The expanding role of GLP-1 receptor agonists: a narrative review of current evidence and future directions

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Summary

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have transformed obesity management, offering substantial weight loss and metabolic benefits. This review examines their expanding role, evaluating efficacy compared to alternative treatments, emerging indications, ongoing challenges, and future directions. Beyond obesity and type 2 diabetes, the therapeutic potential of GLP-1 RAs extends to a range of conditions such as cardiovascular disease, liver disease, neurodegenerative disease, and substance abuse disorders. While early concerns regarding pancreatic and thyroid cancer have been largely attenuated by recent evidence, issues such as gallbladder and biliary disorders, psychiatric safety, and perioperative aspiration risk require ongoing investigation. Additionally, observations of weight regain after treatment discontinuation and reductions in lean mass highlight the need for long-term, individualized strategies to sustain clinical benefits. The high cost and limited access to these medications raise critical policy and equity challenges. Future research must address these gaps, focusing on long-term safety, optimizing combination approaches, and evaluating the broader clinical and economic implications of widespread GLP-1 RA use.

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Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), originally developed for the management of type 2 diabetes, have gained prominence in managing obesity, offering clinically meaningful weight loss of 15–20% in many clinical trials.[1] The approval of liraglutide, semaglutide, and tirzepatide for chronic weight management has significantly expanded their use. Beyond their effects on glycemic control and weight loss, GLP-1 RAs are now being evaluated for a range of other conditions, including cardiovascular disease, chronic kidney disease, metabolic dysfunction-associated steatotic liver disease, obstructive sleep apnea, knee osteoarthritis, polycystic ovary syndrome, neurodegenerative disease, and substance abuse disorders. Despite these advancements, several challenges persist. Long-term safety concerns, particularly regarding potential risks to the thyroid and gallbladder, are still being explored.[2,3] Additionally, weight regain after treatment discontinuation and reductions in lean mass have raised new clinical concerns, while issues surrounding cost and accessibility present barriers to the widespread adoption of these drugs.[4–7] This review explores the evolving role of GLP-1 RAs, highlighting their benefits beyond weight loss, key safety and policy considerations, and future directions for optimizing their use.

Methods

Role of funding source

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Other obesity management approaches

While GLP-1 RAs have demonstrated substantial efficacy in promoting weight loss, it is useful to first examine other treatment modalities in obesity management. Lifestyle interventions, alternative anti-obesity medications, and bariatric surgery offer different approaches for weight loss and may provide useful context for evaluating the overall impact of GLP-1 RAs.

Lifestyle interventions and behavioral therapy

Lifestyle modification remains the cornerstone for treating obesity. Clinical guidelines on obesity management, including the 2013 American Heart Association/American College of Cardiology and the 2016 American Association of Clinical Endocrinologists/American College of Endocrinology guidelines, highlight the importance of a structured lifestyle intervention program.[8] These programs typically include a calorie-restricted diet, increased physical activity, and behavioral therapy, which together are recommended as the first-line treatment for individuals with overweight or obesity. However, these strategies are often insufficient to achieve and sustain weight loss.[9,10] Many patients struggle to maintain the necessary behavioral changes long term, leading to modest results which are often inadequate in addressing the complex physiological, genetic, and environmental factors underlying obesity.[11] On average, patients regain one-third of the weight lost (5–10% of baseline bodyweight) within the first year of treatment discontinuation, and nearly half of patients return to their initial weight within five years.[9] Consequently, lifestyle interventions frequently require supplementation with pharmacological treatments to achieve more substantial weight loss outcomes.

Alternative pharmacotherapy options

Beyond GLP-1 RAs, current FDA-approved pharmacotherapies for chronic weight management include orlistat (a lipase inhibitor that reduces fat absorption), phentermine-topiramate (a sympathomimetic appetite suppressant combined with a gamma-aminobutyric acid receptor modulator), naltrexone-bupropion (an opioid antagonist combined with a dopamine/norepinephrine reuptake inhibitor), and setmelanotide (a melanocortin-4 receptor agonist).[12] Besides setmelanotide, which is indicated for patients with rare genetic forms of obesity, these alternative anti-obesity medications result in modest weight loss, typically ranging from 3 to 9% of baseline body weight.[12] These benefits are smaller than the 15–20% weight loss observed with GLP-1 RAs or co-agonists.[1]

