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# BEYOND GLYCEMIC CONTROL AND WEIGHT REDUCTION: PLEIOTROPIC EFFECTS OF GLP-1 RECEPTOR AGONISTS ON HUMAN PHYSIOLOGY - A NARRATIVE REVIEW

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**ABSTRACT**

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as one of the most important therapeutic advances in the management of type 2 diabetes mellitus and obesity. Originally developed to enhance glucose-dependent insulin secretion and improve glycemic control, these agents have demonstrated a broad spectrum of effects extending beyond traditional metabolic indications. The widespread expression of GLP-1 receptors throughout multiple organ systems provides a biological basis for their pleiotropic actions, which include modulation of inflammatory, vascular, metabolic, and neurohormonal pathways. This narrative review summarizes current evidence regarding the systemic effects of GLP-1RAs beyond diabetes and obesity. Recent landmark clinical trials have demonstrated significant reductions in major adverse cardiovascular events, improvements in heart failure-related outcomes, and slower progression of chronic kidney disease. Emerging evidence also supports beneficial effects in metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH), with improvements observed in hepatic steatosis, inflammation, and fibrosis. In addition, growing interest has focused on the neuroprotective properties of GLP-1RAs, including their potential role in neurodegenerative disorders such as Parkinson's and Alzheimer's disease. Modulation of central reward pathways has further raised the possibility of their application in addiction medicine. Additional findings suggest favorable effects in obesity-associated obstructive sleep apnea and reproductive disorders, particularly polycystic ovary syndrome. Observational studies have also explored potential associations with reduced cancer risk and healthy aging, although evidence in these areas remains preliminary. Despite their favorable safety profile and expanding clinical utility, several emerging indications require further validation through large randomized controlled trials. Overall, current evidence supports the view that GLP-1 receptor agonists should be regarded as multisystem therapeutic agents with clinically meaningful effects extending far beyond glycemic control and weight reduction, highlighting their potential to reshape the management of numerous chronic diseases.

**KEYWORDS**

GLP-1 Receptor Agonists, Semaglutide, Tirzepatide, Cardiovascular Disease, Chronic Kidney Disease, MASLD, Neuroprotection

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# 1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as one of the most significant therapeutic advances in metabolic medicine over the past two decades. GLP-1 is an incretin hormone secreted by intestinal L-cells in response to nutrient intake, where it plays a crucial role in glucose homeostasis by stimulating glucose-dependent insulin secretion, suppressing glucagon release, delaying gastric emptying, and promoting satiety. Due to the short half-life of endogenous GLP-1, pharmacological GLP-1 receptor agonists were developed to provide sustained receptor activation and prolonged therapeutic effects (Zheng et al., 2024; Drucker, 2025).

Initially introduced for the treatment of type 2 diabetes mellitus (T2DM), GLP-1RAs such as liraglutide, semaglutide, and tirzepatide have demonstrated substantial efficacy in improving glycemic control and inducing clinically meaningful weight loss. However, growing evidence suggests that their therapeutic effects extend far beyond traditional metabolic outcomes. The widespread distribution of GLP-1 receptors throughout the cardiovascular system, kidneys, liver, gastrointestinal tract, and central nervous system provides a biological basis for their broad systemic activity (Wilbon & Kolonin, 2024; Zheng et al., 2024).

Over the last several years, large randomized clinical trials have demonstrated significant cardiovascular and renal benefits associated with GLP-1RA therapy, including reductions in major adverse cardiovascular events, improvements in heart failure-related outcomes, and slower progression of chronic kidney disease (Lincoff et al., 2023; Kosiborod et al., 2023; Perkovic et al., 2024). Furthermore, emerging evidence supports their potential role in metabolic dysfunction-associated steatotic liver disease (MASLD), neurodegenerative

disorders, addiction medicine, reproductive health, and obesity-related respiratory diseases (Hong et al., 2024; Hendershot et al., 2025; Malhotra et al., 2024).

These diverse clinical effects are believed to result from a combination of metabolic, anti-inflammatory, vascular, and neuroprotective mechanisms that influence multiple pathological pathways involved in chronic disease development. Consequently, GLP-1RAs are increasingly being regarded as multisystem therapeutic agents.

The aim of this narrative review is to summarize and critically evaluate current evidence regarding the pleiotropic effects of GLP-1 receptor agonists beyond diabetes and obesity, with particular emphasis on cardiovascular, renal, hepatic, neurological, reproductive, respiratory, and aging-related outcomes.

## 2. Methods

A narrative literature review was conducted to evaluate the extra-glycemic and extra-weight effects of GLP-1 receptor agonists. Relevant articles published between January 2021 and June 2026 were identified through searches of PubMed/MEDLINE, Scopus, and Google Scholar. Search terms included combinations of "GLP-1 receptor agonists," "semaglutide," "tirzepatide," "liraglutide," "cardiovascular outcomes," "chronic kidney disease," "heart failure," "MASLD," "MASH," "Parkinson's disease," "Alzheimer's disease," "substance use disorders," "polycystic ovary syndrome," and "pleiotropic effects."

Priority was given to randomized controlled trials, landmark outcome studies, systematic reviews, meta-analyses, and high-quality observational studies published in peer-reviewed journals. The final selection focused on evidence describing organ-specific and systemic effects of GLP-1RAs beyond glycemic control and weight reduction. Studies exclusively addressing glucose-lowering efficacy without broader clinical implications were not prioritized.

The included literature was synthesized narratively and organized into thematic sections covering mechanistic pathways, cardiovascular effects, renal outcomes, liver disease, neurological disorders, addiction-related behaviors, reproductive health, and safety considerations. Particular emphasis was placed on recent clinical evidence supporting the expanding therapeutic role of GLP-1 receptor agonists across multiple organ systems.

## 3. Results

Current evidence indicates that GLP-1 receptor agonists exert broad systemic effects extending beyond glycemic control and weight reduction. Large randomized clinical trials have demonstrated significant cardiovascular and renal benefits, including reductions in major adverse cardiovascular events and slower progression of chronic kidney disease. Emerging data also support favorable effects in metabolic dysfunction-associated steatotic liver disease (MASLD), heart failure with preserved ejection fraction, and obesity-associated obstructive sleep apnea. Growing evidence suggests potential neuroprotective properties, modulation of reward-related pathways involved in addiction, and improvements in reproductive outcomes among women with polycystic ovary syndrome. While observational studies have also reported possible associations with reduced cancer risk and healthy aging, these findings require further confirmation in prospective clinical trials.

