefit, establishing semaglutide as the first obesity medication proven to reduce cardiovascular events.

The medication requires ongoing treatment for weight loss maintenance, as discontinuation results in substantial weight

regain in most patients. Practical implementation requires careful patient selection considering both clinical eligibility and individual factors including prior weight loss attempts, willingness to modify lifestyle behaviors, acceptance of long-term treatment, and financial means to afford medication. Gradual dose escalation minimizes adverse effects and improves tolerability. The medication should always accompany rather than replace lifestyle modifications addressing diet, physical activity, and behavioral factors contributing to obesity. Regular monitoring ensures appropriate response, adverse effect detection, and dose adjustments when necessary.

Critical knowledge gaps constrain comprehensive understanding of semaglutide's role in obesity management. Long-term safety data, strategies for post-discontinuation weight maintenance, optimal patient selection approaches, comparative effectiveness against surgical interventions, effects on body composition, and psychosocial impacts require investigation. Addressing cost and accessibility barriers represents a crucial challenge for ensuring equitable access to effective treatment. As clinical experience accumulates and research addresses current limitations, the field will develop increasingly refined understanding of how to optimize semaglutide use for obesity management across diverse populations and clinical contexts.

References

1. Organization WH. Obesity and overweight Geneva: WHO; 2021 [Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.

2. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. BMC Public Health. 2009;9(1):88.

3. Wing RR, Phelan S. Long-term weight loss maintenance. The American journal of clinical nutrition. 2005;82(1):222S-5S.

4. Arterburn DE, Telem DA, Kushner RF, Courcoulas AP. Benefits and Risks of Bariatric Surgery in Adults. JAMA : the journal of the American Medical Association. 2020;324(9):879.

5. Yanovski SZ, Yanovski JA. Long-term Drug Treatment for Obesity. JAMA : the journal of the American Medical Association. 2014;311(1):74.

6. Rodgers RJ, Tschöp MH, Wilding JPH. Anti-obesity drugs: past, present and future. Disease Models & Mechanisms. 2012;5(5):621-6.

7. Rucker D, Padwal R, Li SK, Curioni C, Lau DCW. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. British medical journal. 2007;335(7631):1194-9.

8. Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, et al. Glucagon-like peptide 1 (GLP-1). Molecular metabolism. 2019;30:72-130.

9. Holst JJ. The Physiology of Glucagon-like Peptide 1. Physiological reviews. 2007;87(4):1409-39.

10. Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. The lancet. 2009;374(9701):1606-16.

11. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, Kofoed J, et al. Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide. Journal of medicinal chemistry. 2015;58(18):7370-80.

12. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. The New England journal of medicine. 2021;384(11):989-1002.

13. Administration UFaD. FDA approves new drug treatment for chronic weight management Silver Spring, MD: U.S. Food and Drug Administration; 2021 [

14. Ryan N, Savulescu J. The Ethics of Ozempic and Wegovy. Journal of medical ethics. 2024:jme-2024-110374.

15. Lim S, Buranapin S, Bao X, Quiroga M, Park KH, Kang J-H, et al. Once-weekly semaglutide 2·4 mg in an Asian population with obesity, defined as BMI ≥25 kg/m2, in South Korea and Thailand (STEP 11): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. 2025;13(10):838-47.

16. Deacon CF. Physiology and Pharmacology of DPP-4 in Glucose Homeostasis and the Treatment of Type 2 Diabetes. Frontiers in Endocrinology. 2019;10.

17. Drucker DJ. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. Cell Metabolism. 2018;27(4):740-56.

18. Nauck MA, Meier JJ. Incretin hormones: Their role in health and disease. Diabetes, obesity & metabolism. 2018;20(S1):5-21.

19. Unger RH, Cherrington AD. Glucagonocentric restructuring of diabetes: a pathophysiologic and therapeutic makeover. Journal of Clinical Investigation. 2012;122(1):4-12.

20. Marathe CS, Rayner CK, Jones KL, Horowitz M. Glucagon-like peptides 1 and 2 in health and disease: A review. Peptides. 2013;44:75-86.

21. Secher A, Jelsing J, Baquero AF, Hecksher-Sørensen J, Cowley MA, Dalbøge LS, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. Journal of Clinical Investigation. 2014;124(10):4473-88.

22. Grill J, Harvey, Hayes R, Matthew. Hindbrain Neurons as an Essential Hub in the Neuroanatomically Distributed Control of Energy Balance. Cell Metabolism. 2012;16(3):296-309.

23. Dickson SL, Shirazi RH, Hansson C, Bergquist F, Nissbrandt H, Skibicka KP. The Glucagon-Like Peptide 1 (GLP-1) Analogue, Exendin-4, Decreases the Rewarding Value of Food: A New Role for Mesolimbic GLP-1 Receptors. The Journal of Neuroscience. 2012;32(14):4812-20.

