

Can Obesity Drugs Replace Surgery? A Review

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Abstract

The potential of obesity medications to serve as viable alternatives to bariatric surgery to treat obesity remains an open question. This review examines whether contemporary anti-obesity pharmacotherapy can replace metabolic and bariatric surgery in the management of obesity, by critically comparing their mechanisms of action, weight loss outcomes, durability, safety profiles, and roles in long-term disease control. While metabolic/bariatric surgery has been the gold standard for substantial and sustained weight loss, advancements in pharmacotherapy are producing weight loss approaching surgical outcomes without associated risks, complications, and recovery time. New drug therapies demonstrate previously unattainable efficacy and long-term control of obesity. Surgery, however, induces superior short- and long-term weight loss via profound hormonal, neurological, and



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metabolic shifts, resulting in durable outcomes without ongoing intervention, though it remains difficult to scale. Pharmacotherapy is scalable and increasingly effective but requires sustained adherence, with loss of treatment-mediated control and weight regain upon cessation. It also does not have as extensive established research on safety as surgery. While obesity medications cannot fully replicate the multifactorial physiological impacts of metabolic/bariatric surgery, they offer a scalable, less invasive treatment path that broadens patient options. So far, pharmacotherapy will not replace surgery, as there are patients who will respond better to it, while others to medication only. However, combining both surgical and pharmacological options can increase the penetrance of treatments to manage the chronic complexities of obesity.

Keywords: Obesity, Metabolic Surgery, Bariatric Surgery, Obesity Drugs

Introduction

Obesity is a chronic, multifaceted condition [1] that affects millions worldwide, with an increasing global prevalence, and may be accompanied by over 200 known complications [2]. Traditional treatments for obesity, including lifestyle modifications, have yielded limited long-term success for many patients [3], leading to the rise of more targeted interventions such as metabolic/bariatric surgery and pharmacotherapy. Metabolic/bariatric surgery has long been considered the gold standard for significant and sustained weight loss, as it induces anatomical changes and profound hormonal, neural, and metabolic shifts that impact the disease of obesity [4, 5]. However, advancements in obesity medications are shifting the landscape, presenting patients with scalable and less invasive alternatives for controlling the disease of obesity [6]. This review aims to evaluate whether pharmacotherapy can be an effective substitute for bariatric surgery, examining both approaches regarding mechanisms of action, weight loss outcomes, and risk profiles.

Mechanisms of Action

Both metabolic/bariatric surgery and pharmacotherapy treat the disease of obesity by targeting the subcortical areas of the brain to change adipocyte mass while having direct organ effects, such as the pancreas, liver, kidneys, and heart, that impact metabolism. Furthermore, emerging evidence highlights the importance of individual biological variability in obesity, including genetic predisposition, which may influence treatment response and support the move toward more personalised therapeutic strategies [7]. Metabolic/bariatric

surgery alters the anatomy of the gastrointestinal tract and induces profound hormonal, neural, and metabolic changes that persist long-term, supporting durable weight loss. In contrast, current pharmacotherapy primarily influences neurohormonal pathways and requires continuous use to maintain its effects, whereby cessation of medication leads to loss of treatment-mediated weight control. [2, 3, 8, 9] . These distinct mechanisms of action result in varied outcomes across patients, as individual responses and preferences for treatment can differ based on each patient. Understanding these divergences provides a nuanced framework for assessing each treatment's advantages and limitations, particularly in managing obesity as a chronic disease. Different from medications, metabolic/bariatric surgery is usually a single procedure that leads to long-lasting physiological responses.

The most common types of bariatric surgery are Roux-en-Y Gastric Bypass (RYGB) and Sleeve Gastrectomy (SG). RYGB and SG reduce the size of the stomach, and the former reroutes the small intestine. This causes enhanced signals from the gut to the brain, which controls the disease of obesity. In the dynamic phase of weight reduction, patients feel less hungry and more full, have reduced appetitive behaviour, and eat smaller portions, partly attributed to the postprandial gut hormone responses [10-12]. Some of these hormones, such as glucagon-like peptide 1 (GLP-1) and oxyntomodulin, can also directly impact receptors on organs such as the pancreas to improve type 2 diabetes mellitus (T2DM) or the liver to improve fibrosis, even before substantial weight loss occurs [13].

To provide greater context and facilitate interpretation of therapeutic advancements, it is helpful to distinguish obesity pharmacotherapies by their primary mechanisms of action. First-generation medications, including orlistat, phentermine and naltrexone/bupropion act through relatively limited or single-pathway mechanisms [2, 14]: orlistat reduces intestinal fat absorption via pancreatic lipase inhibition; phentermine primarily enhances central noradrenergic signaling to suppress appetite; and naltrexone/bupropion modulates hypothalamic appetite regulation and mesolimbic reward pathways. In contrast, second-generation agents such as semaglutide provide more potent and sustained GLP-1 receptor activation, leading to stronger effects on appetite regulation, energy intake, and glycaemic control through enhanced signalling to subcortical appetite centres and peripheral metabolic organs [15, 16]. Emerging third-generation therapies, including Cagrilintide/Semaglutide (Cagri/Sema), retatrutide, and survodutide, are designed as multi-agonist or combination therapies targeting multiple gut hormone pathways (e.g., GLP-1, amylin, GIP, and/or

glucagon receptors), thereby producing synergistic effects on satiety, energy expenditure, and metabolic regulation [14, 17-20]. This progressive shift from single-target to multi-hormonal pathway modulation helps explain the increasingly greater and more surgery-comparable weight loss observed with newer agents [6].

Dynamic phase of weight reduction

Weight reduction is a helpful metric in assessing the efficacy of obesity interventions, especially when considered alongside resolution of obesity complications. Short-term weight loss, typically assessed within 1-2 years post-intervention, provides insight into the potency of a treatment, fosters patient adherence, and helps identify how well the patient responds to the intervention. When comparing metabolic/bariatric surgery to pharmacotherapy, surgery remains the most effective intervention for inducing rapid and significant short-term weight loss. However, third-generation pharmacotherapies may close this gap.

RYGB and SG are effective bariatric interventions, with approximately 25-30% reduction in total body weight within 1 year [11, 13, 21-29]. The pace of weight loss with pharmacotherapy is slower than with surgery. Among the second-generation pharmacotherapies, tirzepatide (15 mg weekly) had a nadir weight loss of 21% (95% CI, -21.8 to -19.9) at 72 weeks in a double-blind, randomized, controlled trial (n=2539) [30], nearing the efficacy of sleeve gastrectomy. Subcutaneous semaglutide (2.4 mg, once a week) had a nadir weight loss of approximately 15% at 68 weeks (estimated treatment difference, -12.4 percentage points; 95% CI, -13.4 to -11.5; P<0.001) in a double-blind randomised controlled trial (n=1961) [31], while oral semaglutide (50mg, once per day) had a nadir weight loss of 15.1% after 68 weeks in a randomized, double-blind controlled trial (n=667) [32]. Cagri/Sema (administered as a fixed-dose of 2.4 mg each of carilintide and semaglutide subcutaneously once weekly) showed a 20.4% reduction in total body weight after week 68, compared to 3% with placebo in a randomized, double-blind controlled trial (n= 3417) [33].