In addition, these agents are associated with a broader range of adverse events compared to GLP-1 RAs.[12–14] Phentermine-topiramate has been linked to psychiatric and cognitive effects, including irritability (relative risk [RR] vs. placebo: 3.31, 95% confidence interval [CI] 1.69, 6.47), anxiety (RR: 1.91, 95% CI 1.09, 3.35), and sleep disorders (RR: 1.55, 95% CI 1.24, 1.93).[13] Naltrexone-bupropion is associated with anxiety (RR vs. placebo: 2.44, 95% CI 1.29, 4.63) and elevated blood pressure (RR: 1.72, 95% CI 1.04, 2.85).[13] In a 2024 network meta-analysis of 61 randomized controlled trials (RCTs) comparing active treatments to lifestyle modification in adults with overweight or obesity, both phentermine-topiramate (odds ratio [OR]: 2.40, 95% CI 1.68, 3.44) and naltrexone-bupropion (OR: 2.69, 95% CI 2.10, 3.44) ranked among the highest for treatment discontinuation due to adverse events.[14] In contrast, GLP-1 RAs have primarily been associated with gastrointestinal side effects and have demonstrated more favorable psychiatric and cardiovascular safety profiles.[13,14] These differences may in part reflect the distinct mechanisms through which GLP-1 RAs act on both central appetite regulation and peripheral metabolic pathways, which we have discussed in detail in a previous review.[15]

Bariatric surgery

Bariatric surgery is a highly effective treatment for obesity, often leading to more pronounced and sustained weight loss than GLP-1 RAs (mean difference: −22.7 kg, 95% CI −31.4, −14.0)[16] and pharmalogical treatment as a whole (−22.1 kg, 95% CI −28.9, −15.2).[17] Long-term studies indicate that individuals who undergo bariatric surgery can sustain their weight loss for years and see notable improvements in obesity-related comorbidities.[18,19] However, this approach is highly invasive compared to pharmacotherapy with GLP-1 RAs, requiring substantial lifestyle changes and continuous monitoring. Additionally, the higher risk of surgical and long-term complications necessitates careful patient selection.[20,21] As such, bariatric surgery is typically reserved for individuals with severe obesity (body mass index [BMI] $\geq$ 40 kg/m^2 or BMI $\geq$ 35 kg/m^2 with obesity-related comorbidities) who have not achieved sufficient weight loss with other interventions.[22] In contrast, GLP-1 RAs are generally recommended for those with a BMI $\geq$ 30 kg/m^2 or a BMI $\geq$ 27 kg/m^2 with obesity-related comorbidities. New data also suggest that the use of GLP-1 RAs before metabolic or bariatric surgery may help high-risk patients with extreme obesity (BMI $\geq$ 70 kg/m^2) lower the risk of post-operative complications.[23] Previous studies have shown that weight loss before surgery can mitigate risk, however conventional lifestyle interventions or older anti-obesity medications have not led to sufficient weight loss to make a difference.[24,25]

Established benefits beyond obesity

Cardiorenal protection

GLP-1 RAs have shown important cardioprotective benefits beyond their role in weight loss. Multiple cardiovascular outcomes trials have demonstrated that use of a GLP-1 RA reduces the risk of major adverse cardiovascular events (MACE) among patients with diabetes and at high cardiovascular risk.[26] Similarly, the SELECT trial found a reduced risk of MACE in patients with established cardiovascular disease and overweight or obesity without diabetes with the use of semaglutide compared to placebo (6.5% vs. 8.0%, hazard ratio [HR]: 0.80, 95% CI 0.72, 0.90).[27] In the STEP-HFpEF and STEP-HFpEF-DM trials, use of semaglutide improved symptoms, reduced physical limitations, and enhanced exercise capacity in patients with heart failure with preserved ejection fraction, both with and without diabetes, when compared to placebo.[28,29]

Subgroup analyses from various cardiovascular outcomes trials have also shown that GLP-1 RAs may benefit kidney-related outcomes, including reductions in albuminuria, slower declines in estimated glomerular filtration rate, and a decreased risk of end-stage kidney disease in patients with and without diabetes.[30,31] The FLOW trial demonstrated that, compared to placebo, randomization to semaglutide reduced the risk of kidney-related complications by 24% (HR: 0.76, 95% CI 0.66, 0.88) in patients with diabetes and chronic kidney disease.[32] An observational study found that GLP-1 RAs users experienced reduced risks of mortality (6.8% vs. 12.9%, adjusted HR [aHR]: 0.57, 95% CI 0.51, 0.64), MACE (14.8% vs. 18.8%, aHR: 0.88, 95% CI 0.80, 0.96), and major adverse kidney events (10.8% vs. 16.0%, aHR: 0.73, 95% CI 0.66, 0.80) in patients with diabetes and acute kidney disease when compared to non-users.[33] Overall, the consistent reduction in the risk of MACE and major adverse kidney events associated with GLP-1 RAs across patient subgroups underscores the potential of these agents in managing cardiorenal risk (Fig. 1).

