



EVIDENCE-BASED MANAGEMENT OF OBESITY - ADVANCES IN LIFESTYLE INTERVENTIONS AND PHARMACOTHERAPY

Agaaj Shaikh^{*1}, Dr. Kelgaonkar Prajakta², Pratiksha Jadhav¹, Vedika Mali¹, Ashwini Khandagale¹

¹Pharm D, Students, Channabasweshwar Pharmacy College, Latur, Maharashtra.

²Pharm D, Assistant Professor, Channabasweshwar Pharmacy College, Latur, Maharashtra.



***Corresponding Author: Agaaj Shaikh**

Pharm D, Students, Channabasweshwar Pharmacy College, Latur, Maharashtra.

DOI: <https://doi.org/10.5281/zenodo.22896553>



How to cite this Article: Agaaj Shaikh^{*1}, Dr. Kelgaonkar Prajakta², Pratiksha Jadhav¹, Vedika Mali¹, Ashwini Khandagale¹ (2026). Evidence-Based Management of Obesity - Advances in Lifestyle Interventions and Pharmacotherapy. European Journal of Biomedical and Pharmaceutical Sciences, 13(9), 320–329.

This work is licensed under Creative Commons Attribution 4.0 International license.

Article Received on 05/08/2026

Article Revised on 25/08/2026

Article Published on 01/09/2026

ABSTRACT

Obesity is a chronic, relapsing, multifactorial disease driven by interactions among biological, behavioural, environmental and social determinants. Contemporary management has therefore moved beyond the traditional concept of short-term calorie restriction toward long-term, complication-oriented care. Lifestyle intervention remains the foundation of treatment and should include an individualized dietary strategy, regular aerobic and resistance exercise, behavioural support, adequate sleep, stress management and attention to weight stigma. No single dietary pattern is consistently superior for all patients; sustained energy deficit, nutritional quality, adherence and preservation of lean mass are more important than macronutrient ideology. Intensive multicomponent programmes produce clinically meaningful weight loss and improve cardiometabolic risk, but physiological adaptations frequently limit long-term maintenance. Pharmacotherapy is increasingly used as an adjunct to lifestyle treatment, particularly when obesity-related complications are present or lifestyle intervention alone is insufficient. Older agents such as orlistat, naltrexone/bupropion and phentermine/topiramate remain useful in selected patients, whereas incretin-based therapies have transformed expectations for non-surgical weight reduction. Semaglutide 2.4 mg and the dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonist tirzepatide can produce double-digit mean weight loss, with evidence of benefits extending to glycaemia, cardiovascular outcomes, heart failure, sleep apnoea and physical function in appropriately selected populations. Weight regain after drug withdrawal emphasizes that obesity pharmacotherapy should generally be viewed as long-term treatment. This review summarizes evidence-based lifestyle management, established and newer anti-obesity medications, integration of treatment modalities, safety considerations and emerging directions in personalized obesity care.

KEYWORDS: Obesity, weight management, lifestyle intervention, anti-obesity medication, GLP-1 receptor agonist and pharmacotherapy.

INTRODUCTION

Obesity has become one of the most important chronic diseases encountered in clinical practice. Its consequences extend well beyond body weight and include type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, obstructive sleep apnoea, osteoarthritis, metabolic dysfunction-associated steatotic liver disease, impaired physical function and several cancers. The modern view recognizes obesity as a chronic, relapsing and progressive disease rather than a simple failure of willpower or an isolated consequence of excessive calorie intake. This shift is clinically important

because it changes the goals of treatment: the aim is not merely to achieve a lower number on the weighing scale, but to improve health, function, quality of life and obesity-related complications.^[1,36,37]

The pathophysiology of obesity is complex. Energy imbalance remains necessary for weight gain, but food intake and energy expenditure are influenced by neuroendocrine signals, adipose-tissue biology, genetic susceptibility, sleep, stress, medications, the food environment and socioeconomic conditions. Leptin resistance, altered ghrelin responses, insulin resistance,

chronic low-grade inflammation and changes in gut-derived signals contribute to persistent hunger and metabolic adaptation. During weight loss, compensatory changes may reduce resting energy expenditure and increase appetite, favouring weight regain. These biological responses explain why a short-term diet can be successful while long-term weight maintenance remains difficult.^[8,10,11,13] The treatment paradigm has changed substantially during the last decade. Intensive lifestyle modification remains the foundation of care, but increasingly effective pharmacological treatments can now produce weight loss that was previously achievable mainly through metabolic-bariatric surgery. The STEP programme established the efficacy of once-weekly semaglutide 2.4 mg, while the SURMOUNT programme demonstrated even larger average reductions in body weight with tirzepatide. Cardiovascular-outcome and complication-specific trials have further shifted treatment from weight-centred prescribing to health-outcome-directed therapy.^[18,42,62]

This review brings together current evidence on adult obesity management, with particular attention to the areas that have changed most rapidly: lifestyle treatment and pharmacotherapy. Drawing on the supplied collection of recent reviews, guidelines and pivotal trials, it considers how nutrition, physical activity and behavioural care can be combined with modern anti-obesity medicines, how treatment can be individualized and why long-term maintenance deserves the same attention as initial weight loss.^[15,37]

CLINICAL ASSESSMENT & TREATMENT GOALS

Effective treatment begins with a structured assessment. Body mass index (BMI) remains a useful screening measure, but it should not be the sole determinant of treatment intensity. Waist circumference, body-fat distribution, recent weight trajectory, physical function, mental health, eating behaviour, sleep, medications that promote weight gain and the presence and severity of obesity-related complications should all be considered. Recent frameworks increasingly emphasize the clinical consequences of excess adiposity rather than BMI alone.^[36,37]