## 4. Mechanistic Basis of the Systemic Effects of GLP-1 Receptor Agonists

### 4.1. GLP-1 Receptor Distribution and Intracellular Signaling

The diverse clinical effects of GLP-1 receptor agonists (GLP-1RAs) are largely explained by the widespread distribution of GLP-1 receptors throughout multiple organ systems, including the pancreas, cardiovascular system, kidneys, gastrointestinal tract, liver, central nervous system, and immune cells (Zheng et al., 2024; Wilbon & Kolonin, 2024). This broad receptor expression provides the biological foundation for the pleiotropic actions of GLP-1-based therapies.

Binding of GLP-1RAs to the GLP-1 receptor, a G protein-coupled receptor, activates adenylate cyclase and increases intracellular cyclic adenosine monophosphate (cAMP) concentrations. Subsequent activation of protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac) regulates numerous downstream pathways involved in cellular metabolism, survival, and stress responses (Zheng et al., 2024). In addition, GLP-1 signaling interacts with phosphatidylinositol 3-kinase (PI3K)/Akt and AMP-activated protein kinase (AMPK) pathways, both of which play essential roles in energy homeostasis and cellular protection.

### 4.2. Anti-Inflammatory and Antioxidative Mechanisms

Chronic low-grade inflammation is a central pathological feature linking obesity, diabetes, cardiovascular disease, chronic kidney disease, MASLD, and neurodegenerative disorders. One of the most important systemic actions of GLP-1RAs is the attenuation of inflammatory signaling.

Experimental and clinical studies have demonstrated that GLP-1RAs reduce the expression of pro-inflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), while simultaneously improving anti-inflammatory signaling pathways (Wilbon & Kolonin, 2024; Lu et al., 2025). Furthermore, GLP-1 receptor activation reduces oxidative stress by decreasing the generation of reactive oxygen species (ROS) and enhancing endogenous antioxidant defenses.

Through suppression of inflammatory and oxidative pathways, GLP-1RAs may mitigate cellular injury and tissue remodeling across multiple organs, contributing to their observed cardiovascular, renal, hepatic, and neurological benefits.

### 4.3. Vascular and Endothelial Protection

Endothelial dysfunction is recognized as a major contributor to atherosclerosis and cardiometabolic disease progression. GLP-1RAs exert several favorable vascular effects that extend beyond improvements in traditional risk factors.

Activation of GLP-1 signaling enhances endothelial nitric oxide synthase (eNOS) activity and increases nitric oxide bioavailability, promoting vasodilation and improving endothelial function (Alexiadou et al., 2024; Zheng et al., 2024). Additionally, reductions in vascular inflammation and oxidative stress may limit endothelial injury and slow atherosclerotic plaque development.

These mechanisms likely contribute to the substantial reductions in major adverse cardiovascular events observed in large cardiovascular outcome trials, including SELECT and other landmark studies (Lincoff et al., 2023).

### 4.4. Neuroprotective, Metabolic, and Anti-Fibrotic Effects

Within the central nervous system, GLP-1 receptors are highly expressed in regions involved in appetite regulation, reward processing, learning, and memory. Activation of these receptors modulates hypothalamic satiety pathways while influencing dopaminergic neurotransmission within mesolimbic reward circuits (Hong et al., 2024). These effects may explain reductions in food intake and addictive behaviors, as well as the growing interest in GLP-1RAs as potential therapies for neurodegenerative disorders.

Beyond the nervous system, GLP-1RAs improve mitochondrial function and cellular energy metabolism by enhancing metabolic efficiency and reducing mitochondrial stress. Experimental studies have also demonstrated inhibition of profibrotic signaling pathways, resulting in reduced extracellular matrix deposition and attenuation of tissue fibrosis (Zheng et al., 2024).

Collectively, improvements in inflammation, oxidative stress, endothelial dysfunction, mitochondrial health, and fibrosis provide a mechanistic framework linking GLP-1 receptor activation to the broad spectrum of cardiovascular, renal, hepatic, neurological, and metabolic benefits observed in contemporary clinical trials (Drucker, 2025; Moiz et al., 2025).

## 5. Renal Effects

### 5.1. Clinical Evidence for Renoprotection

Chronic kidney disease (CKD) is a major complication of type 2 diabetes mellitus, obesity, and cardiovascular disease and remains one of the leading causes of end-stage kidney disease worldwide. Although sodium-glucose cotransporter-2 inhibitors currently represent the cornerstone of cardiorenal protection, accumulating evidence indicates that GLP-1 receptor agonists (GLP-1RAs) provide additional renal benefits extending beyond glycemic control (Perkovic et al., 2024; Drucker, 2025).

Initial cardiovascular outcome trials consistently demonstrated reductions in albuminuria and slower declines in estimated glomerular filtration rate (eGFR) among patients receiving GLP-1RAs. More definitive evidence emerged from the FLOW trial, which evaluated semaglutide in patients with type 2 diabetes and CKD. Semaglutide significantly reduced the composite risk of kidney failure, persistent eGFR decline, and renal or cardiovascular death, establishing GLP-1RAs as an important component of contemporary cardiorenal therapy (Perkovic et al., 2024).

### 5.2. Mechanisms of Renal Protection

The nephroprotective effects of GLP-1RAs appear to result from a combination of hemodynamic, metabolic, and anti-inflammatory mechanisms.

One of the principal mechanisms involves attenuation of chronic low-grade inflammation. Activation of the GLP-1 receptor reduces the production of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and other mediators implicated in progressive renal injury. Simultaneously, GLP-1RAs reduce oxidative stress through decreased generation of reactive oxygen species and improved mitochondrial function, thereby limiting cellular damage within the glomerulus and renal tubulointerstitium (Zheng et al., 2024; Wilbon & Kolonin, 2024).

GLP-1RAs also exert favorable effects on renal hemodynamics. Improvements in blood pressure, endothelial function, and vascular inflammation may reduce intraglomerular pressure and mitigate hyperfiltration-related injury, a key contributor to CKD progression in obesity and diabetes. Enhanced nitric oxide bioavailability further supports microvascular function and renal perfusion (Zheng et al., 2024).

