

Review

Emerging Frontiers in GLP-1 Therapeutics: A Comprehensive Evidence Base (2025)

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have evolved from glucose-lowering agents to transformative therapies across multiple organ systems. This comprehensive review synthesizes current evidence on the mechanisms, established applications, and emerging therapeutic frontiers of GLP-1 RAs. **Methods:** We conducted a systematic literature search of PubMed, Embase, Cochrane Library, and ClinicalTrials.gov from inception through May 2025, using controlled vocabulary and free-text terms related to GLP-1 RAs, their mechanisms, and clinical applications. **Results:** GLP-1 RAs demonstrate pleiotropic effects through fundamental cellular mechanisms, including enhanced mitochondrial function, anti-inflammatory actions, improved cellular quality control, and comprehensive metabolic regulation. Established applications demonstrate robust efficacy in diabetes management (HbA1c reductions of 1.5–2.0%), obesity treatment (weight loss of 7–24%), and cardiovascular protection (14–20% reduction in major adverse cardiovascular events, or MACE). Emerging applications span neurological disorders, dermatological conditions, respiratory diseases, and novel applications in addiction medicine and autoimmune disorders. **Conclusions:** GLP-1 RAs represent a paradigmatic shift toward multi-system therapeutic intervention, with expanding evidence supporting their role as comprehensive metabolic modulators.

Keywords: GLP-1; GLP-1 Receptor peptide Agonists; type 2 diabetes mellitus; obesity; cardiovascular disease



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1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as one of the most transformative therapeutic classes in modern medicine. Initially developed for glycemic control in type 2 diabetes mellitus (T2DM), these medications have demonstrated unprecedented efficacy in managing obesity and protecting the cardiovascular system [1,2].

The therapeutic success of GLP-1 RAs stems from their ability to target fundamental physiological processes underlying metabolic dysfunction while maintaining a favorable safety profile relative to older antidiabetic medications [3,4]. The GLP-1 receptor, a class B G protein-coupled receptor with widespread tissue distribution including pancreatic islets, the central and peripheral nervous systems, cardiovascular tissues, kidneys, lungs, and gastrointestinal tract, mediates diverse physiological effects when activated [5–7].

GLP-1 RA therapeutic development has progressed through sequential generations, classified based on specific pharmacological properties including molecular structure, pharmacokinetic parameters, receptor selectivity, and clinical outcomes. This evolutionary

progression reflects systematic optimization of drug efficacy, duration of action, and tolerability profiles. First-generation short-acting agents (exenatide and lixisenatide), with twice-daily or once-daily administration provided proofs of concept for incretin-based therapy but required frequent injections and offered modest efficacy. Second-generation long-acting molecules (liraglutide, dulaglutide, and semaglutide) introduced enhanced receptor engagement profiles and extended half-lives, enabling once-weekly administration while significantly improving glycemic control and weight reduction outcomes [8–10]. Most recently, third-generation multi-agonists (tirzepatide, retatrutide, and survodutide) targeting complementary incretin receptors have demonstrated unprecedented metabolic efficacy, representing a paradigm shift in both diabetes and obesity management [11,12].

A notable evolution in recent clinical development is the strategic use of GLP-1 RAs as a platform for combinatorial therapy, particularly in the treatment of obesity and metabolic syndrome. Unimolecular and co-formulated combination products such as CagriSema (semaglutide + cagrilintide) and tirzepatide have demonstrated synergistic effects through co-activation of GLP-1 and amylin or GIP receptors, respectively, achieving up to 22–24% weight loss in clinical trials—a magnitude previously only attainable with bariatric surgery [13,14].

2. Methodology

We conducted a comprehensive systematic literature review to identify and synthesize evidence on GLP-1 RAs across all therapeutic applications. Systematic searches were conducted in PubMed/MEDLINE, Embase, Cochrane Library, Web of Science, and ClinicalTrials.gov from database inception through 31 May 2025. The systematic search methodology and eligibility criteria for study selection are presented in Table 1.

Table 1. Search Strategy and Study Selection Criteria.

Search Databases	Inclusion Criteria	Exclusion Criteria
PubMed/MEDLINE	Original research articles	Conference abstracts only
Embase	Systematic reviews, meta-analyses	Case reports with <3 patients
Cochrane Library	Human clinical studies	Overlapping populations
Web of Science	Clear methodology	Inadequate methodology
ClinicalTrials.gov	English language	Language other than English

Core search terms included the following:

- Primary drug terms: “Glucagon-Like Peptide-1 Receptor” OR “GLP-1 receptor agonist”;
- Specific agents: “liraglutide,” “semaglutide,” “exenatide,” “dulaglutide,” “tirzepatide,” “retatrutide”;
- Mechanism terms: “cellular signaling,” “mitochondrial function,” “autophagy,” “inflammation”;
- Clinical terms: “diabetes mellitus,” “obesity,” “cardiovascular disease,” neurological conditions.

3. Core Mechanisms of GLP-1 Action

3.1. Fundamental Cellular Signaling Pathways

The therapeutic efficacy of GLP-1 RAs stems from complex intracellular signaling cascades that operate across multiple organ systems through the GLP-1 receptor, a class B G protein-coupled receptor. Upon activation, the receptor initiates complex signaling networks through three primary pathways with distinct temporal and spatial characteristics (Figure 1) [15,16].

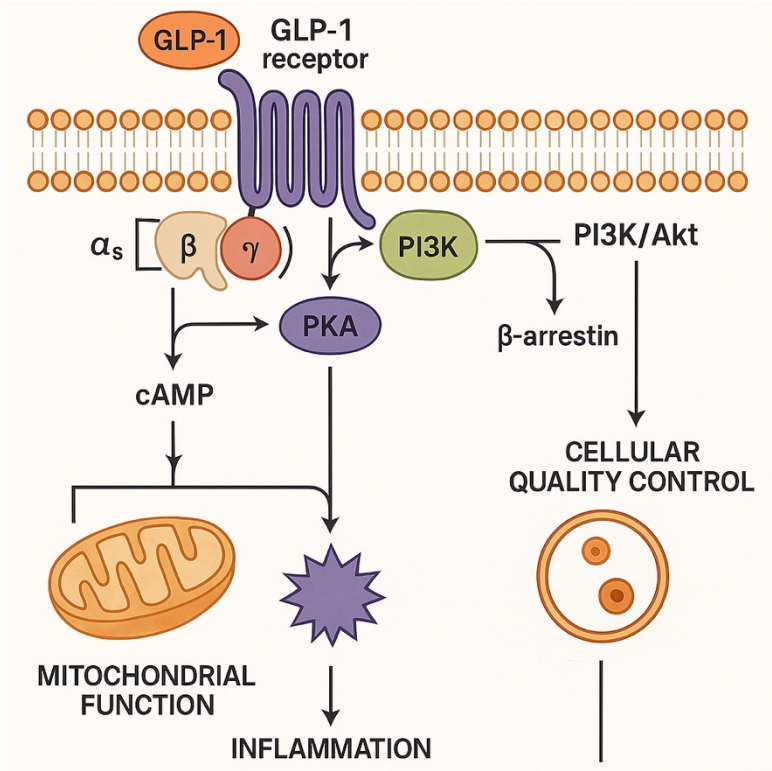


Figure 1. Comprehensive mechanistic diagram showing GLP-1 receptor signaling pathways including cAMP/PKA, PI3K/Akt, β -arrestin pathways, and downstream effects on mitochondrial function, inflammation, and cellular quality control.

