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THE DARK SIDE OF GLP-1 ANALOGS: ADVERSE EFFECTS, LIMITATIONS, AND SAFETY CONCERNS

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ABSTRACT

The aim of this work is to comprehensively review and highlight the adverse effects, clinical limitations, and safety concerns associated with the use of GLP-1 receptor agonists (GLP-1 RAs), with particular emphasis on the digestive, endocrine, and cardiovascular systems, as well as the risks of off-label misuse. A comprehensive literature review was conducted using the PubMed database and Polish Summaries of Product Characteristics (SmPC). While GLP-1 analogs provide significant metabolic benefits, they carry substantial risks, including gastrointestinal distress (nausea, vomiting, delayed gastric emptying), potential skeletal muscle loss, and psychiatric effects such as suicidal ideation.

The use of GLP-1 receptor agonists demonstrates significant hepatoprotective potential, manifested by a beneficial modulation of biochemical liver markers in patients with fatty liver disease. Analysis of the impact on other systems shows that while these drugs are cardioprotective, they may cause a modest increase in resting heart rate. Regarding body composition, GLP-1 RAs lead to a reduction in fat-free mass, which accounts for less than 20% of total weight loss, although this poses a risk of sarcopenia in older populations. To mitigate this, pharmacotherapy should be integrated with resistance training and high protein intake. The growing trend of off-label misuse for cosmetic weight loss further exacerbates safety concerns. Optimizing therapy requires an integrated approach and careful patient monitoring to balance metabolic gains with musculoskeletal and psychological stability.

KEYWORDS

GLP-1 Receptor Agonists, Adverse Effects, Off-Label Use, Muscle Loss, Safety Concerns

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1. Introduction

GLP-1 receptor agonists have been used in medicine since the 1980s. At that time, Svetlana Mojsov from Rockefeller University discovered the sequence of an intestinal hormone belonging to the incretin group (Müller et al., 2019). The incretin effect consists of greater insulin secretion after oral (p.o.) administration of glucose compared to insulin secretion after parenteral administration.

GLP-1 receptor agonists activate the GLP-1 receptor in pancreatic B cells. This results in a glucose-dependent increase in insulin secretion. In addition, they inhibit glucagon secretion, delay gastric emptying, reduce appetite and have beneficial cardiovascular effects (Sfairopoulos, Liatis, Tigas, & Liberopoulos, 2018). Besides of it, GIP directly stimulates lipogenesis, while GLP-1 indirectly promotes lipolysis, together maintaining healthy adipocytes, reducing ectopic fat breakdown and increasing the production and secretion of adiponectin from adipocytes (Liu, 2024). Together, these two incretins contribute to metabolic homeostasis by preventing both hyperglycaemia and hypoglycaemia, alleviating dyslipidaemia and reducing the risk of cardiovascular disease in people with type 2 diabetes and obesity (Liu, 2024).

There is a long list of drugs that utilise the incretin effect and act as GLP-1. In the United States, the FDA has registered a wider group of agonists, while in the European Union, including Poland, drugs such as Exenatide, one of the first GLP-1 RAs approved in the EU, are available (Parker, Slattery, Brennan, & le Roux, 2025). Liraglutide – authorised in the EU since 2009, used to treat type 2 diabetes (Parker et al., 2025). The higher dose of the drug is also indicated for the treatment of obesity (e.g. Saxenda) — registered as an aid to weight loss in overweight or obese patients (European Medicines Agency, 2018a). Lixisenatide and Dulaglutide – approved in the EU for the treatment of type 2 diabetes (Parker et al., 2025). Semaglutide is authorised in the EU both as an antidiabetic medicine (e.g. Ozempic, Rybelsus) and as a weight loss aid (e.g. Wegovy), depending on the dose and indications (European Medicines Agency, 2018b). Tirzepatide, a GIP/GLP-1 agonist (with hybrid activity), is approved for the treatment of type 2 diabetes and is also indicated

for weight reduction in obese or overweight patients with accompanying health problems (European Medicines Agency, 2018c).