24. Buckley ST, Bækdal TA, Vegge A, Maarbjerg SJ, Pyke C, Ahnfelt-Rønne J, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Science translational medicine. 2018;10(467):eaar7047.

25. Knudsen LB, Lau J. The Discovery and Development of Liraglutide and Semaglutide. Frontiers in Endocrinology. 2019;10.

26. Yang X-D, Yang Y-Y. Clinical Pharmacokinetics of Semaglutide: A Systematic Review. Drug Design, Development and Therapy. 2024;Volume 18:2555-70.

27. Müller TD, Blüher M, Tschöp MH, DiMarchi RD. Anti-obesity drug discovery: advances and challenges. Nature reviews. 2022;21(3):201-23.

28. Cowley MA, Smart JL, Rubinstein M, Cerdán MG, Diano S, Horvath TL, et al. Leptin activates anorexigenic POMC neurons

through a neural network in the arcuate nucleus. Nature. 2001;411(6836):480-4.

29. Nauck MA, Niedereichholz U, Ettler R, Holst JJ, Ørskov C, Ritzel R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. American journal of physiology. 1997;273(5):E981-E8.

30. Hayes MR, De Jonghe BC, Kanoski SE. Role of the glucagon-like-peptide-1 receptor in the control of energy balance. Physiology & behavior. 2010;100(5):503-10.

31. Skibicka KP. The central GLP-1: implications for food and drug reward. Frontiers in Neuroscience. 2013;7.

32. Beiroa D, Imbernon M, Gallego R, Senra A, Herranz D, Villarroya F, et al. GLP-1 Agonism Stimulates Brown Adipose Tissue Thermogenesis and Browning Through Hypothalamic AMPK. Diabetes : a journal of the American Diabetes Association. 2014;63(10):3346-58.

33. Karakasis P, Patoulias D, Fragakis N, Mantzoros CS. Effect of glucagon-like peptide-1 receptor agonists and co-agonists on body composition: Systematic review and network meta-analysis. Metabolism, clinical and experimental. 2025;164:156113.

34. van Bloemendaal L, Ijzerman RG, ten Kulve JS, Barkhof F, Konrad RJ, Drent ML, et al. GLP-1 Receptor Activation Modulates Appetite- and Reward-Related Brain Areas in Humans. Diabetes : a journal of the American Diabetes Association. 2014;63(12):4186-96.

35. Farr OM, Sofopoulos M, Tsoukas MA, Dincer F, Thakkar B, Sahin-Efe A, et al. GLP-1 receptors exist in the parietal cortex, hypothalamus and medulla of human brains and the GLP-1 analogue liraglutide alters brain activity related to highly desirable food cues in individuals with diabetes: a crossover, randomised, placebo-controlled. Diabetologia. 2016;59(5):954-65.

36. Iepsen EW, Torekov SS, Holst JJ. Therapies for inter-relating diabetes and obesity – GLP-1 and obesity. Expert opinion on pharmacotherapy. 2014;15(17):2487-500.

37. Klausen MK, Thomsen M, Wortwein G, Fink-Jensen A. The role of glucagon-like peptide 1 (GLP-1) in addictive disorders. British Journal of Pharmacology. 2022;179(4):625-41.

38. O'Neil PM, Birkenfeld AL, McGowan B, Mosenzon O, Pedersen SD, Wharton S, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. The lancet. 2018;392(10148):637-49.

39. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, et al. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity. JAMA : the journal of the American Medical Association. 2021;325(14):1414.

40. Smits MM, Van Raalte DH. Safety of Semaglutide. Frontiers in Endocrinology. 2021;12.

41. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, 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. The lancet. 2021;397(10278):971-84.

42. Kushner RF, Calanna S, Davies M, Dicker D, Garvey WT, Goldman B, et al. Semaglutide 2.4 mg for the Treatment of Obesity: Key Elements of the STEP Trials 1 to 5. Obesity. 2020;28(6):1050-61.

43. Ryan DH, Lingvay I, Colhoun HM, Deanfield J, Emerson SS, Kahn SE, et al. Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) rationale and design. American heart journal : AHJ. 2020;229:61-9.

44. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva 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. JAMA : the journal of the American Medical Association. 2021;325(14):1403.

45. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nature Medicine. 2022;28(10):2083-91.

46. Rubino DM, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sørrig R, et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes. JAMA : the journal of the American Medical Association. 2022;327(2):138.

47. Shi Q, Wang Y, Hao Q, Vandvik PO, Guyatt G, Li J, et al. Retracted: Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. The lancet. 2022;399(10321):259-69.

48. Rubino F, Nathan DM, Eckel RH, Schauer PR, Alberti KGMM, Zimmet PZ, et al. Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations. Diabetes Care. 2016;39(6):861-77.