Table 2 provides a comprehensive overview of the major GLP-1 signaling pathways, including their key mediators, primary cellular effects, and clinical significance.

Table 2. Major GLP-1 Signaling Pathways and Their Effects.

Pathway	Mediators	Primary Effects	Clinical Relevance
cAMP/PKA	Gs, adenylyl cyclase, PKA, CREB	• Gene transcription• BDNF expression• Bcl-2 upregulation	Neuroprotection, cell survival
PI3K/Akt	PI3K, Akt, GSK-3 β , mTORC1	• Cell survival• Protein synthesis• Tau phosphorylation inhibition	Metabolic regulation, neurodegeneration
β -Arrestin	β -arrestin-2, ERK	• Receptor desensitization• Sustained signaling• CREB phosphorylation	Receptor regulation, cellular survival
Wnt/ β -catenin	GSK-3 β inhibition, β -catenin	• Neurogenesis• β -cell proliferation• Tissue regeneration	Regenerative processes

3.2. Primary cAMP/PKA Pathway

The primary signaling pathway involves Gs-mediated activation of adenylyl cyclase, leading to rapid accumulation of cyclic adenosine monophosphate (cAMP) and subsequent activation of protein kinase A (PKA). This canonical cAMP/PKA pathway phosphorylates numerous downstream targets, including the transcription factor CREB (cAMP response element-binding protein), which translocates to the nucleus and induces expression of cytoprotective genes, including brain-derived neurotrophic factor (BDNF) and B-cell lymphoma 2 (Bcl-2) [17,18]. Recent advances have revealed that GLP-1 receptor signaling creates distinct cAMP microdomains within cells, mediated by A-kinase anchoring proteins (AKAPs). This compartmentalization allows for precise spatial control of downstream responses [19,20].

3.3. PI3K/Akt Survival Pathway

Parallel to cAMP signaling, GLP-1 receptor activation stimulates the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, a critical mediator of cell survival and metabolic regulation. Activated Akt phosphorylates multiple substrates with far-reaching consequences. Inhibition of glycogen synthase kinase-3 β (GSK-3 β) at Ser9 prevents tau hyperphosphorylation in neurons and enhances insulin signaling in metabolic tissues [21,22].

3.4. β -Arrestin-Mediated Signaling

The role of β -arrestin-2 in GLP-1 receptor signaling exhibits concentration-dependent complexity that reconciles its seemingly contradictory functions through distinct molecular mechanisms operating at different agonist concentrations. At physiological GLP-1 concentrations (<100 pM), β -arrestin-2 serves as a negative regulator, dampening insulin secretion by partially uncoupling cAMP/PKA signaling pathways, thereby providing homeostatic control under normal postprandial conditions. However, at pharmacological concentrations achieved with therapeutic GLP-1 receptor agonists (≥ 100 pM–10 nM), β -arrestin-2 becomes essential for sustained signaling, specifically mediating extracellular signal-regulated kinase (ERK) activation and CREB phosphorylation that promotes pancreatic β -cell survival and insulin synthesis. This apparent contradiction is mechanistically reconciled through β -arrestin-2's dual molecular functions: classical desensitization via termination of receptor-stimulated G protein coupling (operative at all concentrations), and scaffolding function where receptor- β -arrestin-2 complexes act as signaling nodes modulating intracellular pathways (prominent at higher concentrations). The physiological relevance of this concentration-dependent signaling complexity has been demonstrated in human adipocytes, where picomolar GLP-1 promoted lipogenesis while nanomolar GLP-1 induced lipolysis. Understanding this dual role has important therapeutic implications, as G protein-biased GLP-1 receptor agonists with reduced β -arrestin recruitment show enhanced anti-hyperglycemic efficacy through avoidance of receptor desensitization, while the requirement for β -arrestin-2 in ERK/CREB activation at therapeutic concentrations explains why complete elimination of β -arrestin-2 recruitment may not be optimal for all applications. These findings highlight the importance of assessing the signaling pathways engaged by therapeutic agonists for optimal clinical outcomes. Notably, the majority of mechanistic data supporting this concentration-dependent model derives from preclinical studies using mouse pancreatic β -cells and clonal cell lines, with limited validation in human islet studies, necessitating further clinical investigation to confirm these concentration thresholds in human diabetes treatment [23–26].

3.5. Wnt/ β -Catenin Signaling

GLP-1 receptor activation also engages the Wnt/ β -catenin signaling cascade through PKA-mediated inhibition of GSK-3 β . This stabilizes β -catenin, enabling nuclear translocation and activation of genes that promote neurogenesis, β -cell proliferation, and tissue regeneration [27,28]. Recent discoveries have revealed novel regulation of the Hippo pathway, with GLP-1 promoting the nuclear translocation and activation of YAP/TAZ, leading to the activation of regenerative gene programs [29].

3.6. Mitochondrial Enhancement and Bioenergetics

A unifying feature across GLP-1-responsive tissues is a profound enhancement of mitochondrial function and biogenesis. GLP-1 receptor activation induces expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), the master regulator of mitochondrial biogenesis, through both the cAMP/PKA/CREB and AMP-activated protein kinase (AMPK) pathways [30,31].

This leads to coordinated upregulation of nuclear respiratory factors (NRF-1 and NRF-2) and mitochondrial transcription factor A (Tfam), driving mitochondrial DNA replication and expression of respiratory chain components. GLP-1 signaling also suppresses microRNA-23a, a negative regulator of PGC-1 α , while upregulating the expression of uncoupling protein 2 (UCP2) for additional protection against oxidative stress [32,33].

The functional consequences detailed in Table 3 include improved oxidative phosphorylation efficiency through the upregulation of electron transport chain complexes, particularly complex I and IV, resulting in enhanced ATP production. Mitochondrial calcium buffering capacity improves through regulation of the mitochondrial calcium uniporter (MCU), preventing calcium-induced mitochondrial dysfunction. Structural integrity is maintained through upregulation of OPA1 (optic atrophy 1), which promotes cristae organization and prevents cytochrome c release during stress conditions [34,35].

