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A New Era in the Medical Management of Obesity

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Abstract

A new era in obesity management is emerging, characterized by the development of more effective treatments and healthcare strategies. A paradigm shift in obesity care calls for a more integrated, community-based approach that bridges the gap between medical management and bariatric surgery. This review explores important pillars related to obesity management, encompassing aspects related to the pathophysiology of the disease; treatments related to behavioral, nutritional, pharmacotherapeutic, and surgical approaches; and stigma mitigation.

INTRODUCTION

Obesity is a chronic disease characterized by excess adiposity, which impairs organ or tissue function, resulting in broad and heterogeneous medical and psychosocial complications (1). More than 1 billion people worldwide are living with obesity, including 880 million adults and 159 million children and adolescents. Obesity rates have more than doubled among women (8.8% to 18.8%) and nearly tripled among men (4.8% to 14.8%) since 1990 (2). The World Obesity Federation predicts that by 2035, obesity could affect more than half of the global population, with prevalence among children and adolescents rising from 22% to more than 39% (3).

Rising obesity rates have a significant economic impact worldwide. The global cost of overweight and obesity will reach $4.32 trillion by 2035 (3% of GDP). In 2023, the US Joint Economic Committee reported that excess medical cost due to obesity was $5,155/person, corresponding to $520 billion in total healthcare expenses. This figure is expected to grow to $8.2–$9.1 trillion over the next decade. Beyond the financial toll, obesity significantly impacts life expectancy, with an average reduction of 4.7 years per affected individual (4). These data underscore the urgent need for effective interventions.

People living with obesity (PLWO) often face weight stigma, judgment, and blame, which can result in healthcare avoidance, unmet medical needs, and poor mental health (5). Other patient challenges include a lack of recognition of obesity as a chronic disease, environmental and social factors, cultural norms, financial constraints, and comorbidities that may limit physical activity. Providers, on the other hand, may struggle with limited consultation time, insufficient training in obesity care, biases, and underdiagnosis of the disease (6). Clinicians need to recognize these limitations and adopt holistic, patient-centered interventions focusing on overall well-being rather than treating weight alone (5).

A paradigm shift in obesity care calls for a more integrated, community-based approach that bridges the gap between medical management and bariatric surgery. This can be accomplished by providing earlier access to multidisciplinary care, expanding behavioral interventions, promoting physical activity, increasing access to healthier foods, and expanding insurance coverage for pharmacotherapy and bariatric surgery. Clinician training in medical and surgical management is crucial for successful patient outcomes at the primary care level (7, 8).

PATHOPHYSIOLOGY AND ASSESSMENT

Obesity is a chronic, multifactorial, relapsing disease that can arise from several pathways, including genetic, epigenetic, behavioral/lifestyle, or socioeconomic factors, as shown in **Figure 1**. The pathogenesis of obesity is characterized in **Table 1**.

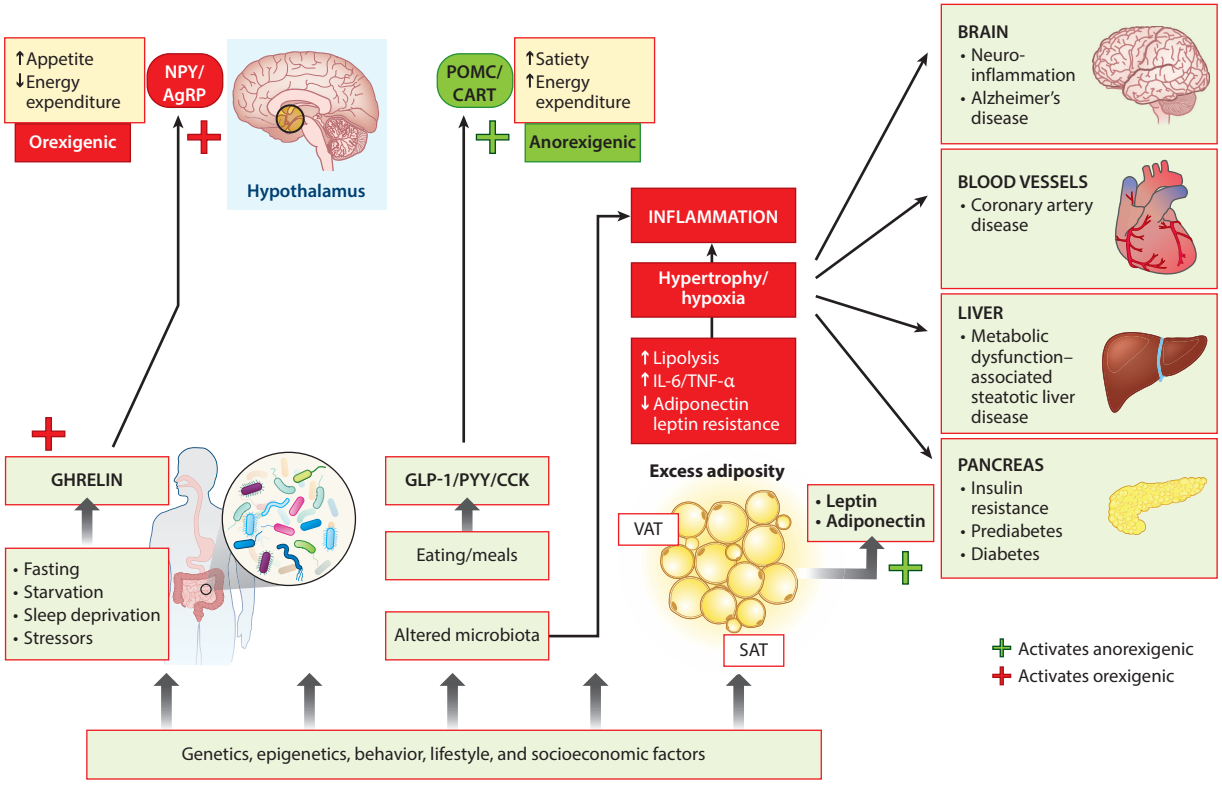

Figure 1

Pathophysiology of energy dysregulation. This figure illustrates the NPY/AgRP and POMC/CART brain pathways and highlights how dysfunctional or excess adipose tissue can lead to metabolic disease. The mechanisms involved include dysregulation of leptin and adiponectin, increased inflammation, and metabolic dysregulation arising from insulin resistance, hyperinsulinemia, and dyslipidemia. Additionally, altered gut microbiota and genetic factors, such as polygenic inheritance and epigenetic modifications, have a strong influence on the development of obesity and metabolic dysfunction. Abbreviations: CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; IL-6, interleukin 6; NPY/AgRP, neuropeptide-Y/Agouti-related protein; POMC/CART, pro-opiomelanocortin cocaine- and amphetamine-regulated transcript; PYY, peptide YY; SAT, subcutaneous adipose tissue; TNF-α, tumor necrotic factor-α; VAT, visceral adipose tissue.

