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Comparison of GLP-1RAs vs Other Pharmacotherapy for Obesity: A Clinical Review

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Abstract

Background: The Centers for Disease Control and Prevention (CDC) reports that 42% of adults in the United States (US) are obese, and 10% are severely obese. Obesity has many known associated health risks, and successful treatment decreases those risks. Management always includes diet and lifestyle changes and drug therapy can improve weight loss. The current United States Food and Drug Administration (FDA) approved pharmaceutical therapy choices for long-term use include a combination of phentermine-topiramate, combination bupropion-naltrexone, orlistat, glucagon-like peptide-1 receptor agonists (GLP-1RAs), and dual action GLP-1RAs and gastric inhibitory peptide agonists (GIP).

Objectives: This review will summarize evidence comparing the safety and efficacy of GLP-1RAs or GLP-1RAs/GIP agonists with other pharmacologic treatments to achieve and maintain weight loss, improve quality of life, and reduce morbidity in obese adults.

Methods: We completed a literature review of multiple databases, including PubMed, Embase, Google Scholar, and Cochrane databases, to identify studies about pharmacologic treatment for overweight or obese adults with or without T2DM and reporting outcomes of mean percentage body weight loss. An emphasis was placed on choosing meta-analyses and primary studies in patients without T2DM. We excluded articles older than 5 years or published in a language other than English. 19 meta-analyses and 2 randomized controlled trials (RCTs) were chosen, and 13 meta-analyses were excluded based on not meeting the inclusion criteria. 6 meta-analyses and 2 RCTs were included.

Results: The literature showed that over 52 weeks, liraglutide reduced mean body weight percentage by 4.81% (95% CI: 4.23%-5.39%). Between a 12-68 week period in patients receiving semaglutide, three meta-analyses reported reduced weight by 12.57% [97% CI 10.35%-14.80%,) 10.55% (95% CI 6.96%-14.13%,) and 10.09% (95% CI: 8.33%-11.84%.) Tirzepatide, a novel GLP-1RA and GIP agonist, recently completed a phase-3 RCT, which showed that over 72 weeks, the mean weight percentage decrease was 18.4% (95% CI: 18.5%-23.2%) vs a 3.1% weight gain with placebo, a change of 21.8%. Each of the GLP-1RA agents (including tirzepatide) improved cardiometabolic risk factors. Phentermine-topiramate reduced mean body weight percentage by 8.45% (95% CI, 7.89%–9.01%) after 52-56 weeks. Bupropion-naltrexone reduced mean body weight percentage by 3.01% (95% CI, 2.47%–3.54%) over 56 weeks. Finally, orlistat reduced mean body weight percentage by 2.78% (95% CI, 2.36%–3.20%) after 1-4 years. Semaglutide is a well-established drug with weight loss, but tirzepatide shows the most promise in being the superior agent.

Conclusion: It is well known that pharmacotherapy with diet and exercise is more effective than diet and exercise alone in achieving weight loss. The GLP-1RAs are effective for weight loss, with semaglutide more effective than phentermine-topiramate, bupropion-naltrexone, orlistat, and liraglutide. Tirzepatide shows promise as a superior agent, but more comprehensive studies need to be done. When choosing pharmacotherapy, utilizing a GLP-1RA (semaglutide) or a dual GLP-1RA/GIP agonist (tirzepatide) can improve cardiometabolic risk factors and quality of life and is more effective than any other FDA-approved agent.

Keywords: GLB-1Ras, Obesity, Pharmacotherapy Obesity, Tirzepatide, Semaglutide, Weight Loss