Table 3. Mitochondrial Effects of GLP-1 Receptor Activation.

Effect	Mechanism	Functional Outcome
Biogenesis	PGC-1 α upregulation	Increased mitochondrial number
Respiratory Capacity	Complex I/IV upregulation	Enhanced ATP production
Calcium Buffering	MCU regulation	Prevented Ca ²⁺ -induced dysfunction
Quality Control	PINK1/Parkin pathway	Damaged mitochondria removal
Dynamics	OPA1 upregulation	Maintained network integrity

3.7. Anti-Inflammatory and Immunomodulatory Actions

The anti-inflammatory properties of GLP-1 RAs represent fundamental mechanisms underlying the therapeutic benefits of these agents across diverse conditions. At the molecular level, GLP-1 receptor activation potently inhibits nuclear factor kappa B (NF- κ B), the master transcriptional regulator of inflammation. This occurs through cAMP-dependent PKA activation, which phosphorylates and inhibits the I κ B kinase (IKK) complex [36,37].

The inflammasome, particularly the NLRP3 complex, represents another critical target. GLP-1 RAs suppress NLRP3 inflammasome activation through multiple mechanisms: inhibition of priming signals via reduced NF- κ B activity, attenuation of reactive oxygen species generation through enhanced mitochondrial function, induction of autophagy that removes damaged mitochondria serving as inflammasome triggers, and direct interference with NLRP3-ASC interaction through PKA-mediated phosphorylation [38,39].

Direct immunomodulatory effects occur through GLP-1 receptors expressed on multiple immune cell populations. In macrophages, GLP-1 signaling promotes polarization from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype through STAT6 activation and metabolic reprogramming [40–42]. T lymphocyte function is modulated through inhibition of pro-inflammatory Th17 differentiation and promotion of regulatory T cell (Treg) expansion via STAT5-dependent mechanisms [42,43].

3.8. Cellular Quality Control and Proteostasis

GLP-1 receptor activation enhances cellular homeostasis through comprehensive protein quality control and autophagy mechanisms. GLP-1 RAs enhance autophagy through coordinated AMPK activation and partial mTORC1 inhibition, promoting the formation of autophagosomes that engulf damaged organelles and protein aggregates [44,45]. Enhanced lysosomal biogenesis occurs through nuclear translocation of transcription factor EB (TFEB), increasing cellular degradation capacity [46–48].

GLP-1 signaling activates selective autophagy pathways, including mitophagy for the removal of damaged mitochondria, lipophagy for the degradation of lipid droplets, and aggrephagy for the clearance of protein aggregates. This is particularly relevant

for neurodegenerative diseases where GLP-1 RAs facilitate the removal of amyloid- β , α -synuclein, and mutant huntingtin [48–50].

3.9. Pancreatic β -Cell Protection and Function

In pancreatic β -cells, GLP-1 receptor activation enhances glucose-stimulated insulin secretion by increasing intracellular cAMP production, which leads to protein kinase A phosphorylation and activation of exchange protein directly activated by cAMP (Epac). This canonical pathway promotes insulin granule exocytosis while simultaneously suppressing inappropriate glucagon secretion from α -cells [51,52]. The glucose-dependent nature of this insulintropic action provides a significant therapeutic advantage by minimizing the risk of hypoglycemia 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 [53].

GLP-1 receptor activation enhances mitochondrial biogenesis through modulation of PGC-1 α , thereby improving oxidative phosphorylation, ATP production, and calcium buffering capacity [54,55]. A critical mechanism involves maintaining the mature β -cell phenotype through the regulation of key transcription factors, including pancreatic duodenal homeobox-1 (PDX1), MAF BZIP transcription factor A (MAFA), and NKX6.1 [56,57].

4. Established and Emerging Applications

4.1. Diabetes Management

4.1.1. Type 2 Diabetes Mellitus

The glucose-dependent insulintropic mechanism of GLP-1 RAs fundamentally transformed type 2 diabetes management by virtually eliminating hypoglycemia risk—a limitation that had constrained earlier antidiabetic therapies [58]. Contemporary evidence has established a clear efficacy hierarchy among agents, with dual and triple receptor agonists demonstrating superior outcomes compared to traditional GLP-1 monotherapy (Table 4).

Table 4. Comparative Efficacy of GLP-1 RAs in Type 2 Diabetes.

Agent	Dose	HbA1c Reduction (%)	Weight Loss (kg)	Key Trial	Reference
Tirzepatide	15 mg weekly	−2.01	−11.2	SURPASS-2	[9]
Semaglutide	1.0 mg weekly	−1.86	−6.9	SURPASS-2	[9]
Dulaglutide	1.5 mg weekly	−1.5	−3.1	REWIND	[59]
Liraglutide	1.8 mg daily	−1.3	−2.8	LEADER	[60]
Oral Semaglutide	14 mg daily	−1.2	−3.7	PIONEER 6	[61]

The SURPASS-2 trial established tirzepatide’s therapeutic superiority over semaglutide 1 mg, demonstrating greater HbA1c reduction (−2.01% vs. −1.86%) and substantially superior weight loss (−10.3% vs. −6.9%) with the 15 mg dose [9]. This efficacy advantage has been confirmed through a comprehensive network meta-analysis of 76 trials encompassing 39,246 participants, which demonstrated tirzepatide 15 mg as the most efficacious agent for HbA1c reduction relative to a placebo (mean difference −2.00%; 95% CI −2.16 to −1.84) [62].

Real-world evidence from the most extensive comparative effectiveness study demonstrated that GLP-1 RA-naïve patients initiating tirzepatide achieved significantly greater HbA1c reduction compared to those initiating semaglutide (−1.3% vs. −0.9%, $p < 0.0001$), confirming that clinical trial efficacy translates to routine practice [63]. Population-level time series analysis of US adults with type 2 diabetes demonstrated that increased utilization of newer GLP-1 RAs correlates with improved population-level glycemic control [64].

Oral semaglutide represents a paradigm shift in GLP-1 therapy accessibility, with extensive real-world evidence from 19 studies confirming comparable effectiveness and tolerability to injectable formulations in routine clinical scenarios [65]. The PIONEER 6 trial demonstrated cardiovascular safety with non-inferiority to placebo for major adverse cardiovascular events [61]. A comprehensive meta-analysis, including SOUL trial data, demonstrated that long-acting GLP-1 RAs reduce the incidence of major adverse cardiovascular events (MACEs), hospitalization for heart failure, kidney events, and all-cause mortality in type 2 diabetes [66]. The SOUL trial specifically demonstrated a 14% reduction in major adverse cardiovascular events (HR 0.86; 95% CI 0.77–0.96; $p = 0.006$) among 9650 participants [67].