The main clinical indications for the use of GLP-1 drugs are type II diabetes. They have been proven to have a significant effect on reducing HbA1c: on average 0.8–1.8% (depending on the molecule and dose). They have a positive effect on weight reduction (the greatest for semaglutide 2.4 mg and tirzepatide) by influencing satiety centres and delaying gastric emptying (Wilding et al., 2021). Some, in particular liraglutide, semaglutide and dulaglutide, have been used in the treatment of heart failure and cardiovascular protection.

The use of this group of drugs is not limited to the above-mentioned indications. More and more review articles are suggesting a positive effect on a number of other diseases, such as liver disease, neurodegenerative syndromes, and addiction syndromes (Moiz, Filion, et al., 2025).

In this paper, we would like to focus on the darker side of these unique drugs. GLP-1 analogues have their limitations and side effects. From the many side effects, we have tried to identify the most important subgroups, with particular emphasis on body systems such as the digestive system, endocrine system, cardiovascular system, etc. We hope that our work will be useful to many clinicians in their daily work and will help them better understand the use of these drugs.

2. Methodology

A comprehensive literature search was conducted to evaluate the safety profile and adverse effects of GLP-1 receptor agonists. The primary database utilized for this review was PubMed. The inclusion criteria were strictly limited to English-language publications. The selected literature primarily consisted of systematic reviews, meta-analyses, narrative reviews, and case series. To supplement the academic literature and ensure regulatory accuracy regarding reported adverse events, warnings, and clinical contraindications, the official Polish Summaries of Product Characteristics (SmPC/ChPL) for specific GLP-1 analogs were also reviewed and incorporated into the analysis.

3. Results

3.1 Gastrointestinal Side Effects

GLP-1 analogs commonly cause gastrointestinal adverse effects as a consequence of their modulatory influence on both digestive tract and nervous system. The most frequently reported side effects include nausea, vomiting, diarrhea and constipation (Liu, 2024; Ismaiel et al., 2025; Quast et al., 2020; Camilleri & Lupianez-Merly, 2024; Lin et al., 2023; Liu, Chen, Wang, Chen, & Chen, 2022; Gleason et al., 2024). Additional reported adverse reactions comprise of: abdominal pain and discomfort gastroesophageal reflux disease, eructation, flatulence, infrequent bowel movements and hard feces (Ismaiel et al., 2025; Quast et al., 2020). Although classified as adverse effects, gastrointestinal symptoms may aid in weight reduction, but their contribution remains less significant than drug's primary pharmacological mechanism (Quast et al., 2020; Camilleri & Lupianez-Merly, 2024).

A key mechanism of action of GLP-1 analogs is a delay of gastric emptying. Promotion of pyrrolic constriction combined with inhibition of antral contractions results in prolonged gastric retention of ingested food, which is presumed to be a cause of nausea and vomiting (Liu, 2024; Ismaiel et al., 2025; Quast et al., 2020; Camilleri & Lupianez-Merly, 2024). However, long-acting GLP1 receptor antagonists (GLP-1 RA) are hypothesised to have reduced occurrence rate of those symptoms, likely attributable to decrease in delay of gastric emptying resulting from tachyphylaxis (Liu, 2024; Camilleri & Lupianez-Merly, 2024). Notably, diabetes may contribute to the occurrence and severity of some adverse effects through gastrointestinal dysmotility or vagal denervation, however further studies need to be conducted (Liu, 2024; Camilleri & Lupianez-Merly, 2024).

The incidence of gastrointestinal adverse effects varies significantly among individual GLP-1 receptor antagonists and are often a cause of treatment discontinuation (Ismaiel et al., 2025; Quast et al., 2020; Liu et al., 2022; Gleason et al., 2024). Therefore it is important to appropriately select GLP-1RA for each patient in order to improve treatment adherence.