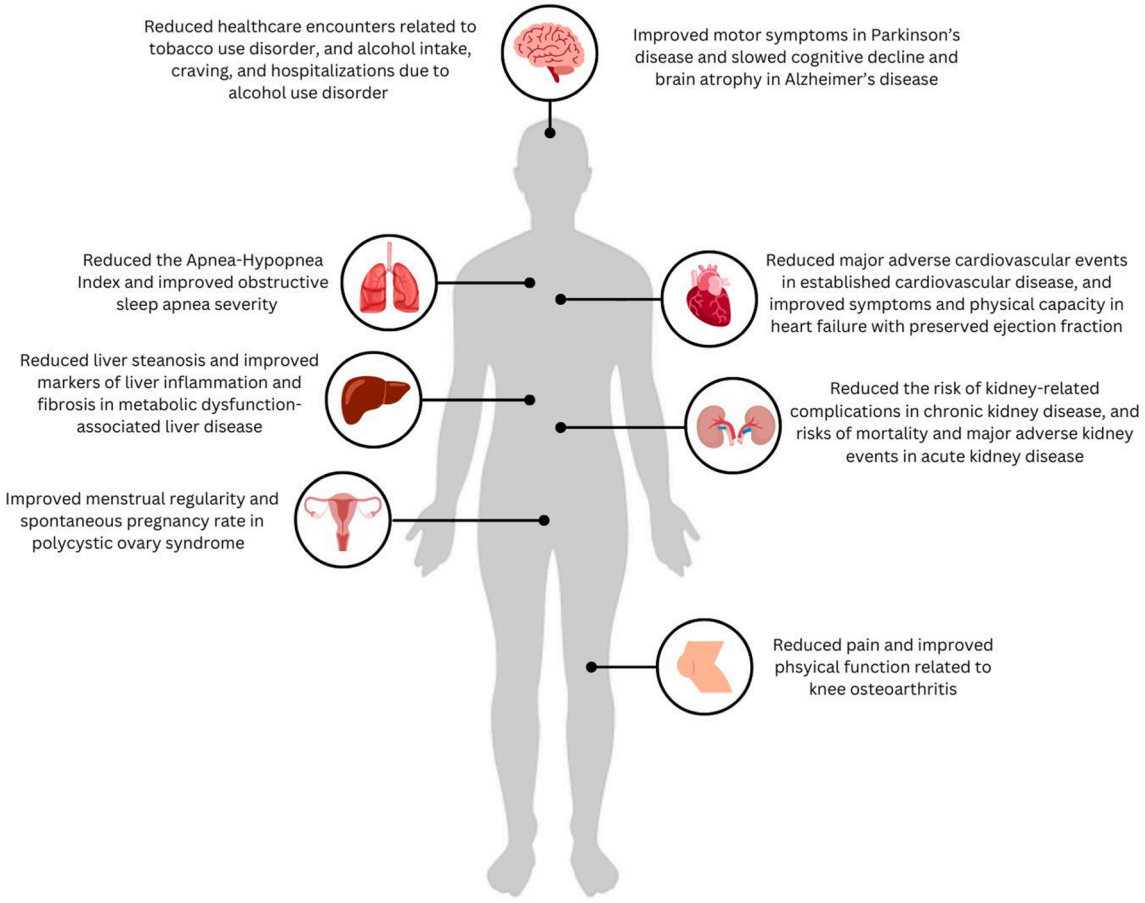

Fig. 1: *Overview of emerging therapeutic roles for glucagon-like peptide-1 receptor agonists*. This figure summarize evidence from randomized controlled trials and observational studies conducted in individuals with overweight or obesity, with and without diabetes. Cardiovascular and renal outcomes are primarily derived from trials in participants with type 2 diabetes or established cardiovascular disease. Other emerging indications are based on studies in participants with obesity-related comorbidities or preliminary trials in broader populations.

Emerging therapeutic roles

Emerging evidence suggests that GLP-1 RAs may be beneficial in the management of several conditions, including metabolic dysfunction-associated steatotic liver disease, obstructive sleep apnea, knee osteoarthritis, polycystic ovary syndrome, neurodegenerative disease, and substance use disorders (Fig. 1). While weight loss likely contributes to improvements in some of these conditions, such as liver disease or sleep apnea, GLP-1 RAs may also exert direct disease-specific effects, particularly in neurodegenerative and substance use disorders, where central mechanisms appear to play a primary role.