NUTRITIONAL AND BEHAVIORAL STRATEGIES

Adopting lifestyle changes is crucial in obesity treatment, whether alone or alongside pharmacological and/or surgical approaches. The main goal is to improve health, with weight loss as an indirect indicator of treatment effectiveness (20). Nutritional and behavioral strategies for obesity management should focus on promoting functional eating behavior, reducing caloric intake, being nutritionally adequate for the individual's life stage and comorbidities, and ensuring long-term sustainability. Maintaining adherence to dietary changes is a significant challenge for PLWO given the chronicity and pathophysiology of obesity. Changes in appetite, satiety, and energy expenditure following weight loss are complex biologic responses that may impact an individual's ability to maintain weight loss (20–22).

Most diets or dietary patterns, whether moderate in macronutrients [e.g., Mediterranean or DASH (dietary approaches to stop hypertension)], low-carb, low-fat, or plant-based, show similar weight loss results in the first 6 months. Still, these results are often not sustained after 12 months

Table 1 Pathophysiology of obesity

Key factors	Mechanism	Pathogenesis
Genetic factors	>250 loci/genes are associated with obesity FTO and MC4R genes play crucial roles in determining BMI and fat mass distribution (9)	Variations in gene expression impact energy storage efficiency and appetite
	Thrifty gene hypothesis (10) Drifty gene hypothesis (10)	The persistence of genes favoring energy storage is disadvantageous in the modern obesogenic environment (survival mechanism during food scarcity period in human evolution) The persistence of obesogenic genes due to the absence of selection pressure during evolution
Epigenetics	Factors that influence conception, pregnancy, and infancy periods Maternal factors: pre-pregnancy BMI, gestational weight gain, maternal nutrition, gestational diabetes Environmental exposures during pregnancy: smoking/pollution Fetal factors: low birth weight, prematurity, postnatal growth patterns Paternal factors: paternal BMI a potential emerging factor (11–14)	Impact long-term gene expression by altering DNA methylation, affecting growth, metabolism, and weight
Central appetite-regulating system	The arcuate nucleus of the hypothalamus receives input from hormones and nutrients (insulin, leptin, ghrelin, glucose, fatty acids) to maintain energy balance	Key neuronal pathways NPY/AgRP neurons (orexigenic) ■ Activates NPY, AgRP, and orexin release in the lateral hypothalamus, causing MCH release ■ ↑ appetite, ↓ energy expenditure POMC/CART neurons (anorexigenic) ■ Releases α-MSH and activates MC4R in the paraventricular nucleus ■ ↑ satiety, ↑ energy expenditure (15)
Adipose tissue biology	Adipose tissue dysfunction and adipokine dysregulation play a central role in obesity White adipose tissue is categorized into SAT and VAT SAT: located beneath the skin VAT: located around internal organs (omental, mesenteric, epicardial/pericardial fat, etc.)	SAT ■ Provides insulation/immune defense/mechanical protection VAT ■ ↑ lipolysis and release of free fatty acids ■ ↑ inflammatory cytokines (IL-1β, IL-6, TNF-α) ■ ↓ levels of anti-inflammatory adipokines (adiponectin) ■ ↑ hypertrophy and hypoxia➔ systemic inflammation/fibrosis ■ ↑ insulin resistance/hyperinsulinemia, impaired lipid metabolism, atherosclerosis ➔ MASLD, diabetes, and CAD ■ Epicardial and pericardial fat cause localized inflammation and oxidative stress, leading to AF and CAD (16)
	Adiponectin: insulin-sensitizing hormone in muscle and liver	■ ↓ levels ■ Weakens insulin sensitivity and anti-inflammatory protection
	Leptin: regulates energy balance/appetite control	■ ↑ levels; central leptin resistance ■ Impaired energy balance/appetite ■ Impairment in leptin/adiponectin signaling leads to neuroinflammation, oxidative stress, brain atrophy, and cognitive decline, potentially accelerating neurodegenerative diseases such as Alzheimer's disease (17)

(*Continued*)

Table 1 (*Continued*)

Key factors	Mechanism	Pathogenesis
Gut–brain axis	A complex bidirectional communication system that links the gut microbiota and brain through neural, immune, and endocrine pathways SFAs, neurotransmitters, and bacterial metabolites influence appetite regulation in the hypothalamus via the vagal nerve	■ Microbiota dysbiosis weakens the intestinal barrier, allowing inflammatory molecules like LPS to enter the bloodstream ■ ↑ chronic systemic inflammation, insulin resistance, and neuroinflammation ■ ↓ beneficial metabolites like GABA worsening stress/mood (18, 19)

Abbreviations: α-MSH, α-melanocyte-stimulating hormone; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; FTO, fat mass and obesity-associated; GABA, γ-aminobutyric acid; IL-1β, interleukin-1β; IL-6, interleukin 6; LPS, lipopolysaccharide; MASLD, metabolic dysfunction–associated steatotic liver disease; MC4R, melanocortin 4 receptor; MCH, melanocorticotropin; NPY/AgRP, neuropeptide Y/Agouti-related peptide; POMC/CART, pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript; SAT, subcutaneous adipose tissue; SFAs, short-chain fatty acids; TNF-α, tumor necrosis factor-α; VAT, visceral adipose tissue.

(23, 24). Nutritional strategies should be personalized to the individual's needs and preferences (25), and evaluating past struggles can help identify more effective approaches to prevent relapse. Dietary interventions should be evidence based and incorporate shared decision-making, addressing factors such as daily routine, food preferences and aversions, cooking skills, relationship with food, and access to food (25).