3.2 Pancreatic and Hepatobiliary Effects

The potential link between GLP-1 agonists and acute pancreatitis (AP) remains a subject of ongoing debate. While some meta-analyses indicate an 82% increase in AP risk, other data suggest this concern primarily involves DPP-4 inhibitors rather than the GLP-1 RA group itself (Guo, Guo, Li, & Wang, 2024; Abd El Aziz, Cahyadi, Meier, Schmidt, & Nauck, 2020). Potential complications most frequently emerge within the first six months of treatment, with a median onset of approximately 92 days (Guo et al., 2024; Tartaglia et al., 2025). Hypotheses regarding harm are based on observed structural changes in the pancreas, such as ductal hyperplasia, as well as the clinically significant elevation of amylase and lipase levels (Wen et al., 2025; Wewer Albrechtsen et al., 2016). However, animal studies suggest these changes are mild and transient; in obese subjects, the therapy may even alleviate pancreatic strain. Although the treatment significantly reduces overall mortality, an individualized risk assessment is essential, particularly for patients with a history of pancreatic disorders (Tartaglia et al., 2025; Wen et al., 2025).

The impact of GLP-1 agonists on the pancreas remains a subject of scientific debate, centered on two primary perspectives. While some preclinical studies suggest these drugs may influence cell proliferation and metaplastic changes—potentially increasing the theoretical risk of dysplasia (Wen et al., 2025)—others argue that elevated pancreatic enzymes represent a benign adaptive response rather than structural damage. Consequently, an isolated increase in amylase and lipase levels is interpreted either as a clinical signal requiring monitoring or as a natural biological effect of the therapy (Wewer Albrechtsen et al., 2016).

The central debate between empirical evidence and academic speculation revolves around the actual mechanism of tumor development. While real-world clinical data indicate a higher odds ratio for pancreatic cancer, researchers hypothesize that this may partially stem from ascertainment bias; patients on these therapies often undergo more frequent diagnostic imaging due to abdominal symptoms, potentially leading to incidental detection of preexisting conditions (Faour, Boktor, Yau, Kinaan, & Mansi, 2025). In contrast, a comprehensive meta-analysis of randomized controlled trials (RCTs) found no such correlation in the general population, suggesting that isolated cases may emerge from the convergence of the treatment with a patient's baseline risk factors rather than being a direct oncogenic consequence of the drug itself (Wen et al., 2025).

Patients with NAFLD exhibit a profound dysregulation of the incretin system, characterized by a reduced density of hepatic GLP-1 receptors and an accelerated degradation of the hormone, as the metabolic environment promotes higher DPP-4 activity that significantly shortens its half-life (Liu, Wei, & Hong, 2014). The administration of GLP-1 analogues enables an effective counteraction of hepatic steatosis by modulating metabolic pathways within hepatocytes and mitigating detrimental oxidative stress (Rezaei et al., 2021). Implementation of this therapeutic class results in a marked improvement in laboratory parameters, specifically a decrease in ALT, ALP, and GGT activity, although the effect on AST levels is not always statistically significant (Liu et al., 2014; Rezaei et al., 2021). Interestingly, the clinical benefits and the reduction in intrahepatic fat content do not directly correlate with the correction of serum cholesterol or triglyceride concentrations (Liu et al., 2014). Beyond these metabolic effects, the treatment demonstrates a hepatoprotective potential by inhibiting progressive structural damage and liver fibrosis (Liu et al., 2014; Rezaei et al., 2021).

3.3 Endocrine and Metabolic Considerations

GLP-1 analogues have drawn attention to their potential endocrine and metabolic effects, besides their well-established role in glycaemic control and weight reduction. In particular, research has focused on the impact of GLP-1 analogues on the function of other endocrine glands, the expression of hormonal receptors, and the possible proliferative consequences in selected cell types. These factors are particularly important because of the inconsistencies between animal model findings and human data, especially in the context of long-term safety assessment of incretin-based therapies.

Thyroid C-cells, which are responsible for calcitonin secretion, express the GLP1 receptor. This suggests that GLP-1 analogues may directly influence C-cell function, highlighting the importance of understanding their potential effects on thyroid physiology and pathology (Gier et al., 2012). GLP-1 receptor is differentially expressed in thyroid C-cells across non-neoplastic tissue, C-cell hyperplasia, and medullary thyroid carcinoma. The findings suggest that GLP-1 receptors may play a crucial role in these disorders (Song et al., 2017).