4.1.2. Type 1 Diabetes

The application of GLP-1 RAs in type 1 diabetes exemplifies precision medicine addressing specific patient phenotypes, with concomitant obesity common among patients and only 20% achieving adequate glycemic control. A systematic review and meta-analysis of five trials involving 2445 participants demonstrated that liraglutide 1.8 mg produced a modest but clinically meaningful reduction in HbA1c (−0.24%; 95% CI −0.32 to −0.16) [68]. The 2023 updated meta-analysis confirmed therapeutic benefits primarily center on weight loss and insulin dose reduction rather than dramatic glycemic improvement [69].

4.2. Obesity Management

GLP-1 RAs have revolutionized obesity pharmacotherapy through comprehensive weight management mechanisms extending beyond simple appetite suppression (Table 5). The combination of delayed gastric emptying, direct hypothalamic appetite regulation, and peripheral metabolic effects achieves sustained weight reduction, approaching levels comparable to those of bariatric surgery with the most advanced agents [70,71].

Table 5. Weight Loss Efficacy of GLP-1 RAs in Obesity.

Agent	Dose	Weight Loss (%)	Study Population	Duration	Reference
Retatrutide	12 mg weekly	−24.2	Obesity without diabetes	48 weeks	[72]
Tirzepatide	15 mg weekly	−22.5	Obesity without diabetes	72 weeks	[73]
Semaglutide	2.4 mg weekly	−14.9	Obesity without diabetes	68 weeks	[74]
Liraglutide	3.0 mg daily	−8.4	Obesity without diabetes	56 weeks	[75]

A comprehensive systematic review of 41 trials involving 15,135 participants found significant weight reduction across all GLP-1 RAs (MD −5.319 kg; 95% CI −6.465 to −4.174), with additional improvements in BMI and waist circumference [76]. However, the therapeutic landscape has been transformed by multi-receptor agonists, which have achieved unprecedented weight loss levels. Network meta-analyses demonstrate a progressive efficacy gradient: GLP-1 monotherapy achieves approximately 7 kg weight reduction, dual agonists reach 11 kg, while triple agonists achieve up to 24 kg weight loss at 52 weeks [77].

Tirzepatide has established itself as highly effective, with the 15 mg dose achieving 22.5% weight loss (95% CI, −23.3 to −21.7), representing a reduction of 23.6 kg (52.0 lb) in phase 3 obesity trials [73,78]. Retatrutide represents the current efficacy frontier, demonstrating up to 24.2% weight reduction in the 12 mg group at 48 weeks, approaching bariatric surgery levels without invasive intervention [72,79,80].

4.3. Cardiovascular and Cardiorenal Protection

Cardiovascular protection has been demonstrated for multiple GLP-1 RAs, though with notable heterogeneity in outcomes across different agents within the class. While

multiple trials have shown significant cardiovascular benefits, the evidence reveals varying magnitudes of effect and some neutral results, indicating that cardiovascular protection may not be universally consistent across all GLP-1 RAs (Table 6) [81].

Table 6. Cardiovascular Outcomes with GLP-1 RAs.

Trial	Agent	Population	MACE Reduction	HR (95% CI)	Reference
SELECT	Semaglutide 2.4 mg	Obesity, no diabetes	20%	0.80 (0.72–0.90)	[82]
LEADER	Liraglutide 1.8 mg	T2DM, high CV risk	13%	0.87 (0.78–0.97)	[60]
SUSTAIN-6	Semaglutide 1.0 mg	T2DM, high CV risk	26%	0.74 (0.58–0.95)	[83]
REWIND	Dulaglutide 1.5 mg	T2DM, mixed risk	12%	0.88 (0.79–0.99)	
SURPASS-4		T2DM, high CV risk	26%	0.74 (0.51–1.08)	[84]
SURMOUNT-1	Tirzepatide (5, 10, 15 mg)	Obesity, no diabetes	Reduction in predicted risk of ASCVD	N/A	[73]
SOUL	Oral Semaglutide	T2DM, high CV risk	14%	0.86 (0.77–0.96)	[67]

As illustrated in Figure 2, pooled analyses of cardiovascular outcome trials have demonstrated that GLP-1 RAs reduce major adverse cardiovascular events (MACEs) by 14% (HR = 0.86, 95% CI 0.79–0.94) in patients with type 2 diabetes, with additional significant benefits including 13% reduction in cardiovascular death, 16% reduction in nonfatal stroke, and 10% reduction in hospitalization for heart failure [85]. However, this overall benefit reflects predominantly positive results from specific agents, with important exceptions such as lixisenatide in the ELIXA trial, which demonstrated cardiovascular safety but no significant reduction in MACEs (HR = 1.02, 95% CI 0.89–1.17) [86].

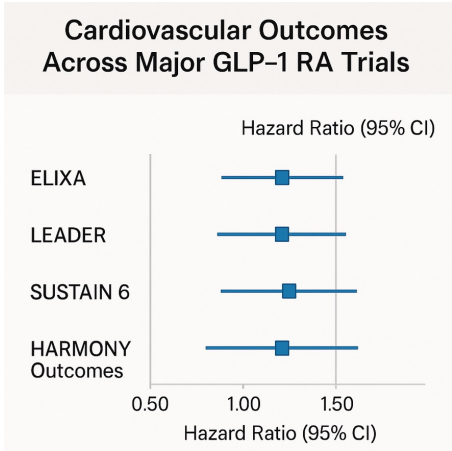


Figure 2. Forest plot showing cardiovascular outcomes across major GLP-1 RA trials, displaying hazard ratios and confidence intervals for MACE reduction.

The largest meta-analysis to date, comprising 13 cardiovascular outcome trials involving 83,258 patients with and without diabetes, confirmed that GLP-1 Ras significantly reduced major adverse cardiovascular events (MACEs), all-cause mortality, cardiovascular mortality, fatal and non-fatal strokes, coronary revascularization, and composite kidney outcomes [87].

The landmark SELECT trial significantly expanded the therapeutic paradigm by demonstrating a 20% relative risk reduction in three-point major adverse cardiovascular events (MACEs) with semaglutide 2.4 mg in 17,604 patients with obesity but without diabetes, leading to FDA approval for cardiovascular risk reduction in March 2024 [82]. This groundbreaking finding extends cardiovascular benefits beyond the diabetic population to individuals with obesity alone.