The traditional regulatory thresholds for anti-obesity medication have generally been BMI at least 30 kg/m², or at least 27 kg/m² in the presence of a weight-related complication. However, several recent medication labels and clinical recommendations increasingly incorporate disease- or complication-specific indications rather than relying exclusively on fixed BMI thresholds. This evolution supports a more individualized approach.^[15,57] Treatment goals are best agreed with the patient and linked to outcomes that matter in everyday life. A 5-10% reduction in body weight can already improve glycaemia, blood pressure, triglycerides, sleep apnoea and mobility, while larger losses may be needed to achieve major improvement or remission of some

complications. Success should therefore include more than kilograms lost: better fitness, less pain, improved sleep, fewer medicines and a better quality of life are equally relevant. Because obesity tends to relapse, maintenance and regular follow-up should be planned from the beginning.^[43,65]

LIFESTYLE THERAPY

Major professional recommendations continue to place lifestyle treatment at the centre of obesity management. The strongest programmes are not single dietary prescriptions but intensive, multicomponent interventions that combine nutrition, physical activity, behavioural counselling and ongoing support. Greater contact frequency and adherence to counselling are consistently associated with better results. Intensive behavioural programmes commonly include at least 12 contacts during the first year and may continue through a maintenance phase.^[19,21,22,23,24,25]

Dietary Intervention

A sustained negative energy balance is necessary for reduction of body fat, but there is no single optimal macronutrient composition for every patient. Low-fat, low-carbohydrate, Mediterranean-style, plant-predominant, higher-protein and intermittent-fasting approaches can all produce weight loss when they reduce overall energy intake and are maintained. Consequently, the best diet is usually the nutritionally adequate pattern that the patient can follow over time.^[19,20] Dietary quality matters. Energy-dense, highly processed foods can facilitate passive overconsumption, whereas vegetables, fruits, legumes, whole grains and minimally processed protein sources increase nutrient density and often improve satiety. The Mediterranean dietary pattern is particularly attractive because it combines plant foods, whole grains, legumes, nuts, olive oil and moderate fish intake and has favourable effects on cardiometabolic risk. Plant-based patterns may also facilitate weight reduction through high fibre content and low energy density, but careful planning is necessary to ensure adequate vitamin B12, iron, calcium, vitamin D, iodine and omega-3 intake in vulnerable groups.^[63,64]

Low-carbohydrate diets can produce greater short-term weight loss and improvements in triglycerides and glycaemic control, particularly in type 2 diabetes, but their superiority over balanced diets generally narrows by 12-24 months. Very-low-carbohydrate ketogenic diets may suppress appetite and produce rapid early weight loss, yet long-term adherence can be difficult and safety requires attention in selected patients. Intermittent fasting, including time-restricted eating, alternate-day fasting and 5:2 regimens, usually produces weight loss comparable to continuous energy restriction rather than consistently superior results. It can nevertheless be useful for patients who prefer a structured eating window.^[19]

Higher-protein diets may improve satiety and help preserve fat-free mass during energy restriction. This

issue has gained new importance in the era of highly effective pharmacotherapy because rapid weight reduction can be accompanied by loss of lean tissue. Adequate protein intake, resistance exercise and attention to micronutrient density should therefore be included in contemporary weight-loss plans, especially in older adults or those at risk of sarcopenia.^[63,64] In practice, dietary advice works best when it is realistic and flexible. Rather than prescribing a rigid 'perfect diet', clinicians can help patients identify changes they are willing to maintain, such as reducing sugar-sweetened drinks, improving portion awareness, eating more minimally processed foods and increasing protein and fibre. Meal planning and self-monitoring can be useful when they suit the patient's preferences. Screening for disordered eating is important so that tracking and restriction do not unintentionally reinforce unhealthy behaviours.^[23,26,28]

Physical activity

Physical activity has benefits that extend far beyond the number of kilograms lost. Exercise improves cardiorespiratory fitness, insulin sensitivity, blood pressure, mood, mobility and cardiovascular health. On its own, exercise usually produces modest average weight loss, but it is crucial for weight-loss maintenance and preservation of lean mass. It should therefore accompany dietary intervention, pharmacotherapy and, when appropriate, metabolic-bariatric surgery.^[20,21] A practical exercise prescription uses the FITT principle: frequency, intensity, time and type. Aerobic training is the principal component for increasing energy expenditure and reducing fat mass, while resistance training helps preserve or increase skeletal muscle and attenuate the decline in resting metabolic rate that can accompany weight loss. A common initial target is progression toward at least 150 minutes per week of moderate-intensity activity, with higher volumes often needed for weight maintenance. Patients who are inactive should begin at a tolerable level and progress gradually.^[20,21] Baseline physical activity, cardiorespiratory limitations, osteoarthritis, neuropathy, balance problems and cardiovascular symptoms should be assessed before prescribing higher-intensity exercise. Wearable devices and step counts can support behaviour change, although increases in steps alone generally produce only modest weight reduction. The goal should be improved fitness and functional capacity, not merely calorie expenditure.^[20]