Hypoglycaemia is a common risk in diabetes therapy, particularly when agents that increase insulin level or secretion are used. GLP-1 analogues are generally associated with a low risk of hypoglycaemia due to their glucose-dependent mechanism of insulin secretion. However, this risk increases when GLP-1 analogues are used in combination with sulfonylureas or exogenous insulin, as these agents can stimulate insulin release independently of blood glucose levels (Wang et al., 2025).

3.4 Cardiovascular Risks

Initial concerns vs. current evidence (CV outcome trials).

Early development of GLP-1 receptor agonists (GLP-1 RA) raised theoretical concerns regarding cardiovascular (CV) safety, primarily due to the need to understand how metabolic modulation might influence cardiovascular physiology. However, multiple large-scale cardiovascular outcome trials (CVOTs) have consistently demonstrated that GLP-1 RA do not increase CV risk and, in many cases, confer cardioprotective benefits in patients with type 2 diabetes mellitus (T2DM) or elevated CV risk. Meta-analyses incorporating data from tens of thousands of participants have shown that GLP-1 RA significantly reduce major adverse cardiovascular events (MACE), all-cause mortality, cardiovascular mortality, nonfatal stroke, and heart failure hospitalizations versus placebo or standard care. Specifically, meta-analytic data report relative hazard reductions of approximately 14% for MACE, 12% for all-cause mortality, and significant reductions in nonfatal stroke and cardiovascular death across multiple CVOTs, including LEADER, SUSTAIN-6, and others (Giugliano et al., 2021; Jia, Alam, Ye, Bajaj, & Birnbaum, 2018; Chen, Zhang, Xiang, Fang, & Feng, 2024).

These findings are supported by comprehensive systematic reviews and meta-analyses that confirm consistent cardiovascular benefit and non-inferiority of GLP-1 RA with regard to CV safety endpoints, aligning with regulatory requirements for antidiabetic therapies (Andrikou et al., 2019; Bahtiyar, Pujals-Kury, & Sacerdote, 2018).

Taken together, the current evidence base from CVOTs and aggregated clinical trials solidly indicates that initial theoretical concerns about CV risk have not materialized in practice, and GLP-1 RAs may be associated with moderate but clinically meaningful cardiovascular protection in high-risk populations.

Despite the broad evidence of cardiovascular safety and benefit, several studies and mechanistic analyses have identified hemodynamic changes associated with GLP-1 RA therapy that warrant careful consideration. A consistent finding across randomized trials and meta-analytic data is a modest increase in resting heart rate (HR), typically in the range of 2–4 beats per minute compared with placebo or active comparators (Sun et al., 2015; Wu et al., 2022).

This heart rate elevation appears to be a class effect of GLP-1 RA and has been observed in both short-acting and long-acting formulations (Lorenz et al., 2017). Mechanistic investigations provide evidence that GLP-1 and its analogs may exert direct chronotropic effects on sinus node pacemaker cells as well as modulate autonomic control of cardiac rhythm, which could underlie these tachycardic responses (Lubberding et al., 2024; Griffioen et al., 2011).

Regarding blood pressure (BP), GLP-1 RA generally produce small reductions in systolic and diastolic blood pressure, likely mediated by weight loss, natriuretic effects, and vasodilatory mechanisms (de Oliveira Almeida et al., 2024; Moiz, Zolotarova, Filion, & Eisenberg, 2025). However, individual patient responses vary and isolated cases reporting tachycardia or transient BP changes have emerged, particularly in specific subpopulations or in early treatment phases (Moiz et al., 2025).

Although these hemodynamic alterations are modest and have not translated into increased rates of serious arrhythmias or clinical hypertension in major CVOTs, they represent important safety considerations. Continued post-marketing surveillance and mechanistic studies are necessary to clarify whether these effects are clinically significant in specific high-risk cohorts or could contribute to adverse outcomes under certain conditions.

