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REVIEW

Obesity management medications: The way forward

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Obesity is now widely recognized as a chronic progressive condition. The altered biological mechanisms that cause obesity frequently require long-term treatment, including pharmacotherapies or bariatric surgery. In recent decades, the pathophysiology of obesity has been understood to an extent that obesity management medication (OMM) discovery could be rationally pursued. Advances in defining the regulation of food intake and energy expenditure by molecular communication from peripheral organs to the brain led to the development of OMMs that appear capable of safely achieving scalable and sustained body weight loss. However, side effects, heterogeneous treatment responses, long-term metabolic adaptations, adherence, and other factors may limit the use of existing OMMs and justify the development of additional medications to improve the health of people living with obesity.

Obesity is classified by the World Health Organization as "a chronic, relapsing disease arising from complex interactions between genetics, neurobiology, eating behaviors, access to healthy diet, market forces, and the broader environment" (*1*). However, there is still a common belief—even in people with a medical education background—that obesity results from insufficient self-discipline and could therefore be treated by behavior changes alone. Such beliefs contributed to the many challenges in the development of obesity management medications (OMMs) in the past (*2*).

The main reason to classify obesity as a disease, rather than a lack of willpower, is the distinct pathophysiology that involves dysfunctional biological mechanisms that cause overeating and reduced energy expenditure with subsequent excess fat accumulation (*3*). The ability to store energy and preserve fat mass has likely been a survival mechanism against environmental pressure with lower availability of food in human evolution. Only in the past ~100 years has almost-unrestricted access to energy-dense foods turned this evolutionary benefit into a factor that promotes obesity and its cardiometabolic complications.

The progressive course of obesity is caused by homeostatic mechanisms that sustain body weight, promote further weight gain, and cause weight regain after weight-loss interventions (*4*). Altered biological mechanisms may further explain why behavior interventions are frequently not sufficient to achieve clinically meaningful long-term weight loss in people living with obesity (*5*). By contrast, bariatric surgery may improve several biological obesity mechanisms and represents the most effective obesity treatment, providing a >30% weight loss on average over 20 years (*6*). However, obesity surgery is not always suitable and can certainly not meet the magnitude of the global medical need for obesity treatment. Given the need for scalable, effective, and safe obesity therapies that target altered biological mechanisms in obesity, OMM development has become a rapidly advancing field.

Obesity pharmacotherapy development is advancing at a speed that few other chronic disease areas have experienced. For a long time, obesity pharmacotherapy had low efficacy, and some medications had to be withdrawn from the market because of safety concerns (for example, rimonabant, sibutramine, lorcaserin) (*2*). With increasing knowledge about the incretin mechanism, gut-brain cross-talk, and drug candidates, including glucagon-like peptide 1 receptor agonists (GLP-1RAs), the hope grew that sustainable, effective, and safe OMMs could be developed. In 2014, the US Food and Drug Administration approved liraglutide for body-weight management as the first incretin-based OMM (*2*). Since then, GLP-1RAs such as semaglutide and the dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor coagonist tirzepatide have transformed the obesity treatment landscape by demonstrating >15 to 23% weight-loss effects (*7*, *8*), and even more weight loss can be expected from triple incretin agonists that are in advanced stages of clinical development, such as retatrutide (*2*).

More importantly, in dedicated clinical trials, semaglutide and tirzepatide provided clinically relevant benefits beyond blood-glucose lowering in the type 2 diabetes indication and weight loss for obesity-related conditions, including prevention of type 2 diabetes, reducing the risk of major adverse cardiovascular events, improving outcomes of heart failure with preserved ejection fraction, regression of steatosis and prevention of fibrosis in steatotic liver disease, and symptomatic improvements in obstructive sleep apnea and knee osteoarthritis (*9*).

Paradigm shift in obesity treatment

GLP-1RAs were initially developed for the treatment of people with type 2 diabetes and demonstrated to be highly effective for improving glycemic control with a low risk of hypoglycemia (*9*). The added benefit of GLP-1RAs to reduce body weight and the risk for major adverse cardiovascular events led to a rethinking of treatment goals and a shift in focus from reducing hyperglycemia toward body-weight reduction and cardiovascular disease management. This paradigm shift is now reflected in existing type 2 diabetes treatment recommendations (*10*).

In addition to data from long-term bariatric surgery effects, outcomes from incretin-based OMM trials inspired a second paradigm change. Obesity treatment goals shifted from simply providing weight loss toward improving health, preventing additional disease development, facilitating remission, and improving quality of life.