Liver disease

Metabolic dysfunction-associated steatotic liver disease is closely linked to obesity, insulin resistance, and metabolic syndrome. GLP-1 RAs, particularly semaglutide, have been shown to reduce liver steatosis and improve markers of liver inflammation and fibrosis in patients with type 2 diabetes and metabolic dysfunction-associated steatotic liver disease.[34–36] In the recent ESSENCE trial, 62.9% of patients receiving semaglutide achieved resolution of metabolic dysfunction-associated steatohepatitis without worsening of fibrosis at 72 weeks, compared to 34.3% in the placebo group (estimated treatment difference [ETD]: 28.7%, 95% CI 21.1, 36.2).[37] While these benefits may be partially mediated by weight loss, other mechanisms likely contribute, including reductions in insulin resistance, systemic inflammation, and hepatic de novo lipogenesis and gluconeogenesis, all of which are related to liver fat accumulation and disease progression.[38] GLP-1 RAs may also improve adipose tissue function by increasing adiponectin and normalizing lipolysis, therefore reducing circulating free fatty acids.[39]

Obstructive sleep apnea

Obstructive sleep apnea is another obesity-associated condition in which GLP-1 RAs may offer therapeutic benefit. Excess adiposity is a key modifiable risk factor for obstructive sleep apnea, and weight loss is a well-established intervention for improving its severity and related complications.[40,41] Recent trials have shown that use of tirzepatide leads to reductions in the Apnea-Hypopnea Index and improvements in obstructive sleep apnea severity compared to placebo (ETD: −23.8 events per hour, 95% CI −29.6, −17.9).[42] While the exact mechanisms are not fully understood, imaging studies suggest that reductions in upper airway adiposity, particularly tongue fat, may contribute to these improvements.[43] GLP-1 RAs also improve systemic inflammation and lipid metabolism, which may further influence obstructive sleep apnea severity.[44]

Knee osteoarthritis

GLP-1 RAs may also have therapeutic potential in knee osteoarthritis, a condition in which excess weight exacerbates joint degeneration, inflammation, and pain. In the STEP-9 trial, use of semaglutide led to greater weight loss and improvements in knee pain and physical function compared to placebo in patients with obesity and moderate-to-severe osteoarthritis-related symptoms.[45] However, the extent to which these benefits reflect weight loss vs. direct anti-inflammatory or structural effects remains unclear, as the trial did not assess imaging or biochemical markers of joint degeneration.[45] Preclinical studies suggest that GLP-1 RAs may exert anti-inflammatory and cartilage-protective effects within the joint,[46] but further research is needed to determine whether these translate into structural improvements beyond symptomatic relief.

Polycystic ovary syndrome

GLP-1 RAs may also offer several benefits for women with polycystic ovary syndrome, a condition characterized by insulin resistance, hyperandrogenism, and ovulatory dysfunction. By improving insulin sensitivity, GLP-1 RAs may reduce hyperinsulinemia-driven androgen production and help restore ovulatory cycles.[47–49] A meta-analysis in women with polycystic ovary syndrome and overweight or obesity found that GLP-1 RA use was associated with improvements in menstrual regularity (standardized mean difference: 1.72, 95% CI 0.60, 2.85) compared to metformin or placebo, and spontaneous pregnancy rate (RR: 1.72, 95% CI 1.22, 2.43) compared to metformin.[50] More research is needed to clarify whether these benefits are primarily mediated by weight loss or if enhanced insulin sensitivity alone is sufficient to influence hormonal and fertility outcomes.

Neurodegenerative disease

There is growing interest in the potential neuroprotective effects of GLP-1 RAs, particularly in the context of neurodegenerative diseases. Preclinical studies have shown that GLP-1 RAs reduce oxidative stress, enhance neuronal survival, and improve synaptic plasticity in animal models of diabetes.[51,52] Clinical trials have begun to explore these effects with promising results. In Parkinson's disease, phase II trials have shown that GLP-1 RAs such as exenatide and lixisenatide improve motor activity compared to placebo,[53,54] and liraglutide has shown improvements in non-motor symptoms, mobility, and quality of life.[55] In Alzheimer's disease, preliminary data suggest that liraglutide may reduce cognitive decline by up to 18% over one year compared to placebo by slowing brain atrophy in regions vital for memory, learning, language, and decision-making.[56] These neuroprotective effects are hypothesized to involve modulation of inflammation, tau protein aggregation, insulin resistance, and amyloid accumulation, analogous to how statins protect the heart through their effects on cholesterol.

