Obesity Pharmacotherapy Beyond Weight Loss: Incretin-Based Therapies, Maintenance, and the Role of Family Physicians

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Abstract

According to the American Association of Clinical Endocrinology, obesity is a chronic disease driven by complex genetic, environmental, metabolic, and neuroregulatory factors that disrupt energy homeostasis and promote excess adiposity (1). This framing has shifted obesity treatment from short-term weight reduction toward long-term chronic disease management. Incretin-based therapies, including glucagon-like peptide-1 receptor agonists and dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonists, have transformed medical obesity treatment, with trials such as STEP 1 and SURMOUNT-1 demonstrating clinically meaningful weight reduction (2,3). However, the clinical value of these therapies increasingly depends on long-term continuation of therapy, cardiometabolic outcomes, and real-world implementation. Maintenance studies show that discontinuation is associated with weight regain and worsening of metabolic and functional measures, while continued therapy helps sustain improvements linked to reduced obesity-related complications (6-8) . Real-world evidence highlights discontinuation, lower-than-trial dosing, access barriers, and follow-up challenges that may limit translation of trial efficacy into routine care (9,10). This narrative review examines landmark efficacy trials, maintenance and withdrawal data, real-world evidence, and selected future therapies, including retatrutide, orforglipron, and CagriSema. For family physicians, the key implication is that obesity pharmacotherapy should be approached as individualized, long-term chronic disease care aimed not only at weight reduction, but also at sustaining cardiometabolic health, function, and quality of life.

Keywords: Obesity; pharmacotherapy; GLP-1 receptor agonists; tirzepatide; semaglutide; primary care; family medicine; weight maintenance

Introduction

Obesity pharmacotherapy has changed rapidly with the emergence of incretin-based therapies capable of producing clinically meaningful weight loss. In particular, GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists have produced mean weight reductions of approximately 15% with semaglutide and more than 20% with tirzepatide, approaching the 25%–35% total body weight loss often reported after metabolic and bariatric surgery (2,3,14). As these agents have moved treatment into a new phase, attention has shifted from achieving clinically meaningful weight loss to maintaining it and defining its longer-term clinical value (2,3,6-8).

The central question is no longer whether substantial pharmacologic weight loss can be achieved, but how it can be sustained, what follows treatment withdrawal, and whether newer therapies can improve long-term outcomes. Against this background, this narrative review examines evidence from landmark semaglutide and tirzepatide trials, the challenge of weight regain after discontinuation, and developing therapies that may shape the future of obesity management.

Landmark Trials That Changed Obesity Treatment

The STEP 1 trial was a pivotal moment in modern obesity medicine. In adults with overweight or obesity without diabetes, once-weekly semaglutide 2.4 mg combined with lifestyle intervention produced mean weight loss of approximately 14.9% at 68 weeks (2). This degree of weight reduction was substantially greater than that achieved with older anti-obesity medications and helped establish GLP-1 receptor agonist therapy as an effective central component of medical obesity treatment rather than a limited adjunct. Weight loss in STEP 1 was also associated with greater improvement in cardiometabolic risk factors, including blood pressure, glycated hemoglobin levels, lipid levels, and markers of inflammation (2).

Tirzepatide further advanced this field. SURMOUNT-1 showed weight reductions exceeding 20% with higher-dose tirzepatide in adults with obesity or overweight without diabetes, supporting the hypothesis that dual GIP and GLP-1 receptor agonism may enhance weight loss beyond GLP-1 receptor agonism alone (3). This was later confirmed in SURMOUNT-5, where tirzepatide produced greater reductions in body weight and waist circumference than semaglutide at 72 weeks in adults with obesity but without diabetes (4).

The SELECT cardiovascular outcomes trial is particularly relevant to family medicine because it showed benefits beyond weight loss. SELECT demonstrated that semaglutide reduced the composite risk of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke over a mean follow-up of 39.8 months in patients with overweight or obesity and pre-existing cardiovascular disease, even in the absence of diabetes (5). For family physicians, this supports viewing incretin-based therapy not only as weight-loss treatment, but also as part of cardiometabolic risk reduction in appropriately selected patients.