Aside from assessing average weight loss, evaluating the percentage of patients experiencing significant weight loss measures how many individuals achieve clinically meaningful outcomes from a treatment. Unlike average total weight loss, which outliers can skew, this metric highlights the consistency of the treatment's effectiveness across the patient population. 86.2% of patients after metabolic/bariatric surgery achieved $\geq 20\%$ total weight loss at the time of survey (reflecting outcomes across approximately 0–24 years post-

surgery), with higher rates observed within 0–9 years post-surgery (89.3%) and sustained but slightly lower rates at 10–24 years (81.2%) [4]. Subcutaneous semaglutide (2.4mg weekly) resulted in 32% of patients losing $\geq 20\%$ at 68 weeks [31]. For tirzepatide (15 mg), 57% achieved $\geq 20\%$ total body weight loss [30]. This difference reflects surgery's broader and more consistent metabolic impact compared to medications that target fewer signaling pathways in the subcortical brain areas involved in controlling adipocyte mass [34].

CagriSema is one of the third-generation obesity medications in development [19], combining Cagrilintide, a long-acting acylated amylin analog, with semaglutide, a GLP-1 agonist. A phase 2, multi-site double-blind randomised control trial, only extending into approximately half of the dynamic phase of weight reduction, showed 15.6% total weight loss at 26 weeks (2.4mg), compared to 5.1% and 8.1% with semaglutide (2.4 mg) and cagrilintide (2.4 mg) alone [20]. Survodutide is another third-generation obesity medication binding the GLP-1 and glucagon receptors with weight reductions of up to 19% while still in the dynamic phase of weight reduction at 48 weeks [35], while also having additional benefits through glucagon receptors in the liver to reverse liver fibrosis [36]. Retatrutide, which binds the glucagon receptor (GCGR), glucose-dependent insulinotropic polypeptide receptor (GIPR), and glucagon-like peptide-1 receptor (GLP-1R), resulted in an average weight loss of 17.5% and 24.4% at 24 and 48 weeks, respectively, while still in the dynamic phase of weight [18], which is a substantially greater weight loss than previous drugs such as semaglutide, tirzepatide at 48 weeks of treatment. At 24 weeks of treatment, 86% of patients with established metabolic dysfunction associated steatohepatitis (MASH) also achieve improved liver function, demonstrating health gains beyond rapid weight loss [37]. However, despite these promising early results, the durability and long-term outcomes are yet to be established and these are still early clinical trials, with less established long-term data.

Pharmacotherapy is still less effective than surgery, but the ability to adjust the dose titration schedule produces weight loss more gradually and has fewer side effects during the dynamic phase of weight reduction. However, this also means a reduction in the rapidity of the metabolic shift, which may delay the resolution of obesity-related complications. However, for patients who prefer non-invasive treatments, the weight loss achieved with pharmacotherapy may be substantial enough [38].

Stable phase of Weight Maintenance

Long-term weight loss, typically evaluated beyond 2 years post-intervention, is crucial for sustained health benefits and reducing obesity-related complications, especially with the treatment of obesity as a chronic disease. Metabolic/bariatric surgery has demonstrated favorable long-term weight loss outcomes, with RYGB and SG patients maintaining 27.2% and 23.7% total body weight reduction at five years and beyond, respectively [22, 25]. RYGB, compared to SG, also has fewer patients who regain more than half of the weight they have lost after 5 years (5.4% vs 17.9%) [22]. Longer-term data after 10 years of RYGB is also reassuring with weight maintenance compared to nadir weight loss, albeit the variation of weight loss does get wider [39-41]. Results from the Swedish Obese Subjects (SOS) study further suggests this weight maintenance is sustained after 20 years in surgical patients with significant reduction in mortality [42]. The majority of surgical patients who do have recurrent weight gain never reach their preoperative weight [34].

The long-term efficacy of obesity medication is only starting to emerge. Semaglutide in patients with established cardiovascular disease in the SELECT study resulted in a mean weight nadir at the end of the dynamic phase of weight reduction of -10.2% at 208 weeks that was sustained until the end of the trial period of 4 years. [16]. Semaglutide in patients without diabetes in the STEP 5 study resulted in a nadir at the end of the dynamic phase of weight reduction at 60 weeks of 15.6%. After 2 years and during the stable phase of weight maintenance, 15.2% weight loss was sustained [15]. For tirzepatide, emerging long-term maintenance data similarly demonstrate a distinct dynamic phase followed by a stable phase of weight maintenance with continued therapy. In the SURMOUNT-4 randomized withdrawal trial, participants achieved a mean weight reduction of 20.9% during the initial 36-week lead-in (dynamic phase) [43]. Those who continued tirzepatide for an additional 52 weeks experienced a further modest reduction (-5.5% from week 36) and maintained the majority of their prior weight loss, with 89.5% preserving at least 80% of the weight lost during the lead-in period [43]. Overall weight reduction reached approximately 25.3% at 88 weeks, indicating sustained efficacy through the maintenance phase, whereas withdrawal led to significant regain [43].

The STEP 1 extension and the Surmount 4 trial showed that long-term use of pharmacotherapy is needed for weight loss maintenance, as in both studies, withdrawing medication incurred in recurrent weight gain [8, 43]. In contrast, after metabolic/bariatric

surgery, a significant number of patients maintain their weight loss with just a single intervention.

Newer agents, including retatrutide, survodutide, and cagrisema, have demonstrated more substantial short-term weight loss in clinical trials [6, 18, 20, 30, 35]. The association of these drugs with more significant weight loss outcomes is promising, suggesting the potential for more profound long-term impacts. However, long-term data is currently lacking for these agents, making it difficult to ascertain their sustained efficacy and compare it to the established long-term efficacy of metabolic/bariatric surgery. Based on the longer-term data from semaglutide and tirzepatide, the expectation is that these third-generation medications will maintain the initial weight loss and have shown promising results thus far [15, 44]. Metabolic/bariatric surgery remains the intervention with the most robust evidence for achieving and maintaining substantial weight loss over decades [45, 46]. While emerging longer-term evidence from semaglutide and tirzepatide suggests sustained weight loss during continued treatment, the absence of multi-decade follow-up for newer medications makes direct comparisons with the established long-term outcomes of metabolic/bariatric surgery premature.

This may be explained by the multifaceted mechanisms that impact both the physical structure of the gastrointestinal (GI) tract and a broad spectrum of metabolic, hormonal, and cellular processes that are implicated in surgery, which extend beyond the effects of pharmacotherapy that are conducive to the maintenance of lower body weight [34]. Furthermore, the third generation medications (i.e., retatrutide, survodutide, cagrisema) affect more than one but still selected hormonal pathways. While substantial weight loss (following both surgical and non-surgical intervention) facilitates a reduction in pro-inflammatory adipokines (e.g., TNF- α , IL-6) and an increase in anti-inflammatory adipokines (such as adiponectin and omentin), specific alterations in adipokine dynamics suggest a more complex, surgery-induced physiological response [5]. Notably, immediate post-surgical shifts in adipokine (e.g., omentin), myokine (e.g., myostatin), and hepatokine (e.g., SHBG, adropin) levels can be observed well before significant weight reduction [5], likely in response to acute metabolic adjustments and nutrient signaling alterations. This early shift points to a direct effect of surgery on these protein expressions [5]. Moreover, reported enhanced leptin sensitivity post-surgery, as suggested by increased leptin receptor expression in subcutaneous adipose tissue, underscores the potential role of bariatric surgery in modulating hypothalamic

signalling pathways [47]. Whether obesity medications may improve leptin sensitivity or how they control the disease of obesity in the subcortical areas of the brain remains unknown [48].