1. **Background**

Obesity is a health concern across the nation that clinicians encounter in their practice and is defined by a body mass index (BMI) of 30 kg/m2 or higher, with 10% of people severely obese (BMI of 40 kg/m2 or higher) (1). BMI may overestimate fat content in muscular patients and underestimate it in those with less muscle mass (2). Using waist circumference with BMI can more accurately represent abdominal adiposity, defined by a waist circumference of ≥40 inches in men or ≥35 inches in women (3, 4). The most common cause of obesity relates to dietary and lifestyle choices, referred to as common obesity. Secondary causes of obesity include medication-induced weight gain, endocrine disorders, and genetic disorders (5) The Centers for Disease Control and Prevention (CDC) reports that 42% of adults in the United States are obese, and the incidence has increased by 70% over the last 30 years (1, 6). Obesity increases cardiometabolic morbidity and mortality, as seen in Table 1 (7-9). It is important to recognize that waist circumference increases cardiometabolic risk, independent of BMI (3, 4). Obese patients often lack motivation to lose weight, have comorbid depression and anxiety, have comorbid hypothyroidism, or have time and other resource constraints preventing healthy diet and exercise (10). The treatment for common and secondary obesity always includes dietary changes, lifestyle changes, and exercise, which serve as the foundation for successful long-term weight loss, reducing risks for chronic comorbidities and risk of cardiovascular events (5, 11-14). If lifestyle changes alone fail to achieve a reduction in body weight by at least 10%, pharmacotherapy can provide additional support and may be considered when BMI ≥30kg/m2 or ≥27kg/m2 with weight-related comorbidities (5). Current Federal Drug Administration (FDA) approved drug therapies for chronic use in the treatment of obesity include combination phentermine-topiramate, combination bupropion-naltrexone, orlistat, and specific glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as liraglutide or semaglutide (15, 16) Additionally, tirzepatide, a novel GLP-1RA and gastric inhibitory

peptide (GIP) agonist, has recently been approved for obesity in November 2023 (17, 18).

Table 1: Obesity increases the risk of cardiometabolic morbidity and mortality (7-9).

Obesity Related Cardiometabolic Morbidity and Mortality	
Cardiovascular Related Sequela	Coronary Artery Disease Stroke Myocardial Infarction Hypertension
Impaired Fasting Blood Sugar	Type 2 Diabetes Mellitus Impaired Fasting Insulin
Liver Disorders	Hepatic Steatosis Non-Alcoholic Fatty Liver Disease
Respiratory Disorders	Obesity Hypoventilation Syndrome Obstructive Sleep Apnea
Cancer	Endometrial Cancer Colon Cancer Breast Cancer Thyroid Cancer Ovarian Cancer Gastric Cancer Esophageal Cancer Renal Cancer Liver Cancer Multiple Myeloma Gallbladder Cancer Meningioma Pancreatic Cancer

2. **Pathophysiology Of Obesity**

Obesity is a complex and chronic pathology of storing excess adipose within the body. Many causal mechanisms are involved, and this storage mechanism likely developed in response to food-scarce environments, including famines. To prevent starvation and weight loss, the human body must account for daily resting energy requirements, thermogenesis, and active energy requirements. When caloric intake exceeds expenditure, mechanisms engage to promote the storage of fat to be utilized later during periods of reduced caloric intake. During periods of food deprivation, such as dieting, energy homeostasis is physiologically reset to increase appetite and decrease resting energy expenditure to prevent weight loss (19). Unfortunately, these homeostatic mechanisms can be pathologically prolonged after returning to pre-diet intake. The result is often rebound weight gain after weight loss in the long-term (20, 21). This mechanism supports the chronicity of obesity and leads to the need for lifelong dietary and exercise changes and pharmacologic treatment for maintenance (22).

3. **GLP-1RA Physiology**

GLP-1RAs have been well-established in the treatment of T2DM. These drugs are also well-studied and efficacious in the treatment of obesity. The GLP-1 receptor is present within the central nervous system (CNS), pancreas, cardiovascular system, lung, kidney, and gastrointestinal (GI) tract. Intrinsic or extrinsic agonism of the GLP-1 receptor produces satiety and decreased awareness of hunger (23-25). Gastrointestinal (GI) L-cells produce intrinsic GLP-1 in response to energy intake and stimulate GLP-1 receptors in the GI tract, which transmit action potentials via vagal afferents to the CNS or GLP-1 receptors in the CNS directly. GLP-1 agonism also slows gastric emptying into the duodenum while promoting insulin secretion by pancreatic β-cells, reducing postprandial blood glucose. It is uncertain if delayed gastric emptying decreases hunger, but gastric stretch may promote CNS GLP-1 production through vagal afferents. Multiple studies demonstrate that these mechanisms decrease energy intake rather than increase energy expenditure (26-28).