Obesity contributes to reduced life expectancy and reduces quality of life mainly by increasing the prevalence of type 2 diabetes; cardiovascular, psychological, neurological, pulmonary, gastrointestinal, renal, musculoskeletal, and endocrine diseases; and some types of cancer (*11*). Data from the Swedish Obese Subjects study have shown that bariatric surgery was associated with increased life expectancy and reduced all cause and cardiovascular mortality compared with conservative obesity treatment (*6*). Importantly, these benefits were shown in people with overweight and obesity but without type 2 diabetes, further supporting the notion that obesity itself constitutes a disease worthy of chronic pharmacotherapy and investment into further drug development.

The evolution of clinical trials mirrors the changing therapeutic goals in obesity: Early studies established efficacy and safety for weight reduction, whereas newer trials increasingly test durability, prevention or treatment of obesity-related organ dysfunction, preservation of physical function, and reduction of hard cardiovascular, renal, and hepatic outcomes. Thus, the principal unmet needs increasingly concern not whether these agents reduce body weight, but rather which clinical outcomes are modified, and in whom, and whether such benefits extend beyond weight loss itself.

Improving obesity diagnostics and individualizing treatment

In clinical practice, obesity diagnosis and treatment decisions remain largely body mass index (BMI) based (>30 kg/m^2 and, for Asian people, a

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BMI >25 kg/m^2), despite increasing evidence that abdominal adiposity and obesity-related complications provide more clinically relevant information on individual risk (*12*). BMI should therefore be complemented by measures of adiposity and its distribution, such as waist circumference, waist-to-height ratio, or waist-to-hip ratio (*3*, *12*).

Recent frameworks from the Lancet Commission and the European Association for the Study of Obesity (EASO) both recognize that BMI alone is insufficient but differ in their clinical emphasis (Table 1). The Lancet Commission distinguishes preclinical from clinical obesity and defines the latter by demonstrable organ and/or tissue dysfunction or functional limitation attributable to excess adiposity (*3*). EASO adopts a broader adiposity-based chronic disease model that incorporates adipose tissue distribution and metabolic, mechanical, and psychological complications, as well as disease staging, to guide individualized treatment (*13*, *14*). Thus, the Lancet framework provides greater conceptual precision in distinguishing established disease from risk, whereas the EASO approach may facilitate earlier, complication-based intervention.

Accordingly, future obesity management medications (OMMs) should be evaluated not only by the magnitude of weight loss achieved but also by which patients should be treated, which obesity-related complications or organ dysfunction should be targeted, and which clinical end points are improved. For existing approved OMMs, EASO has proposed an algorithm linking individual treatment goals with comparative clinical evidence (*13*). For emerging OMMs, however, available evidence remains insufficient to assign specific medications to particular obesity phenotypes without introducing considerable speculation.

Adipose tissue dysfunction as future OMM target?

Adipose tissue (AT) is a heterogeneous endocrine and metabolic organ, and the consequences of its expansion depend strongly on anatomical depot and cellular composition (*15*–*17*). Subcutaneous adipose tissue (SAT), particularly gluteofemoral SAT, provides a relatively safe reservoir for lipid storage and can expand through adipocyte hypertrophy and hyperplasia; when its capacity for healthy expansion is exceeded, lipid spillover into visceral depots and nonadipose organs may increase. By contrast, visceral adipose tissue (VAT), particularly omental fat, is characterized by greater immune and inflammatory activity and is more strongly associated with insulin resistance and cardiometabolic disease (*15*). Thus, obesity-associated metabolic dysfunction reflects not simply the quantity of AT but also where lipid is stored and whether individual depots retain their capacity for healthy expansion, lipid buffering, and endocrine regulation (*15*, *17*). Thermogenic AT adds another dimension: Brown adipose tissue (BAT), including supraclavicular, deep cervical, and perirenal depots in humans, contributes to nonshivering thermogenesis and systemic substrate clearance, whereas beige adipocytes within white depots can acquire thermogenic characteristics (*16*). Although BAT is considerably less abundant in humans than in rodents, contemporary imaging and metabolic studies demonstrate that it is biologically active and associated with glucose and lipid metabolism, raising the possibility that modulation of thermogenic AT could influence metabolic health beyond effects on adiposity alone (*16*).

Expansion of AT is the disease-defining symptom of obesity. In addition to increased AT mass, adverse fat distribution with predominant abdominal and visceral fat mass increase and dysfunction of AT may represent the mechanistic links between obesity and adverse health outcomes (*17*). AT dysfunction is characterized by adipocyte hypertrophy, an increased number of immune cells, altered cellular composition, limited expandability of subcutaneous fat stores, and ectopic fat deposition in visceral depots, the liver, and other organs, resulting in the release of proinflammatory, diabetogenic, and atherogenic signals (*17*, *18*). Moreover, AT dysfunction can lead to low-grade systemic inflammation that may lower OMM efficacy and promote obesogenic memory, contributing to weight regain after weight-loss interventions. Notably, there are no approved OMMs or drug candidates in clinical development that directly target AT dysfunction. However, incretin-based therapies can reduce markers of systemic inflammation such as circulating C-reactive protein, suggesting that part of the effects of OMMs may be due to anti-inflammatory effects (*2*, *7*–*9*).