Substance use disorders

GLP-1 RAs are also being investigated for their potential to modulate substance use behaviors. Preclinical studies suggest that GLP-1 signaling in the mesolimbic reward circuits may reduce the reinforcing effects of substances such as nicotine, alcohol, and opioids.[57,58] In a single-center trial, dulaglutide added to varenicline and behavioral support had no effect on smoking cessation, with identical 52-week abstinence rates in both the active and placebo groups (32%).[59] In contrast, real-world data from a target trial emulation found that semaglutide use was associated with a lower risk of tobacco use disorder-related healthcare encounters, including diagnosis (HR vs. insulin: 0.68, 95% CI 0.63, 0.74), prescriptions for cessation medications (HR: 0.32, 95% CI 0.28, 0.38), and cessation counseling (HR: 0.72, 95% CI 0.58, 0.90).[60]

In a phase 2 trial of individuals with alcohol use disorder, semaglutide reduced alcohol consumption during a laboratory self-administration task (standardized regression coefficient [β]: −0.48, 95% CI −0.85, −0.11) and lowered both drinks per drinking day (β: −0.41, 95% CI −0.73, −0.09) and weekly alcohol craving scores (β: −0.39, 95% CI −0.73, −0.06) compared to placebo.[61] A large observational study in Sweden similarly found that semaglutide and liraglutide use were associated with a lower risk of hospitalization due to alcohol use disorder (aHR for semaglutide: 0.64, 95% CI 0.50, 0.83; aHR for liraglutide: 0.72, 95% CI 0.57, 0.92).[62] In another trial, exenatide did not reduce alcohol intake overall but showed benefit in an exploratory subgroup with obesity (BMI > 30 kg/m^2), reducing heavy drinking days by 23.6% (95% CI −44.4, −2.7) and monthly alcohol intake by 1205 g (≈89 standard drinks, 95% CI −2,206, −204).[63] Additional real-world data from a multi-center American cohort linked GLP-1 RA and GIP/GLP-1 RA use to a reduced incidence of alcohol intoxication (adjusted incidence rate ratio [aIRR]: 0.50, 95% CI 0.40, 0.63) and opioid overdose (aIRR: 0.60, 95% CI 0.43, 0.83) compared to periods of non-use.[64] Altogether, these findings support further clinical investigation of GLP-1 RAs as potential treatments for substance use disorders.

Potential safety issues

Pancreatic and thyroid risk

Beyond gastrointestinal adverse events, which are widely accepted as a class effect of GLP-1 RAs,[65,66] several other safety concerns have been raised over the past decade. Initial observational signals from 2011 suggested an increased risk of acute pancreatitis and pancreatic cancer in patients using GLP-based therapies compared to non-users (adjusted odds ratio [OR]: 2.24, 95% CI 1.36, 3.68),[67,68] leading the FDA to issue a warning on the pancreatic safety of GLP-1 RAs.[69] However, these findings have not been confirmed in subsequent large-scale RCTs. A meta-analysis of seven placebo-controlled cardiovascular outcomes trials found no increased risk of either acute pancreatitis or pancreatic cancer with GLP-1 RA treatment (Peto OR: 1.05, 95% CI 0.78, 1.40),[70] providing reassurance evidence against this concern in high-risk populations.

Similarly, while murine studies initially raised concerns about thyroid C-cell tumors,[71] current human data do not suggest an increased risk.[72,73] A large international cohort study across six population-based databases compared nearly 100,000 GLP-1 RA users to over 2.4 million dipeptidyl peptidase-4 (DPP-4) inhibitor users and found no evidence of increased thyroid cancer risk (pooled weighted HR: 0.81, 95% CI 0.59, 1.12).[73] These findings are reassuring in the short term, though long-term risk cannot be excluded due to the relatively limited follow-up duration (median 1.8–3.0 years). As such, clinical guidelines continue to recommend against prescribing GLP-1 RAs to individuals with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2.[74–76]

Gallbladder and biliary disorders

An increased risk of gallbladder and biliary disorders has been observed in multiple trials assessing GLP-1 RAs, particularly at higher doses, longer treatment durations (>26 weeks), and when used for weight management.[77] A meta-analysis of 76 RCTs, involving over 100,000 adults with overweight, obesity, or type 2 diabetes found that GLP-1 RA treatment, compared to placebo or other active comparators, was associated with a modestly elevated risk of cholelithiasis (RR: 1.27, 95% CI 1.10, 1.47), cholecystitis (RR: 1.36, 95% CI 1.14, 1.62), and overall biliary disease (RR: 1.55, 95% CI 1.08, 2.22), corresponding to an absolute increase of approximately 27 events per 10,000 patients per year.[77] Proposed mechanisms underlying this association include rapid weight loss, reduced gallbladder motility, or alterations in bile composition, although casaulity remains uncertain.[78]

Psychiatric disorders

Concerns about the psychiatric safety of GLP-1 RAs have emerged from post-marketing surveillance. Reports submitted to the FDA Adverse Event Reporting System have included insomnia, anxiety, nervousness, and depressive symptoms,[79] while the European Medicines Agency has flagged cases of depression, self-injury, and suicidal ideation among users of liraglutide or semaglutide.[80] However, adverse event reporting systems are inherently limited by underreporting, confounding, and reporting bias, and cannot establish causality.