4. **Objective**

This review will summarize the evidence about the relative safety and efficacy of pharmacologic treatments to reduce obesity in adults (age >18). In addition, the review will determine the ability of these agents to maintain weight loss, improve quality of life, and reduce risks of chronic disease, emphasizing the relatively new GLP-1RAs and GLP-1RAs/GIP agonists.

5. **Methods**

A literature review was completed with PubMed, Embase, Google Scholar, and Cochrane databases to identify studies about pharmacologic treatment for overweight or obese adults with or without T2DM and reporting outcomes of mean percentage body weight loss. An emphasis was placed on choosing meta-analyses and primary studies in patients without T2DM. We excluded articles older than 5 years or published in a language other than English. 19 meta-analyses and 2 randomized controlled trials (RCTs) were reviewed, and 13 studies were excluded based on not meeting the inclusion criteria. Based on study

criteria, 6 meta-analyses, and 2 RCTs were included.

6. **Results**

FDA-Approved GLP-1RAs and GLP-1RAs/GIP agonists for Obesity

Current approved GLP-1RAs are a daily injection of liraglutide or a weekly injection of semaglutide (29). The only approved GLP-1RA/GIP agonist is tirzepatide (18).

Agent	Approved for Obesity?	Weight Loss Potential
Orlistat	Yes	2.78-3.16%
Naltrexone-Bupropion	Yes	3.01-4.11%
Dulaglutide*	No	3.6-5.4%
Liraglutide	Yes	4.81%-5.32%
Phentermine-Topiramate	Yes	7.87%-8.45%
Semaglutide	Yes	10.55-12.57%
Adjustable Gastric Banding	Yes	13.0%
Tirzepatide**	Yes	18.5%-20.8%
Sleeve Gastrectomy	Yes	23.4%
Roux-en-Y Gastric Bypass	Yes	30.9%

Figure 2: Approved and non-approved obesity therapies with maximum weight loss expected after 1 year follow up in order of lowest weight loss to highest weight loss. Bariatric surgery options were included for reference to drug therapy.
*Dulaglutide is not approved for weight loss and not being studied for obesity.
**Tirzepatide was recently approved for weight loss 11/08/2023. More data is needed to establish agent superiority compared with other agents.

6.1. Liraglutide

Liraglutide is a GLP-1RA that is started at a dose of 0.6mg subcutaneous injection daily with titration up to 3mg daily (30). Grunvald and colleagues (31) performed a meta-analysis (8 RCTs with 5,968 participants) that followed the effect of liraglutide on the percent total body weight loss over 52 weeks in those with and without T2DM. The authors measured with moderate certainty a mean weight loss of 4.81% (95% CI: 4.23%-5.39%) in all participants (31). A meta-analysis (7RCTs with 6,028 participants) by Lin et al32 showed that for a treatment duration of 52-56 weeks, liraglutide 3.0mg was associated with a mean weight loss of 4.81% (95% CI: 4.06%-5.56%). A subgroup analysis of those without T2DM produced a mean weight loss of 5.32% (95% CI: 4.50%-6.13%) (32). Another meta-analysis33 (17 RCTs with 6,356 participants), with a mean follow-up of 0.5-1 year in participants with and without T2DM, found that liraglutide reduced body weight percentage by 4.68% (95% CI: 4.06-5.30%) (33). Liraglutide is associated with reductions in BMI, waist circumference, blood pressure, hemoglobin A1C, low-density lipoproteins (LDL), C-reactive protein, and a significant reduction in visceral fat (34, 35). In addition, liraglutide was associated with an improvement in the quality of life of participants, utilizing the Patient Health Questionaire-9 (PHQ-9) (33). Common side effects include nausea and vomiting due to delayed gastric emptying. There were also reported cases of dehydration, renal failure, acute pancreatitis in <0.1% of patients, and symptomatic cholelithiasis in <0.05%. Although no reports of medullary thyroid cancer (MTC) were seen, liraglutide use is contraindicated in a personal or family history of MTC or multiple endocrine neoplasia type-2 (MEN2). GLP-1RAs should not be used with dipeptidyl-peptidase-4 (DPP-4) inhibitors or in pregnancy (31).