Recurrent Weight Gain and Treatment Adherence

Recurrent weight gain remains a critical challenge in the long-term management of obesity, impacting the sustainability of the benefits accrued by either metabolic/bariatric surgery and pharmacotherapy. Metabolic/bariatric surgery has the advantage that the anatomy does not revert to the presurgical state; therefore, recurrent weight gain is more likely related to a loss of weight control associated with the underlying chronic disease of obesity. For RYGB, all patients' mean recurrent weight gain is 23.4 % of maximum weight loss [49]. For SG, up to 75.6% of SG patients experience some recurrent weight gain for 6 years. However, outcomes varied significantly between patients [50]. Therefore, while metabolic/bariatric surgery offers a more stable solution to weight loss than pharmacotherapy, ongoing support, and behavioural modification remain essential to mitigate recurrent weight gain risks.

Recurrent weight gain may also be a significant challenge with pharmacotherapy. Not enough data exists to understand the impact of the disease of obesity on recurrent weight gain after pharmacotherapy, but recurrent weight gain has especially been linked with medications being discontinued. Thus far, no study has demonstrated sustained weight loss after discontinuation of pharmacotherapy [2]. This is unsurprising because other chronic diseases, such as hypertension, dyslipidaemia, and type 2 diabetes, also lose treatment-mediated control when therapy is withdrawn. [51]. Discontinuation of obesity medications leads to substantial weight gain, emphasizing sustained adherence for continued efficacy [3, 8, 9]. Within 68 weeks of semaglutide cessation, patients regain an average of 67% of their nadir weight loss, leading to a net weight loss of only 5.6% from baseline, albeit more recurrent weight gain can be expected given that the slopes of the recurrent weight gain curves did not suggest a stable phase of weight maintenance [8]. The body weight reached after 68 weeks of stopping semaglutide is comparable to the body weight typically achieved through lifestyle interventions alone if participants had not commenced semaglutide [3]. In another study, after a mean weight loss of 10.6% undergoing 20 weeks of semaglutide (2.4mg), the mean recurrent weight gain at week 68 was 65.1% of the nadir weight at week 20, demonstrating cessation of drug administration reverses weight loss effects [9]. In SURMOUNT-4, participants achieved a mean weight loss of 20.9% during 36 weeks of tirzepatide treatment [43]. After randomization, those who discontinued therapy regained approximately 14% of

body weight over the following 52 weeks, whereas those who continued tirzepatide lost an additional 5.5%. At week 88, only 16.6% of participants who stopped tirzepatide maintained $\geq 80\%$ of their initial weight loss compared with 89.5% in the continuation group, demonstrating substantial weight regain after cessation and sustained efficacy with ongoing treatment [43].

The interpretation of weight loss data from these drugs is further complicated by high dropout rates of obesity pharmacotherapy within clinical trials. In an analysis of 28 randomised controlled trials of various weight-loss medications, attrition rates were 30-45% [14]. A significant portion of discontinuation in clinical trials is due to adverse events [14], however reported side effects of pharmacotherapy and placebo are similar [52]. However, this may also relate to protocol-driven titration schedules used in clinical trials, which can increase adverse events in patients who may not tolerate target doses but could otherwise be maintained on a lower, maximum tolerable dose [53, 54]. Greater flexibility in dose titration may improve tolerability and treatment persistence. However, while flexible titration may improve tolerability and adherence [53, 54], the magnitude of weight loss with anti-obesity pharmacotherapy is partly influenced by the dose tolerated and sustained as discussed earlier in this paper, meaning patients maintained on lower doses may experience smaller weight reductions than in trials employing fixed escalation to higher target doses.

Unlike metabolic/bariatric surgery, which modifies the gastrointestinal anatomy to produce long-lasting control of the disease of obesity, pharmacotherapy relies on the continuation of the medication to control the disease. However, pharmacotherapy offers the advantage of titration, allowing for precise adjustments in dosing to target specific receptors and neuroendocrine pathways in response to changes in weight. This enables clinicians to influence metabolic processes in a controlled manner directly. In contrast, while highly effective, metabolic/bariatric surgery provides less control over its impacts on these neuroendocrine pathways. Over time, the initial alterations in key hormonal mediators of appetite and metabolism, such as leptin and gut hormones induced by metabolic/bariatric surgery, tend to diminish [55]. This attenuation can partly lead to the re-emergence of weight gain, highlighting a limitation in the long-term efficacy of surgical interventions for weight management [55]. Thus, despite the superior weight loss effects of surgery, the adaptability of pharmacotherapy through dose titration provides a distinct advantage in addressing long-term metabolic challenges and mitigating recurrent weight gain.

Importantly, this discussion does not contradict the earlier observation that metabolic/bariatric surgery produces greater and more durable average documented weight loss than pharmacotherapy in current literature at the population level. Rather, the distinction lies in therapeutic flexibility. While surgery induces substantial and sustained anatomical and hormonal changes that underpin superior long-term weight loss as currently documented, these effects are not readily adjustable once performed. In contrast, pharmacotherapy allows dose titration and ongoing modulation of neuroendocrine pathways, which may offer a practical advantage in managing weight regain over time. Thus, although surgical intervention generally achieves larger and more sustained weight reductions, pharmacotherapy provides a dynamic, adjustable approach to long-term disease control, particularly in the context of recurrent weight gain.

Adverse Effects and Side Effects

Both surgery and pharmacotherapy carry distinct profiles of adverse effects, side effects, and discontinuation rates that underscore the need for both options, as each may be more appropriate for different patients depending on their health conditions, treatment goals, and tolerance for potential risks. The adverse effect profiles of bariatric surgery procedures vary based on the type and extent of anatomical alteration. Mortality within 30 days post-surgery is approximately 1 in 1000 [10]. Mortality because of surgical complications within 90 days and beyond is also low, around 4 in 1000 [10]. Severe adverse events were rare and occurred in 5-8%, and often no reoperations were required [23]. Early complications within 30 days post-surgery are also rare, at 0.9% and 4.5% in SG and RYGB respectively [21]. This rises to 14.9% and 17.3% for late complications for SG and RYGB, respectively, but still remains low [21]. The most common adverse effects post-surgery are vomiting and constipation [23, 24]. Given this excellent safety profile and the benefits of surgery, patients may consider it more risky not to have surgery than to have surgery[46] .