Personalized OMM therapy

There is still a long way to go for an etiology-based, targeted therapy for most people with obesity. However, discoveries of rare monogenic or syndromal obesity guided the development of targeted pharmacotherapies, including metreleptin to treat leptin deficiency (*19*) or setmelanotide for children and adults with genetically confirmed biallelic

Table 1. Emerging frameworks for diagnosis and individualized management of obesity.

Criteria	BMI-based approach	Lancet Commission framework (*3*)	EASO framework (*14*)
Primary purpose	Defines obesity based mainly on BMI	Distinguishes health risk from established clinical disease	Characterizes obesity as a chronic disease and guides individualized management
Role of BMI	Primary diagnostic criterion	Surrogate measure; useful mainly for population-level assessment and screening	Insufficient alone; incorporated with broader adiposity assessment
Assessment of adiposity	Primarily BMI	Confirmation of excess adiposity by direct body-fat measurement or anthropometric criteria (e.g., waist circumference, waist-to-height ratio, waist-to-hip ratio)	Considers adiposity level and distribution together with clinical characteristics
Key clinical distinction	Obesity defined by BMI threshold	Preclinical versus clinical obesity	Complication- and stage-based obesity
Criterion for clinical disease	BMI cutoff	Demonstrable organ and/or tissue dysfunction or functional limitation attributable to excess adiposity	Obesity-related metabolic, mechanical, psychological, or other complications
Treatment approach	Largely BMI or anthropometry driven	Based on whether clinical obesity and comorbid conditions or impairments are present	Individualized according to complications, disease stage, and phenotype
Main strengths	Simple, reproducible, widely applicable	Clear distinction between established disease and future risk	Pragmatic framework for early detection and complication-based management
Potential limitations	Poorly captures adiposity distribution, phenotype, and individual risk	Intervention could potentially be delayed until dysfunction is demonstrable	May blur the distinction between established disease and elevated future risk

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loss-of-function variants in POMC, PCSK1, or LEPR; Bardet-Biedl syndrome; and acquired hypothalamic obesity (*20*). Such examples of successfully translating basic research discoveries into therapies may stimulate OMM development.

Recent advances in obesity pharmacotherapy

In principle, an OMM should target both energy intake and expenditure, yet approved OMMs, including orlistat, naltrexone/bupropion, and incretin-based therapies, primarily affect energy intake. The brain is the central regulator of energy homeostasis and integrates peripheral signals from AT, the gastrointestinal tract, liver, and pancreas to control hunger, appetite, satiety, and systemic energy metabolism (*2*, *21*). Advances in understanding the actions of ghrelin, leptin, insulin, cholecystokinin, peptide YY, GLP-1, GIP, glucagon, and amylin have enabled mechanism-guided OMM development (*2*).

The discovery of the insulinotropic and glucose-regulating effects of GLP-1 ultimately led to the development of GLP-1–based therapies, now used by an estimated 15 million to 20 million people worldwide (*22*, *23*). Early GLP-1RAs, including exenatide and liraglutide, were short-acting and produced modest weight loss, whereas longer-acting agents such as semaglutide and dulaglutide enabled once-weekly administration and greater efficacy (*2*, *9*). Semaglutide was the first OMM to achieve ~15% mean weight loss and to demonstrate cardiovascular benefits in the SELECT trial (*7*, *24*). Semaglutide reduced major cardiovascular events by 20% across subgroups defined by BMI, hemoglobin A1c, kidney function, inflammatory status, and other characteristics, although SELECT was not designed to establish cardiovascular benefits independent of weight loss. Additional benefits included improvements in blood pressure, glycemic and lipid parameters, C-reactive protein, progression to diabetes, kidney outcomes, physical functioning, and quality of life (*24*).

Despite these advances, a weight-loss gap remained between pharmacotherapy and bariatric surgery (*2*). This prompted the development of polyagonists, based on the concept that the greater efficacy of bariatric surgery may reflect coordinated gut-hormonal signaling that cannot be reproduced by GLP-1R agonism alone. Dual and triple agonists targeting GLP-1, GIP, and/or glucagon receptors subsequently emerged, including tirzepatide, survodutide, and retatrutide (*2*). Tirzepatide, the first approved GLP-1R–GIP receptor (GIPR) dual agonist, achieved ~20% weight loss for up to 3 years at 15 mg once weekly and improved progression from prediabetes to type 2 diabetes, cardiometabolic risk factors, predicted cardiovascular risk, obstructive sleep apnea symptoms, and kidney function (*8*). More recently, the GLP-1R–GIPR–glucagon receptor triple agonist retatrutide produced almost 30% weight loss at the highest dose in a phase 3 trial (*25*).

