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GLP-1 RECEPTOR AGONISTS IN METABOLIC HEALTH: EXPANDING APPLICATIONS, WEIGHT MANAGEMENT, AND EMERGING SAFETY CONSIDERATIONS

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ABSTRACT

GLP-1 receptor agonists (GLP-1 RAs) have transformed the treatment of type 2 diabetes mellitus (T2DM) and obesity and have recently gained an additional approved indication for metabolic dysfunction-associated steatohepatitis (MASH). Their expanding clinical use has also increased interest in off-label applications and their evolving safety profile. This narrative review summarizes current evidence regarding the off-label use of GLP-1 RAs and evaluates both well-established and emerging adverse effects. A literature search was performed using the PubMed database, and relevant studies addressing approved and off-label applications, efficacy, and safety were qualitatively analyzed. Current evidence suggests that GLP-1 RAs have therapeutic potential beyond approved indications, particularly in polycystic ovary syndrome, antipsychotic-induced weight gain, prediabetes, binge eating disorder, and disorders involving dysregulation of reward-related behavior. The most common adverse effects are gastrointestinal symptoms and gallbladder disorders, whereas emerging safety concerns include weight regain following treatment discontinuation, changes in body composition, hair loss, non-arteritic anterior ischemic optic neuropathy (NAION), and a theoretical risk of medullary thyroid carcinoma in susceptible individuals. Although these findings are promising, the available evidence remains heterogeneous. Further high-quality studies are required to establish the efficacy and long-term safety of off-label applications. Careful patient selection, appropriate monitoring, and integration of pharmacotherapy with lifestyle modification remain essential for optimizing clinical outcomes.

KEYWORDS

GLP-1 Receptor Agonists, Off-Label Use, Adverse Effects, Safety Profile

CITATION

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Introduction

GLP-1 RAs have transformed the T2DM and obesity and have become an integral component of modern metabolic therapy. More recently, semaglutide has also received regulatory approval for the treatment of MASH. Their well-established efficacy in improving glycemic control, promoting weight reduction, and reducing cardiovascular risk has contributed to their widespread adoption in clinical practice. In parallel with their expanding clinical use, GLP-1 RAs have attracted increasing interest in off-label settings. Emerging evidence suggests potential benefits in conditions such as PCOS, antipsychotic-induced weight gain, prediabetes, binge eating disorder and other disorders involving dysregulation of reward-related behavior. In addition, these agents are increasingly used for weight management, reflecting both their accessibility and the growing demand for pharmacological strategies targeting obesity. Despite their favorable efficacy and overall acceptable safety profile, the expanding use of GLP-1 RAs has raised important safety considerations. Well-established adverse effects include gastrointestinal symptoms and gallbladder disease, while emerging and less well-characterized signals include hair loss, changes in body composition associated with rapid weight loss, NAION, and weight regain following treatment discontinuation. Given the widening scope of clinical use, a comprehensive assessment of both off-label applications and the evolving safety profile of GLP-1 RAs is of increasing clinical relevance.

Methodology

This study was conducted as a narrative literature review focusing on the off-label use and safety profile of GLP-1 RAs. A structured literature search was performed using the PubMed database. The search strategy included relevant combinations of keywords related to GLP-1 receptor agonists, off-label use, adverse effects, obesity, type 2 diabetes mellitus, and emerging safety concerns such as hair loss, weight regain, changes in body composition, thyroid cancer risk, and non-arteritic anterior ischemic optic neuropathy. Boolean operators (AND, OR) were used to refine the search. Only English-language publications were included. No strict time limits were applied; however, priority was given to recent high-quality evidence. Additional studies were identified through manual screening of reference lists of selected articles. Studies were selected based on their relevance to the objectives of the review. Data were synthesized qualitatively to provide an overview of current evidence regarding off-label applications of GLP-1 RAs and both established and emerging adverse effects. As a narrative review, no formal protocol, risk-of-bias assessment, or quantitative meta-analysis was performed.

GLP-1 receptor agonists: mechanism of action and clinical application

GLP-1 RAs are a class of drugs that activate the GLP-1 receptor, resulting in improved glycemic control, reduced appetite, and decreased caloric intake. Structurally, GLP-1 analogues closely resemble the endogenous GLP-1 hormone. They are classified as incretin mimetics, as they reproduce the physiological effects of incretin hormones such as GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). [(1)] Currently, GLP-1 receptor agonists are approved for the treatment of T2DM, obesity, and—more recently—MASH, following conditional approval of semaglutide. [(2)] GLP-1 Ras exert their effects through activation of GLP-1 receptors in pancreatic, central nervous system, and peripheral tissues. In T2DM, they improve glycemic control by enhancing glucose-dependent insulin secretion, suppressing glucagon release, and delaying gastric emptying, which collectively reduce postprandial glucose levels. In obesity, their primary mechanism involves central appetite regulation, leading to increased satiety, reduced hunger, and decreased energy intake, as well as slowed gastric emptying. In MASH, the beneficial effects are mainly indirect and result from weight loss, improved insulin sensitivity, and reduced hepatic fat accumulation and inflammation. Emerging evidence also suggests potential direct anti-inflammatory and metabolic effects within hepatic tissue, although these mechanisms remain under investigation. [(1)][(2)]