Individual trials have established agent-specific evidence profiles, revealing differential cardiovascular efficacy within the GLP-1 RA class. The REWIND trial demonstrated dulaglutide’s effectiveness in reducing the primary composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes by 12% [59]. The SURPASS-CVOT trial is an ongoing phase 3 cardiovascular outcomes trial designed to evaluate the non-inferiority and potential superiority of tirzepatide compared to dulaglutide in cardiovascular outcomes [88,89].

Heart Failure Benefits

The most significant recent advancement has been the demonstration of profound benefits in heart failure with preserved ejection fraction (HFpEF) across multiple pivotal trials, establishing GLP-1 RAs as transformative therapy for obesity-related heart failure (Table 7).

Table 7. Heart Failure Outcomes with GLP-1 RAs.

Trial	Agent	Population	Primary Endpoint	Reduction	Reference
SUMMIT	Tirzepatide	HFpEF + obesity	CV death/HF events	38% (HR 0.62)	[90]
STEP-HFpEF	Semaglutide 2.4 mg	HFpEF + obesity	Symptoms/QoL	Significant improvement	[91]
STEP-HFpEF DM	Semaglutide 2.4 mg	HFpEF + obesity + T2DM	Symptoms/QoL	Significant improvement	[92]

The landmark SUMMIT trial with tirzepatide has provided the most compelling evidence to date for heart failure benefits with incretin-based therapy. In 731 patients with HFpEF and obesity, tirzepatide demonstrated a 38% reduction in the composite endpoint of cardiovascular death or worsening heart failure events (HR 0.62, 95% CI 0.41–0.95), representing one of the most significant treatment effects ever observed in HFpEF [90].

The STEP-HFpEF program established comprehensive benefits in heart failure with preserved ejection fraction across diverse populations. Clinical trials have demonstrated the efficacy of semaglutide in HFpEF, with significant benefits in symptoms and quality of life measures [91]. Pooled analyses across the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM trials confirmed a consistent reduction in heart failure events among 3743 participants with HFpEF [93].

4.4. Renal Protection

Recent evidence suggests that GLP-1 RAs exhibit significant nephroprotective effects, extending beyond their cardiovascular benefits. A comprehensive meta-analysis of 11 trials involving 85,373 participants demonstrated that GLP-1 RAs reduced composite kidney outcomes by 18% (HR 0.82, 95% CI 0.73–0.93), kidney failure by 16% (HR 0.84, 0.72–0.99), MACEs by 13% (HR 0.87, 0.81–0.93), and all-cause death by 12% (HR 0.88, 0.83–0.93) in participants with type 2 diabetes [94,95].

The pivotal FLOW trial demonstrated semaglutide’s nephroprotective effects, with a 24% reduction in the primary composite renal outcome (HR 0.76; 95% CI, 0.66 to 0.88; $p = 0.0003$) in 3533 patients with type 2 diabetes and chronic kidney disease, over a median follow-up of 3.4 years [96,97]. The trial was terminated early due to overwhelming efficacy, leading to regulatory approval for the prevention of chronic kidney disease progression in people with type 2 diabetes and early kidney disease evidence.

4.5. Metabolic Dysfunction-Associated Steatotic Liver Disease

Non-alcoholic steatohepatitis (NASH) and fatty liver disease, now termed metabolic dysfunction-associated steatohepatitis (MASH) and steatotic liver disease (MASLD), represent significant therapeutic targets where GLP-1 RAs demonstrate substantial therapeutic potential, as evidenced by multiple clinical trials (Table 8) [98,99].

Table 8. GLP-1 RAs in MASH Clinical Trials.

Trial	Agent	Dose	Primary Endpoint	Response Rate	Reference
ESSENCE	Semaglutide	2.4 mg weekly	MASH resolution	62.9% vs. 34.3% placebo	[100]
SYNERGY-NASH	Tirzepatide	15 mg weekly	MASH resolution	62% vs. 10% placebo	[101,102]
Survodutide Study	Survodutide	4.8 mg weekly	MASH improvement	83% vs. 18.2% placebo	[103]
LEAN	Liraglutide	1.8 mg daily	NASH resolution	39% vs. 9% placebo	[104]

GLP-1 RAs ameliorate hepatic steatosis through improved insulin sensitivity, direct suppression of hepatic de novo lipogenesis through AMPK activation and SREBP-1c inhibition, and enhanced fatty acid oxidation through PPAR α upregulation. AMPK plays a crucial role in the development and progression of MASLD, representing a promising therapeutic target through its diverse signaling input and output networks [105,106].

The pivotal phase 3 ESSENCE trial with semaglutide 2.4 mg weekly demonstrated superior efficacy across both primary endpoints at 72 weeks. For the first primary endpoint, 62.9% of participants treated with semaglutide achieved resolution of steatohepatitis, with no worsening of liver fibrosis, compared to 34.1% on placebo (estimated difference in responder proportions [EDP] of 28.7%; 95% CI, 21.1 to 36.2; $p < 0.001$) [100].

Tirzepatide (5–15 mg weekly) evaluated over 52 weeks in the SYNERGY-NASH trial with participants having MASH and stage F2 or F3 fibrosis showed MASH resolution without worsening fibrosis in 44%, 56%, and 62% of participants on 5 mg, 10 mg, and 15 mg doses, respectively, compared to 10% with placebo [102,107].

Survodutide, a dual glucagon/GLP-1 RA, has demonstrated exceptional efficacy in phase 2 trials. Studies in 293 subjects with biopsy-confirmed MASH showed improved MASH without worsening fibrosis in 47%, 62%, and 43% of participants receiving 2.4 mg, 4.8 mg, and 6.0 mg doses, respectively, versus 14% with placebo [103,108].

5. Neurological Disorders

Emerging clinical evidence reveals significant therapeutic potential for GLP-1 RAs in treating neurological disorders (Table 9).

5.1. Alzheimer’s Disease

In Alzheimer’s disease models, GLP-1 RAs demonstrate multiple beneficial mechanisms, including reduced amyloid- β and tau pathology through enhanced clearance mechanisms, decreased neuroinflammation by modulating microglial activation states, and enhanced synaptic plasticity through improved long-term potentiation and dendritic spine density [35,109].

Table 9. GLP-1 RAs in Neurological Disorders.