Weight loss versus organ-specific disease modification

For many patients, weight loss is the most immediate and tangible treatment goal. This focus is understandable, given the visibility of body weight and the prominent role of weight reduction in contemporary treatment paradigms. However, weight loss should not be considered the sole measure of therapeutic success in obesity management. Although the magnitude and durability of weight loss are important determinants of therapeutic efficacy, body-weight reduction is an intermediate phenotype rather than a universal surrogate for disease outcomes. The biological consequences of weight loss vary across organs and disease states, and some interventions may exert organ-specific effects that are disproportionate to the amount of weight lost. Conversely, substantial weight loss does not necessarily translate into modification of every obesity-associated complication. Accordingly, the therapeutic effects of obesity interventions should be evaluated at two complementary levels: changes in body weight and adiposity, and clinically relevant disease-specific outcomes, including metabolic control, hepatic disease, cardiovascular and renal outcomes, respiratory function, improved mobility, and other measures of organ function or disease progression. This distinction is particularly important when comparing interventions with different mechanisms because similar degrees of weight loss may produce different patterns of organ-specific benefit. These considerations may also shape future OMM development. Although weight loss is likely to remain an important and patient-valued outcome, next-generation therapies could increasingly be evaluated according to their capacity to modify specific obesity-related diseases rather than weight reduction alone. This approach would move beyond BMI-based treatment paradigms toward biologically defined phenotypes and endotypes, using metabolic, imaging, and molecular biomarkers to identify patients at risk for particular organ complications and to match them with therapies that target the relevant biology. Clinical trials should therefore incorporate both patient-centered outcomes (weight loss, physical function, quality of life) and organ-specific end points that capture prevention or modification of disease.

Although clinical trials for future OMMs still use changes in body weight as the primary outcome (table S1), the next generation of OMMs is being (additionally) evaluated not only for magnitude and durability of weight loss but increasingly for their ability to modify obesity-related morbidity. Accordingly, ongoing outcome trials have been designed to address specific unmet needs, including cardiovascular and renal event reduction, prevention or treatment of metabolic dysfunction–associated steatotic liver disease, durability of weight loss, preservation of physical function, and assessment of benefits across populations with different degrees of obesity-related disease.

(Why) Do we need more OMMs?

Incretin-based OMMs have revolutionized obesity treatment by demonstrating an average weight loss of >20% and health benefits for a wide range of obesity complications (*26*, *27*). With the existing approved therapies, which include semaglutide and tirzepatide, and the upcoming expansion of incretin-based therapies to multireceptor agonists targeting GLP-1, GIP, glucagon, amylin, and calcitonin receptors simultaneously, the question arises whether we still need to invest in OMM development (*26*).

Indeed, despite better efficacy, tolerability, and safety of newer OMMs, there are remaining gaps that cause patients in clinical practice to discontinue OMMs because of a lack of efficacy, side effects, costs, or a plateau in health and quality-of-life improvements. Therefore, further OMM development is needed to overcome the limitations of existing obesity pharmacotherapies. Among several challenges of presently approved OMMs (Box 1), further OMM development should aim for even greater weight loss, target the disconnect between weight loss and quality of life, address long-term weight maintenance without the typical weight regain after stopping drugs, minimize side effects, offer oral application, and improve efficacy for nonresponders (*27*).

Box 1. Defining the need for additional OMMs.

- High prevalence of obesity
- Need for greater weight loss
- Heterogeneous response to existing treatments (nonresponders)
- Improved tolerability (gastrointestinal side effects)
- Prevention and treatment of obesity complications and comorbidities
- Weight regain after discontinuation
- Alternative routes of administration
- Adaptations of metabolism and appetite-regulation upon OMM therapy
- Personalized medicine
- Excessive loss of lean body mass and sarcopenic obesity
- Accessibility and costs (adherence)

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A recent network meta-analysis of 262 trials of 19 OMMs (99,791 participants; follow-up after 12 to 172 weeks) concluded that OMMs produce variable weight loss, with larger benefits generally accompanied by more side effects (gastrointestinal symptoms, fatigue, loss of lean mass) and higher discontinuation rates (*28*). Therefore, OMM development should focus on individual patient characteristics, long-term health, and quality-of-life outcomes to facilitate future individualized decision-making in obesity management (*28*).

Unmet needs for future OMMs

Despite major advances in OMM efficacy, important unmet needs remain (Fig. 1). These include durable weight maintenance after treatment discontinuation, improved tolerability, reduced interindividual variability, preservation of lean mass, and more convenient, accessible, and affordable treatment options. Because obesity is a chronic, relapsing disease, future OMMs should ideally provide sustained weight control with reduced maintenance dosing or durable effects after discontinuation. Whether pharmacological interventions can overcome the biological mechanisms that drive weight regain remains an important question.