3.5 Psychiatric and Behavioral Effects

GLP-1 receptor agonists, including semaglutide and liraglutide, have been associated with clinically relevant psychiatric adverse events, particularly depressive symptoms and suicidal ideation, highlighting the need for further research, especially in patients with pre-existing psychiatric disorders (Katranski, Liang, Morris, Suppiah, & Lim, 2025). Interference with the mechanisms controlling food intake through GLP-1 can lead to psychological and behavioral side effects, including anxiety, irritability, and mood disturbances. These effects may result from an imbalance between the systems regulating hunger and satiety, and can be further exacerbated by gastrointestinal symptoms such as nausea, vomiting, or diarrhea (Ameer et al., 2025).

At the same time, other publications describe potential therapeutic benefits of GLP-1 receptor agonists in psychiatric and neurocognitive conditions, suggesting that their overall impact on mental health remains inconclusive (Himmerich, 2025; Meshkat et al., 2025).

There have also been reports of semaglutide misuse for cosmetic weight loss by individuals without medical indications, with analyses of the FDA Adverse Event Reporting System indicating a potential for misuse compared with similar agents. Concerns have also been raised regarding use by patients with restrictive eating disorders, such as anorexia nervosa or atypical anorexia, which may further increase the risk of adverse psychiatric effects (Himmerich, 2025).

3.6 Misuse of GLP-1 Analogs by Healthy Individuals

In recent years, there has been a noticeable increase in the use of GLP-1 receptor agonists among individuals without clear medical indications, such as type 2 diabetes or obesity accompanied by metabolic complications. Data from national health registries, including analyses from France covering 2017 to mid-2023, show a marked rise in the number of users, particularly among young women (du Soulier et al., 2025). The growing proportion of single or short-term prescriptions suggests that some of these medications may be used for temporary weight reduction rather than as part of structured, long-term medical care.

This trend appears to be influenced by social media and celebrity endorsement of so-called "slimming drugs," as well as marketing by private clinics offering off-label prescriptions (Oyama, Okuhara, Furukawa, Okada, & Kiuchi, 2025; Ugwu, Willis, & Pickett, 2026). Online platforms enable rapid sharing of personal experiences and visible weight-loss transformations, which can increase public interest and contribute to the perception that these medications are a quick and effective solution for weight control.

Because GLP-1 receptor agonists are approved and widely prescribed for chronic conditions, they are often viewed as relatively safe—even when used without medical supervision. However, clinical trials and post-marketing data consistently identify gastrointestinal adverse effects as the most common complications, including nausea, vomiting, diarrhea, and constipation (Bellavance, Chua, & Mashimo, 2025). These agents are also associated with delayed gastric emptying, which in some individuals may lead to clinically significant gastroparesis-like symptoms (Jalleh et al., 2024).

Additional concerns involve metabolic disturbances and gallbladder disease (He et al., 2022). Rapid weight loss may increase the risk of cholelithiasis and cholecystitis, findings reported in both clinical trials and real-world studies. Cases of pancreatitis have also been described, although a definitive causal relationship remains under debate (Monami et al., 2017). Persistent gastrointestinal symptoms may further result in dehydration and electrolyte imbalance, particularly in individuals using these agents without adequate medical monitoring.

In non-diabetic individuals, inappropriate use combined with caloric restriction may increase the risk of hypoglycemia. Moreover, discontinuation of GLP-1 therapy is frequently followed by weight regain, which may encourage repeated short-term use and ongoing exposure to adverse effects without sustained metabolic benefit (Tzang et al., 2025; Berg, Stickle, Rose, & Nemec, 2025).

The use of GLP-1 analogues in otherwise healthy individuals raises important clinical and public health questions (Pazzagli & Trolle Lagerros, 2025; Spinelli et al., 2025; Azizi, Rodriguez, & Assimes, 2024). In people without a clear therapeutic need, the potential risks may outweigh the expected benefits. Moreover, increased off-label demand may contribute to reduced drug availability and unequal access for patients who rely on these medications for evidence-based treatment. The growing normalization of pharmacological weight loss, reinforced by social media and digital word-of-mouth, may also shift attention away from sustainable lifestyle interventions and create unrealistic expectations regarding rapid weight reduction.