Behavioural therapy, Sleep, Stress & Weight stigma

Behavioural treatment translates knowledge into repeatable actions. Core techniques include goal setting, self-monitoring, stimulus control, problem solving, relapse planning, motivational interviewing and reinforcement of achievable changes. Frequent contact improves accountability and allows the treatment plan to be modified when weight loss plateaus or adverse effects occur.^[22,23,26] Sleep and stress deserve specific attention. Short or irregular sleep can worsen appetite regulation and reduce adherence to healthy behaviours. Chronic

stress may promote emotional eating, reduced physical activity and sleep disturbance. Although improving sleep or stress alone is not a substitute for energy balance, addressing these domains can improve the sustainability of a broader plan.^[9,10] Weight stigma can quietly undermine otherwise good obesity care. Many people with obesity have experienced blame, embarrassment or dismissive encounters in healthcare settings, which may reduce trust and delay care. Person-first language, permission before discussing weight and shared decision making can make treatment more respectful and more workable. Recognizing obesity as a biologically influenced chronic disease helps move the conversation away from moral judgement and toward practical, sustained care.^[15,16,17]

PHARMACOLOGICAL TREATMENT OF OBESITY

Pharmacotherapy is appropriate when lifestyle intervention alone does not produce sufficient health improvement, when obesity-related complications justify greater weight reduction, or when a patient is unable to sustain prior weight loss. Anti-obesity medications should be prescribed as adjuncts to a reduced-energy dietary pattern and physical activity, not as substitutes for comprehensive care. Medication selection should consider efficacy, contraindications, coexisting diseases, adverse-effect profile, route of administration, cost, access and patient preference.^[51,57] The response to medication is heterogeneous. Clinicians should assess weight change, complication-specific outcomes, tolerability and adherence during dose escalation and thereafter. Many drugs require gradual titration to reduce gastrointestinal, neurological or cardiovascular adverse effects. If the response is inadequate despite an appropriate dose and adherence, options include optimizing the dose, switching agents, adding structured behavioural therapy, considering rational combination treatment, or referral for metabolic-bariatric surgery.^[51,57]

Orlistat

Orlistat is a gastrointestinal and pancreatic lipase inhibitor that reduces absorption of dietary fat. Its weight-loss efficacy is modest compared with newer agents, but it has the advantages of a non-central mechanism and long clinical experience. Gastrointestinal adverse effects, including oily stool, urgency, increased defecation and flatus with discharge, are directly related to unabsorbed fat and are reduced by a lower-fat eating pattern. Because absorption of fat-soluble vitamins may be reduced, supplementation of vitamins A, D, E and K may be required. It should be avoided in chronic malabsorption and used cautiously in patients at risk of oxalate nephropathy or stones. Orlistat remains an option when injectable therapy is not desired or when sympathomimetic or centrally acting agents are unsuitable.^[38,39]

Phentermine/Topiramate

The combination of phentermine and extended-release topiramate acts through complementary appetite-suppressing mechanisms and provides greater average weight reduction than orlistat or naltrexone/bupropion in comparative analyses. Adverse effects can include paraesthesia, dry mouth, constipation, insomnia, cognitive symptoms and increases in heart rate. Topiramate is teratogenic; pregnancy must be avoided and appropriate reproductive counselling is essential. Caution is also needed in glaucoma, nephrolithiasis and significant cardiovascular disease. The medication can be particularly useful when strong appetite suppression is needed and contraindications are absent.^[40,50,80]

Naltrexone/Bupropion

Naltrexone/bupropion acts on hypothalamic appetite pathways and reward-related eating. It produces moderate average weight loss and may be helpful when food cravings or reward-driven eating are prominent. Nausea is common and bupropion can increase blood pressure and heart rate. It is unsuitable in uncontrolled hypertension, seizure disorders, certain eating disorders and chronic opioid use because naltrexone blocks opioid receptors. Careful psychiatric and medication history is required before treatment.^[39,57]

Liraglutide

Liraglutide 3.0 mg was the first GLP-1 receptor agonist widely used specifically for chronic weight management. GLP-1 receptor activation increases satiety, reduces appetite and slows gastric emptying. In the SCALE Obesity and Prediabetes trial, liraglutide produced clinically meaningful weight loss, with substantially more participants achieving at least 5% and 10% loss than with placebo. Daily injection and gastrointestinal adverse effects, particularly nausea, limit acceptability for some patients. Liraglutide nevertheless established incretin therapy as an effective strategy for obesity and demonstrated that pharmacological manipulation of appetite physiology could produce sustained clinically relevant weight loss.^[41,70,79]

Semaglutide

Semaglutide is a longer-acting GLP-1 receptor agonist administered once weekly. In STEP 1, semaglutide 2.4 mg combined with lifestyle treatment produced approximately 15% mean weight loss over 68 weeks, compared with a small reduction with placebo. This magnitude of response substantially exceeded that of most previously available medications. STEP 2 confirmed clinically important weight loss and improved glycaemic control in people with type 2 diabetes and overweight or obesity. Intensive behavioural intervention can be combined with semaglutide, although the incremental weight benefit may be smaller than with less potent agents because the medication itself produces strong appetite suppression.^[24,42,78]

Semaglutide has also changed the way clinicians view obesity outcomes. In SELECT, people with overweight or obesity and established cardiovascular disease but without diabetes had a significant reduction in major adverse cardiovascular events with semaglutide 2.4 mg. Thus, the drug is not only a weight-loss treatment but also an evidence-based cardiovascular risk-reduction therapy in an appropriate high-risk population. Studies in obesity-related heart failure with preserved ejection fraction have shown improvements in symptoms, functional limitations, exercise capacity and body weight. Evidence from osteoarthritis studies also suggests that sufficient weight reduction can translate into meaningful improvement in pain and physical function.^[4,47,49] The principal adverse effects are gastrointestinal, including nausea, vomiting, diarrhoea and constipation, especially during dose escalation. Gradual titration and smaller, lower-fat meals can improve tolerability. Clinicians should evaluate a history of severe gastrointestinal disease, pancreatitis risk and relevant endocrine contraindications according to the product label. Rapid weight reduction also raises concern about loss of lean mass; adequate protein intake and resistance exercise are therefore advisable, particularly in older adults.^[60,63,64]