As suggested by a recent meta-analysis, greater efficacy is presently associated with more adverse effects and treatment discontinuation, highlighting the need for better-tolerated agents and rational drug combinations (*28*). Substantial interindividual variability in efficacy and adverse effects, partly related to genetic, sex, metabolic, and comorbidity-related factors, further supports a precision-medicine approach (*29*). Genetic variation in GLP-1Rs and GIPRs has already been associated with both treatment efficacy and nausea and/or vomiting, suggesting that nonincretin mechanisms may be valuable for nonresponders (*29*). Finally, although weight-loss interventions reduce both fat and lean mass (*30*, *31*), emerging evidence suggests that skeletal-muscle loss with incretin therapy may be less detrimental than initially assumed, with preserved strength and improved body composition reported in a proof-of-concept study (*32*, *33*).

The ultimate goal in OMM development is to maximize fat mass loss while preserving skeletal muscle. Although injectable incretin-based therapies are widely used and accepted, oral applications, such as the recently approved oral semaglutide or orforglipron, could improve adherence, increase prescriptions by nonspecialists, overcome fears of injectable therapies, bypass the need for refrigeration and strict cold-chain logistics to increase access, and reduce treatment costs (*26*).

Accessibility to antiobesity medications can be limited by high cost and limited reimbursement, unequal access between populations and countries, supply shortages and manufacturing constraints, and health care–system capacity (*27*). Therefore, broadening the market by introducing additional competitors, generics, and oral formulations may reduce OMM prices and increase access across different health care systems.

Challenges of future OMM development

With the exception of orlistat, a gastric and pancreatic lipase inhibitor, approved OMMs (Fig. 2) and most drugs in development (table S1) primarily target central mechanisms that regulate food intake. Newer incretin-based polyagonists, including tirzepatide, survodutide, and retatrutide, may additionally modulate substrate utilization and energy expenditure, particularly through glucagon receptor agonism (*34*, *35*). GIPR agonism may also exert weight-independent metabolic effects through AT, where GIPR signaling regulates glucose and lipid uptake, lipolysis, fatty-acid storage and oxidation, and potentially thermogenesis (*36*, *37*). However, the contribution of direct adipose effects to the clinical efficacy of GIPR-based therapies remains uncertain, and the relevance of BAT-mediated effects observed in rodents to human weight loss is unresolved (*36*, *37*). Similarly, although glucagon has been proposed to promote adipose lipolysis, evidence from human studies suggests that this effect is limited at physiological concentrations, with important species- and context-dependent differences (*38*, *39*).

Contemporary drug development therefore increasingly explores mechanisms beyond appetite suppression, including thermogenesis, mitochondrial function, and combination approaches, to enhance energy expenditure. Key challenges include the heterogeneity of obesity, neuroendocrine regulation, translation from animal models to humans, tolerability, safety, and off-target effects (*2*). Genetic, epigenetic, and environmental factors contribute not only to obesity risk but also to variability in treatment response, supporting target-discovery approaches and personalized treatment strategies, including those informed by pathways identified in monogenic obesity (*2*, *26*, *27*).

The physiological defense of body weight represents a further barrier. Peripheral endocrine signals act through hypothalamic and other neurocircuits to defend against negative energy balance; for example, weight loss reduces leptin signaling, increasing orexigenic drive (*2*, *27*). Conversely, persistent elevations of adiposity signals such as leptin and insulin can induce resistance within this homeostatic system (*2*). Moreover, pharmacological effects on food intake often translate less effectively from rodents to humans, highlighting the limitations of existing preclinical models (*4*).