Off-label use

In addition to their approved therapeutic indications, GLP-1 RAs are increasingly being investigated and used off-label across a broad spectrum of clinical conditions. These include pharmacological weight reduction in PCOS, antipsychotic-induced weight gain, prediabetes, binge eating disorder, and other disorders involving dysregulation of reward-related behavior. [(3)]

One of the most extensively studied off-label applications of GLP-1 RAs is PCOS. Evidence from clinical studies and narrative reviews indicates that GLP-1 RAs may improve key metabolic and reproductive parameters in this population. Reported effects include reductions in body weight, visceral adiposity, and insulin resistance, which are central features of the metabolic phenotype of PCOS. In addition, improvements in hyperandrogenism and menstrual cyclicity have been observed, particularly in women with concomitant obesity and metabolic dysfunction. [(4)] These effects are thought to be primarily mediated through weight loss and improvement in insulin sensitivity, although potential direct endocrine effects have also been suggested. Overall, GLP-1 RAs appear to be a promising adjunct to lifestyle intervention and metformin therapy in selected patients with PCOS, particularly those with obesity and significant metabolic impairment.

Another important clinical area in which GLP-1 RAs have been investigated is antipsychotic-induced weight gain, particularly in patients treated with second-generation antipsychotics such as clozapine and olanzapine. GLP-1 RAs, including liraglutide and exenatide, are associated with significant reductions in body weight, body mass index, and waist circumference, as well as improvements in glycated hemoglobin and fasting plasma glucose compared with standard care. [(5)] GLP-1 RAs may represent a promising therapeutic option for the management of cardiometabolic adverse effects induced by antipsychotic treatment.

Another clinically relevant area of interest is prediabetes, where GLP-1 RAs may play a role in delaying or preventing progression to T2DM. GLP-1 RAs are associated with sustained weight loss, improved glycemic control, and enhanced insulin sensitivity in individuals with elevated metabolic risk. These effects are primarily mediated through reduced appetite and energy intake due to central appetite regulation, delayed gastric

emptying, and subsequent improvements in insulin secretion dynamics and pancreatic β -cell function. Collectively, these mechanisms contribute to improved metabolic profiles and may reduce the likelihood of progression from prediabetes to T2DM. [(6)]

Growing evidence also supports a potential role of GLP-1 RAs in binge eating disorder and substance use disorders. Preclinical and early clinical data indicate that GLP-1 signaling is involved in the modulation of central reward pathways, which regulate hedonic eating and addictive behaviors. Mechanistic studies suggest that GLP-1 receptor activation within mesolimbic structures, including the ventral tegmental area and nucleus accumbens, may reduce reward-driven food intake as well as the reinforcing effects of alcohol, nicotine, and other addictive substances. Despite these promising neurobiological and experimental findings, clinical evidence in humans remains limited, and current data are insufficient to support routine use of GLP-1 RAs for the treatment of binge eating disorder or substance use disorders. [(7)] [(8)]

Adverse effects

The adverse effects associated with GLP-1 RAs therapy are heterogeneous in both frequency and strength of evidence. In this review, they are categorized into two groups: well-established adverse effects, supported by robust evidence; and emerging or less well-defined effects, based on limited clinical data, including observational studies, case reports, or early hypotheses. This classification provides a structured framework for interpreting the safety profile of GLP-1 RAs in relation to the current level of evidence.

Well-established adverse effects

The most commonly reported adverse effects of GLP-1 RAs are gastrointestinal symptoms, including nausea, vomiting, diarrhea, constipation, abdominal pain, dyspepsia, and gastroesophageal reflux. These effects are well documented in randomized clinical trials and meta-analyses and represent the most frequent and consistent safety concern associated with this drug class. The incidence of gastrointestinal adverse events is dose-dependent and most pronounced during treatment initiation and dose escalation, with symptoms typically decreasing over time despite continued therapy. In addition to gastrointestinal symptoms, some patients may experience non-specific systemic effects such as fatigue, dizziness, and headache. Overall, gastrointestinal adverse events remain the predominant limitation of GLP-1 RAs therapy, although they are generally mild to moderate in severity and rarely lead to treatment discontinuation. [(9)]