Tirzepatide

Tirzepatide represents a major recent advance because it combines agonism of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors. The once-weekly drug reduces energy intake, enhances satiety and improves glucose regulation. In SURMOUNT-1, adults with obesity but without diabetes achieved approximately 15-21% mean weight reduction depending on dose, with a substantial proportion losing 20% or more. In SURMOUNT-2, people with type 2 diabetes also achieved large reductions in body weight and glycated haemoglobin. Comparative evidence and network meta-analysis place tirzepatide among the most effective currently available non-surgical obesity treatments.^[18,44,62,77] The SURMOUNT programme has also demonstrated the importance of continuing therapy. In SURMOUNT-4, participants who continued tirzepatide after initial weight reduction maintained and extended their loss, whereas those switched to placebo regained substantial weight. A three-year extension in people with prediabetes showed durable weight reduction and markedly reduced progression to type 2 diabetes, reinforcing the role of sustained treatment.^[26,73]

Tirzepatide has emerging complication-specific evidence. In obesity-related heart failure with preserved ejection fraction, the SUMMIT trial showed improvement in health status and reduction in the risk of cardiovascular death or worsening heart-failure events. Trials in obstructive sleep apnoea have reported major reductions in apnoea-hypopnoea index accompanying substantial weight loss. These findings illustrate the transition from prescribing a drug simply to reduce weight toward selecting therapy to improve specific

obesity-related diseases.^[6,48] Gastrointestinal adverse effects are the most frequent and are typically most prominent during titration. Nausea, vomiting, diarrhoea and constipation can often be managed by slower dose escalation, smaller meals and adjustment of meal fat content. As with GLP-1 receptor agonists, prescribing should follow current product-specific warnings and contraindications, including pregnancy and relevant personal or family endocrine history.^[61,63,64]

Comparative efficacy and Clinical selection

Comparative analyses consistently demonstrate a hierarchy of average weight-loss efficacy. Orlistat generally produces the smallest placebo-subtracted effect; naltrexone/bupropion and liraglutide provide intermediate effects; phentermine/topiramate produces larger reductions; and semaglutide and tirzepatide produce the greatest mean losses among established medicines. However, average trial efficacy should not be interpreted as a universal ranking for every patient. A medication with slightly lower mean efficacy may be preferable because of oral administration, lower cost, a

favourable comorbidity profile or better tolerability.^[2,44,51,62]

Comorbidity-directed selection is increasingly important. In type 2 diabetes, semaglutide and tirzepatide simultaneously improve body weight and glycaemia and can reduce the need for glucose-lowering medication. In established cardiovascular disease without diabetes, semaglutide has direct cardiovascular-outcome evidence. In obesity-related HFpEF, both semaglutide and tirzepatide have demonstrated meaningful symptom and event benefits. Conversely, naltrexone/bupropion is less attractive in uncontrolled hypertension and stimulant-containing regimens require careful cardiovascular assessment.^[4,47,48,75,77,78] Real-world treatment is also shaped by cost and access. A highly effective medicine offers little lasting benefit if a patient cannot obtain it consistently. Before starting therapy, clinicians should discuss affordability, supply, route of administration and whether long-term treatment is realistic. This conversation is especially important because stopping an effective anti-obesity medicine is often followed by renewed appetite and weight regain.^[58,59]

Table 1: Evidence-based lifestyle strategies in obesity management.

Strategy	Evidence-based role	Practical application	Key limitation
Energy-restricted dietary pattern	Foundation of weight loss; no single macronutrient pattern is universally superior.	Choose a sustainable, nutrient-dense pattern matched to preferences and comorbidities.	Adherence and metabolic adaptation limit long-term maintenance.
Mediterranean/plant-predominant diet	Supports weight control and cardiometabolic health through low energy density, fibre and unsaturated fats.	Emphasize vegetables, fruits, legumes, whole grains, nuts and minimally processed foods.	Requires attention to nutrient adequacy in highly restrictive plant-based diets.
Low-carbohydrate/ketogenic diet	Can improve short-term weight and glycaemic outcomes.	Useful for selected motivated patients with monitoring.	Long-term superiority is inconsistent; adherence and lipid response vary.
Intermittent fasting	Usually comparable to continuous energy restriction.	Consider when a structured eating window improves adherence.	Long-term data and suitability in vulnerable groups remain limited.
Aerobic plus resistance exercise	Improves fitness, cardiometabolic risk and weight maintenance; resistance training helps preserve lean mass.	Progress toward ≥ 150 min/week moderate activity plus regular resistance exercise.	Weight loss from exercise alone is usually modest.
Behavioural treatment	Improves adherence through self-monitoring, goal setting, problem solving and relapse planning.	Use frequent contact, motivational interviewing and multidisciplinary support.	Access, cost and time can limit intensive programmes.

Table 2: Selected Anti-obesity medications and Contemporary clinical role.