Another important mechanism involves modulation of fibrotic pathways. Experimental studies suggest that GLP-1RAs inhibit profibrotic signaling and reduce extracellular matrix accumulation, thereby limiting renal fibrosis and structural remodeling. Preservation of podocyte integrity and attenuation of inflammatory cell infiltration have also been proposed as contributors to the observed slowing of CKD progression (Zheng et al., 2024).

### 5.3. Effects on Albuminuria and Cardiorenal Risk

Reduction of albuminuria represents one of the most consistent renal findings observed with GLP-1RA therapy. Because albuminuria reflects both glomerular injury and systemic endothelial dysfunction, its reduction may indicate broader vascular protection rather than solely kidney-specific effects (Perkovic et al., 2024).

The renal benefits of GLP-1RAs should also be interpreted within the context of cardiorenal disease. Obesity, diabetes, CKD, and cardiovascular disease share common pathological mechanisms, including inflammation, endothelial dysfunction, insulin resistance, and adipose tissue dysregulation. By targeting these interconnected pathways, GLP-1RAs may simultaneously reduce both renal and cardiovascular risk, contributing to the favorable outcomes observed in large outcome trials (Drucker, 2025; Moiz et al., 2025).

## 6. Liver and Metabolic Dysfunction

### 6.1. Clinical Evidence in MASLD and MASH

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the hepatic manifestation of systemic metabolic dysfunction and is strongly associated with obesity, insulin resistance, type 2 diabetes mellitus (T2DM), and cardiovascular disease. Progressive forms of MASLD may evolve into metabolic dysfunction-associated steatohepatitis (MASH), characterized by hepatocellular injury, inflammation, fibrosis, and an increased risk of cirrhosis and hepatocellular carcinoma. Given the absence of highly effective pharmacological therapies for many years, GLP-1 receptor agonists (GLP-1RAs) have attracted considerable attention as potential disease-modifying agents (Newsome et al., 2021; Drucker, 2025).

Clinical evidence supporting this role has expanded rapidly. In a landmark phase 2 trial, semaglutide significantly increased rates of MASH resolution compared with placebo, highlighting the ability of GLP-1RAs to target key pathogenic mechanisms involved in liver disease progression (Newsome et al., 2021). More recently, tirzepatide demonstrated substantial improvements in both steatohepatitis and fibrosis among patients with MASH, further supporting the therapeutic potential of incretin-based therapies in chronic liver disease (Loomba et al., 2024).

### 6.2. Mechanisms of Hepatic and Metabolic Improvement

The beneficial hepatic effects of GLP-1RAs are largely attributable to their ability to target the underlying metabolic abnormalities driving MASLD.

Insulin resistance plays a central role in hepatic steatosis by promoting increased lipolysis within adipose tissue, elevated free fatty acid flux to the liver, and enhanced de novo lipogenesis. GLP-1RAs improve insulin sensitivity and reduce adipose tissue dysfunction, thereby decreasing hepatic lipid accumulation and reducing lipotoxic stress on hepatocytes (Wilbon & Kolonin, 2024; Zheng et al., 2024).

Significant reductions in body weight and visceral adiposity further contribute to improvements in liver fat content. Because visceral adipose tissue serves as a major source of inflammatory mediators and free fatty

acids, its reduction may attenuate the metabolic burden imposed on the liver. These effects are particularly relevant because visceral adiposity is strongly associated with progression from simple steatosis to steatohepatitis and fibrosis.

### 6.3. Anti-Inflammatory and Anti-Fibrotic Effects

Beyond metabolic improvements, GLP-1RAs appear to influence several pathways directly involved in liver injury and fibrogenesis.

Experimental studies have demonstrated reductions in oxidative stress, inflammatory cytokine production, and activation of hepatic stellate cells following GLP-1 receptor activation (Zheng et al., 2024; Lu et al., 2025). Hepatic stellate cells represent the principal fibrogenic cell population within the liver and are responsible for excessive extracellular matrix deposition during fibrosis progression.

By attenuating inflammatory signaling and fibrotic remodeling, GLP-1RAs may slow the transition from steatosis to advanced liver disease. Improvements in mitochondrial function and cellular energy metabolism may further reduce hepatocyte injury and susceptibility to disease progression (Wilbon & Kolonin, 2024).

## 7. Neurological and Neurodegenerative Effects

### 7.1. Neurobiological Basis of GLP-1 Receptor Signaling

The central nervous system (CNS) has emerged as one of the most promising targets for GLP-1 receptor agonist (GLP-1RA) therapy beyond metabolic disease. GLP-1 receptors are widely distributed throughout the brain, including the hypothalamus, hippocampus, cortex, brainstem, and mesolimbic reward system (Hong et al., 2024; Zheng et al., 2024). These regions regulate energy homeostasis, cognition, memory, motor function, and reward-related behaviors, providing a biological basis for the broad neurological effects observed with GLP-1RA treatment.

Following receptor activation, GLP-1 signaling influences intracellular pathways involved in neuronal survival, synaptic plasticity, mitochondrial function, and cellular stress responses. Experimental studies have demonstrated activation of neuroprotective signaling cascades, including cAMP-dependent pathways, resulting in improved neuronal resilience and reduced susceptibility to degeneration (Zheng et al., 2024).

### 7.2. Neuroinflammation and Neuroprotection

Neuroinflammation is increasingly recognized as a central mechanism contributing to the development and progression of neurodegenerative disorders. Chronic activation of microglia and astrocytes promotes the release of pro-inflammatory cytokines, oxidative stress, and progressive neuronal injury.

GLP-1RAs have been shown to suppress neuroinflammatory signaling by reducing the production of inflammatory mediators and limiting microglial activation (Hong et al., 2024). In parallel, these agents reduce oxidative stress and improve mitochondrial function, thereby decreasing neuronal vulnerability to cellular damage.

Another important mechanism involves modulation of cerebral insulin signaling. Impaired insulin sensitivity within the brain has been implicated in cognitive decline and neurodegeneration, particularly in Alzheimer's disease. By improving systemic and potentially central insulin sensitivity, GLP-1RAs may help restore neuronal metabolic homeostasis and support cognitive function (Hong et al., 2024; Zheng et al., 2024).