6.1.1. Semaglutide.

Semaglutide is started at 0.25mg subcutaneous injection weekly with titration up to 2.4mg weekly (36). Three meta-analyses included assessing percentage change in body weight and comparing semaglutide with placebo in overweight or obese patients without T2DM, with a duration of 12-68 weeks. Zhong et al (4 RCTs with 3,447 participants) measured a weight loss of 12.57% (97% CI 10.35%-14.80%) (37). He and colleagues (5 RCTs with 4,824 participants) measured a weight loss of 10.55% (95% CI 6.96%-14.13%) (38). Finally, Gao et al (8 RCTs with 4,567 participants) measured a weight loss of 10.09% (95% CI: 8.33%-11.84%) (39). Shi et al (5 RCTs with 4421 participants) studied participants with T2DM and found a weight loss of 11.41% (95% CI: 10.27%-12.54%) (33). These meta-analyses also demonstrated a significant reduction in blood pressure, reduced inflammatory markers (C-reactive protein), improved cholesterol, improved glucose levels, and improved quality of life, which were recorded using the PHQ-9. The main adverse

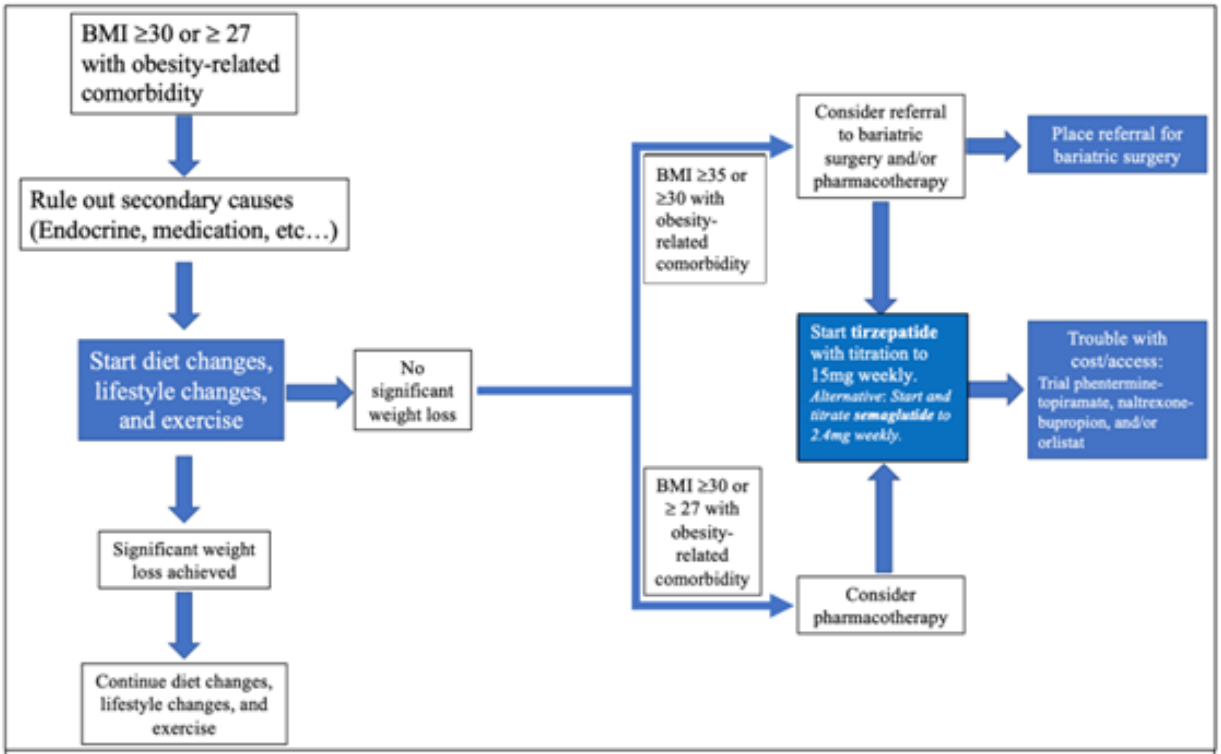

Figure 4: An algorithm for treatment initiation. Successful significant weight loss before pharmacotherapy can be decided with the patient on a case-by-case basis but may be 10% weight loss over a year. Utilization of GLP-1RAs such as semaglutide and tirzepatide can provide a reasonable cost/benefit ratio. If unable to tolerate or obtain due to cost or access, phentermine-topiramate, naltrexone-bupropion, or orlistat can be tried. The risks and benefits of each treatment should also be discussed with patients and chosen on a case-by-case basis.

effects, appearing to be dose-dependent, were GI symptoms, including nausea, vomiting, delayed gastric emptying, diarrhea, constipation, bloating, and gas. These side effects were common and limited adherence and dose titration (33, 37-39). Semaglutide is contraindicated in those with a family or personal history of MTC and MEN2, and in pregnancy. Other adverse effects include pancreatitis, cholelithiasis, acid reflux, and renal impairment, and should not be used in those on a DPP-4 inhibitor (31).