Pharmacotherapy is less invasive and does not carry the same 30- and 90-day mortality risks as surgery [56]. This makes it an attractive option for many patients, especially when weight loss outcomes with newer drugs are approaching closer to those previously only seen with surgical intervention. However, while the rates of reported side effects for patients undergoing pharmacotherapy are high—95.2% on semaglutide and 96.1% on liraglutide—it is worth noting that this is not substantially higher than the 95.3% of participants in the placebo group who also reported adverse events [52]. After 4 years of semaglutide in older

patients with established cardiovascular disease, serious adverse events were reported by 33.4%, which was lower than the 36.4% in the placebo group [57]. This also suggests that taking medications may be safer than not taking medications. Serious adverse events (SAEs), defined as events resulting in death, life-threatening outcomes, hospitalization or prolongation of hospitalization, persistent or significant disability, congenital anomaly, or other medically important events, were noted across all drug groups, though with varying incidences [6, 19, 31, 52, 56]. For semaglutide, 9.8% of participants experienced SAEs, compared to 6.4% in the placebo group, with the higher rate attributed mainly to GI disorders (1.4% in semaglutide vs. 0% in placebo) and hepatobiliary disorders (1.3% in semaglutide vs. 0.2% in placebo) [31]. For tirzepatide, discontinuation rates due to adverse events were dose-dependent: 4.3% in the 5 mg group, 7.1% in the 10 mg group, and 6.2% in the 15 mg group, compared to 2.6% in the placebo group [30]. These discontinuation rates are critical indicators of the severity of side effects and reflect patient tolerability, as continuation is critical for intervention success. Furthermore, a more gentle dose titration schedule may have attenuated many of these adverse events.

Gastrointestinal complications are the most commonly reported adverse event from surgery and pharmacotherapy. Dumping syndrome is a common adverse effect that affects 15.7% of patients for all procedures within six months and can increase up to 25% of patients 1-5 years after surgery [58]. This is most prominent in RYGB due to the lack of a pyloric valve, which usually controls the release of stomach contents into the small intestine and allows hyperosmolar food to enter the jejunum rapidly. This shift leads to an osmotic gradient that draws fluid into the intestine, resulting in bloating, diarrhoea, and abdominal cramping. The rapid glucose absorption also triggers a hyperinsulinemia response, causing postprandial hypoglycaemia in some patients [24]. SG has also been linked with gastroesophageal reflux disease (GERD) in approximately 20% of patients due to increased intragastric pressure and altered gastric anatomy, compared to only 1% in RYGB [23]. The most common GI side effects across procedures include vomiting and constipation [23, 24].

In comparison, vomiting and nausea are extremely common in GLP-1 receptor agonists in a dose-dependent relationship [59]. Rates of nausea are 30-40% in tirzepatide and semaglutide (2.4mg subcutaneously), respectively [45]. Vomiting rates were 12-25%, and constipation rates were 12-23% in the same drugs, respectively, suggesting higher rates than surgery [45]. This apparent difference may partly reflect methodological differences in adverse event

ascertainment [60]. Pharmacotherapy trials typically employ systematic, prospective collection of patient-reported symptoms at predefined intervals [59], increasing the likelihood of capturing mild and transient events such as nausea, vomiting, and diarrhea. In contrast, surgical studies often prioritize perioperative complications and may rely on less standardized patient-reported outcome measures, potentially leading to underreporting of subjective gastrointestinal symptoms, particularly when they are anticipated as part of the immediate postoperative course [61].

The incidence of GI symptoms such as nausea, diarrhoea, vomiting, and constipation is high in patients treated with semaglutide (74.2%), compared to placebo (47.9%), with most cases being mild to moderate in severity and resolving without requiring discontinuation [31]. Similarly, tirzepatide participants reported GI symptoms primarily during forced dose escalation, with an adverse event incidence ranging from 78.9% to 81.8% across different doses, as opposed to 72.0% in the placebo group [30].

Patients after metabolic/bariatric surgery are at a higher risk of nutritional deficiencies [24]. In RYGB, the food bypasses key segments of the intestine where intrinsic factor binds with vitamin B12 for absorption and where nutrients such as iron and calcium are typically absorbed [62]. This may exacerbate nutritional deficiencies [62]. In RYGB patients, the risk of anaemia is 11%, secondary hyperparathyroidism is 14%, hypovitaminosis B12 is 28%, and ferritin deficiency is 5% [24]. In contrast, SG, which retains a larger portion of the small intestine in contact with food, has a lower risk of severe nutrient deficiencies. However, SG can still contribute to deficiencies indirectly, particularly in iron and B12, due to reduced food intake and gastric acid production, which are critical for nutrient absorption [62]. In comparison, the risk for malnutrition is much lower in patients undergoing pharmacotherapy, albeit longer-term data are still awaited.

Unlike pharmacotherapy, metabolic/bariatric surgeries also pose risks of mechanical complications [45]. The rate of anastomotic leaks (leakage at the surgical connection between segments of the gastrointestinal tract) and stenosis (narrowing of the surgical connection causing obstruction) is relatively low but constitutes a severe complication when it occurs. Anastomotic leaks have an incidence rate of 1-7% and 0.6%-4.4% for SG and RYGB, respectively, and stenosis has an incidence rate of 1-9% and 8-19% for SG and RYGB, respectively [45]. Incidences of intestinal obstruction (blockage of the bowel), internal hernias (protrusion of the intestine through mesenteric defects created during surgery), and

intussusception (inward folding of one segment of intestine into another) are rare but still present (<1%, 1% & 1% respectively) [23]. The most common complication following RYGB is ulceration [39]. SG has a similar risk profile but is associated with specific complications such as staple line leaks (1%), gastric stenosis (1%), and haemoperitoneum (bleeding into the abdominal cavity) (<1%) [23]. These complications, though infrequent, can increase morbidity and often require reoperation to prevent mortality. In a 10-year prospective randomised controlled trial, reoperation rates across surgical patients were 18.3% [39]. However, Stenberg et al. reported internal hernias to be the leading cause of this higher reoperations rate, as surgeons did not close the Petersen and mesenteric defects, indicating the impact of this can be mitigated to lower reoperation rates further [46]. Despite reoperation rates being generally low, these are not a feature of pharmacological treatments.

However, unlike metabolic/bariatric surgery, which has a well-established safety profile documented over decades, the newer obesity medications lack comparable data on long-term safety and efficacy. This absence of longitudinal evidence of safety does not mean there will be significant safety concerns, but it presents a significant gap in understanding these drugs' potential risks and sustained benefits. As pharmacological agents achieve weight loss outcomes approaching those traditionally seen with surgery, this may change the profile of patients opting for surgical intervention. Thus, patients requiring surgery may be older, have higher rates of complications of obesity, and be at higher risk for surgical complications.

Combining surgery and pharmacotherapy

The combination of bariatric surgery and pharmacotherapy offers a novel approach to managing obesity, capitalizing on the strengths of each treatment modality to address the limitations observed when either is used alone. This integrated strategy may be particularly beneficial in maximizing initial weight loss, sustaining long-term weight maintenance, reducing complications of obesity, and mitigating weight regain—challenges often encountered in obesity management.