### 7.3. Evidence in Parkinson's and Alzheimer's Disease

Among neurodegenerative disorders, Parkinson's disease currently provides the strongest clinical evidence supporting the therapeutic potential of GLP-1RAs. In a randomized controlled trial, Meissner et al. (2024) demonstrated that lixisenatide slowed the progression of motor disability in patients with early Parkinson's disease compared with placebo. These findings suggest that GLP-1RAs may exert disease-modifying effects rather than merely providing symptomatic improvement.

Several biological mechanisms may explain these observations. Experimental studies have reported reductions in α-synuclein aggregation, attenuation of neuroinflammatory responses, and preservation of dopaminergic neurons following GLP-1 receptor activation (Hong et al., 2024).

In Alzheimer's disease, growing evidence suggests that GLP-1RAs may influence key pathological processes involved in disease progression. Preclinical studies have demonstrated reductions in amyloid-β accumulation, decreased tau-related pathology, and improvements in synaptic function and neuronal survival (Hong et al., 2024). Although clinical evidence remains limited, these findings have generated considerable interest in GLP-1RAs as potential therapeutic agents for cognitive disorders.

### 7.4. Mitochondrial Function, Cognitive Health, and Future Perspectives

Mitochondrial dysfunction and impaired cellular energy metabolism are common features of both aging and neurodegenerative diseases. GLP-1RAs appear to improve mitochondrial efficiency, reduce oxidative injury, and enhance neuronal energy utilization, potentially contributing to long-term neuroprotection (Zheng et al., 2024).

Beyond classical neurodegenerative disorders, these mechanisms may have broader implications for cognitive aging and neurological resilience. Improvements in systemic metabolic health, vascular function, and chronic inflammation may further contribute to preservation of brain function over time (Drucker, 2025; Moiz et al., 2025).

Although current evidence remains less extensive than that available for cardiovascular and renal outcomes, the convergence of mechanistic, preclinical, and early clinical findings strongly supports continued investigation of GLP-1RAs in neurology. Future large-scale randomized trials will be necessary to determine whether these biological effects translate into meaningful long-term reductions in neurodegenerative disease progression and cognitive decline.

## 8. Addiction and Reward-Related Behaviors

### 8.1. GLP-1 Signaling Within the Brain Reward System

Increasing evidence suggests that GLP-1 signaling plays an important role in regulating reward-related behaviors. GLP-1 receptors are expressed in several components of the mesolimbic reward pathway, including the ventral tegmental area (VTA), nucleus accumbens, amygdala, and prefrontal cortex (Hong et al., 2024; Zheng et al., 2024). These structures are critically involved in motivation, reinforcement learning, craving, and addictive behaviors.

Activation of GLP-1 receptors within these regions modulates dopaminergic neurotransmission and reduces the rewarding effects of both natural and drug-related stimuli. Experimental studies suggest that GLP-1 signaling attenuates dopamine release within reward circuits, thereby decreasing reinforcement responses and reducing the motivational drive to seek rewarding substances or behaviors (Zheng et al., 2024). These observations provide a mechanistic link between metabolic regulation and addiction neurobiology.

### 8.2. Mechanisms Underlying Anti-Addictive Effects

Several biological mechanisms have been proposed to explain the effects of GLP-1RAs on addiction-related behaviors. In addition to modulation of dopamine signaling, GLP-1 receptor activation influences neuroinflammatory pathways, neuronal energy metabolism, and synaptic plasticity, all of which have been implicated in the development of substance use disorders (Hong et al., 2024).

Preclinical studies have demonstrated reductions in drug-seeking behavior, craving-like responses, and relapse-related behaviors following GLP-1 receptor activation. These effects have been observed across multiple substances, including alcohol, nicotine, cocaine, and opioids, suggesting that GLP-1 signaling may regulate common neurobiological pathways involved in addiction rather than substance-specific mechanisms (Moiz et al., 2025).

Importantly, obesity and addiction share several pathophysiological features, including dysregulation of reward circuitry, impaired impulse control, and altered dopaminergic signaling. This overlap has led to the hypothesis that GLP-1RAs may target fundamental neural mechanisms underlying compulsive reward-seeking behaviors.

### 8.3. Clinical Evidence in Alcohol Use Disorder

Among addiction-related conditions, alcohol use disorder currently has the strongest clinical evidence. In a randomized clinical trial, Hendershot et al. (2025) demonstrated that once-weekly semaglutide reduced alcohol consumption and alcohol-related outcomes in adults with alcohol use disorder. These findings provided the first prospective clinical evidence supporting the therapeutic potential of GLP-1RAs in addiction medicine.

Further support comes from large observational analyses. Wang et al. (2024) reported lower rates of both incident and recurrent alcohol use disorder among individuals receiving semaglutide compared with alternative treatments. Although observational findings cannot establish causality, they reinforce the hypothesis that GLP-1 receptor activation may influence addictive behaviors in real-world settings.

# 9. Reproductive and Endocrine Effects

## 9.1. Metabolic–Reproductive Interactions and the Rationale for GLP-1RA Therapy

Reproductive dysfunction is closely linked to metabolic health, particularly in women with obesity and polycystic ovary syndrome (PCOS). PCOS is characterized by hyperandrogenism, ovulatory dysfunction, insulin resistance, and frequently obesity, making it one of the most common endocrine disorders among women of reproductive age. Increasing evidence suggests that metabolic abnormalities play a central role in the pathogenesis of PCOS, creating a strong rationale for therapies targeting insulin resistance and excess adiposity (Szczesnowicz et al., 2023).

Hyperinsulinemia contributes directly to ovarian androgen production and amplifies luteinizing hormone-mediated steroidogenesis. Elevated androgen concentrations subsequently impair follicular maturation and ovulation, leading to menstrual irregularities and reduced fertility. Because GLP-1 receptor agonists (GLP-1RAs) improve insulin sensitivity and promote substantial weight loss, they may target key mechanisms underlying both the metabolic and reproductive manifestations of PCOS (Lin et al., 2025; Szczesnowicz et al., 2023).

## 9.2. Mechanisms of Endocrine and Reproductive Improvement

The beneficial reproductive effects of GLP-1RAs are believed to arise primarily through improvements in metabolic homeostasis. By reducing body weight, visceral adiposity, and insulin resistance, GLP-1RAs decrease circulating insulin concentrations and attenuate insulin-mediated ovarian androgen synthesis (Szczesnowicz et al., 2023).