Although there is no gold standard or one-size-fits-all diet for managing obesity (23), there are some general dietary recommendations, including a variety of fruits and vegetables, healthy fats, nuts, whole grains, low-fat dairy, and lean proteins (25). Reducing energy-dense foods high in sugar, salt, and fats while prioritizing nutrient-dense options is recommended. This includes limiting unhealthy foods, reducing sugar-sweetened beverages and fat intake, controlling portions, and increasing fruit and vegetable consumption (25, 26).

Time-restricted eating, lower meal frequency, and earlier caloric distribution may reduce weight compared to the standard nutritional approach for individuals with overweight and obesity without eating disorders, but the clinical relevance remains unclear (27). This approach may also be challenging in PLWO considering the changes in hunger and satiety signaling, homeostatic imbalance, and hedonic abnormalities that play a role in the pathophysiology of obesity (21, 22). Establishing regular meal times and increasing the intake of dietary fiber and protein may influence appetite, induce satiety, and improve metabolic balance (28–30), potentially reducing overeating triggers and supporting adherence to a dietary plan. Adequate protein consumption is also highlighted to prevent more significant muscle loss commonly associated with weight loss (31).

Given the complexity of eating behaviors in obesity management, it is crucial to address not only what an individual eats but also factors like where, when, how, how much, why, and with whom they eat (32, 33). Achievable dietary and behavioral changes, combined with cognitive restructuring, are essential to promote lasting improvements in eating behavior and self-regulation for PLWO (22, 26, 34, 35). Sustained nutritional strategies should be paired with behavior change techniques, such as self-monitoring and goal setting, and enhanced by self-regulatory strategies like problem-solving, coping, relapse prevention, and frequent individual or group contact with patients (25, 36). Cognitive-behavioral therapy is effective in treating obesity by addressing cognitive distortions related to dysfunctional eating behaviors or eating disorders, improving self-esteem and emotional dysregulation, and supporting self-efficacy (37–39). To implement effective long-term dietary and behavioral changes in PLWO, healthcare providers' counseling skills are essential for motivational communication to address internalized bias, manage expectations, encourage healthy behaviors, and recognize and accept internal modulators (40).

STIGMA MITIGATION

Weight stigma is experienced almost daily and can have profound effects on PLWO. It refers to the social devaluation of individuals based on body size. It can lead to negative attitudes, stereotypes, prejudice, and discrimination, all based on the unfounded assumption that their body weight results from a lack of self-discipline and personal responsibility (5).

Weight stigma is driven by various societal sources, including the entertainment industry, media, the food industry, policy and legislation, public health campaigns, and unequal opportunities, reinforcing negative perceptions of PLWO (41). Experiences of weight stigma are associated with physiological and psychological consequences such as depression, anxiety, reduced quality of life, worse healthcare experiences, chronic stress, and increased morbidity and mortality (41).

Healthcare providers should approach PLWO with empathy, recognizing the lived experience of obesity, which, as a result of widespread weight stigma and discrimination, may include marginalization, social isolation, guilt, shame, and low self-esteem. Healthcare professionals should be trained in counseling and communication skills to engage nonjudgmentally with PLWO, using active listening and individualized care to promote positive outcomes, reduce stigma, and empower long-term self-care (42, 43). Emphasizing person-centered conversations that focus on overall health and healthier behaviors, rather than just weight, is essential, as well as avoiding terminology and language that can harm the patient–practitioner relationship (44). Healthcare providers' communication should be positive, focusing on the benefits of obesity management, offering support, guiding individuals to relevant resources, and recognizing that different approaches work for other people (43). Healthcare providers should avoid assuming treatment failures result solely from noncompliance, recognizing the need for a comprehensive approach to obesity management.

Mitigating stigma also requires that healthcare facilities are equipped to accommodate PLWO, including comfortable waiting room chairs, scales that support up to 150 kg in private spaces, and appropriately sized blood pressure cuffs (43). A well-designed environment addresses the physical needs of PLWO while fostering a sense of care and inclusion within the healthcare system. Additionally, technological solutions such as telehealth, mobile apps, and wearable devices improve access to obesity care and enhance the quality of interventions because PLWO avoid seeking care due to previous discriminatory experiences (45).

Addressing weight stigma in healthcare requires integrating education on obesity management into professional curricula, focusing on stigma awareness, bias prevention, and the human aspects of care (46). Fostering empathy and understanding the discrimination faced by PLWO are essential to creating inclusive, supportive healthcare environments.

PHARMACOTHERAPY OPTIONS

Pharmacotherapy plays a critical role in obesity management when combined with lifestyle intervention. Anti-obesity medications are indicated in patients who have a body mass index (BMI) $\geq$30 or a BMI $\geq$27 and one or more obesity-associated comorbidities. **Table 2** provides an overview of US Food and Drug Administration–approved medications for obesity treatment, highlighting their key properties. The decision to initiate anti-obesity medication should be guided by a shared decision-making process and tailored to the individual patient's needs, preferences, and comorbidities (see **Table 3**). Although off-label use of these agents can be considered, it should be approached with caution given the lack of long-term outcomes data and limited insurance coverage associated with off-label prescribing.

Table 3 outlines how pharmacologic selection can be targeted to treat certain comorbid conditions, but it is equally important to consider factors such as treatment adherence, long-term

Table 2 Summary of US Food and Drug Administration–approved obesity medications and key characteristics