Pharmacotherapy has the potential to enhance surgical outcomes both preoperatively and postoperatively. When administered before surgery, obesity medications may facilitate initial weight loss, lower surgical risks, and improve operative conditions. Although preoperative weight loss is not a prerequisite for metabolic/bariatric surgery [63], moderate evidence suggests that patients experience fewer perioperative complications with increased

preoperative weight loss, which pharmacotherapy can facilitate [63, 64]. Patients who achieved preoperative weight loss show modest reductions in surgical complications, such as anastomotic leaks and deep infections, and improved operative factors, including reduced liver size, less intraoperative blood loss, and decreased operating time [64, 65]. Greater preoperative weight loss is associated with a slightly reduced risk of perioperative complications (9.1% vs. 10.3%), though the overall impact remains modest [64, 66]. This observation is not specific to the weight loss method; however, given pharmacotherapy's increasing availability and efficacy, it is reasonable to hypothesize that incorporating pharmacological treatments before surgery is beneficial. In 2008, the American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery Medical Guidelines for Clinical Practice guidelines concluded that preoperative weight loss could improve the technical aspects of bariatric surgery based on moderate-quality evidence [67]. Subsequent studies and reviews, including a systematic review by Livhits et al., found that preoperative weight loss reduced operating time by an average of 23 minutes and recommended a 10% excess weight loss to optimize surgical outcomes [68]. Livhits et al. conclude that there does not appear to be a significant perioperative risk for patients with obesity who lose 10% of their excess body weight prior to undergoing bariatric surgery [68]. With the advent of new pharmacotherapies to achieve significant weight loss that surpasses lifestyle intervention alone, combining medical weight management with surgical preparation offers a promising approach to enhance obesity management outcomes further.

Postoperatively, pharmacotherapy can serve as an adjunct to mitigate recurrent weight gain by sustaining neurohormonal adaptations and appetite suppression, addressing one of the primary challenges in maintaining long-term weight loss after surgery [55, 69]. The benefit of this is two-fold: to enhance weight loss in the remission of the disease of obesity and the dynamic phase of weight loss and to mitigate the impacts of weight regain. While bariatric surgery induces favorable metabolic shifts, the addition of pharmacotherapy extends these benefits, especially for patients with severe metabolic dysfunction or for non-responders to surgery [69-71]. When used alongside bariatric surgery, these agents help to stabilize metabolic improvements, providing a sustained remission of obesity-related complications [69-71]. In the long-term, post-surgical alterations in the levels of ghrelin, leptin, and incretins diminish, resulting in recurrent weight gain due to physiological adaptations [55]. The

addition of postoperative pharmacotherapy may help to counterbalance these adaptations, providing a sustained suppression of hunger and stabilization of weight [70-72]. Miras et al. found that adjunct therapy with liraglutide post-surgery was beneficial in increasing weight loss and improving glycaemic profile without serious adverse events related to treatment [70]. A trial of 50 patients with recurrent weight gain showed that adjunct treatment with GLP-1 receptor agonists resulted in a loss of 67.4% of the recurrent weight gain over six months with no serious adverse events [72]. Furthermore, the metabolic shift induced through surgery may not be significant enough in some surgical patients, resulting in insufficient weight loss post-surgery [71]. For these patients with suboptimal post-surgical weight loss and GLP-1 response, a trial of 3.0mg daily liraglutide adjunct treatment resulted in -7.67% adjusted mean difference in body weight post-surgery after 24 weeks, with significantly more patients achieving $>5\%$ weight loss than placebo (71.9% vs 8.8%), and no serious adverse events [71]. Patients did not reach weight nadir by the end of the trial either, further suggesting that more weight loss and health benefits are achievable if continued [71]. By reinforcing the effects of surgery through continuous neurohormonal modulation, the combination of surgery and pharmacotherapy addresses the limitations of each intervention, offering a more comprehensive treatment option.

While the combined use of bariatric surgery and pharmacotherapy is promising, optimal combination strategies or a unified protocol about dosing, initiation, and treatment is yet to be established. Additionally, the altered pharmacokinetics in post-bariatric patients, especially those undergoing significant gastrointestinal modifications, may influence drug absorption and efficacy, necessitating careful monitoring and potential dose adjustments [73]. In available trial results, patient responses to pharmacotherapy post-surgery vary [70, 71], with different bariatric procedures inducing distinct metabolic and hormonal changes that may influence the effectiveness of adjunct treatments. The studies focus on patients with specific characteristics, such as poorly controlled diabetes or those with insufficient GLP-1 response, implying the importance of tailoring treatments based on metabolic profiles. Until better predictors of response can be identified, a comprehensive and holistic approach remains essential for effective long-term management of obesity [74].

In this context, the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) recently published a landmark guideline on the role of obesity medications in the context of metabolic/bariatric surgery [75]. Based on expert consensus and extensive

evidence, this guideline provides a roadmap for healthcare providers worldwide, offering practical recommendations on when and how to incorporate pharmacotherapy into surgical care. These guidelines underscore the importance of a multimodal approach, integrating medications both preoperatively (neoadjuvant therapy) to reduce surgical risks and postoperatively (adjuvant therapy) to maintain weight loss and prevent regain.

Conclusion

In comparing metabolic/bariatric surgery and pharmacotherapy as interventions for obesity, it is evident that obesity medications, though increasingly effective, do not substitute the multifactorial impacts of surgery. Surgical procedures leverage anatomical changes that initiate profound and sustained alterations to control the disease of obesity. While newer medications such as retatrutide, Cagrisema, and survodutide approach weight loss outcomes previously only achieved through surgery, their efficacy depends on continuous adherence, and cessation results in the loss of treatment-mediated control of the disease of obesity with subsequent weight regain. This limitation contrasts with the durability of weight loss seen post-surgery. Moreover, long-term safety and efficacy data for pharmacotherapy is limited, particularly beyond five years for the newest medications, albeit the more than 20 years of safety data of the GLP-1 class of medication for treating type 2 diabetes is very reassuring. The complication rates associated with bariatric surgery are likely at a nadir currently; however, these rates may increase as a greater proportion of patients presenting with severe obesity and more severe obesity-related complications are referred for surgical intervention. Challenges for pharmacotherapy include high rates of mild to moderate side effects and patient discontinuation, but these may be addressed by slowing down titration schedules and moving obesity management into a chronic disease model. At present, surgery remains a very effective intervention for achieving lasting control of the disease of obesity with substantial weight reduction and improvements in the complications of obesity, but surgery remains difficult to scale. However, pharmacotherapy also offers a viable, scalable, less invasive alternative that can yield meaningful control of the disease of obesity, weight loss, and metabolic benefits. The combination of surgery and pharmacotherapy does hold promise to not only address recurrent weight gain after surgery but also to achieve treatment targets in patients with more severe forms of obesity and obesity complications. Together, these treatments represent complementary strategies in the comprehensive management of obesity, allowing for more personalized approaches based on patient needs and treatment targets. With

fewer than 10% of all people with obesity currently receiving either medication or surgery [76], it is less productive to debate which treatment is superior; instead, efforts should prioritize expanding access to both effective obesity interventions to benefit a greater number of patients.