49. Majid SF, Ahmed S, Benson-Davies S, Voellinger D, Davis M, Ajmal S, et al. Proposed Definitions and Clinical Recommendations for the Management of Weight Recurrence, Partial Response, and Nonresponse Following Metabolic and Bariatric Surgery. Obesity Surgery. 2025.

50. Blonde L, Pencek R, Macconell L. Association among weight change, glycemic control, and markers of cardiovascular risk with exenatide once weekly: a pooled analysis of patients with type 2 diabetes. Cardiovascular Diabetology. 2015;14(1):12.

51. Bergmann K, Sypniewska G. Diabetes as a complication of adipose tissue dysfunction. Is there a role for potential new biomarkers? Clinical Chemistry and Laboratory Medicine (CCLM). 2013;51(1):177-85.

52. Ferdinand KC, Nasser SA. Racial/ethnic disparities in prevalence and care of patients with type 2 diabetes mellitus. Current Medical Research and Opinion. 2015;31(5):913-23.

53. Kumanyika S. Ethnic minorities and weight control research priorities: Where are we now and where do we need to be? Preventive medicine. 2008;47(6):583-6.

54. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. The New England journal of medicine. 2021;385(6):503-15.

55. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England journal of medicine. 2016;375(19):1834-44.

56. Lundgren JR, Janus C, Jensen SBK, Juhl CR, Olsen LM, Christensen RM, et al. Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined. New England Journal of Medicine. 2021;384(18):1719-30.

57. Kelly AS, Auerbach P, Barrientos-Perez M, Gies I, Hale PM, Marcus C, et al. A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. New England Journal of Medicine. 2020;382(22):2117-28.

58. Weghuber D, Barrett T, Barrientos-Pérez M, Gies I, Hesse D, Jeppesen OK, et al. Once-Weekly Semaglutide in Adolescents with Obesity. New England Journal of Medicine. 2022;387(24):2245-57.

59. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. Current opinion in endocrinology, diabetes and obesity. 2017;24(1):73-9.

60. Inge TH, Laffel LM, Jenkins TM, Marcus MD, Leibel NI, Brandt ML, et al. Comparison of Surgical and Medical Therapy for Type 2 Diabetes in Severely Obese Adolescents. JAMA pediatrics. 2018;172(5):452.

61. Nauck MA, Petrie JR, Sesti G, Mannucci E, Courrèges J-P, Lindegaard ML, et al. A Phase 2, Randomized, Dose-Finding Study of the Novel Once-Weekly Human GLP-1 Analog, Semaglutide, Compared With Placebo and Open-Label Liraglutide in Patients With Type 2 Diabetes. Diabetes care. 2016;39(2):231-41.

62. Aroda VR, Ahmann A, Cariou B, Chow F, Davies MJ, Jódar E, et al. Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: Insights from the SUSTAIN 1–7 trials. Diabetes & metabolism. 2019;45(5):409-18.

63. Pratley RE, Aroda VR, Lingvay I, Lüdemann J, Andreassen C, Navarria A, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. The Lancet. 2018;6(4):275-86.

64. Azoulay L, Filion KB, Platt RW, Dahl M, Dormuth CR, Clemens KK, et al. Incretin based drugs and the risk of pancreatic cancer: international multicentre cohort study. BMJ : British medical journal. 2016:i581.

65. Ayoub M, Chela H, Amin N, Hunter R, Anwar J, Tahan V, et al. Pancreatitis Risk Associated with GLP-1 Receptor Agonists, Considered as a Single Class, in a Comorbidity-Free Subgroup of Type 2 Diabetes Patients in the United States: A Propensity Score-Matched Analysis. Journal of Clinical Medicine. 2025;14(3):944.

66. Bjerre Knudsen L, Madsen LW, Andersen S, Almholt K, de Boer AS, Drucker DJ, et al. Glucagon-Like Peptide-1 Receptor Agonists Activate Rodent Thyroid C-Cells Causing Calcitonin Release and C-Cell Proliferation. Endocrinology. 2010;151(4):1473-86.

67. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes – state-of-the-art. Molecular metabolism. 2021;46:101102.

68. Overgaard RV, Navarria A, Ingwersen SH, Bækdal TA, Kildemoes RJ. Clinical Pharmacokinetics of Oral Semaglutide: Analyses of Data from Clinical Pharmacology Trials. Clinical Pharmacokinetics. 2021;60(10):1335-48.

69. Agency EM. EMA statement on ongoing review of GLP-1 receptor agonists Amsterdam: EMA; 2023 [

70. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. New England Journal of Medicine. 2015;373(1):11-22.

71. Kushner RF. Weight Loss Strategies for Treatment of Obesity: Lifestyle Management and Pharmacotherapy. Progress in cardiovascular diseases. 2018;61(2):246-52.

