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Review

GLP-1 Receptor Agonists: Chemical Evolution and Expanding Clinical Applications

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Abstract: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have transformed modern medicine, progressing from diabetes treatments to versatile therapeutics with applications across multiple medical specialties. This review examines the fundamental mechanisms, established applications, and emerging therapeutic roles of GLP-1 RAs. We provide a comprehensive analysis of their structural evolution, from first-generation short-acting agents to sophisticated multi-receptor agonists. Through systematic evaluation of clinical evidence and mechanistic foundations, we highlight how strategic peptide engineering has enabled unprecedented metabolic outcomes. The expanding therapeutic applications of GLP-1 RAs across diverse conditions—including metabolic dysfunction-associated steatotic liver disease, neurodegenerative disorders, and psychiatric conditions—demonstrate their potential to address underlying pathophysiological mechanisms across seemingly unrelated disorders. As research advances, GLP-1 RAs are poised to fundamentally reshape treatment paradigms across medicine.

Keywords: Glucagon GLP-1; semaglutide; liraglutide; diabetes; weight loss; receptor agonist.

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represent one of the most significant therapeutic breakthroughs in modern medicine. Initially developed for glycemic control in type 2 diabetes mellitus (T2DM), these medications have revolutionized treatment across multiple therapeutic areas, most notably obesity management. Their success stems from a unique mechanism of action that addresses fundamental physiological processes underlying metabolic dysfunction while demonstrating a remarkably favorable safety profile.

The GLP-1 receptor, a G protein-coupled receptor, is expressed throughout the body—in pancreatic islets, central and peripheral nervous systems, cardiovascular tissues, kidneys, lungs, and the gastrointestinal tract. This widespread distribution explains the pleiotropic effects of GLP-1 RAs and supports their expanding therapeutic applications (Müller and Lau, 2021; Drucker et al., 2023). As our understanding of GLP-1 biology has advanced, the perception of these agents has evolved from simple incretin mimetics to multifaceted modulators of metabolism, inflammation, and cellular function across multiple organ systems.

The therapeutic landscape of GLP-1 RAs has evolved through distinct generations:

- First-generation short-acting agents (exenatide BID, lixisenatide)
- Second-generation long-acting molecules (liraglutide, dulaglutide, semaglutide, exenatide QW)

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- Third-generation multi-agonists (tirzepatide, retatrutide, survodutide) that engage multiple incretin receptors

Each generation has demonstrated incremental improvements in efficacy, with the most recent agents achieving unprecedented metabolic outcomes across multiple indications (Chen et al., 2024).

Core Mechanisms of GLP-1 Action

Before examining specific applications, it is essential to understand the fundamental mechanisms through which GLP-1 RAs exert their diverse physiological effects. These mechanisms extend far beyond glucose regulation and collectively explain the pleiotropic benefits observed across organ systems.

2.1 Pancreatic Effects

In pancreatic β-cells, GLP-1 receptor activation potentiates glucose-stimulated insulin secretion through enhanced intracellular cAMP production, leading to phosphorylation of protein kinase A and activation of exchange protein directly activated by cAMP (Epac). This cascade ultimately promotes insulin release while simultaneously suppressing glucagon secretion from α-cells (Nauck and Meier, 2022). The glucose-dependent nature of this insulinotropic action provides a significant therapeutic advantage by minimizing hypoglycemia risk compared to earlier antidiabetic medications.

Beyond immediate glycemic control, GLP-1 signaling enhances β-cell function, promotes β-cell proliferation, and inhibits apoptosis in preclinical models, potentially addressing the progressive β-cell dysfunction characteristic of T2DM pathophysiology (Holst et al., 2022).

2.2 Central Nervous System Effects

GLP-1 RAs provide metabolic benefits extending beyond pancreatic effects through central appetite regulation. They delay gastric emptying, creating premature satiety through mechanoreceptor activation and afferent vagal signaling to brainstem nuclei.

Additionally, GLP-1 receptor activation in hypothalamic nuclei, particularly the arcuate nucleus, regulates appetite by directly stimulating proopiomelanocortin (POMC) neurons and indirectly suppressing neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons (López-Ferreras et al., 2024). These central nervous system effects substantially contribute to the significant weight reduction observed with GLP-1 RA therapy.