A second well-established adverse effect of GLP-1 RAs is an increased risk of gallbladder and biliary diseases, including cholelithiasis and cholecystitis. Evidence from large systematic reviews and meta-analyses of randomized controlled trials has demonstrated a statistically significant association between GLP-1 RA therapy and gallbladder-related adverse events. The proposed mechanisms include rapid weight loss, reduced gallbladder motility, and bile stasis, all of which may contribute to gallstone formation and subsequent biliary complications. These findings are consistent across multiple GLP-1 RAs and have been observed both in patients with and without diabetes, particularly in individuals experiencing substantial and rapid weight reduction. Overall, the risk appears to be class-related and clinically relevant, although the absolute incidence remains relatively low. [(10)] [(11)]

GLP-1 RAs are associated with a low risk of hypoglycemia due to their glucose-dependent mechanism of action, which stimulates insulin secretion only in the presence of elevated blood glucose levels. Consequently, GLP-1 RAs as monotherapy rarely cause clinically significant hypoglycemia. [(12)] However, the risk of hypoglycemia increases when GLP-1 RAs are used in combination with insulin or sulfonylureas, due to the additive effects on insulin secretion and glucose lowering. Regimens combining GLP-1 RAs with sulfonylureas are associated with a higher incidence of hypoglycemic events compared with other antidiabetic drug combinations. Therefore, dose adjustment of concomitant insulin or sulfonylurea therapy is recommended to minimize the risk of hypoglycemia in clinical practice. [(13)]

Emerging adverse effects

Long-term maintenance of weight loss achieved with GLP-1 RAs is generally dependent on continued pharmacotherapy and sustained lifestyle modification. Evidence from the STEP 1 trial extension demonstrates that discontinuation of semaglutide is associated with significant weight regain, accompanied by partial reversal of cardiometabolic benefits. These findings suggest that, after treatment discontinuation, the mechanisms responsible for weight reduction are no longer fully maintained. The effects of GLP-1 receptor agonists on appetite regulation and energy balance gradually diminish, which may contribute to progressive weight regain over time. [(14)] However, in the context of obesity, this interpretation may be overly simplistic. Experimental evidence suggests that obesity may be associated with impaired endogenous GLP-1 signaling and reduced sensitivity to nutrient-induced GLP-1 responses. In preclinical models, high-fat diet-induced obesity has been associated with impaired GLP-1-mediated gut–brain signaling. This alteration may contribute to reduced satiety responses and dysregulated energy intake. These findings support the hypothesis that impaired incretin signaling may play a role in the pathophysiology of obesity and suggest that pharmacological GLP-1 receptor activation may act not only as a symptomatic intervention but also as a potential mechanism-based therapeutic approach. [(15)] Nevertheless, this perspective should not imply that pharmacotherapy alone is sufficient for achieving or maintaining long-term weight control. Evidence emphasizes that optimal and sustained outcomes with GLP-1 RAs are achieved when pharmacological treatment is integrated with comprehensive lifestyle and behavioral interventions, including dietary modification and physical activity. Accordingly, expectations regarding long-term weight maintenance should not rely solely on continued pharmacotherapy, but rather on a multifactorial approach that combines pharmacological, behavioral, and lifestyle-based strategies. [(16)] Individuals using GLP-1 RAs, particularly in off-label settings, should be aware that pharmacologically induced weight loss may occur relatively rapidly. Evidence on rapid weight reduction highlights that such changes can be associated not only with reductions in fat mass but also with alterations in lean body mass and broader physiological adaptations related to energy balance. For this reason, GLP-1 RA therapy should be combined with structured lifestyle interventions, including regular physical activity, particularly resistance training, and a balanced diet with adequate macronutrient and protein intake. [(17)]

Pharmacologically induced weight loss may occur relatively rapidly and may lead to visible phenotypic changes, including alterations in facial appearance characterized by reduced subcutaneous fat, increased skin laxity, and accentuation of pre-existing wrinkles. These changes have been described in both clinical literature and public discourse using the informal term “Ozempic face.” [(18)] Although largely driven by loss of facial adipose tissue rather than direct drug effects on the skin, emerging reports also discuss potential associations between GLP-1 RA–induced weight loss and perceived skin aging. [(19)]

Another aspect warranting consideration is hair loss observed in some individuals receiving GLP-1 RAs therapy. This adverse effect is not primarily related to direct dysfunction of the hair follicle. Instead, it is more likely associated with rapid weight loss and metabolic changes induced by treatment, which may trigger a telogen effluvium–like process. [(20)]