In addition, reductions in adipose tissue mass may contribute to improved endocrine function through decreased secretion of pro-inflammatory cytokines and adipokines associated with metabolic dysfunction. Because chronic inflammation and adipose tissue dysregulation have been implicated in ovarian dysfunction, these changes may support restoration of normal reproductive physiology (Wilbon & Kolonin, 2024).

Emerging evidence also suggests that improvements in metabolic flexibility and systemic insulin sensitivity may enhance follicular development and ovulatory function (Szczesnowicz et al., 2023; Zhou et al., 2023). Although direct ovarian effects of GLP-1 receptor activation remain incompletely understood, current data indicate that metabolic improvement is the primary driver of the observed reproductive benefits (Szczesnowicz et al., 2023; Lin et al., 2025).

## 9.3. Clinical Evidence in Polycystic Ovary Syndrome

Clinical studies have consistently demonstrated favorable effects of GLP-1RAs in women with PCOS. Treatment is associated with significant reductions in body weight, body mass index (BMI), waist circumference, and markers of insulin resistance, outcomes that are particularly relevant given the strong association between obesity and PCOS severity (Lin et al., 2025).

A meta-analysis by Zhou et al. (2023) reported improvements in menstrual cyclicity and increased pregnancy rates among women receiving GLP-1RA therapy. These findings suggest that metabolic improvements may translate into clinically meaningful reproductive outcomes. Similarly, recent reviews have highlighted the growing role of GLP-1RAs as adjunctive therapies for women with obesity-related PCOS who fail to achieve adequate results with lifestyle interventions alone (Szczesnowicz et al., 2023).

# 10. Sleep and Respiratory Outcomes

## 10.1. Obesity and Sleep-Disordered Breathing: Pathophysiological Background

Obstructive sleep apnea (OSA) is one of the most common obesity-related respiratory disorders and is characterized by recurrent episodes of upper airway collapse during sleep, resulting in intermittent hypoxia, sleep fragmentation, and increased cardiovascular risk. Excess adiposity, particularly in the neck, upper airway, and visceral compartments, contributes to airway narrowing, impaired respiratory mechanics, and reduced pharyngeal stability. Consequently, obesity is considered one of the strongest modifiable risk factors for OSA development and progression (Malhotra et al., 2024).

Beyond mechanical airway obstruction, OSA is increasingly recognized as a systemic disorder associated with chronic inflammation, insulin resistance, endothelial dysfunction, and cardiometabolic disease. These overlapping pathological mechanisms provide a strong rationale for investigating GLP-1 receptor agonists (GLP-1RAs) and related incretin-based therapies in patients with obesity-associated sleep-disordered breathing.

### 10.2. Mechanisms Underlying Respiratory Benefits

The beneficial effects of GLP-1RAs on OSA are thought to be mediated primarily through substantial and sustained weight reduction. Decreases in visceral and upper-body adiposity may reduce pharyngeal tissue compression, improve airway patency, and decrease upper airway collapsibility during sleep (Malhotra et al., 2024).

In addition to weight loss, GLP-1RAs improve insulin sensitivity and reduce systemic inflammation, factors that may contribute to improved respiratory physiology. Chronic inflammation has been implicated in upper airway dysfunction and cardiometabolic complications associated with OSA. By attenuating inflammatory signaling and improving metabolic homeostasis, GLP-1RAs may indirectly influence respiratory outcomes beyond simple reductions in body weight (Wilbon & Kolonin, 2024; Moiz et al., 2025).

Furthermore, improvements in cardiovascular function and reductions in fluid retention associated with weight loss may positively affect cardiorespiratory interactions, which play an important role in the pathophysiology of sleep-disordered breathing.

### 10.3. Clinical Evidence in Obstructive Sleep Apnea

The strongest evidence supporting the role of incretin-based therapies in OSA comes from the SURMOUNT-OSA trial. In this study, tirzepatide significantly reduced the apnea–hypopnea index (AHI), body weight, and overall disease severity in adults with obesity and moderate-to-severe OSA compared with placebo (Malhotra et al., 2024).

Importantly, clinically meaningful improvements were observed both in patients receiving positive airway pressure therapy and in those not using such treatment. These findings suggest that pharmacological management of obesity may directly translate into improvements in respiratory outcomes and disease burden.

The magnitude of improvement observed in SURMOUNT-OSA further supports the concept that obesity treatment should be considered an integral component of OSA management rather than solely a strategy for reducing cardiometabolic risk.

## 11. Cancer and Aging-Related Outcomes

### 11.1. Biological Rationale: Obesity, Inflammation, and Metabolic Dysfunction

The potential relationship between GLP-1 receptor agonists (GLP-1RAs), cancer risk, and aging-related outcomes is closely linked to the biological effects of obesity, insulin resistance, and chronic low-grade inflammation. Excess adiposity promotes hyperinsulinemia, increased insulin-like growth factor signaling, adipokine imbalance, oxidative stress, and persistent inflammatory activation, all of which may contribute to carcinogenesis and age-related functional decline (Drucker, 2025; Wilbon & Kolonin, 2024).

GLP-1RAs may influence these pathways primarily by reducing body weight, improving insulin sensitivity, decreasing visceral adiposity, and attenuating systemic inflammation. These mechanisms are relevant because obesity-related cancers and aging-related diseases share several common biological drivers, including metabolic dysregulation, endothelial dysfunction, mitochondrial stress, and inflammatory tissue remodeling (Moiz et al., 2025; Zheng et al., 2024).

### 11.2. Mechanisms Potentially Linking GLP-1RAs to Cancer Risk Reduction

Several mechanisms may explain the observed associations between GLP-1RA use and lower incidence of selected obesity-related cancers. First, improvements in insulin sensitivity may reduce chronic hyperinsulinemia, which is believed to promote cellular proliferation and inhibit apoptosis in several obesity-associated malignancies. Second, reductions in visceral adiposity may decrease the production of pro-inflammatory cytokines and adipokines that contribute to tumor-promoting microenvironments (Drucker, 2025; Wilbon & Kolonin, 2024).

Third, GLP-1RAs reduce oxidative stress and inflammatory signaling, both of which are involved in DNA damage, cellular senescence, and malignant transformation. By improving mitochondrial function and limiting reactive oxygen species generation, GLP-1RAs may theoretically reduce cellular injury associated with carcinogenesis (Zheng et al., 2024). However, it remains unclear whether these effects directly modify cancer biology or mainly reflect improved metabolic health.