A recent large population-based cohort study using UK primary care data evaluated the risk of suicidality among patients with type 2 diabetes initiating GLP-1 RAs (n = 36,371) compared to DPP-4 inhibitors

(n = 232,511) or sodium-glucose cotransporter-2 (SGLT-2) inhibitors (n = 104,386).[81] After adjusting for baseline differences, GLP-1 RA use was not associated with an increased risk of composite suicidality compared to DPP-4 inhibitors (HR: 1.02, 95% CI 0.85, 1.23) or SGLT-2 inhibitors (HR: 0.91, 95% CI 0.73, 1.12).[81] These null findings were consistent across individual outcomes, including suicidal ideation (HR vs. DPP-4i: 1.03, 95% CI 0.71, 1.49), self-harm (HR: 0.92, 95% CI 0.73, 1.17), and suicide (HR: 0.75, 95% CI 0.30, 1.86).[81] Notably, there was no increased risk even among patients with pre-existing psychiatric illness, including depression or prior self-harm. Overall, while pharmacovigilance reports have described a range of psychiatric symptoms, real-world evidence to date does not support an increased risk of suicidality with GLP-1 RAs in patients with type 2 diabetes. Further research is warranted to evaluate long-term psychiatric outcomes in broader populations, including those using GLP-1 RAs for obesity or other emerging indications.

Non-arteritic anterior ischemic optic neuropathy

Recent studies have raised concerns about a potential association between GLP-1 RAs and non-arteritic anterior ischemic optic neuropathy. A nationwide Danish-Norwegian cohort study of over 60,000 individuals with type 2 diabetes reported a nearly three-fold increased risk of non-arteritic anterior ischemic optic neuropathy with semaglutide use compared to SGLT-2 inhibitors (HR: 2.81, 95% CI 1.67, 4.75), corresponding to an absolute risk difference of 1.41 events per 10,000 person-years.[82] A complementary analysis using 14 databases from the Observational Health Data Sciences and Informatics network similarly observed an increased risk, but only when non-arteritic anterior ischemic optic neuropathy was defined using a specific diagnostic code (HR vs. empagliflozin: 2.27, 95% CI 1.16, 4.46); no association was seen using a more sensitive definition.[83] A meta-analysis of 69 RCTs found a total of 12 cases of ischemic optic neuropathy reported across five trials (8 in GLP-1 RA groups vs. 4 in comparators), yielding a non-significant OR of 1.53 (95% CI 0.53, 4.44).[84] Although current findings are inconsistent, the potential severity of non-arteritic anterior ischemic optic neuropathy warrants the need for trials specifically designed to assess this outcome using standardized and well-defined diagnostic criteria.

Perioperative aspiration risk

GLP-1 RAs delay gastric emptying, a pharmacodynamic effect that contributes to appetite suppression but may increase residual gastric volume during procedures involving deep sedation or general anesthesia. Early case reports of regurgitation and pulmonary aspiration in patients using GLP-1 RAs raised concerns about their perioperative safety.[85] A 2024 scoping review found seven comparative studies reporting higher rates of gastric content retention among GLP-1 RA users (19–56%) vs. non-users (5–20%), though most studies were confounded by comorbidities and varied in methodology.[86] In a Mayo Clinic analysis of 4134 GLP-1 RA users undergoing upper endoscopy, only two confirmed aspiration events were identified (4.8 events per 10,000 procedures), closely mirroring a historical rate of 4.6 per 10,000 prior to widespread GLP-1 RA use.[87] However, the study acknowledged that not all patients may have been actively using the medication at the time of the procedure, potentially inflating the denominator. Separately, a large retrospective cohort study involving over 360,000 surgical patients found no significant difference in 30-day postoperative aspiration pneumonia between GLP-1 RA users and non-users (OR: 0.78, 95% CI 0.57, 1.06).[88] Although the absolute risk appears low, several surgical societies recommend precautionary withholding of GLP-1 RAs prior to elective procedures.[85,89] Further prospective studies are needed to clarify perioperative risks associated with GLP-1 RA use and inform individualized management.