GLP-1 RAs have been associated with a theoretical risk of MTC, particularly in individuals with a personal or familial predisposition to this malignancy or with conditions such as multiple endocrine neoplasia type 2 (MEN2). This concern is primarily based on preclinical findings in rodent models exposed to supraphysiological doses, in which C-cell hyperplasia and tumor formation were observed. To date, there is no conclusive evidence demonstrating a causal association between GLP-1 RAs therapy and thyroid cancer in humans. Nevertheless, current guidelines and regulatory recommendations advise caution in patients with a history of MTC or MEN2. Clinical decision-making in such cases should be individualized, balancing potential benefits of therapy against theoretical risks. [(21)]

NAION is a rare but potentially vision-threatening condition that has recently emerged as a possible safety signal in patients treated with GLP-1 RAs. [22,23] Observational studies have suggested an increased incidence of NAION among semaglutide users. [22,23]. The pathophysiological mechanism remains uncertain. Current hypotheses suggest that GLP-1 RAs therapy may interact with pre-existing vascular susceptibility rather than directly inducing optic nerve ischemia, but no mechanism has been conclusively demonstrated [22,24]. Consequently, available evidence should be interpreted with caution, and further prospective studies are needed to clarify this potential association [22,23]. Although NAION remains an extremely rare adverse event, clinicians should advise patients to seek immediate ophthalmological evaluation if they experience sudden, painless visual loss during GLP-1 RA therapy [24]. At present, there is no evidence that newer dual- or triple-receptor agonists, such as tirzepatide or retatrutide, confer a lower risk of NAION than selective GLP-1 receptor agonists. While these agents differ in their pharmacological profile, their ocular safety has not yet been established and requires further investigation [25,26].

Results

GLP-1 receptor agonists have been reported to demonstrate potential therapeutic effects beyond their approved indications, particularly in polycystic ovary syndrome, antipsychotic-induced weight gain, and prediabetes. More recently, semaglutide has also been approved for the treatment of MASH with moderate to advanced fibrosis. The most commonly reported adverse effects include gastrointestinal symptoms and gallbladder disorders. In addition, emerging safety signals described in the literature include weight regain following treatment discontinuation, changes in body composition and facial appearance associated with rapid weight loss, hair loss, a theoretical risk of MTC in predisposed individuals, and NAION.

Discussion

GLP-1 receptor agonists have transformed the management of T2DM and obesity and, more recently, have expanded into the treatment of MASH. Their proven efficacy in improving glycemic control and promoting weight loss has also contributed to a growing interest in off-label applications, including PCOS, antipsychotic-induced weight gain, prediabetes, binge eating disorder, and addictive disorders. Although many of these indications show promising results, the current level of evidence varies considerably, and routine clinical use outside approved indications is not yet supported for most of these conditions. This review also highlights that the safety profile of GLP-1 RAs extends beyond the well-recognized gastrointestinal adverse effects. While gastrointestinal symptoms, biliary disease, and hypoglycemia associated with concomitant insulin or sulfonylurea therapy are supported by clinical evidence, increasing attention has been directed toward less common or emerging safety signals. These include weight regain following treatment discontinuation, changes in body composition associated with rapid weight loss, hair loss, perceived facial aging, the theoretical risk of MTC, and the possible association NAION. For most of these events, current evidence remains limited and does not establish a causal relationship. The expanding use of GLP-1 receptor agonists, particularly in off-label settings, underscores the importance of careful patient selection, individualized risk–benefit assessment, and appropriate counseling regarding both the expected benefits and the limitations of therapy. Pharmacological treatment should be considered part of a comprehensive management strategy that includes lifestyle modification, adequate nutritional support, and regular physical activity to maximize long-term efficacy and minimize treatment-related complications. Overall, GLP-1 RAs remain among the most effective evidence-based therapies for obesity and T2DM. However, as their indications continue to expand, further high-quality prospective studies are needed to better define the efficacy and long-term safety of off-label applications and to clarify the clinical relevance of emerging adverse effects.

Conclusions

GLP-1 receptor agonists are highly effective pharmacological agents for the treatment of T2DM, obesity, and MASH. Their expanding use has also led to increasing interest in several off-label applications, although the level of supporting evidence varies considerably across these indications. While the safety profile of GLP-1 RAs is generally favorable, clinicians should distinguish between well-established adverse effects and emerging safety signals that require further investigation. Careful patient selection, individualized risk–benefit assessment, and appropriate counseling regarding treatment expectations remain essential, particularly when these agents are prescribed outside approved indications. Future prospective studies are needed to better define the long-term efficacy and safety of off-label use and to clarify the clinical relevance of emerging adverse effects. Integrating pharmacotherapy with lifestyle modification remains fundamental to achieving optimal and sustained therapeutic outcomes.

Conflict of Interest Statement: The authors declare no conflicts of interest.

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