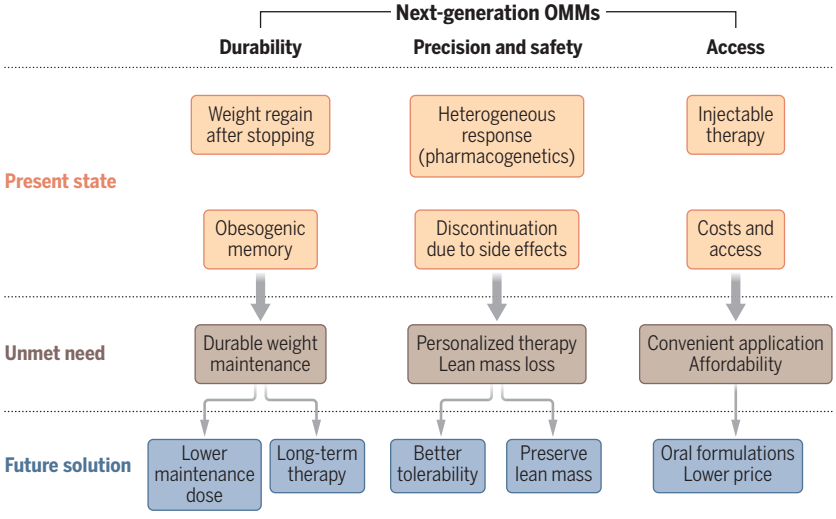

Fig. 1. Unmet needs and priorities for next-generation OMMs. Existing OMMs achieve substantial weight loss, but important unmet needs remain. Future therapies should provide more durable weight control, ideally with reduced maintenance dosing or sustained effects after treatment discontinuation, while addressing the biological mechanisms underlying weight regain. Greater tolerability is needed because higher treatment efficacy is associated with increased adverse effects and treatment discontinuation (*28*). Substantial interindividual variability in efficacy and adverse effects supports a more personalized approach, potentially guided by genetic and clinical characteristics (*29*). Preservation of lean mass and physical function should also be considered when evaluating treatment efficacy, although emerging evidence suggests that skeletal muscle loss with incretin-based therapies may be less detrimental than initially assumed (*30*–*32*). Finally, oral formulations, improved tolerability, lower costs, and broader accessibility could facilitate long-term treatment. Together, these priorities define key directions for the development of next-generation OMMs.

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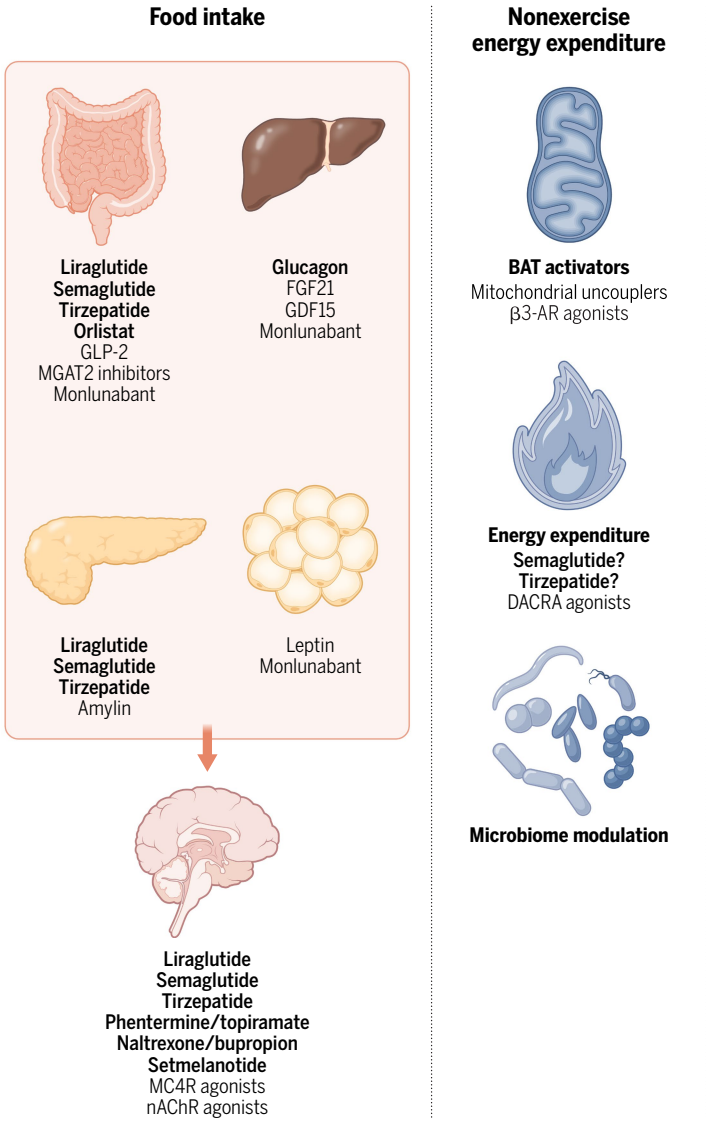

Fig. 2. Integrated therapeutic strategies that target energy balance in obesity. The schematic illustrates existing and emerging pharmacological approaches designed to restore energy balance by reducing food intake and/or increasing energy expenditure. Approved antiobesity medications—including liraglutide, semaglutide, tirzepatide, phentermine/topiramate, naltrexone/bupropion, and setmelanotide—primarily act through the central nervous system and the gut-brain axis to suppress appetite and enhance satiety. Additional therapies target peripheral organs such as the gastrointestinal tract, liver, pancreas, AT, and skeletal muscle through mechanisms including glucagon-like peptide 2 (GLP-2) signaling, glucagon, FGF21, GDF15, amylin, leptin, MGAT2 inhibition, CB1 receptor antagonism, BAT activation, myostatin inhibition, and microbiome modulation. Emerging therapeutic strategies aim to complement appetite suppression by increasing thermogenesis, preserving skeletal muscle mass, and enhancing basal energy expenditure, thereby providing a more comprehensive and durable approach to obesity treatment. MC4R, melanocortin-4 receptor; nAChR, nicotinic acetylcholine receptor.