Observational studies provide early clinical support for these hypotheses. Wang et al. (2024a) reported lower risks of several obesity-associated cancers among patients with type 2 diabetes receiving GLP-1RAs, while Wang et al. (2024b) observed a reduced risk of colorectal cancer among GLP-1RA users. These findings are biologically plausible but should be interpreted cautiously because observational studies cannot establish causality.

### 11.3. Aging-Related Mechanisms and Healthspan

Aging is characterized by progressive metabolic impairment, chronic inflammation, endothelial dysfunction, mitochondrial decline, and increased susceptibility to cardiovascular, renal, hepatic, and neurodegenerative diseases. Many of these processes overlap with pathways modified by GLP-1RA therapy (Drucker, 2025; Moiz et al., 2025).

By improving insulin sensitivity, reducing adipose tissue dysfunction, and attenuating systemic inflammation, GLP-1RAs may theoretically support healthier aging trajectories. Improvements in mitochondrial function and cellular energy metabolism may further contribute to tissue resilience, while reductions in vascular inflammation and endothelial dysfunction may help preserve cardiovascular and renal function during aging (Zheng et al., 2024; Wilbon & Kolonin, 2024).

These potential geroprotective effects remain indirect and should not be interpreted as evidence that GLP-1RAs slow biological aging. Rather, current evidence suggests that GLP-1RAs may reduce the burden of age-related cardiometabolic diseases, which could translate into improved healthspan in selected populations.

## 12. Safety, Controversies, and Clinical Translation

### 12.1. Common Adverse Effects and Tolerability

The rapid expansion of GLP-1 receptor agonist (GLP-1RA) use beyond the treatment of type 2 diabetes mellitus (T2DM) has generated significant enthusiasm among clinicians and researchers. However, as these agents are increasingly prescribed, careful consideration of their safety profile becomes essential.

The most commonly reported adverse effects are gastrointestinal in nature and include nausea, vomiting, diarrhea, constipation, and abdominal discomfort. These events are generally mild to moderate in severity and occur most frequently during treatment initiation and dose escalation. Although symptoms often improve over time, gastrointestinal intolerance remains one of the leading causes of treatment discontinuation in clinical practice (Drucker, 2025; Sheth et al., 2025). Appropriate dose titration and patient education are therefore critical components of successful therapy.

Another important safety consideration involves gallbladder and biliary disease. Rapid weight loss induced by GLP-1RAs has been associated with an increased risk of cholelithiasis and cholecystitis, particularly among individuals experiencing substantial reductions in body weight. Clinicians should therefore remain vigilant when treating patients with pre-existing gallbladder disease or risk factors for biliary complications (Moiz et al., 2025).

### 12.2. Long-Term Safety Concerns

Historically, concerns have been raised regarding pancreatitis, pancreatic cancer, and thyroid malignancies. Early post-marketing reports and animal studies prompted extensive investigation into these potential associations. However, current evidence from large clinical trials and observational studies has not demonstrated a consistent increase in pancreatic cancer risk attributable to GLP-1RA therapy (Drucker, 2025).

One of the most debated issues relates to thyroid safety. Rodent studies identified an increased incidence of medullary thyroid carcinoma following exposure to certain GLP-1RAs, leading to regulatory warnings and contraindications in individuals with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2). Large population-based human studies have not confirmed a substantial increase in thyroid cancer risk, providing reassurance regarding the overall safety of these agents in routine clinical practice (Pasternak et al., 2024).

### 12.3. Emerging Controversies

Beyond traditional adverse events, emerging concerns have focused on excessive loss of lean body mass during profound weight reduction. Although weight loss is a major therapeutic goal in obesity management, preservation of skeletal muscle mass is essential for maintaining physical function, metabolic health, and healthy aging. Consequently, increasing attention is being directed toward combining GLP-1RA therapy with resistance exercise, adequate protein intake, and lifestyle interventions to optimize body composition outcomes (Drucker, 2025; Moiz et al., 2025).

Another controversy concerns the interpretation of benefits observed across multiple organ systems. While cardiovascular, renal, and hepatic improvements are increasingly well established, it remains difficult to determine the extent to which these outcomes result directly from GLP-1 receptor activation versus secondary effects of weight loss. This distinction is particularly relevant when considering potential applications in neurodegenerative diseases, addiction medicine, and healthy aging, where mechanistic pathways are less clearly defined and clinical evidence remains limited (Moiz et al., 2025; Spezani et al., 2025).

### 12.4. Clinical Translation and Real-World Challenges

Clinical translation of GLP-1RAs presents several practical challenges. The high cost of treatment remains a significant barrier to widespread implementation, particularly in healthcare systems with limited reimbursement. Furthermore, the chronic nature of obesity and metabolic disease raises important questions regarding treatment duration.

Evidence suggests that discontinuation of GLP-1RA therapy is frequently associated with partial weight regain and deterioration of metabolic benefits, indicating that long-term treatment may be necessary for many patients (Ryan et al., 2024; Drucker, 2025). This observation has fueled ongoing debate regarding whether obesity should be managed similarly to other chronic diseases requiring lifelong pharmacotherapy.

As the indications for GLP-1RAs continue to expand, careful patient selection, monitoring strategies, and integration with lifestyle interventions will become increasingly important to maximize therapeutic benefit and minimize treatment-related risks.

### 12.5. Future Perspectives

Despite these challenges, the overall safety profile of GLP-1RAs remains favorable when compared with many alternative pharmacological interventions. Large randomized clinical trials have consistently demonstrated substantial benefits across cardiovascular, renal, metabolic, and obesity-related outcomes, often outweighing the risks associated with treatment (Lincoff et al., 2023; Perkovic et al., 2024).

Continued post-marketing surveillance, long-term safety studies, and mechanistic research will be essential to clarify unresolved questions and support the safe expansion of GLP-1RA therapy into new clinical domains. As evidence continues to accumulate, these agents are likely to play an increasingly important role in the management of chronic diseases characterized by metabolic dysfunction and systemic inflammation.

## 13. Future Directions and Emerging Indications

### 13.1. Expanding Therapeutic Applications

The rapid evolution of GLP-1 receptor agonist (GLP-1RA) research has transformed these agents from glucose-lowering medications into a therapeutic platform with potential applications across multiple medical specialties. While substantial evidence already supports their use in obesity, cardiovascular disease, chronic kidney disease, and metabolic dysfunction-associated steatotic liver disease (MASLD), ongoing research continues to explore new indications and refine their role within precision medicine (Drucker, 2025; Moiz et al., 2025).