Body composition and muscle preservation

As GLP-1 RAs become more widely used for weight management, attention has turned to their effects on body composition. Evidence from dual-energy X-ray absorptiometry and MRI sub-studies suggests that 25–45% of total weight loss with semaglutide and tirzepatide may come from reductions in lean body mass.[90] Although this proportion is similar to that seen with lifestyle interventions,[91] the decline in lean mass may have implications for mobility, metabolic rate, and physical function, particularly in older adults or those with sarcopenic obesity. These concerns have prompted interest in strategies to mitigate muscle loss. In addition to resistance training and adequate protein intake, investigational therapies such as myostatin inhibitors and selective androgen receptor modulators are being evaluated for their ability to preserve or enhance lean mass in conjuction with GLP-1 RA use.[92,93]

Weight regain and cardiometabolic effects after treatment discontinuation

Another important concern regarding GLP-1 RA use is potential weight regain upon discontinuation of treatment. In an extension of the STEP-1 trial, participants originally randomized to semaglutide regained 68% of their lost weight after one year of discontinuing treatment.[7] Cardiometabolic improvements achieved with semaglutide also reverted towards baseline for most risk factors after one year. The STEP-4 trial included a 20-week run-in period during which participants achieved a mean weight loss of 10.6% after treatment with weekly semaglutide. From week 20 to week 68, participants who discontinued the drug regained an average of 6.9% of

their baseline body weight, while those who continued treatment lost an additional 7.9%.[6] These findings suggest ongoing treatment with GLP-1 RAs is required to maintain improvements in weight and health, highlighting the chronicity of obesity. Recognizing obesity as a chronic disorder underscores the need for long-term pharmacological treatment, similar to the approach used for managing type 2 diabetes or hypertension to achieve optimal control.[9]

Cost and policy implications

Addressing the high cost and supply shortages of GLP-1 RAs is essential for improving patient access and optimizing treatment outcomes. In the United States, the cost of GLP-1 RAs can range from $800 to $1300 per month without insurance, which poses a substantial barrier to access and adherence for many patients.[4,5] This highlights the need for policy interventions to improve affordability and insurance coverage for these medications. In jurisdictions with socialized medicine, such as Canada, the high demand for these drugs places large burdens on public insurance plans, resulting in the presence of formulary restrictions which further inequities between those with and without private insurance. Addressing equity issues is critical to ensure that all individuals, regardless of socioeconomic status, can benefit from these advancements in obesity treatment. Previous shortages of GLP-1 RAs impacted patient care, leading to concerns that these medications should be reserved for patients with diabetes rather than weight loss in otherwise healthy individuals.[94] These concerns highlight the importance of stable supply chains and strategies to mitigate shortages, including increasing production and ensuring fair distribution.[95] Public awareness campaigns are also essential to educate individuals about the benefits and potential risks of GLP-1 RAs, fostering informed decision-making and broader acceptance of these treatments.

Future research

Long-term efficacy and safety

The long-term effects of GLP-1 RA use for weight loss remains an important area for future research. While current studies have demonstrated substantial short-term weight loss and metabolic improvements, the sustainability of these outcomes over extended periods requires further exploration. Longitudinal studies should investigate how these agents impact long-term health outcomes, such as the incidence of cardiovascular diseases and mortality. Additionally, long-term safety needs to be established. Comprehensive long-term studies will help clarify the risk-benefit ratio of prolonged GLP-1 RA therapy.

Oral formulations

The development of oral GLP-1 RAs offers an alternative to injectable formulations, potentially improving access and adherence for some patients. Oral semaglutide has demonstrated efficacy in both diabetes and obesity management.[96,97] Cardiovascular safety was first established in the PIONEER 6 trial,[98] with the more recent SOUL trial demonstrating a significant reduction in MACE compared to placebo among individuals with type 2 diabetes and high cardiovascular or renal risk.[99] These findings support the potential of oral semaglutide for broader clinical use. Orforglipron, a novel non-peptide oral GLP-1 RA, has also shown promising glycemic and weight-lowering effects in phase 2 trials.[100,101] While oral formulations have demonstrated acceptable tolerability overall, gastrointestinal side effects remain common and may occur at similar or slightly higher rates than with injectable agents.[102,103] Daily dosing and pill burden may also pose practical challenges in long-term use, highlighting the need to tailor treatment choices to individual patient needs and preferences.