6.1.2. Tirzepatide

Tirzepatide is a novel dual GLP-1RA and GIP agonist. A phase-3 RCT, SURMOUNT-318 (670 participants), was recently completed in October 2023 and assessed the effect of tirzepatide for weight loss in obese adults without diabetes at doses between 5mg and 15mg for 72 weeks vs placebo (18). Tirzepatide is usually started and titrated from a weekly 2.5mg injection (40). Results show that the mean weight percentage loss was 18.4% (95% CI: 18.5%-23.2%) vs a 3.1% weight gain with placebo, a change of 21.8% (18). The SURMOUNT-441 RCT (670 participants) completed in December 2023 assessed the effect of stopping the tirzepatide. Participants were started on tirzepatide and titrated from weeks 0-36, with a weight reduction of 20.8%. After 36 weeks, half of the participants were stopped. In those stopping tirzepatide, 14% of their weight was regained between weeks 36-88. In those who continued tirzepatide, a further weight reduction of 5.5% was seen, a change of 19.4% (95% CI: 17.7%-21.2%) (41). Significant improvements in cardiometabolic risks, cholesterol, fasting glucose, waist circumference, and blood pressure were also observed compared with placebo. Like semaglutide, tirzepatide is associated with dose-dependent GI side effects, including nausea,

vomiting, delayed gastric emptying, and diarrhea. There was a 0.2% incidence of mild pancreatitis and a 0.6% incidence of cholecystitis, but no reports of MTC (18).

7. Other FDA-Approved Pharmacotherapy for Obesity

7.1. Phentermine-Topiramate

Phentermine-topiramate is a combination drug approved for obesity at a maximum dose of 15mg/92mg daily. Phentermine, as an analog of amphetamine, acts as a CNS sympathomimetic to increase norepinephrine neurotransmission (42). Topiramate likely increases dopaminergic neurotransmission, inhibits glutamate receptors, and modulates neuropeptide-Y, a hormone that promotes increased energy intake (43). Combined use of phentermine-topiramate results in reduced energy consumption (42). Grunvald and colleagues31 performed a meta-analysis (3 RCTs with 3,141 participants) with and without T2DM. After 52-56 weeks, the mean percentage loss was 8.45% (95% CI, 7.89%–9.01%) (31). Another meta-analysis (5 RCTs with 3407 participants), with a mean follow-up of 0.5-1 year in participants with and without T2DM, found that phentermine-topiramate was associated with a percentage weight loss of 7.87% (95% CI: 6.66%-9.28%) (33). Cosentino and colleagues43 reviewed the clinical approval trials (EQUIP, EQUATE, CONQUER, SEQUEL, FORTRESS) for phentermine-topiramate. They reported improvements in systolic and diastolic blood pressure, blood sugar, and waist circumference (43). A different meta-analysis also established improved quality of life via the PHQ-9 (33). No studies to date have assessed whether there is a reduction in vascular events with phentermine-topiramate (43). Common side effects include paresthesia, insomnia, change in taste, constipation, dizziness, and headaches (43). The CONQUER44 trial did reveal a dose-dependent increase in neuropsychiatric effects, including cognitive changes, attention difficulties, depression, and anxiety (44). Further serious adverse event risks include arrhythmias, myocardial infarction, cardiac arrest, tachycardias, syncope, cholelithiasis, seizures, blurry vision, nephrolithiasis, and pancreatitis (31). Topiramate is teratogenic and increases the risk of orofacial clefts in an exposed fetus (5). Phentermine-topiramate is contraindicated in hyperthyroidism, pregnancy, glaucoma, and within 14 days of taking a monoamine oxidase inhibitor (MAOI) (31), and is not recommended for those with cardiovascular disease (5).