Among the most promising emerging applications are neurodegenerative disorders, substance use disorders, reproductive medicine, and age-related diseases. The expanding spectrum of clinical benefits observed in recent years suggests that GLP-1RAs may become central components of future strategies aimed at addressing complex chronic diseases characterized by metabolic dysfunction and systemic inflammation.

### 13.2. Neurological and Behavioral Disorders

One of the most rapidly developing areas of investigation involves neurology and behavioral medicine. Early clinical findings in Parkinson’s disease and growing mechanistic evidence in Alzheimer’s disease have generated considerable interest in the neuroprotective properties of GLP-1RAs (Meissner et al., 2024; Hong et al., 2024). Future large-scale randomized controlled trials will be essential to determine whether these agents can meaningfully alter disease progression, delay cognitive decline, or improve long-term neurological outcomes.

Similarly, preliminary evidence suggests potential applications in addiction medicine. Modulation of central reward pathways and dopaminergic signaling may explain the observed reductions in alcohol consumption and addictive behaviors reported in early clinical studies and observational analyses (Hendershot et al., 2025; Wang et al., 2024). Further research is needed to evaluate their efficacy across a broader range of substance use disorders.

### 13.3. Healthy Aging and Next-Generation Incretin Therapies

Future investigations are also likely to focus on healthy aging and multimorbidity. Aging is increasingly recognized as a process driven by chronic inflammation, metabolic dysfunction, mitochondrial impairment, and progressive loss of physiological resilience. Because GLP-1RAs appear to influence many of these pathways, they have been proposed as potential agents capable of improving healthspan and reducing the burden of age-related diseases (Drucker, 2025; Moiz et al., 2025).

At the same time, advances in pharmacology are accelerating the development of novel incretin-based therapies. Dual- and triple-receptor agonists targeting combinations of GLP-1, glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptors are already demonstrating impressive metabolic effects and may offer enhanced efficacy compared with traditional GLP-1RAs (Sheth et al., 2025). These innovations may further broaden the therapeutic landscape and create opportunities for more individualized treatment approaches.

### 13.4. Precision Medicine and Future Research Priorities

An important priority for future research will be distinguishing direct receptor-mediated effects from benefits secondary to weight loss. Although many favorable outcomes are likely attributable to reductions in adiposity and improvements in metabolic health, accumulating evidence suggests that GLP-1RAs may exert independent anti-inflammatory, vascular, renal, and neuroprotective actions (Zheng et al., 2024; Wilbon & Kolonin, 2024). Clarifying these mechanisms will be critical for identifying patient populations most likely to benefit from treatment and for developing next-generation therapies.

Future studies should also address long-term safety, treatment durability, cost-effectiveness, and accessibility. Improved understanding of optimal treatment duration, combination therapies, and strategies to enhance adherence will be essential as the demand for GLP-1-based therapies continues to grow globally.

## 14. Conclusions

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have undergone a remarkable therapeutic evolution, progressing from glucose-lowering agents used primarily in type 2 diabetes mellitus to multifunctional therapies with benefits extending across multiple organ systems. Evidence accumulated over recent years demonstrates that the effects of GLP-1RAs reach far beyond glycemic control and weight reduction, encompassing cardiovascular protection, renal preservation, improvement of metabolic dysfunction-associated steatotic liver disease (MASLD), and favorable outcomes in obesity-related conditions such as heart failure and obstructive sleep apnea.

In addition to these established indications, emerging data suggest potential applications in neurodegenerative disorders, substance use disorders, reproductive dysfunction associated with polycystic ovary syndrome, and possibly cancer prevention and healthy aging. Although the strength of evidence varies considerably between clinical domains, the collective findings support the concept that GLP-1RAs exert broad pleiotropic effects mediated through interconnected metabolic, anti-inflammatory, vascular, and neuroprotective mechanisms.

The expanding clinical scope of GLP-1RAs highlights the growing recognition of metabolic dysfunction and chronic inflammation as shared drivers of numerous chronic diseases. By targeting these fundamental pathological processes, GLP-1-based therapies may offer benefits that extend beyond the treatment of individual conditions and contribute to a more integrated approach to chronic disease management.

Despite these promising developments, important challenges remain. Further research is needed to clarify long-term safety, determine the durability of therapeutic benefits, distinguish direct pharmacological effects from those mediated by weight loss, and identify patient populations most likely to benefit from treatment. Large randomized controlled trials will be particularly important for validating emerging indications in neurology, addiction medicine, and age-related diseases.

In conclusion, accumulating evidence indicates that GLP-1 receptor agonists are evolving beyond their traditional role as metabolic therapies into multisystem therapeutic agents, with established and emerging benefits spanning cardiovascular, renal, hepatic, neurological, reproductive, and behavioral health. Continued advances in clinical research, mechanistic understanding, and drug development are likely to further expand their therapeutic applications, positioning GLP-1-based therapies among the most influential pharmacological innovations in contemporary medicine.