Combination therapies

Combination therapies represent a promising strategy to enhance the efficacy and tolerability of GLP-1 RAs. Several novel agents now combine GLP-1 receptor agonism with other metabolic targets. Dual agonists such as tirzepatide (GLP-1/GIP) have demonstrated superior weight loss and glycemic control compared to GLP-1 RAs alone,[104] likely due to complementary mechanisms involving both incretin pathways. Triple agonists that target GLP-1, GIP, and glucagon receptors, such as retatrutide, are also in development and have shown even greater weight loss effects in early-phase trials.[105] Other potential combinations include GLP-1 RAs with SGLT-2 inhibitors,[106] amylin analogs, or central nervous system appetite modulators, such as phentermine or bupropion.[107] These combination therapies could provide synergistic effects on weight loss, glycemic control, or cardiometabolic risk while potentially minimizing the gastrointestinal side effects commonly associated with GLP-1 RAs.[108] Future studies should also explore optimal sequencing, dosing strategies, and patient selection to maximize clinical benefit.

Precision medicine

Precision medicine aims to tailor treatments based on individual patient characteristics, including genetic, epigenetic, and metabolic profiles.[109] Identifying biomarkers that predict response to GLP-1 RAs can help customize treatment plans to maximize efficacy and minimize adverse events. Research efforts should focus on understanding the variability in individual responses to GLP-1 RAs, developing predictive models, and integrating these insights into clinical practice.[110]

Search strategy and selection criteria

Data for this review were identified through searches of PubMed and Google Scholar using the following search terms, among others: "glucagon-like peptide-1 receptor agonists", "glucagon-like peptide-1-based therapies", "liraglutide", "semaglutide", "tirzepatide", "obesity", "weight loss", "metabolic effects", "bariatric surgery", "anti-obesity pharmacotherapy", "cardiovascular outcomes", "metabolic dysfunction-associated steatotic liver disease", "nonalcoholic fatty liver disease", "neurodegenerative disorders", "polycystic ovary syndrome", "obstructive sleep apnea", "safety", "adverse effects", "pancreatitis", "thyroid cancer", "gallbladder disease", "psychiatric safety", "weight regain", "combination therapies", "precision medicine", and "health economics". The search spanned from database inception to February 2025. References were selected for originality and relevance to the review's broad scope.

Personalized approaches could lead to more effective weight management, improved patient satisfaction, and better long-term health outcomes.[111]

Health economics

The economic implications of widespread GLP-1 RA use necessitate thorough evaluation. Future research should include comprehensive cost-benefit analyses to assess the long-term financial impact of these therapies on healthcare systems. These analyses should consider the potential reductions in healthcare costs associated with treating obesity-related comorbidities and the improvements in quality of life and productivity.[112] Additionally, studies should explore strategies to enhance the cost-effectiveness of GLP-1 RAs, such as through the development of generic formulations or alternative delivery methods (e.g., oral formulations).

Conclusions

The therapeutic landscape for obesity and related metabolic conditions has evolved substantially with the emergence of GLP-1 RAs. These agents now play a central role not only in weight management and diabetes care but are also being investigated in a growing number of conditions, including cardiovascular, renal, hepatic, neurologic, and substance use disorders. As their indications expand, so must our understanding of long-term efficacy, safety, and patient-centered treatment strategies. Recent insights into body composition changes, potential psychiatric effects, and perioperative risks highlight the importance of individualized care and ongoing monitoring. Advances in oral formulations, multi-targeted therapies, and precision medicine offer new opportunities to refine and personalize GLP-1 RA therapy. At the same time, issues of cost and access necessitate policy reforms to ensure equitable availability of these treatments. Continued efforts to improve real-world implementation will be essential to ensuring that GLP-1 RAs deliver meaningful clinical and public health benefits across a range of chronic conditions.

Outstanding questions

As GLP-1 RAs continue to expand beyond their original indications, several important questions remain. What are the long-term effects of sustained GLP-1 RA use on cardiovascular, pancreatic, thyroid, hepatobiliary, and neurocognitive outcomes across diverse populations? Can biomarkers or clinical characteristics reliably predict individual response to guide personalized therapy? What strategies can be employed to preserve lean body mass and mitigate weight regain after treatment discontinuation? How can we ensure equitable access to these therapies amidst rising demand and cost? Addressing these questions will be critical to optimizing the clinical and public health impact of GLP-1 RAs.

Contributors

Ms. Moiz contributed to the conception and design of the study, analysis and interpretation of data, and drafting of the manuscript. Dr. Filion was involved in the conception and design of the study, provided statistical expertise, and critically revised the manuscript for important intellectual content. Drs. Tsoukas, Yu, and Peters provided clinical expertise and critically revised the manuscript for important intellectual content. Dr. Eisenberg contributed to the conception and design of the study, provided clinical expertise, and critically revised the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

Declaration of interests

Dr. Tsoukas has received speaker honoraria from Novo Nordisk, Eli Lilly, Boehringer-Ingelheim, and Sanofi. The other authors have no conflicts of interest to disclose.

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