Condition	Agent	Study	Primary Finding	Status	Reference
Alzheimer’s Disease	Liraglutide	ELAD	50% less brain volume loss	Completed	[110]
	Oral Semaglutide	EVOKE/EVOKE+	CDR-Sum of Boxes	Ongoing	[111–113]
Parkinson’s Disease	Exenatide	EXENATIDE-PD3	No disease modification	Completed	[114]
	Lixisenatide	LixiPark	Slower motor progression	Completed	[115]
	Semaglutide	Oslo University	Motor symptoms	Ongoing	[116,117]

The ELAD trial, a randomized, double-blind, placebo-controlled study of 204 patients with mild Alzheimer’s disease, demonstrated that liraglutide treatment resulted in nearly 50% less brain volume loss in frontal, temporal, parietal, and total gray matter regions compared to placebo, suggesting significant neuroprotective effects [110,118]. Clinical evaluation continues with the EVOKE and EVOKE+ trials, the first large-scale phase 3 studies evaluating oral semaglutide in people aged 55–85 years with mild cognitive impairment or mild dementia and evidence of Alzheimer’s pathology [112,118,119].

5.2. Parkinson’s Disease

GLP-1 RAs exhibit neuroprotective effects by reducing α -synuclein aggregation through enhanced chaperone-mediated autophagy, attenuating neuroinflammation via microglial modulation, and promoting dopaminergic neuron survival through anti-apoptotic signaling and mitochondrial protection [22,35,120].

Clinical investigations have yielded mixed results, with the LixiPark trial demonstrating potential disease-modifying effects in patients with early Parkinson’s disease, showing slower motor symptom progression compared to the placebo group [115]. However, the most significant phase 3 trial (EXENATIDE-PD3), which used exenatide once weekly over 96 weeks in 194 people with Parkinson’s disease, found no evidence to support exenatide as a disease-modifying treatment [121].

Real-world data from a comprehensive US Veterans Affairs Health Care system study of 215,970 individuals with type 2 diabetes revealed that GLP-1 medications were associated with reduced rates of neurocognitive disorders, including Alzheimer’s disease (HR 0.88) and dementia (HR 0.92), as well as decreased risks of substance use disorders and seizures [122].

6. Reproductive Health Applications

Polycystic ovary syndrome (PCOS) represents a metabolic-reproductive disorder where GLP-1 RAs show therapeutic potential by addressing core pathophysiological mechanisms of insulin resistance and compensatory hyperinsulinemia that exacerbate ovarian androgen production [123,124]. GLP-1 RAs enhance insulin sensitivity by increasing signaling in skeletal muscle, liver, and adipose tissue, reduce hyperinsulinemia through improved pancreatic β -cell function, and facilitate weight loss by addressing adipose tissue dysfunction [125–127].

Clinical evidence from multiple randomized controlled trials and meta-analyses demonstrates significant therapeutic benefits of GLP-1 RAs in women with PCOS. A meta-analysis by Han et al. of eight RCTs involving 375 women showed that compared with metformin, GLP-1 RAs were more effective in improving insulin sensitivity (SMD -0.40 , 95% CI -0.74 to -0.06 , $p = 0.02$) and reducing body mass index (SMD -1.02 , 95% CI -1.85 to -0.19 , $p = 0.02$) [128]. A recent meta-analysis by Morais et al. of four RCTs with 176 participants demonstrated that GLP1-RAs significantly reduced waist circumference

(MD: −5.16 cm), BMI (MD: −2.42 kg/m²), serum triglycerides (MD: −0.20), and total testosterone levels (MD: −1.33) compared to placebo [129].

Reproductive outcomes showed meaningful improvements, with Zhou et al.’s meta-analysis revealing that GLP1RAs improved natural pregnancy rate (RR: 1.72, 95% CI 1.22 to 2.43, *p* = 0.002) and menstrual regularity (SMD: 1.72, 95% CI 0.60 to 2.85, *p* < 0.001) [130].

7. Dermatological Applications

Inflammatory skin disorders represent promising therapeutic targets for GLP-1RAs, with psoriasis receiving particular attention due to its strong associations with metabolic syndrome. GLP-1 receptors are extensively expressed on keratinocytes, dermal fibroblasts, and skin-resident immune cells, providing a mechanistic rationale for therapeutic intervention [131]. Table 10 highlights key dermatological benefits of GLP-1 RAs.

Table 10. Dermatological Benefits of GLP-1 RAs.

Condition	Agent	Primary Outcome	Effect Size	Reference
Psoriasis	Various GLP-1 RAs	PASI score reduction	Significant improvement	[132–134]
Hidradenitis Suppurativa	GLP-1 RAs	Hurley stage improvement	<i>p</i> = 0.002	[135,136]
Wound Healing	Liraglutide	Healing acceleration	Demonstrated in T2DM	[137,138]

The primary anti-inflammatory mechanisms include the inhibition of JAK-STAT and NF-κB signaling pathways in keratinocytes, enhanced keratinocyte barrier function through increased expression of tight junction proteins, reduced Th17 polarization that drives psoriatic pathology, and reduced oxidative stress through enhanced expression of antioxidant enzymes [131,139,140]. Additionally, GLP-1RAs inhibit key inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), nuclear factor-kappa B (NF-κB), interleukin (IL)–23, IL–17, and IL–22 [141–143].

Clinical evidence demonstrates significant therapeutic benefits of GLP-1RAs in the management of psoriasis. A comprehensive systematic review and meta-analysis published in 2024 demonstrated that treatment with GLP-1 RAs results in significant reductions in disease severity among patients with psoriasis, irrespective of whether they have diabetes mellitus [134,144].

8. Respiratory Applications

Chronic respiratory conditions, particularly asthma and chronic obstructive pulmonary disease, represent significant emerging applications supported by GLP-1 receptor expression throughout the bronchial epithelium, airway smooth muscle, and pulmonary immune cells (Table 11) [145,146].

Table 11. Respiratory Benefits of GLP-1 RAs.

Condition	Effect	Risk Reduction	Population	Reference
General Respiratory Disease	Overall protection	14% (RR 0.86)	77,485 participants	[147,148]
COPD Exacerbations	Reduced exacerbations	18% (HR 0.82)	T2DM + COPD patients	[149]
Asthma Exacerbations Pneumonia	Fewer exacerbations Prevention	Significant reduction 28% (HR 0.72)	T2DM + asthma patients COPD patients	[150–152] [149]

A comprehensive meta-analysis of 28 randomized controlled trials involving 77,485 participants demonstrated that GLP-1 RAs were associated with a 14% lower risk of respiratory disease

compared to controls (relative risk, 0.86; 95% confidence interval, 0.81–0.93; $p < 0.0001$). Among individual agents, semaglutide showed the most potent protective effect (RR 0.82, 95% CI 0.68–0.97, $p = 0.02$), followed by liraglutide (RR 0.86, 95% CI 0.75–0.98, $p = 0.03$), and dulaglutide (RR 0.82, 95% CI 0.70–0.96, $p = 0.02$) [147,153].