Medication	Mechanism	Approximate efficacy	Common/important adverse effects	Clinical considerations
Orlistat	Gastrointestinal/pancreatic lipase inhibition	Modest	Oily stool, urgency, fat-soluble vitamin loss	Oral option; use lower-fat diet; avoid in chronic malabsorption.
Naltrexone/bupropion	Appetite and reward pathway modulation	Moderate	Nausea, blood-pressure/heart-rate	Avoid in uncontrolled

			increase	hypertension, seizure risk and chronic opioid use.
Phentermine/topiramate ER	Sympathomimetic plus anticonvulsant appetite suppression	Moderate to high	Paraesthesia, insomnia, cognitive effects, heart-rate increase	Teratogenic; assess cardiovascular and pregnancy-related risks.
Liraglutide 3.0 mg	GLP-1 receptor agonist	Approximately 5-8% mean loss in trials	Nausea, vomiting, diarrhoea, constipation	Daily injection; established incretin option.
Semaglutide 2.4 mg	Long-acting GLP-1 receptor agonist	Approximately 15% mean loss in STEP 1	Predominantly gastrointestinal	Weekly injection; cardiovascular-outcome and HFpEF evidence.
Tirzepatide	Dual GIP/GLP-1 receptor agonist	Approximately 15-21% mean loss in SURMOUNT-1	Predominantly gastrointestinal	Weekly injection; high efficacy, diabetes-prevention and HFpEF evidence.

Safety, Special populations and monitoring

Safety monitoring should be individualized and should begin before the first prescription. Baseline assessment commonly includes blood pressure, glycaemic status, renal and hepatic function when clinically indicated, a medication review and evaluation for pregnancy potential. The clinician should also identify conditions that may influence the choice of drug, including seizure history, uncontrolled hypertension, opioid use, glaucoma, nephrolithiasis, severe gastrointestinal disease, pancreatitis history and endocrine disorders relevant to incretin therapy. Product-specific prescribing information should always guide final decisions because warnings and approved indications continue to evolve.^[57,63]

Pregnancy is a special situation in which intentional pharmacological weight loss is generally inappropriate. Women of reproductive potential receiving medications with fetal risk, particularly topiramate-containing therapy, require effective contraception and counselling. Older adults require a different emphasis: preservation of muscle and function may be more important than maximal weight reduction. Rapid weight loss can worsen frailty if protein intake and resistance exercise are inadequate. Similarly, patients with chronic kidney disease, advanced liver disease or complex cardiovascular disease may need slower titration and closer monitoring.^[40,57] The gastrointestinal effects of GLP-1 and GIP/GLP-1 therapies deserve practical management rather than automatic discontinuation. Nausea and early satiety can often be reduced by smaller portions, slower eating, lower-fat meals, adequate hydration and extending the interval before a dose

increase. Persistent vomiting, severe abdominal pain or inability to maintain hydration warrants prompt reassessment. Because appetite may fall markedly, clinicians should actively ask about protein intake and overall nutritional adequacy instead of assuming that lower food intake is inherently beneficial.^[60,61,63,64]

Cardiovascular monitoring is particularly relevant for sympathomimetic therapy and naltrexone/bupropion. Blood pressure, pulse, insomnia, anxiety and palpitations should be reviewed during titration. Neuropsychiatric symptoms should be monitored when centrally acting drugs are used. Orlistat requires counselling about gastrointestinal effects and fat-soluble vitamin intake. Across all therapies, adverse effects should be balanced against improvements in obesity-related disease rather than judged in isolation^[39,40,57] Weight alone should not determine whether treatment is working. Follow-up should document waist or body-composition change when useful, blood pressure, glycated haemoglobin, lipid profile, sleep-apnoea symptoms, mobility, pain, medication burden and patient-reported quality of life. This broader monitoring reflects the central aim of evidence-based obesity therapy: improvement in health and function with acceptable treatment burden.^[15,51]

INTEGRATING LIFESTYLE & DRUG THERAPY

The emergence of highly effective pharmacotherapy does not make lifestyle treatment obsolete. Instead, the role of lifestyle intervention is evolving. With older drugs, intensive behavioural therapy often increased total weight loss. With semaglutide and tirzepatide, the incremental effect on the scale may be smaller, but lifestyle treatment remains important for nutritional

adequacy, preservation of muscle, physical fitness, management of gastrointestinal adverse effects and long-term self-efficacy.^[23,24,25,63,64] Nutrition during incretin therapy should prioritize adequate protein, fiber, fluids and micronutrients despite reduced appetite. Very large portions and high-fat meals can aggravate nausea and postprandial discomfort; smaller meals may be better tolerated. Resistance exercise is particularly important for patients losing weight rapidly or those with low baseline muscle mass. Aerobic activity should continue because cardiovascular fitness independently predicts health outcomes even when body weight changes only modestly.^[63,64]

The chronic-disease model also changes how treatment success is judged. If a medication produces clinically important weight loss and improves complications, continuing the drug is analogous to continuing antihypertensive or lipid-lowering therapy. Withdrawal studies show substantial regain after discontinuation of liraglutide, semaglutide and tirzepatide. In the STEP 1 extension, a large proportion of semaglutide-associated weight loss was regained after treatment stopped, with deterioration of several cardiometabolic improvements. Patients should therefore be counselled before initiation that pharmacotherapy may be long term.^[29,59] When response is disappointing, the next step should be reassessment rather than blame. It is useful to review adherence, dose, eating patterns, sleep, weight-promoting medicines, binge eating, mood and other contributors before deciding that treatment has failed. Depending on the findings, care can be intensified with structured lifestyle support, a different medicine, combination treatment in selected cases, or referral for metabolic-bariatric surgery. In this way, obesity treatment becomes an adaptive long-term plan rather than a single intervention.^[53,57]