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## REFERENCES


1. Alexiadou, K., Hartley, A., Tan, T. M.-M., & Khamis, R. (2024). The cardiovascular effects of GLP-1 receptor agonists beyond obesity and type 2 diabetes: An anti-atherosclerotic action. *Trends in Cardiovascular Medicine*, *34*(8), 552–557. https://doi.org/10.1016/j.tcm.2024.03.003
2. Deanfield, J., et al. (2025). Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: A prespecified analysis of the SELECT trial. *The Lancet*, *404*(10454), 773–786. https://doi.org/10.1016/S0140-6736(24)01498-3
3. Drucker, D. J. (2025). GLP-1-based therapies for diabetes, obesity and beyond. *Nature Reviews Drug Discovery*, *24*(8), 631–650. https://doi.org/10.1038/s41573-025-01183-8
4. Hendershot, C. S., et al. (2025). Once-weekly semaglutide in adults with alcohol use disorder: A randomized clinical trial. *JAMA Psychiatry*, *82*(4), 395–405. https://doi.org/10.1001/jamapsychiatry.2024.4789
5. Hong, C. T., Chen, J. H., & Hu, C. J. (2024). Role of GLP-1 receptor agonists in Alzheimer's disease and Parkinson's disease. *Journal of Biomedical Science*, *31*, 102. https://doi.org/10.1186/s12929-024-01090-x
6. Kosiborod, M. N., et al. (2023). Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *The New England Journal of Medicine*, *389*(12), 1069–1084. https://doi.org/10.1056/NEJMoa2306963
7. Kosiborod, M. N., et al. (2024). Semaglutide in patients with obesity-related heart failure with preserved ejection fraction and type 2 diabetes. *The New England Journal of Medicine*, *390*(15), 1394–1407. https://doi.org/10.1056/NEJMoa2313917
8. Lin, S., et al. (2025). Efficacy and safety of GLP-1 receptor agonists on weight management and metabolic parameters in PCOS women: A meta-analysis of randomized controlled trials. *Scientific Reports*, *15*(1), 16512. https://doi.org/10.1038/s41598-025-99622-4
9. Lincoff, A. M., et al. (2023). Semaglutide and cardiovascular outcomes in obesity without diabetes. *The New England Journal of Medicine*, *389*(24), 2221–2232. https://doi.org/10.1056/NEJMoa2307563
10. Lingvay, I., et al. (2024). Semaglutide and cardiovascular outcomes by baseline HbA1c and change in HbA1c in people with overweight or obesity but without diabetes in SELECT. *Diabetes Care*, *47*(8), 1360–1369. https://doi.org/10.2337/dc24-0764
11. Loomba, R., et al. (2023). Semaglutide 2.4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: A randomised, placebo-controlled phase 2 trial. *The Lancet Gastroenterology & Hepatology*, *8*(6), 511–522. https://doi.org/10.1016/S2468-1253(23)00068-7
12. Loomba, R., et al. (2024). Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *The New England Journal of Medicine*, *391*(14), 1296–1308. https://doi.org/10.1056/NEJMoa2401943
13. Lu, C., et al. (2025). The beneficial effects of GLP-1 receptor agonists other than their anti-diabetic and anti-obesity properties. *Medicina*, *61*(1), 17. https://doi.org/10.3390/medicina61010017
14. Malhotra, A., et al. (2024). Tirzepatide for the treatment of obstructive sleep apnea and obesity. *The New England Journal of Medicine*, *391*, 1193–1205. https://doi.org/10.1056/NEJMoa2404881
15. Meissner, W. G., et al. (2024). Trial of lixisenatide in early Parkinson disease. *The New England Journal of Medicine*, *390*(13), 1176–1185. https://doi.org/10.1056/NEJMoa2312323
16. Moiz, A., et al. (2025). The expanding role of GLP-1 receptor agonists: A narrative review of current evidence and future directions. *EClinicalMedicine*, *86*, 103363. https://doi.org/10.1016/j.eclinm.2025.103363
17. Newsome, P. N., et al. (2021). A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *The New England Journal of Medicine*, *384*, 1113–1124. https://doi.org/10.1056/NEJMoa2028395
18. Pasternak, B., et al. (2024). Glucagon-like peptide 1 receptor agonist use and risk of thyroid cancer: Scandinavian cohort study. *BMJ*, *385*, e078225. https://doi.org/10.1136/bmj-2023-078225
19. Perkovic, V., et al. (2024). Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *The New England Journal of Medicine*, *391*, 109–121. https://doi.org/10.1056/NEJMoa2403347
20. Ryan, D. H., et al. (2024). Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial. *Nature Medicine*, *30*(10), 2977–2985. https://doi.org/10.1038/s41591-024-02996-7
21. Sheth, K., Kim, S., Porterfield, L., Virani, S. S., Wadhwani, S., & Vaughan, E. M. (2025). The expanding scope of GLP-1 receptor agonists: Six uses beyond diabetes. *Current Atherosclerosis Reports*, *27*(1), 76. https://doi.org/10.1007/s11883-025-01319-6
22. Spezani, R., et al. (2025). Beyond diabetes and obesity: GLP-1 receptor agonists in disrupting the vicious cycle of metabolic dysfunction and neuroinflammation. *Diabetes, Obesity and Metabolism*, *27*(8), e70400. https://doi.org/10.1111/dom.70400
23. Szczesnowicz, A., Szeliga, A., Niwczyk, O., Bala, G., & Meczekalski, B. (2023). Do GLP-1 analogs have a place in the treatment of PCOS? New insights and promising therapies. *Journal of Clinical Medicine*, *12*(18), 5915. https://doi.org/10.3390/jcm12185915
24. Targher, G., et al. (2025). Phase 3 trial of semaglutide in metabolic dysfunction–associated steatohepatitis. *The New England Journal of Medicine*, *392*(19), 1867–1880. https://doi.org/10.1056/NEJMoa2413258

25. Wang, L., Wang, W., Kaelber, D. C., et al. (2024a). Glucagon-like peptide 1 receptor agonists and 13 obesity-associated cancers in patients with type 2 diabetes. *JAMA Network Open*, *7*(7), e2421305. https://doi.org/10.1001/jamanetworkopen.2024.21305
26. Wang, L., Wang, W., Kaelber, D. C., et al. (2024b). GLP-1 receptor agonists and colorectal cancer risk in drug-naive patients with type 2 diabetes, with and without overweight/obesity. *JAMA Oncology*, *10*(2), 256–258. https://doi.org/10.1001/jamaoncol.2023.5573
27. Wang, W., Volkow, N. D., Berger, N. A., et al. (2024). Associations of semaglutide with incidence and recurrence of alcohol use disorder in real-world population. *Nature Communications*, *15*, 4548. https://doi.org/10.1038/s41467-024-48780-6
28. Wilbon, S. S., & Kolonin, M. G. (2024). GLP-1 receptor agonists - effects beyond obesity and diabetes. *Cells*, *13*(1), 65. https://doi.org/10.3390/cells13010065
29. Zheng, Z., et al. (2024). Glucagon-like peptide-1 receptor: Mechanisms and advances in therapy. *Signal Transduction and Targeted Therapy*, *9*, 170. https://doi.org/10.1038/s41392-024-01931-z
30. Zhou, L., et al. (2023). Effects of GLP-1 receptor agonists on pregnancy rate and menstrual cyclicity in women with polycystic ovary syndrome: A meta-analysis and systematic review. *BMC Endocrine Disorders*, *23*, 245. https://doi.org/10.1186/s12902-023-01500-5