72. Gelhorn H, Bacci ED, Poon JL, Boye K, Suzuki S, Babineaux SM. Evaluating preferences for profiles of glucagon-like peptide-1 receptor agonists among injection-naive type 2 diabetes patients in Japan. Patient Preference and Adherence. 2016;Volume 10:1337-48.

73. Storgaard H, Cold F, Gluud LL, Vilsbøll T, Knop FK. Glucagon-like peptide-1 receptor agonists and risk of acute pancreatitis in patients with type 2 diabetes. Diabetes, obesity & metabolism. 2017;19(6):906-8.

74. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. Diabetes, obesity & metabolism. 2017;19(4):524-36.

75. Faillie J-L, Yu OH, Yin H, Hillaire-Buys D, Barkun A, Azoulay L. Association of Bile Duct and Gallbladder Diseases With the Use of Incretin-Based Drugs in Patients With Type 2 Diabetes Mellitus. JAMA internal medicine. 2016;176(10):1474.

76. Hegedüs L, Sherman SI, Tuttle RM, von Scholten BJ, Rasmussen S, Karsbøl JD, et al. No Evidence of Increase in Calcitonin Concentrations or Development of C-Cell Malignancy in Response to Liraglutide for Up to 5 Years in the LEADER Trial. Diabetes care. 2018;41(3):620-2.

77. Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, Pancreatic, and Thyroid Cancer With Glucagon-Like Peptide-1–Based Therapies. Gastroenterology. 2011;141(1):150-6.

78. Rosenstock J, Allison D, Birkenfeld AL, Blicher TM, Deenadayalan S, Jacobsen JB, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea. JAMA : the journal of the American Medical Association. 2019;321(15):1466.

79. Lingvay I, Hansen T, Macura S, Marre M, Nauck MA, de la Rosa R, et al. Superior weight loss with once-weekly semaglutide versus other glucagon-like peptide-1 receptor agonists is independent of gastrointestinal adverse events. BMJ open diabetes research & care. 2020;8(2):e001706.

80. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine. 2016;375(4):311-22.

81. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. The lancet. 2019;394(10193):121-30.

82. Mann JFE, Ørsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. New England Journal of Medicine. 2017;377(9):839-48.

83. Davies MJ, Bain SC, Atkin SL, Rossing P, Scott D, Shamkhalova MS, et al. Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial. Diabetes care. 2016;39(2):222-30.

84. Usman MS, Siddiqi TJ, Khan MS, Patel UK, Shahid I, Ahmed J, et al. Is there a smoker's paradox in COVID-19? BMJ evidence-based medicine EBM. 2020;26(6):279-84.

85. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BWJH, et al. Overweight, Obesity, and Depression. Archives of general psychiatry. 2010;67(3):220.

86. Castaneda D, Popov VB, Wander P, Thompson CC. Risk of Suicide and Self-harm Is Increased After Bariatric Surgery—a Systematic Review and Meta-analysis. Obesity surgery. 2019;29(1):322-33.

87. Sarwer DB, Wadden TA, Moore RH, Baker AW, Gibbons LM, Raper SE, et al. Preoperative eating behavior, postoperative dietary adherence, and weight loss after gastric bypass surgery. Surgery for obesity and related diseases. 2008;4(5):640-6.

88. Kalarchian MA, Marcus MD, Levine MD, Courcoulas AP, Pilkonis PA, Ringham RM, et al. Psychiatric Disorders Among Bariatric Surgery Candidates: Relationship to Obesity and Functional Health Status. American Journal of Psychiatry. 2007;164(2):328-34.

89. Shapses SA, Sukumar D. Bone Metabolism in Obesity and Weight Loss. Annual review of nutrition. 2012;32(1):287-309.

90. Mechanick JI, Apovian C, Brethauer S, Garvey WT, Joffe AM, Kim J, et al. Clinical Practice Guidelines For The Perioperative Nutrition, Metabolic, and Nonsurgical Support of Patients Undergoing Bariatric Procedures – 2019 Update: Cosponsored By American Association of Clinical Endocrinologists/American College of Endocrinology,. Endocrine Practice. 2019;25(Supplement 2):1-75.

91. Alpert MA, Omran J, Mehra A, Ardhanari S. Impact of Obesity and Weight Loss on Cardiac Performance and Morphology in Adults. Progress in cardiovascular diseases. 2014;56(4):391-400.

92. Sarwer DB, Spitzer JC, Wadden TA, Rosen RC, Mitchell JE, Lancaster K, et al. Sexual functioning and sex hormones in men who underwent bariatric surgery. Surgery for obesity and related diseases. 2015;11(3):643-51.

93. Nauck MA, Meier JJ. MANAGEMENT OF ENDOCRINE DISEASE: Are all GLP-1 agonists equal in the treatment of type 2 diabetes? European journal of endocrinology. 2019;181(6):R211-R34.

94. Faillie J-L, Montastruc F, Montastruc J-L, Pariente A. Pharmacoepidemiology and its input to pharmacovigilance. Therapies. 2016;71(2):211-6.