Figure 1. Evolution of obesity pharmacotherapy toward long-term, personalized chronic disease management

Earlier pharmacotherapy	GLP-1 receptor agonists	Dual incretin agonists	Emerging therapies
Modest mean weight loss; short-term weight-loss focus	Semaglutide 2.4 mg; approximately 15% mean weight loss	Tirzepatide; more than 20% mean weight loss	Retatrutide, orforglipron, and CagriSema; greater efficacy, oral options, and combination approaches
Weight-centric treatment	*Substantial pharmacologic weight loss*	*Weight-loss magnitudes approaching those previously associated mainly with bariatric surgery*	*Personalized long-term chronic disease management*

Together, these trials redefined obesity pharmacotherapy by establishing substantial weight loss as achievable, broadening treatment goals beyond body weight alone, and shifting attention toward the challenge of long-term maintenance.

The major trials informing current practice are summarized in Table 1.

Table 1. Key trials informing the clinical use of incretin-based obesity pharmacotherapy, including efficacy, maintenance, cardiovascular outcomes, and implications for family medicine practice.

Trial	Agent / design	Duration	Key finding	Clinical message
STEP 1[2]	Semaglutide 2.4 mg vs placebo in adults with overweight or obesity without diabetes	68 weeks	Mean weight change −14.9% vs −2.4% with placebo	Established high-efficacy GLP-1 receptor agonist therapy for obesity
SURMOUNT-1[3]	Tirzepatide 5, 10, or 15 mg vs placebo in adults without diabetes	72 weeks	Mean weight loss up to −20.9%; ≥20% loss in up to 56.7%	Approached weight-loss magnitudes previously associated mainly with bariatric surgery
SELECT[5]	Semaglutide 2.4 mg vs placebo in adults with overweight/obesity and cardiovascular disease, without diabetes	Mean 39.8 months	Major cardiovascular events 6.5% vs 8.0%; hazard ratio 0.80	Supports cardiometabolic benefit beyond weight reduction
STEP 4[6]	Continued semaglutide vs placebo after semaglutide run-in	68 weeks total	Continued semaglutide: additional −7.9%; placebo switch: +6.9% regain	Shows importance of continued therapy for maintenance
SURMOUNT-4[7]	Continued tirzepatide vs placebo after open-label lead-in	88 weeks total	Overall weight change −25.3% with continued tirzepatide vs −9.9% after placebo switch	Reinforces long-term treatment rather than short-term use
SURMOUNT-MAINTAIN[8]	Continued or reduced-dose tirzepatide vs placebo after weight-loss phase	112 weeks total	Week 112 weight change: −21.9% maximum tolerated dose, −16.6% 5 mg, −9.9% placebo	Supports individualized maintenance strategies

Long term maintenance and treatment discontinuation

The success of incretin-based therapy has exposed a major unresolved issue in obesity care: long-term maintenance. Withdrawal and maintenance studies increasingly show that weight loss achieved with pharmacotherapy is difficult to sustain after treatment discontinuation.

The STEP 4 randomized clinical trial demonstrated the effect of continued once-weekly subcutaneous semaglutide 2.4 mg on maintenance of body weight loss in adults with overweight or obesity without diabetes. After an initial 20-week run-in, participants who continued semaglutide lost an additional 7.9% of body weight from weeks 20 to 68, whereas those switched to placebo regained 6.9% (6). Continued treatment also helped preserve improvements in waist circumference, blood pressure, lipid levels, glucose metabolism, and physical functioning, while discontinuation and switch to placebo were associated with worsening of these measurements (6). This is clinically important because these markers are closely linked to obesity-related complications. For patients, the benefit of treatment may therefore extend beyond the number on the scale; for family physicians, the trial reinforces the need to discuss obesity pharmacotherapy as long-term chronic disease management rather than a short-term course of treatment.

SURMOUNT-4 further demonstrated that continued tirzepatide therapy is important for maintaining weight reduction and associated health benefits. At week 88, participants who remained on tirzepatide were more likely than those switched to placebo to maintain at least 80% of the weight loss achieved during the initial treatment period, with sustained improvements in BMI, waist circumference, cardiometabolic measures, and patient-reported outcomes (7). These findings reinforce that discontinuation of anti-obesity pharmacotherapy can lead to weight regain and attenuation of broader clinical benefits.