RECENT ADVANCES AND FUTURE DIRECTIONS

The most important recent advance is the shift toward therapies that target the biological regulation of appetite and produce double-digit mean weight loss. Semaglutide and tirzepatide have narrowed the efficacy gap between medication and surgery and have generated a pipeline of multi-agonist therapies targeting GLP-1, GIP, glucagon and other metabolic pathways. Future treatment is likely to focus increasingly on greater efficacy, better preservation of lean mass, oral formulations and complication-specific outcome benefits.^[18,42,62,74]

Precision obesity medicine is another emerging area. Genomic, epigenetic, metabolomic and microbiome-related markers may eventually help predict who responds best to a particular dietary pattern or drug. At present, however, routine nutrigenetic testing has limited validated clinical utility and should not replace established assessment and evidence-based therapy. Digital health tools, continuous monitoring, mobile applications and remote coaching can improve self-

monitoring and access, but algorithms need validation and should not widen health inequities.^[12,13,14]

A third advance is the move from weight-loss percentages toward disease outcomes. Cardiovascular events, heart-failure symptoms, sleep apnoea severity, osteoarthritis pain, progression to diabetes, liver disease and quality of life are increasingly incorporated into trials. This is a more clinically meaningful framework because two patients with the same percentage weight loss may experience very different health benefits.^[4,6,7,46,47,48,49] Important uncertainties remain. Long-term comparative safety, optimal sequencing of therapies, treatment after major weight loss, prevention of sarcopenia, cost-effectiveness and equitable access require further study. Head-to-head trials are still limited and real-world discontinuation is higher than in many randomized trials. Future guidelines will therefore need to integrate efficacy with affordability, patient preference, comorbidity profile and health-system capacity.^[51,58,59,62]

CONCLUSION

Evidence-based obesity care is most effective when it is treated as long-term, individualized care rather than a short course of dieting. A sustainable energy deficit, good dietary quality, regular aerobic and resistance activity, behavioural support, adequate sleep and respectful communication remain the foundation. The evidence does not support one universally superior diet; the most useful eating pattern is one that is nutritionally sound, clinically appropriate and sustainable for the individual. Medication becomes important when lifestyle treatment alone does not provide enough improvement or when obesity-related disease calls for greater weight reduction. Established medicines still have a role, but semaglutide and tirzepatide have substantially raised expectations for non-surgical treatment and have demonstrated benefits that extend beyond weight itself. At the same time, withdrawal studies remind clinicians and patients that effective obesity treatment often needs to continue. The direction of modern care is therefore clear: combine lifestyle therapy, pharmacotherapy and metabolic-bariatric surgery when appropriate and choose the intensity of treatment according to complications, patient goals, safety, access and long-term sustainability.

REFERENCES

1. LeBlanc ES, Patnode CD, Webber EM, et al. Behavioral and pharmacotherapy weight loss interventions to prevent obesity-related morbidity and mortality in adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*, 2018; 320: 1172-91.
2. Shi Q, Wang Y, Hao Q, et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. *Lancet*, 2024; 403: e21-31.
3. Qin W, Yang J, Ni Y, et al. Efficacy and safety of once-weekly tirzepatide for weight management