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Authorship

Louise Ko drafted the original manuscript. Carel le Roux supervised the work, provided conceptual guidance, and, along with Ricardo Cohen, reviewed and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

References

1. Coral, D.E., et al., *Subclassification of obesity for precision prediction of cardiometabolic diseases*. Nature Medicine, 2024.
2. Bray, G.A., et al., *The Science of Obesity Management: An Endocrine Society Scientific Statement*. Endocr Rev, 2018. **39**(2): p. 79-132.
3. Kheniser, K., D.R. Saxon, and S.R. Kashyap, *Long-Term Weight Loss Strategies for Obesity*. J Clin Endocrinol Metab, 2021. **106**(7): p. 1854-1866.
4. Xie, W., et al., *Bariatric surgery and weight loss in the short- and long-term: Evidence from NHANES 2015–2018*. Clinical Obesity, 2023. **13**(1): p. e12563.
5. Faramia, J., et al., *Metabolic adaptations after bariatric surgery: adipokines, myokines and hepatokines*. Current Opinion in Pharmacology, 2020. **52**: p. 67-74.
6. Papamargaritis, D., et al., *New therapies for obesity*. Cardiovasc Res, 2024. **119**(18): p. 2825-2842.
7. Ko, T.Y.L., et al., *The role of genetic testing in obesity care: the patient perspective*. Obesity and Endocrinology, 2025. **1**(1).
8. Wilding, J.P.H., et al., *Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension*. Diabetes, Obesity and Metabolism, 2022. **24**(8): p. 1553-1564.
9. Rubino, D., et al., *Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial*. Jama, 2021. **325**(14): p. 1414-1425.
10. Chang, S.H., et al., *The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012*. JAMA Surg, 2014. **149**(3): p. 275-87.
11. Kim, J.C., et al., *Outcomes and Adverse Events After Bariatric Surgery: An Updated Systematic Review and Meta-analysis, 2013-2023*. J Metab Bariatr Surg, 2023. **12**(2): p. 76-88.
12. Chong, M.C., et al., *Changes in Eating Behaviour During Treatment With Obesity Medications*. Clin Obes, 2026. **16**(1): p. e70065.
13. Courcoulas, A.P., et al., *Bariatric Surgery vs Lifestyle Intervention for Diabetes Treatment: 5-Year Outcomes From a Randomized Trial*. J Clin Endocrinol Metab, 2020. **105**(3): p. 866-76.

14. Khera, R., et al., *Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events: A Systematic Review and Meta-analysis*. *Jama*, 2016. **315**(22): p. 2424-34.
15. Garvey, W.T., et al., *Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial*. *Nat Med*, 2022. **28**(10): p. 2083-2091.
16. Ryan, D.H., et al., *Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial*. *Nat Med*, 2024. **30**(7): p. 2049-2057.
17. le Roux, C.W., et al., *Glucagon and GLP-1 receptor dual agonist survodutide for obesity: a randomised, double-blind, placebo-controlled, dose-finding phase 2 trial*. *The Lancet Diabetes & Endocrinology*, 2024. **12**(3): p. 162-173.
18. Kaur, M. and S. Misra, *A review of an investigational drug retatrutide, a novel triple agonist agent for the treatment of obesity*. *Eur J Clin Pharmacol*, 2024. **80**(5): p. 669-676.
19. Yao, H., et al., *Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis*. *Bmj*, 2024. **384**: p. e076410.
20. Frias, J.P., et al., *Efficacy and safety of co-administered once-weekly cagrilintide 2.4 mg with once-weekly semaglutide 2.4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial*. *The Lancet*, 2023. **402**(10403): p. 720-730.
21. Peterli, R., et al., *Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss in Patients With Morbid Obesity: The SM-BOSS Randomized Clinical Trial*. *Jama*, 2018. **319**(3): p. 255-265.
22. Ignat, M., et al., *Randomized trial of Roux-en-Y gastric bypass versus sleeve gastrectomy in achieving excess weight loss*. *Br J Surg*, 2017. **104**(3): p. 248-256.
23. Verrastro, O., et al., *Bariatric–metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial*. *The Lancet*, 2023. **401**(10390): p. 1786-1797.
24. Schiavon, C.A., et al., *Effects of Bariatric Surgery in Obese Patients With Hypertension: The GATEWAY Randomized Trial (Gastric Bypass to Treat Obese Patients With Steady Hypertension)*. *Circulation*, 2018. **137**(11): p. 1132-1142.
25. Wölnerhanssen, B.K., et al., *Laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy: 5-year outcomes of merged data from two*

- randomized clinical trials (SLEEVEPASS and SM-BOSS)*. Br J Surg, 2021. **108**(1): p. 49-57.
26. Ikramuddin, S., et al., *Lifestyle Intervention and Medical Management With vs Without Roux-en-Y Gastric Bypass and Control of Hemoglobin A1c, LDL Cholesterol, and Systolic Blood Pressure at 5 Years in the Diabetes Surgery Study*. Jama, 2018. **319**(3): p. 266-278.
 27. Schauer, P.R., et al., *Bariatric surgery versus intensive medical therapy in obese patients with diabetes*. N Engl J Med, 2012. **366**(17): p. 1567-76.
 28. Simonson, D.C., et al., *Clinical and Patient-Centered Outcomes in Obese Patients With Type 2 Diabetes 3 Years After Randomization to Roux-en-Y Gastric Bypass Surgery Versus Intensive Lifestyle Management: The SLIMM-T2D Study*. Diabetes Care, 2018. **41**(4): p. 670-679.
 29. Hofsø, D., et al., *Gastric bypass versus sleeve gastrectomy in patients with type 2 diabetes (Oseberg): a single-centre, triple-blind, randomised controlled trial*. Lancet Diabetes Endocrinol, 2019. **7**(12): p. 912-924.
 30. Jastreboff, A.M., et al., *Tirzepatide Once Weekly for the Treatment of Obesity*. N Engl J Med, 2022. **387**(3): p. 205-216.
 31. Wilding, J.P.H., et al., *Once-Weekly Semaglutide in Adults with Overweight or Obesity*. N Engl J Med, 2021. **384**(11): p. 989-1002.
 32. Knop, F.K., et al., *Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial*. The Lancet, 2023. **402**(10403): p. 705-719.
 33. Garvey, W.T., et al., *Coadministered Cagrilintide and Semaglutide in Adults with Overweight or Obesity*. N Engl J Med, 2025. **393**(7): p. 635-647.
 34. Akalestou, E., et al., *Mechanisms of Weight Loss After Obesity Surgery*. Endocr Rev, 2022. **43**(1): p. 19-34.
 35. Klein, T., R. Augustin, and A.M. Hennige, *Perspectives in weight control in diabetes – Survodutide*. Diabetes Research and Clinical Practice, 2024. **207**: p. 110779.
 36. Sanyal, A.J., et al., *A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis*. N Engl J Med, 2024. **391**(4): p. 311-319.