2.3 Anti-inflammatory and Cytoprotective Effects

GLP-1 receptor activation exerts anti-inflammatory effects across multiple tissues:

- Reduction of pro-inflammatory cytokine production (TNF-α, IL-6, IL-1β)
- Shift of macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2 phenotypes (Mantovani et al., 2021)
- Attenuation of oxidative stress through enhanced antioxidant enzyme expression
- Decreased activation of inflammatory signaling pathways (NF-κB, JAK-STAT) (Rakipovski et al., 2022)

These anti-inflammatory effects are critical to understanding the therapeutic potential of GLP-1 RAs in conditions characterized by low-grade chronic inflammation, including atherosclerosis, fatty liver disease, and neurodegenerative disorders.

2.4 Cardiovascular Effects

The cardiovascular benefits of GLP-1 RAs stem from multiple mechanisms:

- Direct receptor-mediated actions on cardiomyocytes, vascular endothelium, and inflammatory cells
- Improved endothelial function and decreased arterial stiffness

- Attenuation of atherogenesis through reduced foam cell formation (Rakipovski et al., 2022)
- Direct myocardial protection against ischemia-reperfusion injury
- Enhanced cardiac metabolism, contractility, and favorable remodeling (Sharma et al., 2023)

The combination of these direct cardiovascular effects with indirect improvements in metabolic parameters explains the consistent cardiovascular outcome benefits observed across multiple GLP-1 RAs in clinical trials.

Established Applications

3.1 Type 2 Diabetes Management

The efficacy hierarchy among GLP-1 RAs in T2DM management has been firmly established through comparative clinical trials. The SURPASS-2 trial directly compared tirzepatide with semaglutide 1 mg, demonstrating superior HbA1c reduction (-2.01% vs -1.86%) and substantially greater weight loss (-10.3% vs -6.9%) with tirzepatide 15 mg (Frías et al., 2021).

For patients with T2DM and established cardiovascular disease, high-dose semaglutide has become first-line therapy based on robust cardiovascular outcome trial data, while tirzepatide has emerged as the preferred agent when maximal glycemic control and weight reduction are prioritized. The combination of GLP-1 RAs with SGLT-2 inhibitors has become standard practice for patients with multiple cardiometabolic risk factors, offering complementary mechanisms and synergistic clinical benefits.

3.2 Obesity Management

For obesity treatment, network meta-analyses have established an efficacy gradient with mean weight losses of 5-7% for first-generation agents, 10-15% for second-generation molecules, and 15-24% for multi-agonists (Chen et al., 2024). Retatrutide has emerged as the most efficacious agent for weight management, with the TRIUMPH-3 trial demonstrating mean weight reductions of 24.2% at the highest dose (15 mg) over 72 weeks, positioning it as a pharmacological alternative approaching the efficacy of bariatric surgery (Jastreboff et al., 2025).

Tirzepatide has emerged as the preferred agent for obesity management when substantial but not maximal weight reduction is needed, while retatrutide is positioned for severe obesity when approaching bariatric surgery-level weight loss is the goal. The remarkable efficacy of these agents has fundamentally transformed obesity treatment paradigms, shifting from modest goals of 5-10% weight reduction to clinically meaningful 15-25% reductions that substantially ameliorate obesity-related complications.

3.3 Cardiovascular and Cardiorenal Protection

Cardiovascular protection has been established across multiple GLP-1 RAs, with recent evidence indicating class-wide benefits but differing magnitudes of effect. A pooled analysis of cardiovascular outcome trials demonstrated MACE relative risk reductions ranging from 12% with dulaglutide to 20% with semaglutide 2.4 mg in non-diabetic populations (Sattar et al., 2021).

In heart failure models, GLP-1 RAs demonstrate beneficial effects on cardiac metabolism, contractility, and remodeling. The reduction in heart failure hospitalization observed in clinical trials represents a particularly important benefit in diabetic populations with elevated heart failure risk (Sharma et al., 2023). The STRIDE trial expanded semaglutide's indications to peripheral artery disease, demonstrating a 13% improvement in walking distance and reduced claudication symptoms, while the STEP-HFpEF trials established benefits in heart failure with preserved ejection fraction.

The nephroprotective effects of GLP-1 RAs, evidenced by reduced albuminuria progression and preserved estimated glomerular filtration rate (eGFR), contribute to their comprehensive cardiorenal protective profile (Tuttle et al., 2021). This cardiorenal protection has prompted a paradigm shift in treatment algorithms, with GLP-1 RAs increasingly positioned as first-line therapy for T2DM patients with established cardiovascular disease or high cardiovascular risk.