Medication	Mechanism of action	Administration	Average total body weight loss	Effect on obesity-associated complications	Side effects	Contraindications
Phentermine (Adipex-P®, Lomaira®) (47)	Sympathomimetic amine	Daily oral capsule or tablet	6% on 15-mg dose at 6 months (48)		Tachycardia, palpitations, hypertension, anxiety, insomnia, dry mouth, headache	Uncontrolled hypertension, cardiovascular disease, arrhythmia, glaucoma, hyperthyroidism, MAOI use, agitated states Use with caution in patients with insomnia, substance use disorder, constipation
Orlistat (Xenical®, Alli®) (49)	Reversible lipase inhibitor	Oral tablet three times a day with meals	10% on 120-mg TID dose at 1 year (50)	↓ BP (51) ↓ HbA1c (52) ↓ LDL-C (53)	Flatulence, steatorrhea, fecal urgency or incontinence	Chronic malabsorption or cholestasis Use with caution in patients with oxalate nephrolithiasis and polypharmacy due to medication interactions
Phentermine/ topiramate ER (Qsymia®) (54)	Sympathomimetic amine and GABA enhancer	Daily oral capsule	11% on 15/92-mg dose at 1 year (55)	↓ BP (56) ↓ HbA1c (56)	See phentermine side effects above Additional side effects include drowsiness, cognitive fog, paresthesia, metabolic acidosis, teratogenic effects	See phentermine contraindications above; additional contraindications include patients with a history of nephrolithiasis or those who are able to get pregnant and not on contraception Use with caution in patients with CKD, insomnia, serious mental illness
Naltrexone/ bupropion ER (Contrave®) (57)	Opioid antagonist and norepinephrine and dopamine reuptake inhibitor	Oral tablet twice daily	6% on 32/360-mg dose at 1 year (58)	↓ HbA1c (59)	Headache, dizziness, anxiety/irritability, insomnia, nausea/ vomiting, change in bowel habits	Seizure disorder, narrow-angle glaucoma, uncontrolled hypertension, chronic opioid therapy, MAOI use, anorexia or bulimia Use with caution in patients with serious mental illness, CKD, or liver disease

(*Continued*)

Table 2 (*Continued*)

Medication	Mechanism of action	Administration	Average total body weight loss	Effect on obesity-associated complications	Side effects	Contraindications
Liraglutide[a] (Saxenda®) (60)	GLP-1 receptor agonist	Daily subcutaneous injection	8% on 3.0-mg dose at 1 year (61)	↓BP (61) ↓ HbA1c (61) ↓ LDL-C (61)	Nausea/vomiting, diarrhea/ constipation, headache, injection site reaction, dyspepsia, gallbladder-related events, pancreatitis	Personal or family history of medullary thyroid cancer or MEN2 Use with caution in patients with cholelithiasis, pancreatitis, gastroparesis
Semaglutide[a] (Wegovy®, Rybelsus®[b]) (62, 63)	GLP-1 receptor agonist	Wegovy: weekly subcutaneous injection Rybelsus: daily oral tablet administered on empty stomach with up to 4 oz plain water only	Wegovy: 15% on 2.4-mg dose at 68 weeks (64) Rybelsus: 15.1% on 50 mg of oral semaglutide at week 68 (65)	Wegovy: ↓BP (64) ↓ HbA1c (64) ↓ MACE (66) ↓HF symptoms and limitations (67) ↓ Knee OA pain (68) Rybelsus: ↓BP (65) ↓ HbA1c (65)	Nausea/vomiting, diarrhea/ constipation, abdominal pain, fatigue, injection site reaction, pancreatitis, gallbladder-related events	Personal or family history of medullary thyroid cancer or MEN2 Use with caution in patients with cholelithiasis, pancreatitis, gastroparesis, diabetic retinopathy, NAION
Tirzepatide[a] (Zepbound®) (69)	GLP-1/GIP dual agonist	Weekly subcutaneous injection	21% on 15-mg dose at 72 weeks (70)	↓ BP (70) ↓ HbA1c (70) ↓ LDL-C (70) ↓ AHI (71)	Nausea/vomiting, diarrhea/ constipation, abdominal pain, dyspepsia, injection site reaction, pancreatitis, gallbladder-related events	Personal or family history of medullary thyroid cancer or MEN2 Use with caution in patients with cholelithiasis, pancreatitis, gastroparesis, diabetic retinopathy

Abbreviations: AHI, apnea-hypopnea index; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; GABA, γ-aminobutyric acid; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; HbA1c, hemoglobin A1c; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MAOI, monoamine oxidase inhibitor; MEN2, multiple endocrine neoplasia type 2; NAION, nonarteritic ischemic optic neuropathy; OA, osteoarthritis; TID, three times daily.

[a]Indicates medications that are also approved for the treatment of type 2 diabetes, including Victoza® (liraglutide), Ozempic® (semaglutide), and Mounjaro® (tirzepatide).

[b]Rybelsus® is currently approved only for the treatment of type 2 diabetes but has been found to significantly reduce body weight in patients with obesity. Its use for the treatment of obesity is considered off-label.

Table 3 Obesity medication selection by patient population[a]

Patient population	Agents to consider	Agents to avoid or use with caution
Patients without obesity medication coverage	**Phentermine: lowest cost** Phentermine/topiramate Bupropion/naltrexone	
Patients with type 2 diabetes or prediabetes	**Tirzepatide: greatest reduction in hemoglobin A1c (72)** Semaglutide Liraglutide Bupropion/naltrexone Phentermine/topiramate Orlistat	
Patients with hypertension	**Tirzepatide: greatest reduction in blood pressure (73)** Semaglutide Liraglutide Orlistat	Phentermine/topiramate (use with caution) Bupropion/naltrexone (use with caution) Phentermine (use with caution)
Patients with cardiovascular disease	**Semaglutide: reduced major adverse cardiovascular events (66)** Tirzepatide Liraglutide Orlistat	Phentermine/topiramate (avoid) Bupropion/naltrexone (use with caution) Phentermine (avoid)
Patients with obstructive sleep apnea	**Tirzepatide: reduced apnea-hypopnea index (71)** Semaglutide Liraglutide Orlistat	Phentermine/topiramate (use with caution) Bupropion/naltrexone (use with caution) Phentermine (use with caution)
Patients with chronic kidney disease	Tirzepatide Semaglutide Liraglutide Orlistat	Phentermine/topiramate (use with caution) Bupropion/ naltrexone (use with caution)

[a]Bolded medications represent preferred agents for this population, demonstrating superior efficacy in enhancing key biomarkers and improving clinical outcomes.

efficacy, and side-effect profiles when selecting an anti-obesity agent. Prescribers should consider the patient's preferred route of administration to optimize adherence. In addition, certain medications may warrant caution or avoidance in individuals at elevated risk for adverse effects. For example, glucagon-like peptide 1 (GLP-1) receptor agonists may be inappropriate for patients with baseline gastrointestinal disorders or sarcopenia given the potential for exacerbation of gastrointestinal symptoms and further muscle mass loss (74). Because obesity is a chronic health condition requiring long-term treatment, insurance coverage and out-of-pocket expenses also should be considered to ensure sustained access to therapy.