The most comprehensive evidence to date comes from a landmark 2025 study by See et al., which utilized the TriNetX Analytics Network database to analyze 6898 patients with COPD and type 2 diabetes who received single-inhaler triple therapy (SITT). After propensity score matching, 1751 GLP-1 analog users showed significant improvements compared to 1751 DPP-4 inhibitor users across multiple outcomes. GLP-1 analog users had an 18% lower risk of COPD exacerbation (hazard ratio 0.82, 95% CI 0.71–0.94, $p = 0.003$), a 28% reduced risk of pneumonia (HR 0.72, 95% CI 0.61–0.85, $p < 0.001$), a 34% reduced risk of oxygen dependence (HR 0.66, 95% CI 0.47–0.91, $p = 0.010$), and a 40% decreased risk of all-cause mortality (HR 0.60, 95% CI 0.47–0.77, $p < 0.001$) [149].

9. Sleep Disorders

Obstructive sleep apnea (OSA) represents a significant clinical breakthrough for GLP-1 RAs in sleep medicine, culminating in the historic FDA approval of tirzepatide (Zepbound) on December 20, 2024, as the first medication specifically indicated for moderate-to-severe OSA in adults with obesity [154]. Current evidence supporting GLP-1 RAs applications in sleep disorders is outlined in Table 12.

Table 12. Sleep Disorder Applications.

Agent	Indication	Primary Outcome	Improvement	FDA Status	Reference
Tirzepatide	Moderate–severe OSA	AHI reduction Clinical remission	Up to 62.8% 42–50% vs. 14–16% placebo	Approved Dec 2024	[154–156]
Semaglutide	OSA (investigational)	Sleep parameters	Under investigation	Investigational	[157–160]

This approval was based on the pivotal SURMOUNT-OSA phase 3 trials, which involved 469 participants and demonstrated unprecedented efficacy. Tirzepatide achieved up to a 62.8% reduction in the apnea–hypopnea index (AHI), equivalent to 25–30 fewer events per hour compared to placebo. In patients not using positive airway pressure therapy, tirzepatide reduced the AHI by 27.4 events per hour, compared to 4.8 with placebo (55% reduction). Remarkably, 42–50% of participants achieved clinical remission or mild OSA severity compared to only 14–16% with a placebo [155,156,161].

The therapeutic mechanisms underlying OSA improvement extend beyond weight loss alone, encompassing both weight-dependent and weight-independent pathways. Weight-dependent mechanisms include reduced upper airway collapsibility through decreased parapharyngeal fat deposition [162,163]. Weight-independent mechanisms involve enhanced upper airway dilator muscle function, reduced systemic inflammation contributing to airway edema, enhanced central respiratory drive through brainstem modulation, and improved sleep architecture through enhanced slow-wave sleep duration [164,165].

10. Musculoskeletal Applications

Musculoskeletal applications of GLP-1 RAs gained substantial momentum in 2024–2025, particularly for the management of osteoarthritis and sarcopenia, with systematic reviews identifying consistent signals supporting favorable structural, protective, immunomodulatory, and analgesic effects [166].

The STEP-9 trial, which examined semaglutide in 407 patients with obesity and knee osteoarthritis, documented meaningful improvements in pain and physical function scores associated with a 13.7% weight loss. From baseline to week 68, the mean change in knee pain, assessed using the WOMAC pain score, was a reduction of 41.7 points for semaglutide and a decrease of 27.5 points for placebo, with an estimated treatment difference of 14.1 points, which was statistically significant [167].

Groundbreaking research published in *Science* in 2024 revealed a novel gut–joint axis mechanism for osteoarthritis treatment via GLP-1-mediated pathways. This research identified altered microbial bile acid metabolism, characterized by reduced glyoursodeoxycholic acid (GUDCA), in patients with osteoarthritis. It demonstrated that GLP-1 RAs can modulate intestinal farnesoid X receptor (FXR) signaling to improve joint health [168].

For sarcopenia and age-related muscle dysfunction, GLP-1 RAs preserve muscle health through prevention of catabolic muscle protein breakdown, enhanced insulin and amino acid-stimulated muscle protein synthesis through improved mTOR pathway activation, reduced skeletal muscle inflammation and fibrosis, and enhanced mitochondrial biogenesis improving muscle metabolic efficiency [169–172].

However, concerns about muscle mass loss with GLP-1 RAs have been raised by recent research. Studies suggest muscle loss with these medications (as indicated by decreases in fat-free mass) ranges from 25% to 39% of the total weight lost over 36–72 weeks [173,174]. In the STEP-1 trial of semaglutide, lean mass was reduced by 6.92 kg or 13.2%, with a weight reduction of 15.3 kg or 14.9%, resulting in a fraction of weight lost from lean mass of 45.2%. Similarly, in the SURMOUNT-1 trial of tirzepatide, lean mass was reduced by −5.67 kg or −10.9% from baseline, with a weight reduction of −22.1 kg or −20.9% (with the highest dose), yielding a fraction of weight lost from lean mass of 25.7% [175].

11. Pediatric Applications

The application of GLP-1 RAs in pediatric populations has experienced dramatic growth, with prescription rates for adolescents aged 12–17 years increasing by nearly 600% from 2020 to 2024 [176]. The 2024 average semaglutide prescription rate among adolescents with obesity was 23.7-fold higher than liraglutide prescription rates [177].

The landmark STEP TEENS trial demonstrated the remarkable efficacy of semaglutide in adolescents aged 12–17 years with obesity. After 68 weeks of treatment, participants receiving semaglutide 2.4 mg weekly achieved a mean BMI reduction of 16.1%, compared to 0.6% with placebo. Additionally, 73% of participants achieved a weight loss of $\geq 5\%$, compared to 18% with placebo [178].

The safety profile in adolescents appears comparable to that in adults, with gastrointestinal symptoms predominating as transient adverse events. Importantly, no significant adverse effects on linear growth, pubertal development, or bone health were observed during treatment periods [179].

Current FDA-approved GLP-1 RAs for adolescents include semaglutide (Wegovy), approved in December 2022, and liraglutide (Saxenda), approved in December 2020 for individuals aged 12 and older [180]. Tirzepatide (Mounjaro/Zepbound) remains approved exclusively for adults aged 18 years and older, as pediatric safety and efficacy data are pending from ongoing phase 3 trials in adolescents with type 2 diabetes [181]. The American Academy of Pediatrics updated its guidelines in 2023 to recommend offering medications to patients 12 years and older with obesity alongside lifestyle treatment [182].

12. Hematological Applications

The most significant development in hematological applications has been in the management of sickle cell disease. A 2024 retrospective analysis examined adults with sickle

cell disease treated with GLP-1 RAs, demonstrating improvement in estimated glomerular filtration rate (eGFR) slope in 80% of patients receiving GLP-1 RA treatment [183].