SURMOUNT-MAINTAIN addressed a practical maintenance question: whether patients who achieved weight loss on maximum tolerated tirzepatide need to remain at that dose or may maintain benefit with dose reduction. Continuing the maximum tolerated dose maintained body-weight reduction and health-related benefits, while reduction to tirzepatide 5 mg offered a potential alternative to discontinuation, although individual responses varied (8). These findings support ongoing pharmacotherapy while allowing for individualized, patient-centered decisions.

Real-practice data suggest that GLP-1 receptor agonist–based obesity therapies may perform differently outside trials, with reported first-year discontinuation rates of approximately 20%–50% and frequent use of doses below those tested in pivotal studies (9). Key evidence gaps include optimal dosing, discontinuation rates, comparative effectiveness, withdrawal effects, long-term outcomes, safety, and cost-effectiveness (9). These gaps matter in primary care, where sustained benefit depends on access, adherence, individualized dosing, and longitudinal monitoring (9, 10).

For family physicians, the benefits of GLP-1 receptor agonists and dual incretin agonists are increasingly clear, but maintenance in routine practice is rarely a simple choice between continuing maximum-dose therapy and stopping treatment. Access, cost, tolerability, dose escalation, persistence, comorbidities, and patient preference all shape what is feasible. Many patients have experienced repeated weight-loss attempts followed by regain, and acknowledging this history can help position family physicians as allies in long-term obesity care(10). The practical task is to individualize therapy so that weight loss, cardiometabolic gains, and functional improvements can be preserved (9,10).

These maintenance and implementation challenges have shaped interest in newer agents that may improve efficacy, delivery, tolerability, or individualized long-term treatment options.

Future therapies

The future obesity-treatment landscape is likely to become more complex as newer agents aim not only to increase weight-loss efficacy, but also to broaden therapeutic options and address practical barriers to long-term treatment.

Retatrutide is a subcutaneous injection with triple action at the GIP, GLP-1, and glucagon receptors. In a phase 2 trial of adults with obesity without diabetes, the 12-mg dose produced a mean weight reduction of 24.2% at 48 weeks, with weight loss still ongoing at the end of treatment (11). Its adverse-effect profile was broadly similar to other incretin-based therapies, but longer-term data are needed to define sustained effectiveness, safety, maintenance needs, and its place in routine obesity care.

Orforglipron is a nonpeptide oral GLP-1 receptor agonist that activates the GLP-1 receptor and is designed for once-daily administration. In phase 2 testing, it produced clinically meaningful weight loss over 36 weeks and improved prespecified weight-related and cardiometabolic measures (12). Further studies are needed to determine whether orforglipron provides the broader health benefits demonstrated with injectable GLP-1 receptor agonists.

CagriSema combines once-weekly semaglutide with cagrilintide, a long-acting amylin analogue, targeting complementary appetite-regulating pathways. In adults with overweight or obesity and type 2 diabetes, it produced greater weight loss than placebo over 68 weeks and improved glycemic outcomes, including achievement of HbA1c targets (13). Further data are needed to clarify its comparative effectiveness, tolerability, and place in routine primary care.

For family physicians, future obesity pharmacotherapy will likely involve choosing among agents that act on overlapping appetite and incretin pathways but differ in how they are delivered, combined, and tolerated. Retatrutide may test whether triple agonism can produce greater weight reduction; orforglipron may make oral GLP-1 receptor agonism a practical option; and CagriSema may combine appetite and glycemic benefits, particularly for patients with type 2 diabetes. In routine practice, the key question will be how to match these therapies to the right patient while considering comorbidities, tolerability, adherence, cost, access, and long-term maintenance.

Conclusion

For family physicians, the central message is that obesity pharmacotherapy is evolving from short-term weight-loss treatment toward individualized long-term chronic disease management. Semaglutide and tirzepatide have shown that substantial weight reduction and cardiometabolic benefits are achievable, but maintenance studies and real-world evidence show that long-term benefit depends on continued therapy, access, tolerability, dosing, adherence, and follow-up. Current guidance supports a person-centered, complication-centric approach, including personalized lifestyle and behavioural interventions, in which treatment goals extend beyond weight to metabolic health, comorbidity burden, function, and quality of life (1,10). As newer agents become available, family physicians will be central to matching therapy to the right patient and sustaining meaningful benefit over time.

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