Finally, greater efficacy of incretin-based therapies is associated with more adverse effects (*28*). Previous OMMs, including rimonabant and sibutramine, were withdrawn because of neuropsychiatric or cardiovascular safety concerns, respectively (*2*). Because neurocircuits that regulate energy balance also control reward, emotion, cognition, and behavior, central targeting may produce unintended neuropsychiatric effects, including depression, anxiety, and suicidal ideation (*40*–*43*). Thus, future OMM development must balance efficacy against tolerability and safety while achieving greater selectivity for metabolic pathways.

Trends in OMM development to address key unmet needs

Future OMM development should aim for addressing the limitations of approved medications that already provide clinically meaningful weight loss and health benefits, such as semaglutide or tirzepatide (*26*, *27*). Average weight loss with these medications ranges from 15 to 23% in people with obesity, whereas in patients with obesity and type 2 diabetes, average weight loss is only 10 to 15% in maximal doses (*9*). There are important trends in OMM development that aim at higher efficacy and additional cardiometabolic benefits (Box 2).

The benchmark for sustained weight loss remains bariatric surgery, with an average weight loss of >30% (*2*, *6*). Beyond weight loss, bariatric surgery has been associated with remission and prevention of type 2 diabetes, improvements in hypertension and dyslipidemia, reduced cardiovascular events and mortality, lower cancer mortality, and longer overall life expectancy (*6*, *44*, *45*). Despite offering the highest efficacy of all obesity treatments, bariatric surgery does not provide a solution for the obesity pandemic, is not scalable, is only indicated for people with a BMI >40 kg/m^2 or BMI >35 kg/m^2 with obesity comorbidities, and has long- and short-term risks, including perioperative mortality. By contrast, pharmacotherapy has the potential to meet the broader medical needs for people living with obesity across the entire disease spectrum. However, pharmacotherapy and bariatric surgery should be viewed as complementary rather than competing approaches to obesity treatment. Pharmacological therapies provide a scalable and potentially reversible means of modifying the biological pathways that regulate energy intake and body weight, whereas bariatric surgery induces more profound and durable anatomical and physiological changes. These approaches can occupy different positions along the treatment continuum: Pharmacotherapy may be used as an alternative to surgery, before surgery to facilitate weight reduction and risk optimization, or after surgery to address inadequate weight loss or weight regain. Conversely, surgery remains an important option for people living with severe obesity or obesity-related complications who do not achieve adequate disease control with nonsurgical therapies. The two approaches are not mutually exclusive: Pharmacotherapy may complement the effects of surgery, although the optimal sequencing, duration, and combination of these interventions need to be defined.

OMM development aims at further improving weight-loss effects (*25*, *46*) and closing the efficacy gap to bariatric surgery. Pipelines of pharmaceutical companies are full of compounds that aim to target combinations of peripheral (gut, pancreas, and liver) and brain signals such as GLP-1, GIP, and glucagon (triple agonists) or amylin with GLP-1

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Box 2. OMM development.

Emerging trends and examples

- Optimized multireceptor agonists (retatrutide)
- Oral application (semaglutide, orforglipron, elecoglipron)
- Longer treatment intervals (monthly application)
- Combination therapies (CagriSema)
- "Trojan horse" concept: Intracellular delivery of small molecules (*26*)
- New targets (FGF21, GDF15, myostatin)

To do

- Achieve higher efficacy—close the efficacy gap to bariatric surgery
- Improve tolerability (fewer side effects, combining complementary modes of action at lower doses)
- Overcome heterogeneous responses
- Target long-term weight maintenance
- Target adipose tissue dysfunction
- Address chronic low-grade inflammation
- Improve preservation of skeletal muscle mass and function

For clinical practice

- Start treatment earlier (at BMI of 27 to 33 kg/m^2)
- Include pharmacotherapies into multimodal approaches
- Personalize treatment (best-responder approach)
- Collect long-term data on efficacy and safety

to achieve weight loss thresholds that historically required bariatric surgery (table S1).

Newer drugs provide not only clinically meaningful weight loss but also a wide range of comorbidity management, including targeting systemic inflammation, nonalcoholic steatohepatitis [metabolic dysfunction–associated steatohepatitis (MASH)], cardiovascular disease, heart failure, obstructive sleep apnea, osteoarthritis, chronic kidney disease, and others to expand clinical applications beyond obesity and type 2 diabetes management (*9*, *25*, *46*).

Another strategy to take advantage of incretin-based therapies in a broader range of patients is to develop oral formulations to avoid weekly injections and cold-storage logistics. The approved drugs oral semaglutide (US and Europe) and the small-molecule alternative orforglipron (US and UK) were key developments that addressed this gap (*47*).