- compared to placebo: an updated systematic review and meta-analysis including the latest SURMOUNT-2 trial. *Endocrine*, 2024; 86: 70-84.
4. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med.*, 2023; 389: 2221-32.
 5. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.*, 2016; 375: 311-22.
 6. Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. *N Engl J Med.*, 2024; 391: 1193-205.
 7. Sanyal AJ, Newsome PN, Kliers I, et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N Engl J Med.*, 2025; 392: 2089-99.
 8. Korner J, Aronne LJ. The emerging science of body weight regulation and its impact on obesity treatment. *J Clin Invest*, 2003; 111: 565-70.
 9. Lowe MR. Self-regulation of energy intake in the prevention and treatment of obesity: is it feasible? *Obes Res.*, 2003; 11 Suppl: 44S-59S.
 10. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med.*, 2011; 365: 1597-604.
 11. Fothergill E, Guo J, Howard L, et al. Persistent metabolic adaptation 6 years after 'The Biggest Loser' competition. *Obesity (Silver Spring)*, 2016; 24: 1612-9.
 12. Moiz A, Filion KB, Toutounchi H, et al. Efficacy and safety of glucagon-like peptide-1 receptor agonists for weight loss among adults without diabetes: a systematic review of randomized controlled trials. *Ann Intern Med.*, 2025; 178: 199-217.
 13. Roh E, Choi KM. Hormonal gut-brain signaling for the treatment of obesity. *Int J Mol Sci.*, 2023; 24: 3384.
 14. Bray GA, Purnell JQ, et al. An historical review of steps and missteps in the discovery of anti-obesity drugs. In: Feingold KR, Ahmed SF, Anawalt B, editors. *Endotext*. South Dartmouth (MA): MDText.com, Inc., 2000.
 15. Bannuru RR, ADA Professional Practice Committee. Introduction and methodology: Standards of Care in Overweight and Obesity-2025. *BMJ Open Diabetes Res Care*, 2025; 13: e004928.
 16. Mitropoulou P, Gruner-Hegge N, Reinhold J, et al. Shared decision making in cardiology: a systematic review and meta-analysis. *Heart*, 2023; 109: 34-9.
 17. Elias S, Chen Y, Liu X, et al. Shared decision-making in cardiovascular risk factor management: a systematic review and meta-analysis. *JAMA Netw Open*, 2024; 7: e243779.
 18. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med.* 2022; 387: 205-16.
 19. Franz MJ, VanWormer JJ, Crain AL, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *J Am Diet Assoc.*, 2007; 107: 1755-67.
 20. Recchia F, Leung CK, Yu AP, et al. Dose-response effects of exercise and caloric restriction on visceral adiposity in overweight and obese adults: a systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med.*, 2023; 57: 1035-41.
 21. Lundgren JR, Janus C, Jensen SBK, et al. Healthy weight loss maintenance with exercise, liraglutide, or both combined. *N Engl J Med.*, 2021; 384: 1719-30.
 22. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring)*, 2011; 19: 110-20.
 23. Wadden TA, Walsh OA, Berkowitz RI, et al. Intensive behavioral therapy for obesity combined with liraglutide 3.0 mg: a randomized controlled trial. *Obesity (Silver Spring)*, 2019; 27: 75-86.
 24. Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. *JAMA.*, 2021; 325: 1403-13.
 25. Wadden TA, Chao AM, Machineni S, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. *Nat Med.*, 2023; 29: 2909-18.
 26. Tronieri JS, Fabricatore AN, Wadden TA, et al. Effects of dietary self-monitoring, physical activity, liraglutide 3.0 mg and placebo on weight loss in the SCALE IBT trial. *Obes Facts.*, 2020; 13: 572-83.
 27. Tronieri JS, Wadden TA, Walsh O, et al. Effects of liraglutide on appetite, food preoccupation and food liking: results of a randomized controlled trial. *Int J Obes (Lond)*, 2020; 44: 353-61.
 28. Chao AM, Wadden TA, Walsh OA, et al. Effects of liraglutide and behavioral weight loss on food cravings, eating behaviors and eating disorder psychopathology. *Obesity (Silver Spring)*, 2019; 27: 2005-10.
 29. Hales CM, Gu Q, Ogden CL, et al. Use of prescription medications associated with weight gain among US adults, 1999-2018: a nationally representative survey. *Obesity (Silver Spring)*, 2022; 30: 229-39.
 30. Almazan E, Schwartz JL, Gudzone KA. Use of medications associated with weight change among participants in the All of Us research programme. *Clin Obes.*, 2023; 13: e12609.
 31. Galindo RJ, Uppal TS, McCoy RG, et al. Use and continuity of weight-modifying medications among adults with diabetes and overweight/obesity: US

- population study. *Obesity (Silver Spring)*. 2023; 31: 2924-35.
32. Domecq JP, Prutsky G, Leppin A, et al. Drugs commonly associated with weight change: a systematic review and meta-analysis. *J Clin Endocrinol Metab.*, 2015; 100: 363-70.
 33. Stanford FC, Cena H, Biino G, et al. The association between weight-promoting medication use and weight gain in postmenopausal women: findings from the Women's Health Initiative. *Menopause*, 2020; 27: 1117-25.
 34. Desalermos A, Russell B, Leggett C, et al. Effect of obesogenic medications on weight-loss outcomes in a behavioral weight-management program. *Obesity (Silver Spring)*. 2019; 27: 716-23.
 35. Moon RC, Almuwaqqat Z. Effect of obesogenic medication on weight- and fitness-change outcomes: evidence from the Look AHEAD study. *Obesity (Silver Spring)*, 2020; 28: 2003-9.
 36. Sharma AM, Kushner RF. A proposed clinical staging system for obesity. *Int J Obes (Lond)*. 2009; 33: 289-95.
 37. Rubino F, Cummings DE, Eckel RH, et al. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol.*, 2025; 13: 221-62.
 38. Sjostrom L, Rissanen A, Andersen T, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *Lancet.*, 1998; 352: 167-72.
 39. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.*, 2010; 376: 595-605.
 40. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet.*, 2011; 377: 1341-52.
 41. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med.*, 2015; 373: 11-22.
 42. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med.*, 2021; 384: 989-1002.
 43. Douketis JD, Macie C, Thabane L, et al. Systematic review of long-term weight loss studies in obese adults: clinical significance and applicability to clinical practice. *Int J Obes (Lond)*, 2005; 29: 1153-67.
 44. Pan XH, Tan B, Chin YH, et al. Efficacy and safety of tirzepatide, GLP-1 receptor agonists and other weight loss drugs in overweight and obesity: a network meta-analysis. *Obesity (Silver Spring)*, 2024; 32: 840-56.
 45. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care*, 2011; 34: 1481-6.
 46. Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N Engl J Med.*, 2024; 391: 299-310.
 47. Kosiborod MN, Abildstrom SZ, Borlaug BA, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N Engl J Med.*, 2023; 389: 1069-84.
 48. Packer M, Zile MR, Kramer CM, et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. *N Engl J Med.*, 2025; 392: 427-37.
 49. Bliddal H, Bays H, Czernichow S, et al. Once-weekly semaglutide in persons with obesity and knee osteoarthritis. *N Engl J Med.*, 2024; 391: 1573-83.
 50. Aronne LJ, Wadden TA, Peterson C, et al. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity (Silver Spring)*, 2013; 21: 2163-71.
 51. McGowan B, Ciudin A, Baker JL, et al. A systematic review and meta-analysis of the efficacy and safety of pharmacological treatments for obesity in adults. *Nat Med.*, 2025; 31: 3317-29.
 52. Haddock CK, Poston WSC, Dill PL, et al. Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials. *Int J Obes Relat Metab Disord.*, 2002; 26: 262-73.
 53. Tronieri JS, Ghanbari E, Chevinsky J, et al. Anti-obesity medication for weight loss in early nonresponders to behavioral treatment: a randomized controlled trial. *Nat Med.*, 2025; 31: 1653-60.
 54. Hollander P, Bays HE, Rosenstock J, et al. Coadministration of canagliflozin and phentermine for weight management in overweight and obese individuals without diabetes: a randomized clinical trial. *Diabetes Care*, 2017; 40: 632-9.
 55. Lewis KH, Fischer H, Ard J, et al. Safety and effectiveness of longer-term phentermine use: clinical outcomes from an electronic health record cohort. *Obesity (Silver Spring)*, 2019; 27: 591-602.
 56. Bays HE, Lazarus E, Primack C, et al. Obesity pillars roundtable: phentermine - past, present and future. *Obes Pillars*, 2022; 3: 100024.
 57. Grunvald E, Shah R, Hernaez R, et al. AGA clinical practice guideline on pharmacological interventions for adults with obesity. *Gastroenterology*, 2022; 163: 1198-1225.
 58. Berning P, Adhikari R, Schroer AE, et al. Longitudinal analysis of obesity drug use and public awareness. *JAMA Netw Open*, 2025; 8: e2457232.
 59. Rodriguez PJ, Zhang V, Gratzl S, et al. Discontinuation and reinitiation of dual-labeled GLP-1 receptor agonists among US adults with overweight or obesity. *JAMA Netw Open*, 2025; 8: e2457349.