3.7 Skeletal Muscle Loss Associated with GLP-1 Analogs

Rapid weight loss induced by GLP-1 receptor agonists (GLP-1RAs) involves both fat mass (FM) and fat-free mass (FFM). Although the loss of FFM raises concerns about patients' functional status and decreased muscle strength, this phenomenon does not always correlate with an absolute decrease in strength, and the real risk of neuromuscular decline applies mainly to the geriatric population (Anyiam, Ardavani, Rashid, Panesar, & Idris, 2025; Prokopidis, 2026).

A 2025 meta-analysis showed that in patients with type 2 diabetes, these drugs induce a statistically non-significant decrease in FFM alongside a significant reduction in fat mass. On the other hand, in obese individuals without diabetes, muscle mass loss is statistically significant, but still significantly smaller than fat mass loss. In both studied groups, the decrease in muscle mass accounted for less than 20% of the total weight loss (Anyiam et al., 2025).

For comparison, in the surgical treatment of obesity, the loss of FFM reaches almost 30% of the total weight loss. In this regard, GLP-1 receptor agonist therapy seems to have a more favorable profile for proportional muscle tissue protection compared to other obesity treatment methods (Haghighat et al., 2021).

However, it should be emphasized that the scale of muscle tissue loss reported in clinical trials may be overestimated due to the specifics of the measurement methods. Standard diagnostic tools (DXA, BIA) measure the total fat-free mass (FFM) of the body, which also includes water and connective tissue located inside the fat tissue. For this reason, a drastic reduction in fat tissue naturally leads to a drop in intracellular

water, which measuring devices incorrectly classify as a loss of functional skeletal muscle (Anyiam et al., 2025).

The phenomenon of muscle tissue loss is multifactorial. The direct cause is a significant suppression of appetite, leading to a negative energy balance and a drop in dietary protein intake. This triggers important hormonal adaptations in the body. On one hand, decreased secretion of insulin and IGF-1 factor inhibits the mTOR signaling cascade, drastically slowing down the synthesis of new muscle proteins. On the other hand, caloric deficit activates the hypothalamic-pituitary-adrenal axis, which results in an increase in cortisol levels. This hormone directly increases protein breakdown (proteolysis) by stimulating the ubiquitin-proteasome pathway (Rossi, Bucciarelli, Mananguite, Giovarelli, & Fiorina, 2025).

Evaluating the safety of GLP-1 analogs requires distinguishing between quantitative changes (mass) and qualitative changes (strength). The reduction of fat-free tissue mass does not directly correlate with a drop in muscle strength. In younger and middle-aged obese patients, short- and medium-term studies (lasting up to 6 months) on semaglutide or liraglutide show that handgrip strength remains statistically preserved, despite clear losses of fat-free mass. The situation is completely different in older patients with type 2 diabetes. While older generations of drugs (such as dulaglutide) have a milder effect on fat-free mass (Chen et al., 2024), this risk changes with more potent molecules. Long-term observational studies indicate an increased risk of complications, decreased handgrip strength, and accelerated sarcopenia with prolonged semaglutide use (Prokopidis, 2026).

3.8 Limitations in Clinical Use

In Europe, three glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are currently approved for clinical use: semaglutide, liraglutide, and dulaglutide. Although they share a common mechanism of action, their contraindications, warnings, and precautionary measures differ slightly depending on the specific molecule and formulation. All GLP-1 receptor agonists are contraindicated in patients with hypersensitivity to the active substance or any of the excipients and are not indicated for use in type 1 diabetes or in the treatment of diabetic ketoacidosis, as they are not substitutes for insulin therapy.

Liraglutide should be used with caution in selected patient populations. Its use is not recommended in individuals with NYHA class IV heart failure, inflammatory bowel disease, or diabetic gastroparesis due to limited clinical experience and an increased risk of gastrointestinal adverse events. Cases of acute pancreatitis have been reported, and treatment should be discontinued if pancreatitis is suspected or confirmed. Additional precautions include the risk of aspiration during general anesthesia or deep sedation due to delayed gastric emptying, potential thyroid-related adverse effects (particularly in patients with pre-existing thyroid disease), dehydration secondary to gastrointestinal symptoms, and an increased risk of hypoglycaemia when used in combination with insulin or sulfonylureas (European Medicines Agency, 2018a).