95. Pan D, Gerald J. Ongoing Challenges in Pharmacovigilance. Drug Safety. 2014;37(1):1-8.

96. Lee IO, Ghiasi M, Wong K, Walker M. Pregnancy Outcomes of Maternal Periconceptional Exposure to Glucagon-Like Peptide-1 Receptor Agonists: A Scoping Review of Evidence and Reporting Trends. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstétrique et gynécologie du Canada : JOGC. 2025:103191.

97. Jalleh RJ, Rayner CK, Hausken T, Jones KL, Camilleri M, Horowitz M. Gastrointestinal effects of GLP-1 receptor agonists: mechanisms, management, and future directions. The Lancet Gastroenterology & Hepatology. 2024;9(10):957-64.

98. Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines For Medical Care of Patients with Obesity. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2016;22(Supplement 3):1-203.

99. Excellence NIfHaC. Obesity: identification, assessment and management London: NICE; 2014 [

100. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults. Circulation. 2014;129(25_suppl_2):S102-S38.

101. Wadden TA, Tronieri JS, Butryn ML. Lifestyle modification approaches for the treatment of obesity in adults. American psychologist. 2020;75(2):235-51.

102. Hall KD, Kahan S. Maintenance of Lost Weight and Long-Term Management of Obesity. Medical clinics of North America. 2018;102(1):183-97.

103. Gómez-Donoso C, Sánchez-Villegas A, Martínez-González MA, Gea A, Mendonça RdD, Lahortiga-Ramos F, et al. Ultra-processed food consumption and the incidence of depression in a Mediterranean cohort: the SUN Project. European journal of nutrition. 2020;59(3):1093-103.

104. Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. The lancet. 2022;399(10322):394-405.

105. Foster GD, Wadden TA, Vogt RA, Brewer G. What is a reasonable weight loss? Patients' expectations and evaluations of obesity treatment outcomes. Journal of consulting and clinical psychology. 1997;65(1):79-85.

106. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, et al. Shared Decision Making: A Model for Clinical Practice. Journal of General Internal Medicine. 2012;27(10):1361-7.

107. Nordisk N. Wegovy prescribing information. Bagsværd (Denmark); 2021.

108. Blonde L, Russell-Jones D. The safety and efficacy of liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the LEAD 1–5 studies. Diabetes, obesity & metabolism. 2009;11(s3):26-34.

109. Flint A, Nazzal K, Jagielski P, Hindsberger C, Zdravkovic M. Influence of hepatic impairment on pharmacokinetics of the human GLP-1 analogue, liraglutide. British Journal of Clinical Pharmacology. 2010;70(6):807-14.

110. Blonde L, Jendle J, Gross J, Woo V, Jiang H, Fahrbach JL, et al. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. The lancet. 2015;385(9982):2057-66.

111. Ryan DH, Yockey SR. Weight Loss and Improvement in Comorbidity: Differences at 5%, 10%, 15%, and Over. Current obesity reports. 2017;6(2):187-94.

112. Galli M, Benenati S, Laudani C, Simeone B, Sarto G, Ortega-Paz L, et al. Cardiovascular Effects and Tolerability of GLP-1 Receptor Agonists. JACC. 2025;86(20):1805-19.

113. Kumarathurai P, Anholm C, Larsen BS, Olsen RH, Madsbad S, Kristiansen O, et al. Effects of Liraglutide on Heart Rate and Heart Rate Variability: A Randomized, Double-Blind, Placebo-Controlled Crossover Study. Diabetes care. 2017;40(1):117-24.

114. Aronne LJ, Sattar N, Horn DB, Bays HE, Wharton S, Lin W-Y, et al. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity. JAMA : the journal of the American Medical Association. 2024;331(1):38.

115. Aills L, Blankenship J, Buffington C, Furtado M, Parrott J. ASMBS Allied Health Nutritional Guidelines for the Surgical Weight Loss Patient. Surgery for obesity and related diseases. 2008;4(5):S73-S108.

116. Swift DL, McGee JE, Earnest CP, Carlisle E, Nygard M, Johannsen NM. The Effects of Exercise and Physical Activity on Weight Loss and Maintenance. Progress in cardiovascular diseases. 2018;61(2):206-13.

117. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ. 2006;333(7557):15.

118. Association AD. 6. Glycemic targets: standards of medical care in diabetes—2021. Diabetes Care. 2021;44(Suppl 1):S73–84.

119. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. Diabetes care. 2021;44(Supplement_1):S15-S33.

120. SM G, NJ S, AL B, C B, KK B, RS B. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73(24):e285–350.

121. Fock KM, Khoo J. Diet and exercise in management of obesity and overweight. Journal of Gastroenterology and Hepatology. 2013;28(S4):59-63.