7.1.1. Naltrexone-Bupropion

Naltrexone-bupropion is a combination drug approved for obesity at a max dose of 16mg/180mg twice daily, titrated stepwise (5). Naltrexone is an opioid receptor antagonist useful in opioid/alcohol dependence, and bupropion is a CNS norepinephrine-dopamine reuptake inhibitor useful in depression and smoking cessation (5). In the hypothalamus, bupropion may excite anorexigenic neurons. Beta-endorphin has inhibitory feedback on these neurons and, when antagonized by naltrexone, may lead to weight loss (45). The combination reduces energy intake and increases energy expenditure (42). A meta-analysis31 (5 RCTs with 12,659 participants) on percent weight loss with a regimen of 8mg/90mg titration found a mean weight percentage reduction of 3.01% (95% CI: 2.47%-3.54%) over 56 weeks (31). However, 2/5 of the studies included participants with T2DM, comprising about 63% of all participants, and participants were primarily female. Another meta-analysis33 (7 RCTs with 10,191 participants), with a mean follow-up of 0.5-1 year in participants with and without T2DM, found that naltrexone-bupropion was associated with a reduction in body weight of 4.11% (95% CI: 3.02%-5.19%) (33). Naltrexone-bupropion may slightly improve hemoglobin A1C, increase HDL, and reduce LDL and triglycerides (46). It also improved the quality of life of participants, utilizing the PHQ-9 (33). However, long-term cardiovascular outcome data has yet to be studied (31). Common adverse effects included nausea/vomiting, headaches, constipation, and dizziness, but no significant increases in depression, anxiety, and insomnia. There was a slight transient increase in systolic and diastolic

blood pressure, which resolved after 12 weeks of treatment. Bupropion may reduce the seizure threshold, therefore, should not be used in those with seizures. The drug is also contraindicated in those with concurrent opioid therapy, uncontrolled hypertension, pregnancy, or within 14 days after taking an MAOI (31).

7.1.2. Orlistat

Orlistat prevents triglyceride hydrolysis in the GI tract by inhibiting gastric/pancreatic lipase, thus decreasing dietary fat absorption by 30% (42). It has been approved for over-the-counter use at a dose of 120mg 3 times daily with meals (5). A meta-analysis (15 RCTs with 6,518) showed how orlistat was associated with a weight reduction of 2.78% (95% CI: 2.36%-3.20%) with and without T2DM, found that orlistat was associated with body weight percentage loss of3.16% (95% CI: 2.78%-3.53%) (33). Orlistat is associated with reduced LDL cholesterol duration of 48 weeks to 4 years (31). Another meta-analysis (67 RCTs with 18,425 participants), with a mean follow-up of 0.5-1 year in participants syndromes, and a multivitamin supplement of fat-soluble vitamins should be taken with orlistat (31).

8. Non-FDA-Approved GLP-1RAs with Efficacy for Obesity

Dulaglutide. Dulaglutide has not been studied for weight loss in patients without T2DM and is not

9. **Discussion**

Pharmacotherapeutic regimens for weight loss must account for potential benefits, risks/side effects, and costs. Obesity pharmacotherapy, along with diet and exercise, is more effective than diet and exercise alone (31). GLP-1RAs have an established value for weight loss therapy. Meta-analyses that directly compare liraglutide and semaglutide are not available, but both are effective for weight loss, with semaglutide being the most effective and well-studied drug. An RCT by O'Neil supports the ability of semaglutide to produce superior weight loss efficacy compared to liraglutide (54). Tirzepatide, which has been recently approved for obesity, shows promise to be the most effective of existing drugs for weight loss, and further research and meta-analyses are needed to establish its superiority (17, 18). Head-to-head trials between current GLP-1RAs and GLP-1RA/GIP agonists are also important for future research. Utilizing GLP-1RA and/or dual GLP-1RA/GIP agonists can im prove cardiometabolic risk factors and quality of life, although they have significant GI side effects, such as delayed gastric emptying, nausea, vomiting, and diarrhea. Phentermine-topiramate may increase cardiovascular risk, especially in patients with established cardiovascular disease. Still, it remains an effective choice for obesity management and is otherwise associated with a reduction in cardiometabolic risk factors and obesity-related comorbidities. Although cautious utilization in those with isolated hypertension may be considered, dose-dependent systolic and diastolic blood pressure reductions after 12 weeks are expected (44). Naltrexone-bupropion is less effective than the GLP-1RAs but still has meaningful use for treating obesity with a suitable side effect profile. It may be useful in those with concurrent smoking or depression (31). Orlistat provides little meaningful weight loss and a high gastrointestinal side effect profile and should be avoided as a first-line treatment for obesity (31). No head-to-head trials directly compare the GLP-1RAs to weight loss after bariatric surgery.