Semaglutide shares many class-related warnings, including the risk of gastrointestinal adverse effects leading to dehydration and potential deterioration of renal function, as well as acute pancreatitis. Caution is advised in patients with a history of pancreatitis. Semaglutide has also been associated with an increased risk of diabetic retinopathy complications, particularly in patients treated concomitantly with insulin and experiencing rapid improvement in glycaemic control. Rare cases of non-arteritic anterior ischaemic optic neuropathy (NAION) have been reported, requiring immediate ophthalmological evaluation and discontinuation of therapy if confirmed. As with other GLP-1 RAs, semaglutide is not recommended in patients with severe gastroparesis or NYHA class IV heart failure (European Medicines Agency, 2018b).

Dulaglutide is similarly contraindicated in type 1 diabetes and diabetic ketoacidosis and should be used cautiously in patients with renal impairment due to the risk of dehydration associated with gastrointestinal adverse effects. Its use is not recommended in patients with severe gastrointestinal disease, including severe gastric emptying disorders, as these populations have not been adequately studied. Acute pancreatitis has been reported during treatment, and therapy should be discontinued if pancreatitis is suspected or confirmed. The risk of hypoglycaemia is increased when dulaglutide is combined with insulin or sulfonylureas, necessitating dose adjustments. Clinical experience in patients with congestive heart failure remains limited (European Medicines Agency, 2018c).

4. Discussion

The expanding clinical application of GLP-1 receptor agonists has revolutionized the management of type 2 diabetes and obesity, yet it brings to light significant safety concerns that require careful clinical navigation. As highlighted in our review, gastrointestinal events remain the most common cause of treatment discontinuation, while debates regarding pancreatic safety and rare cardiovascular or endocrine effects necessitate individualized risk assessments.A particularly pressing issue is the alteration in body composition, specifically the loss of fat-free mass. In light of the above data, optimizing GLP-1 analog therapy requires an integrated clinical approach aimed at protecting muscle tissue. According to current evidence, the foundation of prevention is combining pharmacotherapy with regular resistance training and a properly balanced diet. It is crucial for maintaining anabolism to ensure a daily intake of high-quality protein at the level of 1.2-1.6 g/kg of adjusted body weight.The psychiatric effects of GLP-1 receptor agonists appear to be complex, with studies reporting both potential therapeutic benefits and clinically relevant adverse events such as depressive symptoms and suicidal ideation. Additionally, misuse of these drugs for cosmetic weight loss and their use in patients with restrictive eating disorders may further increase the risk of psychological and behavioral complications, highlighting the need for careful patient monitoring.

5. Conclusions

GLP-1 receptor agonists have fundamentally transformed the management of type 2 diabetes and obesity by providing significant metabolic and cardiovascular benefits. However, as this review indicates, their clinical success is accompanied by a wide spectrum of adverse effects that require careful management. The most prevalent concerns are gastrointestinal disturbances, such as nausea and delayed gastric emptying, which remain the primary reason for treatment discontinuation. While these agents demonstrate potential hepatoprotective effects by reducing liver enzymes and mitigating oxidative stress, the ongoing debate regarding their link to acute pancreatitis and pancreatic malignancies necessitates individualized risk assessments and vigilant monitoring. Furthermore, although large-scale trials confirm their cardiovascular safety, the observed modest increase in resting heart rate and potential hemodynamic changes represent important considerations for long-term therapy.

The use of GLP-1 analogs also introduces significant challenges regarding body composition and mental health. The loss of fat-free mass, particularly in non-diabetic and older populations, highlights a risk of sarcopenia that must be countered by integrating pharmacotherapy with resistance training and high-protein nutrition. Additionally, the emergence of psychiatric adverse events, such as depressive symptoms and suicidal ideation, alongside the growing trend of off-label misuse for cosmetic weight loss, underscores the danger of using these medications without strict medical supervision. Ultimately, optimizing GLP-1 therapy requires a holistic clinical approach. To ensure patient safety and sustainable outcomes, it is essential to balance the metabolic gains of these drugs with rigorous monitoring of musculoskeletal health, psychological stability, and the prevention of inappropriate use in healthy individuals.

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