60. Wharton S, Calanna S, Davies M, et al. Gastrointestinal tolerability of once-weekly semaglutide 2.4 mg in adults with overweight or obesity and the relationship between gastrointestinal adverse events and weight loss. *Diabetes Obes Metab.*, 2022; 24: 94-105.
61. Rubino DM, Pedersen SD, Connery L, et al. Gastrointestinal tolerability and weight reduction associated with tirzepatide in adults with obesity or overweight with and without type 2 diabetes in the SURMOUNT-1 to -4 trials. *Diabetes Obes Metab.*, 2025; 27: 1826-35.
62. Aronne LJ, Horn DB, le Roux CW, et al. Tirzepatide as compared with semaglutide for the treatment of obesity. *N Engl J Med.*, 2025; 393: 26-36.
63. Almandoz JP, Wadden TA, Tewksbury C, et al. Nutritional considerations with antiobesity medications. *Obesity (Silver Spring)*, 2024; 32: 1613-31.
64. Mozaffarian D, Agarwal M, Aggarwal M, et al. Nutritional priorities to support GLP-1 therapy for obesity: a joint advisory from the American College of Lifestyle Medicine, the American Society for Nutrition, the Obesity Medicine Association and The Obesity Society. *Am J Clin Nutr.*, 2025; 122: 344-67.
65. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care*, 2006; 29: 2102-7.
66. Garvey WT, Ryan DH, Henry R, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. *Diabetes Care*, 2014; 37: 912-21.
67. Carlsson LMS, Peltonen M, Ahlin S, et al. Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects. *N Engl J Med.*, 2012; 367: 695-704.
68. Booth H, Khan O, Prevost T, et al. Incidence of type 2 diabetes after bariatric surgery: population-based matched cohort study. *Lancet Diabetes Endocrinol.*, 2014; 2: 963-8.
69. Torgerson JS, Hauptman J, Boldrin MN, et al. 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*, 2004; 27: 155-61.
70. le Roux CW, Astrup A, Fujioka K, 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. *Lancet.*, 2017; 389: 1399-409.
71. McGowan BM, Bruun JM, Capehorn M, et al. Efficacy and safety of once-weekly semaglutide 2.4 mg versus placebo in people with obesity and prediabetes (STEP 10): a randomised, double-blind, placebo-controlled, multicentre phase 3 trial. *Lancet Diabetes Endocrinol.*, 2024; 12: 631-42.
72. Kahn SE, Deanfield JE, Jeppesen OK, et al. Effect of semaglutide on regression and progression of glycemia in people with overweight or obesity but without diabetes in the SELECT trial. *Diabetes Care.* 2024; 47: 1350-9.
73. Jastreboff AM, le Roux CW, Stefanski A, et al. Tirzepatide for obesity treatment and diabetes prevention. *N Engl J Med.*, 2025; 392: 958-71.
74. Nauck MA, Quast DR, Wefers J, et al. The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: a pathophysiological update. *Diabetes Obes Metab.*, 2021; 23 Suppl 3: 5-29.
75. Bajaj M, McCoy RG, Balapattabi K, et al. Obesity and weight management for the prevention and treatment of diabetes: Standards of Care in Diabetes-2026. *Diabetes Care*, 2026; 49: S166-82.
76. Bays HE. Why does type 2 diabetes mellitus impair weight reduction in patients with obesity? A review. *Obes Pillars*, 2023; 7: 100076.
77. Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.*, 2023; 402: 613-26.
78. Davies M, Faerch L, Jeppesen OK, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet.* 2021; 397: 971-84.
79. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE Diabetes randomized clinical trial. *JAMA.*, 2015; 314: 687-99.
80. Garvey WT, Ryan DH, Bohannon NJV, et al. Weight-loss therapy in type 2 diabetes: effects of phentermine and topiramate extended release. *Diabetes Care*, 2014; 37: 3309-16.