122. Kristeller JL, Wolever RQ. Mindfulness-Based Eating Awareness Training for Treating Binge Eating Disorder: The Conceptual Foundation. Eating disorders : the journal of treatment and prevention. 2010;19(1):49-61.

123. Mozaffarian D. Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity. Circulation. 2016;133(2):187-225.

124. Pasiakos SM, Cao JJ, Margolis LM, Sauter ER, Whigham LD, McClung JP, et al. Effects of high-protein diets on fat-free mass and muscle protein synthesis following weight loss: a randomized controlled trial. The FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2013;27(9):3837-47.

125. Jéquier E, Constant F. Water as an essential nutrient: the physiological basis of hydration. European journal of clinical nutrition. 2010;64(2):115-23.

126. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The Physical Activity Guidelines for Americans. JAMA : the journal of the American Medical Association. 2018;320(19):2020.

127. Westcott WL. Resistance Training is Medicine. Current sports medicine reports. 2012;11(4):209-16.

128. Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, et al. Weight Loss, Exercise, or Both and Physical Function in Obese Older Adults. New England Journal of Medicine. 2011;364(13):1218-29.

129. Teixeira PJ, Carraça EV, Markland D, Silva MN, Ryan RM. Exercise, physical activity, and self-determination theory: A systematic review. International Journal of Behavioral Nutrition and Physical Activity. 2012;9(1):78.

130. Butryn ML, Webb V, Wadden TA. Behavioral Treatment of Obesity. Psychiatric Clinics of North America. 2011;34(4):841-59.

131. Wadden TA, Volger S, Sarwer DB, Vetter ML, Tsai AG, Berkowitz RI, et al. A Two-Year Randomized Trial of Obesity Treatment in Primary Care Practice. New England Journal of Medicine. 2011;365(21):1969-79.

132. Nauck MA, Homberger E, Siegel EG, Allen RC, Eaton RP, Ebert R, et al. Incretin Effects of Increasing Glucose Loads in Man Calculated from Venous Insulin and C-Peptide Responses*. Journal of clinical endocrinology and metabolism. 1986;63(2):492-8.

133. Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, et al. Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial. Diabetes care. 2018;41(2):258-66.

134. Nauck MA, Kemmeries G, Holst JJ, Meier JJ. Rapid Tachyphylaxis of the Glucagon-Like Peptide 1–Induced Deceleration of Gastric Emptying in Humans. Diabetes. 2011;60(5):1561-5.

135. Group UPDSU. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-53.

136. le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DCW, Van Gaal L, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. The lancet. 2017;389(10077):1399-409.

137. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. The lancet. 2018;391(10120):541-51.

138. Wilding JPH, Batterham RL, Davies M, Van Gaal LF, Kandler K, Konakli K, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. Diabetes, obesity & metabolism. 2022;24(8):1553-64.

139. Ling J, Chow E. Glucagon-like peptide receptor-1 receptor agonists: The emerging fourth pillar in type 2 diabetes and chronic kidney disease? Med. 2024;5(8):845-7.

140. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension. Journal of hypertension. 2023;41(12):1874-2071.

141. Iepsen EW, Lundgren J, Dirksen C, Jensen J-E, Pedersen O, Hansen T, et al. Treatment with a GLP-1 receptor agonist diminishes the decrease in free plasma leptin during maintenance of weight loss. International Journal of Obesity. 2015;39(5):834-41.

142. Rizzo M, Nikolic D, Patti AM, Mannina C, Montalto G, McAdams BS, et al. GLP-1 receptor agonists and reduction of cardiometabolic risk: Potential underlying mechanisms. Biochimica et biophysica acta. 2018;1864(9):2814-21.

143. Goldstein BJ, Scalia RG, Ma XL. Protective vascular and myocardial effects of adiponectin. Nature clinical practice cardiovascular medicine. 2009;6(1):27-35.

144. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. European heart journal. 2016;37(39):2999-3058.

145. Caussy C, Aubin A, Loomba R. The Relationship Between Type 2 Diabetes, NAFLD, and Cardiovascular Risk. Current diabetes report. 2021;21(5).

146. Turer AT, Scherer PE. Adiponectin: mechanistic insights and clinical implications. Diabetologia. 2012;55(9):2319-26.

147. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860-7.

148. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. The New England journal of medicine. 2023;389(24):2221-32.

149. Pi-Sunyer X. The Medical Risks of Obesity. Postgraduate medicine. 2009;121(6):21-33.

150. Brown CD, Higgins M, Donato KA, Rohde FC, Garrison R, Obarzanek E, et al. Body Mass Index and the Prevalence of Hypertension and Dyslipidemia. Obesity Research. 2000;8(9):605-19.

151. Libby P. Inflammation in atherosclerosis. Nature. 2002;420(6917):868-74.

152. Nauck MA, Wefers J, Meier JJ. Treatment of type 2 diabetes: challenges, hopes, and anticipated successes. The Lancet. 2021;9(8):525-44.