BARIATRIC SURGERY CONSIDERATIONS

Metabolic and bariatric surgery (MBS) is a well-established and effective intervention offering significant and sustained weight loss. According to the 2022 American Society for Metabolic and Bariatric Surgery guidelines (75), MBS should be considered for the following groups:

1. Individuals with a BMI $\geq$35 kg/m^2, regardless of presence, absence, or severity of comorbidities.

2. Patients with type 2 diabetes mellitus and BMI $\geq$30 kg/m^2.
3. Individuals with a BMI of 30–34.9 kg/m^2 who do not achieve substantial or durable weight loss or comorbidity improvement with nonsurgical management.
4. Individuals of Asian ethnicity with a BMI $\geq$27.5 kg/m^2 (BMI $\geq$25 kg/m^2 suggests clinical obesity in this population).
5. Appropriately selected children and adolescents with a BMI >120% of the 95th percentile (Class II) and a major comorbidity or a BMI >140% of the 95th percentile (Class III) after multidisciplinary team evaluation at a specialty center.

MBS can be divided into three types: restrictive, malabsorptive, and combined. Sleeve gastrectomy and gastric bypass are the most common surgeries in the United States (75). Long-term data from the Swedish Obese Subjects study and other clinical trials confirm that bariatric surgery leads to substantial weight loss, often 20–35% of total body weight, depending on the procedure, along with reductions in cardiometabolic complications. Importantly, many of these benefits have been shown to persist at 10-year follow-up (75). Although these procedures are generally safe, complications such as nutritional deficiencies and gastrointestinal issues can occur, making careful patient selection and long-term follow-up critical.

Weight Regain After Bariatric Surgery

A significant proportion of patients experience weight regain (WR) during long-term follow-up. WR has been observed in up to 37% of Roux-en-Y gastric bypass (RYGB) patients at 7 years and 76% of sleeve gastrectomy patients at 6 years. In a large cohort of RYGB patients, WR averaged 5.7% one year after reaching the lowest postoperative weight (nadir weight) and progressively increased to 15% by five years. The incidence of $\geq$10% WR rose from 23% after one year to 72% after five years, with the largest change occurring within two years of reaching nadir weight. Contributing factors include anatomical changes (enlarged gastric pouch or stoma), maladaptive eating behaviors, loss-of-control eating or binge eating, hormonal shifts increasing hunger, psychological factors (depression, stress, low social support), demographic differences, and lifestyle factors. Effective long-term management requires addressing behavioral and physiological contributors to sustain weight loss (76).

Anti-obesity medications can enhance postbariatric surgery outcomes. Data from a multicenter study demonstrated an average additional weight loss of 7.6%. Medications were effective after weight plateau or regain, with 56% of patients achieving $\geq$5% additional weight loss. Topiramate was the most prescribed drug, often resulting in $\geq$10% total weight loss. Greater weight loss was associated with the RYGB procedure, higher preoperative BMI, and psychiatric comorbidities. These findings suggest anti-obesity medications can support sustained weight loss in bariatric patients (77).

EMERGING MEDICATIONS AND BRIDGING THE GAP TO BARIATRIC SURGERY

Although surgery remains the most effective weight loss intervention to date, emerging therapies targeting key metabolic regulatory pathways in the body show promise in achieving outcomes that rival bariatric surgery. These medications, when combined with lifestyle interventions, can provide solutions for patients who are not candidates for weight loss surgery, have suboptimal weight loss response to surgery, or experience weight regain postoperatively. **Table 4** details the emerging therapies currently under development. Rigorous clinical trials are needed, however, to ensure the safety and efficacy of these agents before their widespread implementation.

Table 4 Summary of upcoming obesity medication and key characteristics

	Mechanism of action	Administration	Average total body weight loss	Upcoming clinical trial[a]	Estimated study completion[a]
Orforglipron	GLP-1 receptor agonist	Once daily oral pill	14.7% on 45-mg dose at 36 weeks (78)	ATTAIN-1 (NCT05869903)	2027
Danuglipron[b]	GLP-1 receptor agonist	Twice daily oral pill	12.9% on 200-mg BID at 32 weeks (79)		
Efinopegdutide	GLP-1/glucagon dual receptor agonist	Once weekly subcutaneous injection	11.8% on 10-mg dose at 26 weeks (80)	NCT06701305	2025
Survodutide	GLP-1/glucagon dual receptor agonist	Once weekly subcutaneous injection	8.7% on 1.8 mg biweekly (DG6) at 16 weeks (81)	SYNCHRONIZE-1 (NCT06066515) SYNCHRONIZE-2 (NCT06066528)	2026 2026
Pemvidutide	GLP-1/glucagon dual receptor agonist	Once weekly subcutaneous injection	15.6% on 2.4-mg at 48 weeks (82)	IMPACT (NCT05989711)	2025
Maridebart cafraglutide (MariTide)	GLP-1 agonist/ GIPR antagonist	Once every 4 weeks subcutaneous injection	14.5% on 420-mg at day 85 (83)	NCT05669599	2026
CagriSema (semaglutide-cagrilintide)	GLP-1/ amylin dual receptor agonist	Once weekly subcutaneous injection	15.6% at 2.4-mg dose at 32 weeks (84)	NCT06131437	2025
Retatrutide	GLP-1/GIP/ glucagon triple receptor agonist	Once weekly subcutaneous injection	24.2% on 12-mg dose at 48 weeks (85)	TRIUMPH-5 (NCT06662383)	2027
Bremelanotide	Melanocortin-4 receptor agonist	Twice daily subcutaneous injection[c]	−1.7 kg on twice daily subcutaneous injections after 4 days (86)	NCT06565611	2025
Garetosmab[d]	Anti-activin A monoclonal antibody	Once every 4 weeks intravenous injection		COURAGE (NCT06299098)	2026
Efruxifermin	FGF21 analog	Once weekly subcutaneous injection	−3.3 kg on 70-mg dose at 16 weeks (87)	NCT06161571	2026
Bimagrumab	Activin receptor type II monoclonal antibody	Once every 4 weeks intravenous injection	6.5% on 10-mg/kg dose at 48 weeks (88)	NCT05616013 NCT06643728	2025 2026

Abbreviations: BID, twice daily; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1, glucagon-like peptide 1.

[a]Trial information was obtained through ClinicalTrials.gov.

[b]Danuglipron development was discontinued in 2025, and there are no ongoing clinical trials (89).