In addition, OMM development pursues the goal of designing medications that allow for longer treatment intervals. The most advanced compound presently in phase 3 trials, maridebart cafraglutide (MariTide), is a once-monthly antibody-peptide conjugate that works by blocking GIP receptors while simultaneously activating GLP-1 receptors (*48*).

Another challenge in obesity drug development is to provide the best efficacy with lower side effects. Frequently reported nausea, vomiting, diarrhea, obstipation, and other gastrointestinal symptoms often lead to treatment discontinuation. Newer medications, including those with a GIPR agonism component and amylin receptor agonists, are specifically designed to optimize efficacy while yielding more favorable side-effect profiles (*26*). Preservation of skeletal muscle mass and function and a healthy body composition after weight loss became a target of drug development (table S1). For example, bimagrumab binds to the type II activin receptor and blocks myostatin to prevent skeletal muscle loss while promoting skeletal muscle growth and led, in combination with semaglutide, to an ~45% reduction of fat mass while preserving lean mass over 72 weeks (*49*).

Most OMM development in advanced stages of clinical trials is pursued within compound classes of GLP-1RAs, incretin-based unimolecular polyagonists, amylin receptor agonists alone or in combination with GLP-1RAs, dual amylin and calcitonin receptor agonists (DACRA), or activin type II receptor antagonists (table S1).

However, there are additional conceptually different approaches to OMM development in early stages that include incretin-shuttled intracellular delivery of small molecules, BAT activators, mitochondrial uncouplers, leptin sensitizers, a cannabinoid receptor type 1 (CB1R) inverse agonist, fibroblast growth factor 21 (FGF21)– and growth differentiation factor 15 (GDF15)–targeting therapies, a monoacylglycerol transferase 2 (MGAT2) inhibitor, and others (table S1).

Only a few therapeutic concepts target energy expenditure. Among those, the mitochondrial uncoupler BAM15 is in preclinical development as an orally administered drug that can increase nutrient oxidation and decrease body-fat mass without altering food intake, lean body mass, body temperature, or hematological markers of toxicity (*50*).

Moreover, BAT is an attractive therapeutic target because mitochondrial uncoupling increases energy expenditure and promotes glucose and lipid oxidation. However, the relatively low and heterogeneous BAT mass in adults and uncertainty regarding its contribution to whole-body energy expenditure have complicated translation from rodents to humans (*2*, *16*). Historical experience with the mitochondrial uncoupler 2,4-dinitrophenol (DNP), which induced weight loss but had a narrow therapeutic window and potentially fatal hyperthermia, further illustrates the challenge of safely increasing energy expenditure systemically (*51*). Consequently, existing approaches seek more selective activation of BAT or adipose thermogenesis, including tissue-targeted mitochondrial uncouplers and other thermogenic strategies, although most remain preclinical and their capacity to produce clinically meaningful, durable weight loss in humans remains to be established (*52*).

Another strategy to improve the efficacy of OMMs while reducing side and off-target effects is the development of drugs that are specifically delivered into cells that express incretin receptors. A GLP-1R–GIPR–PPARα/γ/δ quintuple agonist based on this concept has been shown to correct obesity and diabetes in mice (*42*). This peptide-based small-molecule conjugate specifically targets tissues expressing GLP-1R and GIPR and allows the PPARα/γ/δ agonist lanifibranor to exert its insulin-sensitizing and anti-inflammatory effects directly in incretin-responsive cells (*42*).

Another incretin-independent mode of action has been pursued in the development of the CB1R inverse agonist monlunabant that demonstrated encouraging weight-loss efficacy and tolerability in a recent phase 2 trial (*53*). Even if weight loss effects of newer OMMs are inferior to existing incretin-based therapies, such compounds are needed for patients who do not respond or have poor tolerance to existing medications.

Conclusions

GLP-1R and dual incretin-receptor agonists have revolutionized pharmacological obesity treatment by demonstrating a >15% average weight loss and multiple cardiometabolic health benefits. However, there are limitations that lead to discontinuation of these drugs in clinical practice. Among the unmet needs that justify further OMM development are a need for greater weight loss, nonresponse, gastrointestinal side effects, and loss of lean body mass, as well as weight regain after discontinuation. More recent approaches to obesity medications are shifting toward multimechanistic therapies with the aim to achieve greater weight loss while reducing side effects and preserving skeletal muscle mass. In advanced stages of clinical trials, key developments include triple incretin-receptor agonists and amylin analogs. In addition, oral formulations of incretin-based therapies and agents targeting the myostatin-activin pathway to prevent skeletal muscle loss during fat

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reduction are being developed. Whether targeting AT dysfunction or pharmacologically increasing energy expenditure are viable concepts in OMM drug development remains open. More likely, incretin-based polypharmacology will shape the obesity treatment landscape in the near future and will extend its benefits to obesity comorbidities and other diseases. The ultimate goal would be to develop therapies that do not simply make patients weigh less but also make them healthier.

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