37. Sanyal, A.J., et al., *Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial*. *Nat Med*, 2024. **30**(7): p. 2037-2048.
38. Weintraub, M.A., et al., *Five-year Weight Loss Maintenance With Obesity Pharmacotherapy*. *J Clin Endocrinol Metab*, 2023. **108**(9): p. e832-e841.
39. Nguyen, N.T., et al., *Ten-year Outcomes of a Prospective Randomized Trial of Laparoscopic Gastric Bypass Versus Laparoscopic Gastric Banding*. *Ann Surg*, 2018. **268**(1): p. 106-113.
40. Salminen, P., et al., *Effect of Laparoscopic Sleeve Gastrectomy vs Roux-en-Y Gastric Bypass on Weight Loss, Comorbidities, and Reflux at 10 Years in Adult Patients With Obesity: The SLEEVEPASS Randomized Clinical Trial*. *JAMA Surg*, 2022. **157**(8): p. 656-666.
41. Sjöholm, K., et al., *Association of Bariatric Surgery With Cancer Incidence in Patients With Obesity and Diabetes: Long-term Results From the Swedish Obese Subjects Study*. *Diabetes Care*, 2021. **45**(2): p. 444-450.
42. Sjöström, L., *Review of the key results from the Swedish Obese Subjects (SOS) trial – a prospective controlled intervention study of bariatric surgery*. *Journal of Internal Medicine*, 2013. **273**(3): p. 219-234.
43. Aronne, L.J., et al., *Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial*. *Jama*, 2024. **331**(1): p. 38-48.
44. Jastreboff, A.M., et al., *Tirzepatide for Obesity Treatment and Diabetes Prevention*. *N Engl J Med*, 2024.
45. Elmaleh-Sachs, A., et al., *Obesity Management in Adults: A Review*. *Jama*, 2023. **330**(20): p. 2000-2015.
46. Carlsson, L.M.S., et al., *Life expectancy after bariatric surgery or usual care in patients with or without baseline type 2 diabetes in Swedish Obese Subjects*. *International Journal of Obesity*, 2023. **47**(10): p. 931-938.
47. Khosravi-Largani, M., et al., *Evaluation of all Types of Metabolic Bariatric Surgery and its Consequences: a Systematic Review and Meta-Analysis*. *Obesity Surgery*, 2019. **29**(2): p. 651-690.
48. Coutinho, W. and B. Halpern, *Pharmacotherapy for obesity: moving towards efficacy improvement*. *Diabetol Metab Syndr*, 2024. **16**(1): p. 6.

49. Cooper, T.C., et al., *Trends in Weight Regain Following Roux-en-Y Gastric Bypass (RYGB) Bariatric Surgery*. *Obes Surg*, 2015. **25**(8): p. 1474-81.
50. Lauti, M., et al., *Weight Regain Following Sleeve Gastrectomy—a Systematic Review*. *Obesity Surgery*, 2016. **26**(6): p. 1326-1334.
51. Burnier, M., *The role of adherence in patients with chronic diseases*. *European Journal of Internal Medicine*, 2024. **119**: p. 1-5.
52. Rubino, D.M., et al., *Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial*. *Jama*, 2022. **327**(2): p. 138-150.
53. Caffrey, A.R. and E.P. Borrelli, *The art and science of drug titration*. *Ther Adv Drug Saf*, 2020. **11**: p. 2042098620958910.
54. Pledger, G., *Proof of efficacy trials: choosing the dose*. *Epilepsy Research*, 2001. **45**(1): p. 23-28.
55. El Ansari, W. and W. Elhag, *Weight Regain and Insufficient Weight Loss After Bariatric Surgery: Definitions, Prevalence, Mechanisms, Predictors, Prevention and Management Strategies, and Knowledge Gaps-a Scoping Review*. *Obes Surg*, 2021. **31**(4): p. 1755-1766.
56. Iannone, A., et al., *Clinical outcomes associated with drugs for obesity and overweight: A systematic review and network meta-analysis of randomized controlled trials*. *Diabetes, Obesity and Metabolism*, 2023. **25**(9): p. 2535-2544.
57. Lincoff, A.M., et al., *Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes*. *New England Journal of Medicine*, 2023. **389**(24): p. 2221-2232.
58. D'Hoedt, A. and T. Vanuytsel, *Dumping syndrome after bariatric surgery: prevalence, pathophysiology and role in weight reduction - a systematic review*. *Acta Gastroenterol Belg*, 2023. **86**(3): p. 417-427.
59. Bettge, K., et al., *Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: A systematic analysis of published clinical trials*. *Diabetes, Obesity and Metabolism*, 2017. **19**(3): p. 336-347.
60. Sartor, O., *Adverse Event Reporting in Clinical Trials: Time to Include Duration as Well as Severity*. *The Oncologist*, 2017. **23**(1): p. 1-1.
61. Coulman, K.D., et al., *Patient-reported outcomes in bariatric surgery: a systematic review of standards of reporting*. *Obes Rev*, 2013. **14**(9): p. 707-20.

62. Mohapatra, S., K. Gangadharan, and C.S. Pitchumoni, *Malnutrition in obesity before and after bariatric surgery*. Disease-a-Month, 2020. **66**(2): p. 100866.
63. Rubio-Herrera, M.A., et al., *Impact of Treatment with GLP1 Receptor Agonists, Liraglutide 3.0 mg and Semaglutide 1.0 mg, While on a Waiting List for Bariatric Surgery*. Biomedicines, 2023. **11**(10).
64. Kushner, B.S. and J.C. Eagon, *Systematic Review and Meta-Analysis of the Effectiveness of Insurance Requirements for Supervised Weight Loss Prior to Bariatric Surgery*. Obesity Surgery, 2021. **31**(12): p. 5396-5408.
65. Tewksbury, C., et al., *Preoperative Medical Weight Management in Bariatric Surgery: a Review and Reconsideration*. Obes Surg, 2017. **27**(1): p. 208-214.
66. Livhits, M., et al., *Preoperative predictors of weight loss following bariatric surgery: systematic review*. Obes Surg, 2012. **22**(1): p. 70-89.
67. Mechanick, J.I., et al., *American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery Medical Guidelines for Clinical Practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient*. Surg Obes Relat Dis, 2008. **4**(5 Suppl): p. S109-84.
68. Livhits, M., et al., *Does weight loss immediately before bariatric surgery improve outcomes: a systematic review*. Surg Obes Relat Dis, 2009. **5**(6): p. 713-21.
69. Cohen, R.V. and T.B.Z. Petry, *How to address weight regain after bariatric surgery in an individualized way*. Reviews in Endocrine and Metabolic Disorders, 2023. **24**(5): p. 993-1002.
70. Miras, A.D., et al., *Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (GRAVITAS): a randomised, double-blind, placebo-controlled trial*. The Lancet Diabetes & Endocrinology, 2019. **7**(7): p. 549-559.
71. Mok, J., et al., *Safety and Efficacy of Liraglutide, 3.0 mg, Once Daily vs Placebo in Patients With Poor Weight Loss Following Metabolic Surgery: The BARI-OPTIMISE Randomized Clinical Trial*. JAMA Surg, 2023. **158**(10): p. 1003-1011.
72. Jensen, A.B., et al., *Efficacy of the Glucagon-Like Peptide-1 Receptor Agonists Liraglutide and Semaglutide for the Treatment of Weight Regain After Bariatric surgery: a Retrospective Observational Study*. Obes Surg, 2023. **33**(4): p. 1017-1025.