Emerging Metabolic Applications

4.1 Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD/MASH)

Non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD), now termed metabolic dysfunction-associated steatohepatitis (MASH) and metabolic dysfunction-associated steatotic liver disease (MASLD), represent significant hepatic disorders where GLP-1 RAs show therapeutic promise (Newsome et al., 2022).

GLP-1 RAs ameliorate hepatic steatosis through multiple mechanisms:

- Improved insulin sensitivity, reducing hyperinsulinemia-driven lipogenesis
- Direct suppression of hepatic de novo lipogenesis through AMPK activation and SREBP-1c inhibition
- Enhanced fatty acid oxidation through PPARα upregulation and increased mitochondrial β-oxidation capacity
- Decreased adipose tissue lipolysis and subsequent hepatic free fatty acid flux (Saponaro et al., 2023)

Several GLP-1 RAs have shown substantial promise (Figure 1)

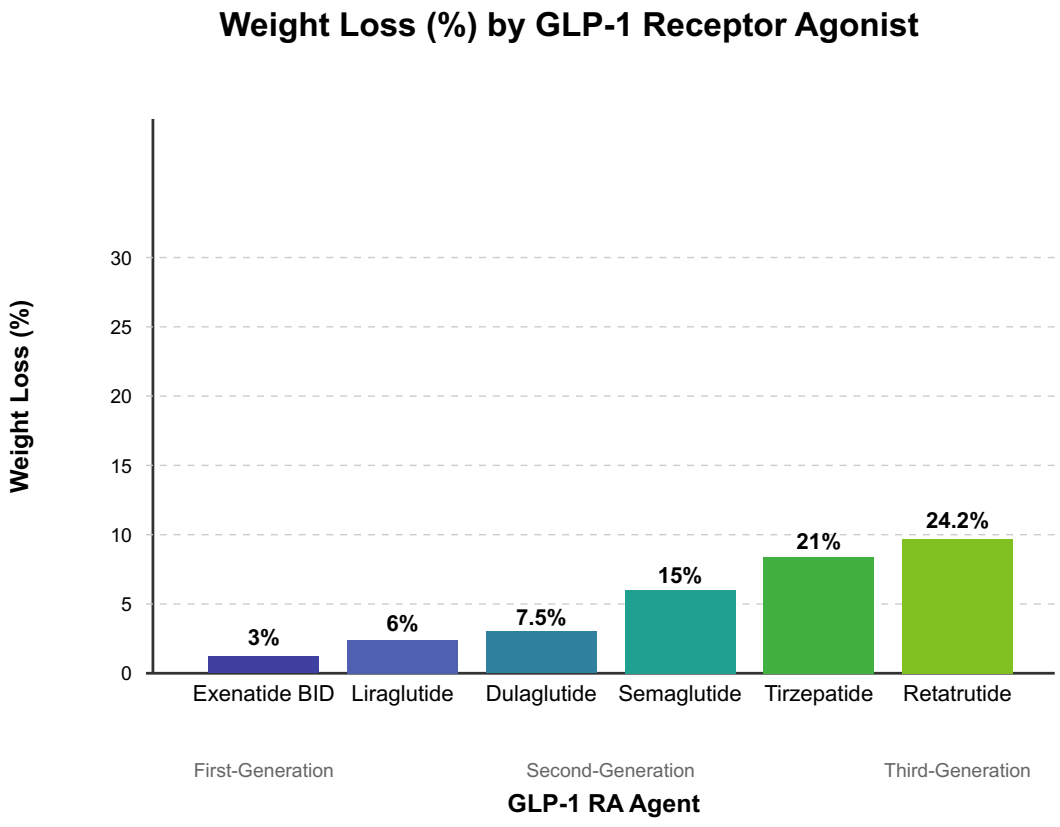

Table 1: Weight Loss (%) by GLP-1 Receptor Agonist

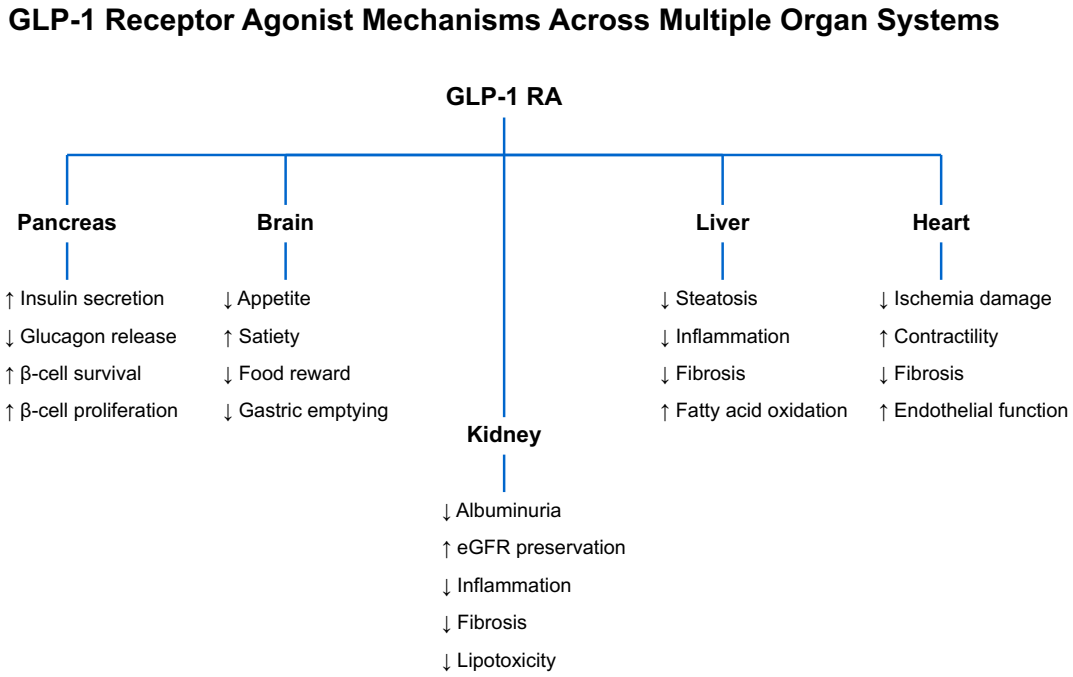

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Table 2. 161

Evolution of GLP-1 Receptor Agonist Structure and Half-Life