153. Robinson LE, Holt TA, Rees K, Randeva HS, O'Hare JP. Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: systematic review and meta-analysis. BMJ Open. 2013;3(1):e001986.

154. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84.

155. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. The lancet. 2016;387(10019):679-90.

156. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. New England Journal of Medicine. 2021;384(12):1113-24.

157. Loomba R, Abdelmalek MF, Armstrong MJ, Jara M, Kjær MS, Krarup N, et al. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. The Lancet Gastroenterology & Hepatology. 2023;8(6):511-22.

158. Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: Mechanisms and treatment options. JHEP reports : innovation in hepatology. 2019;1(4):312-28.

159. Gupta NA, Mells J, Dunham RM, Grakoui A, Handy J, Saxena NK, et al. Glucagon-Like Peptide-1 Receptor Is Present on Human Hepatocytes and Has A Direct Role in Decreasing Hepatic Steatosis in Vitro by Modulating Elements of the Insulin Signaling Pathway. Hepatology. 2010;51(5):1584-92.

160. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328-57.

161. Perkovic V, Tuttle KR, Rossing P, Mahaffey KW, Mann JFE, Bakris G, et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. The New England journal of medicine. 2024;391(2):109-21.

162. Tuttle KR, Lakshmanan MC, Rayner B, Busch RS, Zimmermann AG, Woodward DB, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. The Lancet. 2018;6(8):605-17.

163. Muskiet MHA, Tonneijck L, Smits MM, van Baar MJB, Kramer MHH, Hoorn EJ, et al. GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. Nature reviews. 2017;13(10):605-28.

164. De Boer IH, Caramori ML, Chan JCN, Heerspink HJL, Hurst C, Khunti K, et al. Executive summary of the 2020 KDIGO Diabetes Management in CKD Guideline: evidence-based advances in monitoring and treatment. Kidney International. 2020;98(4):839-48.

165. Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. The lancet. 2010;376(9739):419-30.

166. Crajoinas RO, Oricchio FT, Pessoa TD, Pacheco BPM, Lessa LMA, Malnic G, et al. Mechanisms mediating the diuretic and natriuretic actions of the incretin hormone glucagon-like peptide-1. American journal of physiology. 2011;301(2):F355-F63.

167. Rosenbaum M, Leibel RL. Adaptive thermogenesis in humans. International journal of obesity. 2010;34(S1):S47-S55.

168. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, et al. Long-Term Persistence of Hormonal Adaptations to Weight Loss. New England Journal of Medicine. 2011;365(17):1597-604.

169. Astrup A, Rössner S. Lessons from obesity management programmes: greater initial weight loss improves long-term maintenance. Obesity reviews. 2000;1(1):17-9.

170. Bray GA, Frühbeck G, Ryan DH, Wilding JPH. Management of obesity. The lancet. 2016;387(10031):1947-56.

171. Puhl RM, Heuer CA. Obesity Stigma: Important Considerations for Public Health. American Journal of Public Health. 2010;100(6):1019-28.

172. Perri MG, Limacher MC, Durning PE, Janicke DM, Lutes LD, Bobroff LB, et al. Extended-Care Programs for Weight Management in Rural Communities. Archives of internal medicine. 2008;168(21):2347.

173. Jeffery RW, Epstein LH, Wilson GT, Drewnowski A, Stunkard AJ, Wing RR. Long-term maintenance of weight loss: Current status. Health psychology : the official journal of the Division of Health Psychology, American Psychological Association. 2000;19(1, Suppl):5-16.

174. Anderson JW, Konz EC, Frederich RC, Wood CL. Long-term weight-loss maintenance: a meta-analysis of US studies. The American journal of clinical nutrition. 2001;74(5):579-84.

175. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, et al. Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events. JAMA : the journal of the American Medical Association. 2016;315(22):2424.

176. Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, 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. The lancet. 2010;376(9741):595-605.

177. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 5-Year Outcomes. New England Journal of Medicine. 2017;376(7):641-51.

178. Stanford FC, Alfaris N, Gomez G, Ricks ET, Shukla AP, Corey KE, et al. The utility of weight loss medications after bariatric surgery for weight regain or inadequate weight loss: A multi-center study. Surgery for obesity and related diseases. 2017;13(3):491-500.

179. Pajecki D, Halpern A, Cercato C, Mancini M, Cleva RD, Santo MA. Tratamento de curto prazo com liraglutide no reganho de peso após cirurgia bariátrica. Revista do Colégio Brasileiro de Cirurgiões. 2013;40(3):191-5.

180. Maclean PS, Wing RR, Davidson T, Epstein L, Goodpaster B, Hall KD, et al. NIH working group report: Innovative research to improve maintenance of weight loss. Obesity. 2015;23(1):7-15.