73. Konstantinidou, S.K., et al., *The Effects of Bariatric Surgery on Pharmacokinetics of Drugs: a Review of Current Evidence*. *Curr Nutr Rep*, 2023. **12**(4): p. 695-708.
74. Ko, T.Y.L., et al., *Beyond BMI: Practical Guide for Clinicians to Integrate the Lancet Commission's Obesity Framework and King's Obesity Staging System*. *Clinical Obesity*, 2026. **16**(1): p. e70045.
75. Cohen, R.V., et al., *International consensus position statement on the role of obesity management medications in the context of metabolic bariatric surgery: expert guideline by the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO)*. *Br J Surg*, 2024. **111**(12).
76. Coulman, K.D., et al., *Access to publicly funded weight management services in England using routine data from primary and secondary care (2007-2020): An observational cohort study*. *PLoS Med*, 2023. **20**(9): p. e1004282.

Table 1. Comparative mechanisms of action, physiological effects, and strengths/limitations of metabolic/bariatric surgery versus obesity pharmacotherapies

Intervention Class	Specific Intervention	Primary Mechanisms of Action	Key Neurohormonal & Metabolic Effects	Physiological Impact	Strengths	Limitations
Metabolic-Bariatric Surgery	Roux-en-Y Gastric Bypass (RYGB)	Anatomical gastrointestinal rerouting; reduced gastric reservoir; exclusion of proximal intestine; altered nutrient flow and gut-brain signalling	Marked postprandial increases in GLP-1, PYY, oxyntomodulin; reduced ghrelin signalling; enhanced central satiety signalling; rapid improvements in insulin sensitivity independent of weight loss; altered bile acid signalling and microbiome	Multisystem: central appetite regulation, pancreas, liver, adipose tissue, gut hormones, bile acid pathways, adipokine and hepatokine modulation	Produces rapid and substantial weight loss (~25–30% TBW at 1 year); durable long-term weight maintenance; single intervention with long-lasting physiological effects; early remission of metabolic disease (e.g., T2DM) before significant weight loss; strong long-term safety and mortality data	Invasive and non-scalable; perioperative risk (though low); lifelong micronutrient deficiencies (B12, iron, calcium); risk of dumping syndrome, hypoglycaemia, and mechanical complications (e.g., internal hernia, stenosis); weight regain
	Sleeve Gastrectomy (SG)	Longitudinal gastric resection; reduced gastric volume; accelerated gastric emptying; enhanced distal gut stimulation	Increased GLP-1 and PYY secretion; reduced ghrelin (fundus removal); improved leptin sensitivity; altered gut-brain axis signalling	Broad but slightly narrower than RYGB; strong effects on appetite pathway	Effective and technically simpler than RYGB; substantial weight loss (~20-30% TBW); lower malabsorption risk than bypass; durable outcomes without	Risk of gastroesophageal reflux disease (GERD); weight regain; less potent metabolic effects than RYGB in some patients

			and appetite regulation	ys and metabolic organs	continuous therapy	
First-Generation Pharmacotherapy (Single/limited pathway)	Orlistat	Pancreatic lipase inhibition leading to reduced intestinal fat absorption	Minimal direct neurohormonal effects; modest caloric deficit through fat malabsorption	Narrow (primarily gastrointestinal nutrient malabsorption)	Non-systemic mechanism; low systemic adverse effects; scalable and non-invasive	Modest efficacy; gastrointestinal side effects (steatorrhea); limited effects on appetite, neuroendocrine pathways, and metabolic disease; adherence challenges
	Phentermine	Central noradrenergic stimulation leading to appetite suppression	Increased hypothalamic satiety signalling; reduced hunger drive	Primarily central nervous system (CNS) appetite pathways	Rapid appetite suppression; low cost; oral administration	Limited long-term efficacy; sympathomimetic adverse effects; not suitable for long-term chronic disease control; minimal metabolic improvements
	Naltrexone/Bupropion	Hypothalamic POMC activation and mesolimbic reward pathway modulation	Appetite regulation and reduced hedonic eating; dopaminergic reward pathway modulation	CNS appetite and reward circuits	Targets both homeostatic and hedonic eating behaviours; oral therapy	Moderate weight loss; neuropsychiatric adverse effects; limited metabolic improvements; adherence dependent
Second-Generation Pharmacotherapy	Semaglutide (GLP-1 receptor agonist)	Sustained GLP-1 receptor activation	Strong hypothalamic appetite	Broad neuroendocrine and	Substantial weight loss (~15%); favourable	Requires continuous treatment for maintenance;

(Incretin-based, single dominant hormonal axis)		leading to delayed gastric emptying, enhanced satiety, reduced energy intake	suppression; improved insulin secretion and sensitivity; cardiometabolic benefits; central and peripheral GLP-1 signalling	metabolic pathways	cardiometabolic outcomes; scalable and non-invasive; flexible dose titration; low risk of severe complications compared with surgery	weight regain after cessation; high prevalence of GI adverse events (nausea, vomiting); long-term (>5–10 year) obesity-specific safety data still emerging
	Tirzepatide (GIP/GLP-1 dual agonist)	Dual incretin receptor agonism (GLP-1R + GIPR) leading to synergistic appetite suppression and metabolic regulation	Enhanced satiety signalling; improved glycaemic control; potential effects on adipocyte metabolism and insulin sensitivity	Broad neuroendocrine and metabolic pathways	Greater weight loss approaching surgical ranges (~20%+); strong metabolic improvements; sustained weight loss with continued therapy	Continued adherence required; dose-dependent GI adverse events; long-term durability data still evolving; withdrawal leads to significant weight regain
Third-Generation / Emerging Multi-Agonist Pharmacotherapy (Multi-hormonal pathway targeting)	Cagrilintide + Semaglutide (Amylin + GLP-1 co-agonism)	Dual amylin and GLP-1 receptor activation leading to enhanced satiety, reduced food intake, and complementary neurohormonal modulation	Synergistic appetite suppression; improved glycaemic and metabolic regulation; prolonged satiety signals to subcortical appetite centres	Wider than single agonists but still targeted to selected hormonal axes	Greater efficacy than monotherapy; more surgery-comparable weight loss; flexible titration; non-invasive	Limited long-term (>5 year) safety and durability data; still investigational
	Retatrutide (GLP-1/GIP/Gluca)	Triple receptor agonism	Enhanced satiety; increased	Very broad pharm	High magnitude weight loss	Limited long-term (>5 year)

	gon triple agonist)	targeting GLP-1R, GIPR, and GCGR leading to combined appetite suppression and increased energy expenditure	energy expenditure via glucagon signalling; improvements in liver metabolism and steatosis	acological targeting across multiple receptors	in trials; potential disease-modifying effects (e.g., liver, adipose tissue)	safety and durability data; still investigational
	Survodutide (GLP-1/Glucagon dual agonist)	Dual GLP-1 and glucagon receptor activation leading to appetite suppression plus increased energy expenditure and hepatic metabolic effects	Weight loss plus improvements in liver fibrosis and metabolic dysfunction; central and peripheral signalling	Broad metabolic and hepatic impact	Promising efficacy with additional organ-specific benefits (e.g., liver); multi-pathway targeting	Early-phase data; limited long-term evidence

Abbreviations: TBW, total body weight; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; GCGR, glucagon receptor; PYY, peptide YY; CNS, central nervous system; T2DM, type 2 diabetes mellitus.