GENERATION	MOLECULE	STRUCTURE MODIFICATIONS	HALF-LIFE
First Generation			
	Exenatide BID	• Exendin-4 derivative (lizard peptide) • Natural DPP-4 resistance (G2 position)	2.4 hours
	Lixisenatide	• Exendin-4 derivative • C-terminal modifications with 6 lysine residues	3-4 hours
Second Generation			
	Liraglutide	• Human GLP-1 (97% homology) • C16 fatty acid acylation at position 26 • K34R substitution to prevent ubiquitination	13 hours
	Dulaglutide	• GLP-1 analog with A8G, G22E, R36G substitutions • Fusion to modified IgG4 Fc fragment • Dimeric structure (63 kDa)	5 days
	Semaglutide	• Human GLP-1 (94% homology) • Aib8 substitution for superior DPP-4 resistance • C18 fatty diacid via γGlu-2xOEG spacer	165 hours
Third Generation (Multi-agonists)			
	Tirzepatide	• GIP backbone with GLP-1 receptor co-activation • Strategic substitutions at positions 13, 14, 16-27 • C20 fatty diacid conjugation	5 days
	Retatrutide	• Glucagon backbone-derived triagonist • Multiple substitutions for balanced receptor activity	5-6 days

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Figure 4: Emerging Clinical Applications of GLP-1 Receptor Agonists