However, a cohort study of surgical options (n=2410) compared to non-surgical options (n=5305) for obesity found that after 1 year, weight reduction with Roux-en-Y gastric bypass (n=1785) was 30.9% (95% CI: 30.2%-31.6%), adjustable gastric banding (n=246) was 13.0% (95% CI, 11.1%-14.9%), and sleeve gastrectomy (n=379) was 23.4% (95% CI, 21.8%-24.7%) (55). The American Society for Metabolic and Bariatric Surgery recommends bariatric surgery for any individual, regardless of comorbidities or absence of comorbidities, with a BMI of ≥35. Bariatric surgery is also recommended in those with metabolic disease with a BMI between 30-34.9. In

addition, BMI ranges for the Asian population should be modified, where obesity is diagnosed with a BMI of ≥25, and bariatric surgery is recommended with a BMI ≥27.5 (56). Therefore, an indirect comparison shows the superiority of surgical options over pharmacotherapy, but risks and benefits should be discussed with patients on a case-by-case basis.

Unfortunately, chronic therapy is usually required to maintain long-term weight loss. Adaptive mechanisms during weight loss can lead to weight gain when lifestyle changes and/or drug therapy are stopped (57). Wilding and colleagues (58) found that patients regained around 60% of the weight lost after 52 weeks off treatment following 68 weeks of treatment with weekly semaglutide 2.4mg. However, half of the participants still had clinically meaningful weight loss. This finding is consistent with the evidence that obesity is a chronic condition requiring chronic treatment. Still, there may be some positive lasting effects even after an effective course of treatment (58). Ongoing chronic hormonal pharmacotherapy may help normalize physiology and promote long-term weight loss maintenance compared to behavior/lifestyle modifications alone (59-61). Further studies are needed to establish the long-term use of GLP-1RA or GLP-1RA/GIP agonists in maintenance therapy and the results after a course of therapy. Cost and access are major factors limiting the choice of therapy by clinicians. Levi and colleagues assessed the cost of a 30-day supply of current pharmacotherapy for obesity. In 2023 US dollars , orlistat costs between $77-$100, phentermine-topiramate $120-$199, naltrexone-bupropion $163-$326, semaglutide $804, liraglutide $928-$1418, and tirzepatide $715-$1100 (62). Many insurance companies do not cover anti-obesity agents, requiring patients to pay out-of-pocket. Medicare Part D does not include coverage for obesity therapy; only 11% of commercial payers cover obesity therapy, and Medicaid includes some coverage in only 7 states (63). Obesity pharmacotherapy has the potential for societal impacts. A simulation by Kabiri and colleagues64 showed how Medicare could save 231.5 billion dollars over 75 years by covering obesity pharmacotherapy (64). In addition, over a two-year follow-up, a retrospective cohort65 study of 1405 anti-obesity drug therapy users compared to 218,566 non-users produced stabilization and/or reduction in healthcare costs overall (65). Expanding coverage for obesity pharmacotherapy is a difficult problem to solve, but can include medications eventually becoming generic, identifying obesity as a chronic medical condition, and shifting medical culture to focus on preventative health vs fee for service (66). GLP-1RAs and GLP-1RAs/GIP agonists are safer and more effective than other pharmacologic treatments to reduce obesity, improve quality of life, and reduce the risk of chronic disease in obese adults. Dual GLP-1RA/GIP agonists show promising results as the most effective agent for obesity and should be an area of interest for future research. Maintaining weight loss after stopping pharmacotherapy is difficult but requires lifelong diet and lifestyle modifications, and the main barrier to chronic use of pharmacotherapy is the cost.

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Conflicts of Interest

The authors report no conflicts of interest.

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