[c]The optimal dosing frequency has not yet been established. Early-phase studies have evaluated once-daily, twice-daily, and three-times-daily regimens.

[d]Awaiting weight loss data in humans with obesity.

CONCLUSIONS

A new era in obesity management is emerging, characterized by the development of more effective treatments and healthcare strategies. However, access to advanced therapies, particularly pharmacological interventions, remains limited due to high costs, restricted availability, and inadequate coverage. Despite significant progress in the scientific understanding of obesity, its management remains challenging due to the complex interplay of biological, psychological, social, and environmental factors. Sustained long-term lifestyle modifications and adherence to adjunctive treatments require behavioral change, cognitive restructuring, and emotional regulation. Therefore, investment in frequent patient contact and long-term follow-up by interdisciplinary healthcare teams is essential. The integration of telehealth, digital applications, wearable devices, and artificial intelligence offers novel personalized, accessible, and cost-effective strategies to support PLWO.

The systemic approach to obesity care must evolve to address its multifactorial nature and mitigate associated health disparities, which disproportionately affect marginalized populations (42, 90). Policymakers, healthcare systems, educational institutions, professional organizations, and the pharmaceutical and food industries must collaborate to create environments that better support PLWO. Persistent stigma and discrimination exacerbate the challenges these individuals face, with internalized weight bias representing both a significant social determinant of health and a human rights concern (90). A comprehensive understanding of obesity etiology is critical to delivering compassionate, patient-centered care. Education and training for healthcare professionals and policymakers on obesity, weight bias, and stigma are essential to improving population health worldwide. Furthermore, the responsibility for effective obesity care extends beyond obesity specialists, requiring the engagement of all healthcare providers. The healthcare community must collectively assume responsibility as key stakeholders to ensure that PLWO receive the care and respect they deserve.

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LITERATURE CITED

1. Rubino F, Cummings DE, Eckel RH, et al. 2025. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol*. 13(3):221–62
2. NCD Risk Factor Collaboration. 2024. Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *Lancet* 403(10431):1027–50
3. World Obesity Federation. 2024. *Obesity atlas 2024*. Rep., World Obesity Federation. **https://data.worldobesity.org/publications/?cat=22**
4. Joint Economic Committee. 2024. *2024 economic report of the President: reaching fiscal solutions through healthcare innovation*. Rep., Joint Economic Committee, US Congress
5. Rubino F, Puhl RM, Cummings DE, et al. 2020. Joint international consensus statement for ending stigma of obesity. *Nat. Med.* 26(4):485–97

6. Kim TN. 2020. Barriers to obesity management: patient and physician factors. *J. Obes. Metab. Syndr.* 29(4):244–47
7. O'Hara H, Miras AD. 2024. Shift the paradigm to shift the weight: obesity care in the community. *Br. J. Gen. Pract.* 74(743):275–78
8. Hampl SE, Hassink SG, Skinner AC, et al. 2023. Executive summary: clinical practice guideline for the evaluation and treatment of children and adolescents with obesity. *Pediatrics* 151(2):e2022060641
9. Narciso J, Silva AJ, Rodrigues V, et al. 2019. Behavioral, contextual and biological factors associated with obesity during adolescence: a systematic review. *PLOS ONE* 14(4):e0214941
10. Speakman JR. 2008. Thrifty genes for obesity, an attractive but flawed idea, and an alternative perspective: the 'drifty gene' hypothesis. *Int. J. Obes.* 32(11):1611–17
11. Heslehurst N, Vieira R, Akhter Z, et al. 2019. The association between maternal body mass index and child obesity: a systematic review and meta-analysis. *PLOS Med.* 16(6):e1002817
12. Rogers JM. 2019. Smoking and pregnancy: epigenetics and developmental origins of the metabolic syndrome. *Birth Defects Res.* 111(17):1259–69
13. Drozdz D, Alvarez-Pitti J, Wójcik M, et al. 2021. Obesity and cardiometabolic risk factors: from childhood to adulthood. *Nutrients* 13(11):4176
14. Campbell JM, McPherson NO. 2019. Influence of increased paternal BMI on pregnancy and child health outcomes independent of maternal effects: a systematic review and meta-analysis. *Obes. Res. Clin. Pract.* 13(6):511–21
15. Jais A, Brüning JC. 2022. Arcuate nucleus-dependent regulation of metabolism-pathways to obesity and diabetes mellitus. *Endocr. Rev.* 43(2):314–28
16. Lee MJ, Kim J. 2024. The pathophysiology of visceral adipose tissues in cardiometabolic diseases. *Biochem. Pharmacol.* 222:116116
17. Forny-Germano L, De Felice FG, Vieira M. 2018. The role of leptin and adiponectin in obesity-associated cognitive decline and Alzheimer's disease. *Front. Neurosci.* 12:1027
18. Field BC, Chaudhri OB, Bloom SR. 2010. Bowels control brain: gut hormones and obesity. *Nat. Rev. Endocrinol.* 6(8):444–53
19. Asadi A, Shadab Mehr N, Mohamadi MH, et al. 2022. Obesity and gut-microbiota-brain axis: a narrative review. *J. Clin. Lab. Anal.* 36(5):e24420
20. Lingvay I, Cohen RV, Roux CWL, Sumithran P. 2024. Obesity in adults. *Lancet* 404(10456):972–87
21. Becetti I, Bwenyi EL, de Araujo IE, et al. 2023. The neurobiology of eating behavior in obesity: mechanisms and therapeutic targets: a report from the 23rd Annual Harvard Nutrition Obesity Symposium. *Am. J. Clin. Nutr.* 118(1):314–28
22. Ferreira-Hermosillo A, de Miguel Ibañez R, Pérez-Dionisio EK, Villalobos-Mata KA. 2023. Obesity as a neuroendocrine disorder. *Arch. Med. Res.* 54(8):102896
23. Ge L, Sadeghirad B, Ball GDC, et al. 2020. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials. *BMJ* 369:m696
24. Turner-McGrievy GM, Wilcox S, Frongillo EA, et al. 2023. Effect of a plant-based versus omnivorous soul food diet on weight and lipid levels among African American adults: a randomized clinical trial. *JAMA Netw. Open* 6(1):e2250626
25. Morgan-Bathke M, Raynor HA, Baxter SD, et al. 2023. Medical nutrition therapy interventions provided by dietitians for adult overweight and obesity management: an Academy of Nutrition and Dietetics evidence-based practice guideline. *J. Acad. Nutr. Diet.* 123(3):520–45.e10
26. Varkevisser RDM, van Stralen MM, Kroeze W, et al. 2019. Determinants of weight loss maintenance: a systematic review. *Obes. Rev.* 20(2):171–211
27. Liu HY, Eso AA, Cook N, et al. 2024. Meal timing and anthropometric and metabolic outcomes: a systematic review and meta-analysis. *JAMA Netw. Open* 7(11):e2442163
28. Davis R, Rogers M, Coates AM, et al. 2022. The impact of meal timing on risk of weight gain and development of obesity: a review of the current evidence and opportunities for dietary intervention. *Curr. Diab. Rep.* 22(4):147–55
29. de Carvalho KMB, Pizato N, Botelho PB, et al. 2020. Dietary protein and appetite sensations in individuals with overweight and obesity: a systematic review. *Eur. J. Nutr.* 59:2317–32