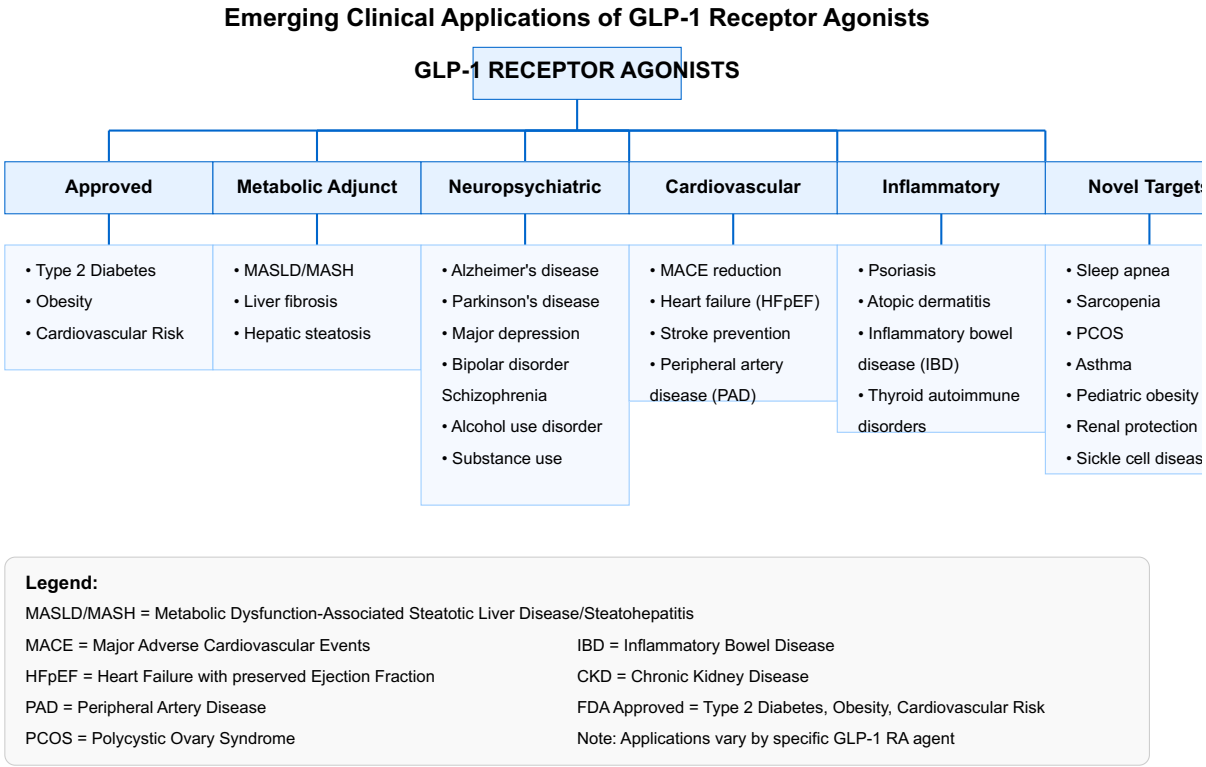

Table 2: Comparative Efficacy of GLP-1 Receptor Agonists

Agent	HbA1c Reduction (%)	Weight Loss (%)	Dosing Frequency
Exenatide BID	-0.8	3	Twice daily
Liraglutide	-1.0	6	Daily
Dulaglutide	-1.1	7.5	Weekly
Semaglutide	-1.8	15	Weekly
Tirzepatide	-2.4	21	Weekly
Retatrutide	-2.5	24.2	Weekly

Table 3: Key Clinical Trials of GLP-1 RAs in Emerging Indications

Indication	GLP-1 RA Studied	Clinical Trial ID / Status
MASLD/MASH	Tirzepatide, Semaglutide	SURMOUNT-NASH, ESSENCE (Completed)
Chronic Kidney Disease	Semaglutide	FLOW (Completed)
Alzheimer's Disease	Semaglutide	EVOKE, EVOKE+ (Ongoing)
Parkinson's Disease	Exenatide	LEAP-PD, Exenatide-PD (Completed)
Psoriasis	Semaglutide	PSOGLP (Ongoing)
Obstructive Sleep Apnea	Tirzepatide	SLEEP STEP (Completed)
Sickle Cell Disease	Liraglutide	SICKLGLP (Ongoing)

Table 4: Comparative Chemical Structure Features of GLP-1 Receptor Agonists

Agent	Sequence Origin	Key Modifications	Half-Life Extension Strategy	Molecular Weight
Exenatide	Exendin-4 (lizard)	Native G2 substitution	None (short-acting)	4.2 kDa
Liraglutide	Human GLP-1 (97%)	K34R substitution	C16 fatty acid acylation	3.8 kDa
Dulaglutide	Human GLP-1 with substitutions	A8G, G22E, R36G	IgG4 Fc fusion	63 kDa
Semaglutide	Human GLP-1 (94%)	Aib8, K34R	C18 fatty diacid with spacer	4.1 kDa
Tirzepatide	GIP backbone	GLP-1R co-activation regions	C20 fatty diacid	4.8 kDa
Retatrutide	Glucagon backbone	Multiple (positions 1,2,3,10,12,16,17,20,21,23,24,27-29)	C16 fatty diacid via γGlu-2xOEG	5.1 kDa

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