181. Sjöström L, Peltonen M, Jacobson P, Ahlin S, Andersson-Assarsson J, Anveden Å, et al. Association of Bariatric Surgery With Long-term Remission of Type 2 Diabetes and With Microvascular and Macrovascular Complications. JAMA : the journal of the American Medical Association. 2014;311(22):2297.

182. Colman E, Golden J, Roberts M, Egan A, Weaver J, Rosebraugh C. The FDA's Assessment of Two Drugs for Chronic Weight Management. The New England journal of medicine. 2012;367(17):1577-9.

183. Lim F, Bellows BK, Tan SX, Aziz Z, Woo Baidal JA, Kelly AS, et al. Cost-Effectiveness of Pharmacotherapy for the Treatment of Obesity in Adolescents. JAMA Network Open. 2023;6(8):e2329178.

184. Herges JR, Neumiller JJ, McCoy RG. Navigating Cost and Access Barriers for Medications in the Treatment of Obesity: A Guide for Patients and Primary Care Clinicians. Clinical diabetes : a publication of the American Diabetes Association. 2025;43(4):587-96.

185. Kyle TK, Puhl RM. Putting people first in obesity. Obesity. 2014;22(5):1211-.

186. Padula WV, Allen RR, Nair KV. Determining the cost of obesity and its common comorbidities from a commercial claims database. Clinical obesity. 2014;4(1):53-8.

187. Ippolito B, Levy JF. Expanding Medicare Coverage Of Anti-Obesity Medicines Could Increase Annual Spending By $3.1 Billion To $6.1 Billion. Health affairs Web exclusive. 2024;43(9):1254-62.

188. Weinstein MC, Torrance G, McGuire A. QALYs: The Basics. Value in Health. 2009;12:S5-S9.

189. Kim N, Wang J, Burudpakdee C, Song Y, Ramasamy A, Xie Y, et al. Cost-effectiveness analysis of semaglutide 2.4 mg for the treatment of adult patients with overweight and obesity in the United States. Journal of managed care & specialty pharmacy. 2022;28(7):740-52.

190. Drummond ME, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. Oxford ; New York :: Oxford University Press.

191. Herman WH. The Economics of Diabetes Prevention. Medical Clinics of North America. 2011;95(2):373-84.

192. Neumann PJ, Cohen JT, Weinstein MC. Updating Cost-Effectiveness — The Curious Resilience of the $50,000-per-QALY Threshold. The New England journal of medicine. 2014;371(9):796-7.

193. Pearce K. The Ozempic shortage is over. What now? 2025 [

194. Fralick M, Jenkins AJ, Khunti K, Mbanya JC, Mohan V, Schmidt MI. Global accessibility of therapeutics for diabetes mellitus. Nature reviews. 2022;18(4):199-204.

195. Longo DL, Heymsfield SB, Wadden TA. Mechanisms, Pathophysiology, and Management of Obesity. The New England journal of medicine. 2017;376(3):254-66.

196. Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and Impact of Real-World Clinical Data for the Practicing Clinician. Advances in Therapy. 2018;35(11):1763-74.

197. Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres A, Weiner R, et al. Interdisciplinary European Guidelines on Metabolic and Bariatric Surgery. Obesity surgery. 2014;24(1):42-55.

198. Partnership for Safe Medicines. Compounded weight loss injections — knock-offs are not the same 2025 [

199. Gahart BL, Nazareno AR. Gahart's 2021 Intravenous Medications: A Handbook for Nurses and Health Professionals. 37 ed. St. Louis (MO): Elsevier; 2021.

200. Gudeman J, Jozwiakowski M, Chollet J, Randell M. Potential Risks of Pharmacy Compounding. Drugs in R&D. 2013;13(1):1-8.

201. Chang VW, Lauderdale DS. Income Disparities in Body Mass Index and Obesity in the United States, 1971-2002. Archives of internal medicine. 2005;165(18):2122.

202. National Academies of Sciences E, and Medicine,. Social determinants of health inequities in obesity prevention and control. In: Callahan EA, editor. A health equity approach to obesity efforts: proceedings of a workshop. Washington (DC): National Academies Press (US); 2019.

203. Commodore-Mensah Y, Turkson-Ocran R-A, Foti K, Cooper LA, Himmelfarb CD. Associations Between Social Determinants and Hypertension, Stage 2 Hypertension, and Controlled Blood Pressure Among Men and Women in the United States. American Journal of Hypertension. 2021;34(7):707-17.

204. Derose KP, Escarce JJ, Lurie N. Immigrants And Health Care: Sources Of Vulnerability. Health affairs Web exclusive. 2007;26(5):1258-68.

205. Heisler M. Mechanisms for Racial and Ethnic Disparities in Glycemic Control in Middle-aged and Older Americans in the Health and Retirement Study. Archives of internal medicine. 2007;167(17):1853.