30. Deehan EC, Mocanu V, Madsen KL. 2024. Effects of dietary fibre on metabolic health and obesity. *Nat. Rev. Gastroenterol. Hepatol.* 21(5):301–18
31. Prado CM, Phillips SM, Gonzalez MC, Heymsfield SB. 2024. Muscle matters: the effects of medically induced weight loss on skeletal muscle. *Lancet Diabetes Endocrinol.* 12(11):785–87
32. Zhang X, Wang H, Kilpatrick LA, et al. 2023. Discrimination exposure impacts unhealthy processing of food cues: crosstalk between the brain and gut. *Nat. Ment. Health* 1(11):841–52
33. Täuber S, Gausel N, Flint SW. 2018. Weight bias internalization: the maladaptive effects of moral condemnation on intrinsic motivation. *Front. Psychol.* 9:1836
34. Bates S, Norman P, Breeze P, et al. 2022. Mechanisms of action in a behavioral weight-management program: latent growth curve analysis. *Ann. Behav. Med.* 56(1):64–77
35. Phelan S, Cardel MI, Lee AM, et al. 2023. Behavioral, psychological, and environmental predictors of weight regain in a group of successful weight losers in a widely available weight-management program. *Obesity* 31(11):2709–19
36. Hawkins LK, Burns L, Swancutt D, et al. 2024. Which components of behavioral weight management programs are essential for weight loss in people living with obesity? A rapid review of systematic reviews. *Obes. Rev.* 25(10):e13798
37. Comșa L, David O, David D. 2020. Outcomes and mechanisms of change in cognitive-behavioral interventions for weight loss: A meta-analysis of randomized clinical trials. *Behav. Res. Ther.* 132:103654
38. Monteleone AM, Pellegrino F, Croatto G, et al. 2022. Treatment of eating disorders: a systematic meta-review of meta-analyses and network meta-analyses. *Neurosci. Biobehav. Rev.* 142:104857
39. Kurnik Mesarič K, Pajek J, Logar Zakrajšek B, et al. 2023. Cognitive behavioral therapy for lifestyle changes in patients with obesity and type 2 diabetes: a systematic review and meta-analysis. *Sci. Rep.* 13(1):12793
40. Vallis TM, Macklin D, Russell-Mayhew S. 2020. Canadian Adult Obesity Clinical Practice Guidelines: effective psychological and behavioural interventions in obesity management. Obesity Canada. **https://obesitycanada.ca/wp-content/uploads/2025/03/10-Canadian-Adult-Obesity-CPG-Psych-Interventions.pdf**
41. Westbury S, Oyebode O, van Rens T, Barber TM. 2023. Obesity stigma: causes, consequences, and potential solutions. *Curr. Obes. Rep.* 12(1):10–23
42. Nutter S, Eggerichs LA, Nagpal TS, et al. 2024. Changing the global obesity narrative to recognize and reduce weight stigma: a position statement from the World Obesity Federation. *Obes. Rev.* 25(1):e13642
43. Albury C, Strain WD, Brocq SL, et al. 2020. The importance of language in engagement between health-care professionals and people living with obesity: a joint consensus statement. *Lancet Diabetes Endocrinol.* 8(5):447–55
44. Brown A, Flint SW. 2021. Preferences and emotional response to weight-related terminology used by healthcare professionals to describe body weight in people living with overweight and obesity. *Clin Obes.* 11(5):e12470
45. Ryan L, Coyne R, Heary C, et al. 2023. Weight stigma experienced by patients with obesity in healthcare settings: a qualitative evidence synthesis. *Obes. Rev.* 24(10):e13606
46. Flint SW. 2021. Time to end weight stigma in healthcare. *EClinicalMedicine* 34:100810
47. Adipex-P® [package insert]. Teva Pharmaceuticals; 2012. **https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/085128s065lbl.pdf**
48. Aronne LJ, Wadden TA, Peterson C, et al. 2013. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity* 21(11):2163–71
49. Xenical® [package insert]. CHEPLAPHARM; 2022. **https://xenical.com/pdf/PI_Xenical-brand_FINAL.pdf**
50. Sjöström L, Rissanen A, Andersen T, et al. 1998. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. *Lancet* 352(9123):167–72
51. Siebenhofer A, Winterholer S, Jeitler K, et al. 2021. Long-term effects of weight-reducing drugs in people with hypertension. *Cochrane Database Syst. Rev.* 1(1):CD007654
52. Norris SL, Zhang X, Avenell A, et al. 2005. Pharmacotherapy for weight loss in adults with type 2 diabetes mellitus. *Cochrane Database Syst. Rev.* 2005(1):CD004096

53. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. 2004. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 27(1):155–61
54. Qsymia® [package insert]. VIVUS; 2025. **https://qsymia.com/patient/include/media/pdf/prescribing-information.pdf**
55. Allison DB, Gadde KM, Garvey WT, et al. 2012. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity* 20(2):330–42
56. Garvey WT, Ryan DH, Bohannon NJ, et al. 2014. Weight-loss therapy in type 2 diabetes: effects of phentermine and topiramate extended release. *Diabetes Care* 37(12):3309–16
57. Contrave® [package insert]. Nalpropion Pharmaceuticals; 2021. **https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/200063s020lbl.pdf**
58. Greenway FL, Fujioka K, Plodkowski RA, et al. 2010. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 376(9741):595–605
59. Hollander P, Gupta AK, Plodkowski R, et al. 2013. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care* 36(12):4022–29
60. Saxenda® [package insert]. Novo Nordisk A/S; 2014. **https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206321orig1s000lbl.pdf**
61. Pi-Sunyer X, Astrup A, Fujioka K, et al. 2015. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N. Engl. J. Med.* 373(1):11–22
62. Wegovy® [package insert]. Novo Nordisk; 2022. **https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215256s007lbl.pdf**
63. Rybelsus® [package insert]. Novo Nordisk; 2023. **https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213051s018lbl.pdf**. Accessed July 28, 2025
64. Wilding JPH, Batterham RL, Calanna S, et al. 2021. Once-weekly semaglutide in adults with overweight or obesity. *N. Engl. J. Med.* 384(11):989–1002
65. Knop FK, Aroda VR, do Vale RD, et al. 2023. Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 402(10403):705–19
66. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. 2023. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N. Engl. J. Med.* 389(24):2221–32
67. Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. 2023. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N. Engl. J. Med.* 389(12):1069–84
68. Bliddal H, Bays H, Czernichow S, et al. 2024. Once-weekly semaglutide in persons with obesity and knee osteoarthritis. *N. Engl. J. Med.* 391(17):1573–83
69. Zepbound® [package insert]. Eli Lilly; 2025. **https://uspl.lilly.com/zepbound/zepbound.html#pi**
70. Jastreboff AM, Aronne LJ, Ahmad NN, et al. 2022. Tirzepatide once weekly for the treatment of obesity. *N. Engl. J. Med.* 387(3):205–16
71. Malhotra A, Grunstein RR, Fietze I, et al. 2024. Tirzepatide for the treatment of obstructive sleep apnea and obesity. *N. Engl. J. Med.* 391(13):1193–205
72. Frías JP, Davies MJ, Rosenstock J, et al. 2021. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N. Engl. J. Med.* 385(6):503–15
73. Krumholz HM, de Lemos JA, Sattar N, et al. 2024. Tirzepatide and blood pressure reduction: stratified analyses of the SURMOUNT-1 randomised controlled trial. *Heart* 110(19):1165–71
74. Neeland IJ, Linge J, Birkenfeld AL. 2024. Changes in lean body mass with glucagon-like peptide-1-based therapies and mitigation strategies. *Diabetes Obes. Metab.* 26 (Suppl. 4):16–27
75. Eisenberg D, Shikora SA, Aarts E, et al. 2022. 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): indications for metabolic and bariatric surgery. *Surg. Obes. Relat. Dis.* 18(12):1345–56
76. Noria SF, Shelby RD, Atkins KD, et al. 2023. Weight regain after bariatric surgery: scope of the problem, causes, prevention, and treatment. *Curr. Diab. Rep.* 23(3):31–42

77. Stanford FC, Alfaris N, Gomez G, et al. 2017. The utility of weight loss medications after bariatric surgery for weight regain or inadequate weight loss: a multi-center study. *Surg. Obes. Relat. Dis.* 13(3):491–500
78. Wharton S, Blevins T, Connery L, et al. 2023. Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. *N. Engl. J. Med.* 389(10):877–88
79. Buckeridge C, Cobain S, Bays HE, et al. 2025. Efficacy and safety of danuglipron (PF-06882961) in adults with obesity: a randomized, placebo-controlled, dose-ranging phase 2b study. *Diabetes Obes. Metab.* 27(9):4915–26
80. Alba M, Yee J, Frustaci ME, et al. 2021. Efficacy and safety of glucagon-like peptide-1/glucagon receptor co-agonist JNJ-64565111 in individuals with obesity without type 2 diabetes mellitus: a randomized dose-ranging study. *Clin. Obes.* 11(2):e12432
81. Blüher M, Rosenstock J, Hoefler J, et al. 2024. Dose-response effects on HbA_{1c} and bodyweight reduction of survodutide, a dual glucagon/GLP-1 receptor agonist, compared with placebo and open-label semaglutide in people with type 2 diabetes: a randomised clinical trial. *Diabetologia* 67(3):470–82
82. Aronne L, Scott Harris M, Roberts MS, et al. 2024. 262-OR: pemvidutide, a GLP-1/glucagon dual receptor agonist, in subjects with overweight or obesity—a 48-week, placebo-controlled, phase 2 (MOMENTUM) trial. *Diabetes* 73(Suppl. 1):262-OR
83. Véniant MM, Lu SC, Atangan L, et al. 2024. A GIPR antagonist conjugated to GLP-1 analogues promotes weight loss with improved metabolic parameters in preclinical and phase 1 settings. *Nat. Metab.* 6(2):290–303
84. Frias JP, Deenadayalan S, Erichsen L, et al. 2023. Efficacy and safety of co-administered once-weekly cagrilintide 2·4 mg with once-weekly semaglutide 2·4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial. *Lancet* 402(10403):720–30
85. Jastreboff AM, Kaplan LM, Frías JP, et al. 2023. Triple-hormone-receptor agonist retatrutide for obesity—a phase 2 trial. *N. Engl. J. Med.* 389(6):514–26
86. Spana C, Jordan R, Fischkoff S. 2022. Effect of bremelanotide on body weight of obese women: data from two phase 1 randomized controlled trials. *Diabetes Obes. Metab.* 24(6):1084–93
87. Harrison SA, Ruane PJ, Freilich BL, et al. 2021. Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2a trial. *Nat. Med.* 27(7):1262–71
88. Heymsfield SB, Coleman LA, Miller R, et al. 2021. Effect of bimagrumab versus placebo on body fat mass among adults with type 2 diabetes and obesity: a phase 2 randomized clinical trial. *JAMA Netw. Open* 4(1):e2033457
89. Pfizer Inc. 2025. *Pfizer provides update on oral GLP-1 receptor agonist danuglipron*. Press Release, April 14. **https://www.pfizer.com/news/press-release/press-release-detail/pfizer-provides-update-oral-glp-1-receptor-agonist**
90. Pearl RL, Donze LF, Rosas LG, et al. 2024. Ending weight stigma to advance health equity. *Am. J. Prev. Med.* 67(5):785–91