Among five patients treated with GLP-1 RAs (liraglutide or dulaglutide) for a median duration of 21.8 months, serum glucose concentrations improved from a median of 213 mg/dL to 152 mg/dL during treatment. The eGFR slope improved from a median of -2.37 mL/min/ 1.73 m² per year before treatment to $+0.49$ mL/min/ 1.73 m² per year during treatment, indicating significant renoprotective benefits [183].

Limited evidence from a large retrospective cohort study of 2025 observed statistical association between GLP-1 RA use and a reduced incidence of hematologic cancers, including leukemia and myelodysplastic syndromes, in patients with type 2 diabetes. However, these findings represent observational correlations rather than established causality and require confirmation through randomized controlled trials [184].

13. Autoimmune and Inflammatory Disorders

13.1. Autoimmune Thyroid Disorders

Current evidence for GLP-1 RAs in autoimmune thyroid disorders remains primarily mechanistic with limited clinical data, though the theoretical rationale is compelling. GLP-1 RAs demonstrate well-established anti-inflammatory and metabolic regulatory properties that may benefit autoimmune thyroid disorders through multiple mechanisms. These include decreased systemic inflammatory cytokines (TNF- α , IL-1 β , and IL-6), reduced thyroid-infiltrating inflammatory cells through PI3K-Akt pathway modulation, improved metabolic function, and reduced oxidative damage through increased antioxidant capacity [185–187].

However, thyroid cancer risk remains a complex and evolving safety consideration. Meanwhile, large-scale prospective cohort studies from 2024 to 2025, including a multisite analysis of 98,147 GLP-1RA users across six countries, show no evidence of increased thyroid cancer risk [188]. However, pharmacovigilance data presents a contrasting signal. FDA Adverse Event Reporting System analysis revealed significant disproportionate reporting of thyroid cancer with GLP-1 RAs, with reporting odds ratios ranging from 2.09 (tirzepatide) to 15.59 (liraglutide) [189]. Additionally, temporal detection patterns emerge, as US claims data revealed increased thyroid cancer diagnoses within the first year of GLP-1RA initiation, potentially reflecting enhanced medical surveillance rather than true carcinogenesis. Additionally, in patients with pre-existing thyroid nodules using GLP-1 analogs, approximately 9% developed thyroid cancer during follow-up, highlighting the importance of enhanced surveillance in this higher-risk population [190].

13.2. Inflammatory Bowel Disease

Inflammatory bowel disease represents a promising therapeutic target with emerging evidence supporting beneficial effects in both Crohn's disease and ulcerative colitis. A 2024 retrospective analysis of 244 IBD patients treated with GLP-1 RAs demonstrated significant weight loss (mean 5% reduction at 12 weeks) and, importantly, a decrease in C-reactive protein levels, suggesting potential anti-inflammatory effects [191,192].

14. Substance Abuse Disorders and Addiction Treatment

The role of GLP-1 RAs in substance use disorders has gained substantial momentum in 2024–2025, with multiple large-scale observational studies and ongoing clinical trials. GLP-1 receptors are extensively expressed in brain reward circuits, particularly mesolimbic and mesocortical pathways involved in addictive behaviors [193].

A pivotal study analyzing 503,747 patients with opioid use disorder and 817,309 patients with alcohol use disorder found that prescriptions of GLP-1 RAs were associated with

significantly lower rates of opioid overdose and alcohol intoxication [194]. Clinical evidence includes studies documenting reduced alcohol consumption, fewer drinks per day, and decreased alcohol craving with semaglutide treatment. Observational data from Sweden revealed that semaglutide and liraglutide were associated with decreased hospitalization risk due to alcohol use disorder in people with type 2 diabetes and obesity [195,196].

15. Psychiatric Disorders

The bidirectional relationship between metabolic disorders and mental health conditions has prompted the investigation of GLP-1 RAs in psychiatric applications. GLP-1 receptors are expressed in mood regulation brain regions, including the amygdala, hippocampus, prefrontal cortex, ventral tegmental area (VTA), and nucleus accumbens (NAc), where signaling modulates monoaminergic neurotransmission and hypothalamic–pituitary–adrenal axis function [197,198].

Systematic reviews and meta-analyses have provided compelling evidence for the antidepressant effects of GLP-1 RAs. A recent meta-analysis of six studies involving 2071 participants found that GLP-1 RA treatment significantly reduced depression rating scale scores compared to control treatments (standardized mean difference, −0.12; 95% CI, −0.21 to −0.03) [199].

Healthcare resource utilization data from 774,968 adults with type 2 diabetes revealed that GLP-1 RA use was associated with significant reductions in outpatient hospital visits for depression (IRR: 0.96; 95% CI: 0.95–0.98) and office visits for both depression (IRR: 0.87; 95% CI: 0.82–0.92) and anxiety (IRR: 0.85; 95% CI: 0.81–0.90) compared to DPP-4 inhibitors [200].

16. Safety Considerations

Comprehensive safety considerations for GLP-1 RA therapy are systematically presented in Table 13.

Table 13. Safety Profile of GLP-1 RAs.

Category	Common AEs	Serious AEs	Contraindications	Monitoring Required
Gastrointestinal	• Nausea (20–40%)• Vomiting• Diarrhea	• Pancreatitis (rare)• Gastroparesis	• Gastroparesis• IBD (relative)	• Amylase/lipase• GI symptoms
Endocrine	• Injection site reactions	• Thyroid cancer risk• Hypoglycemia (with insulin)	• MTC history• MEN2 syndrome	• Thyroid monitoring• Glucose levels
Perioperative	• Delayed gastric emptying	• Aspiration risk	• Recent surgery	• NPO guidelines• Anesthesia consultation
Psychiatric	• Mood changes	• Suicidal ideation (rare)	• Active psychosis	• Mental health screening

While the safety profile remains generally favorable with predominantly transient gastrointestinal effects, emerging considerations include potential thyroid cancer risk, perioperative complications, psychiatric effects, and significant muscle mass loss with rapid weight reduction. These necessitate careful patient selection, comprehensive monitoring, and risk mitigation strategies [4,201,202].

The SUSTAIN-6 and PIONEER 6 trials showed increased diabetic retinopathy complications with semaglutide, particularly in patients with existing retinopathy (HR 1.76; 95% CI 1.11–2.78; *p* = 0.02) [61,83]. This risk appears linked to rapid glycemic improvement, consistent with established mechanisms observed with intensive insulin therapy. However, retrospective real-world evidence observed the progression rates from severe non-proliferative to proliferative diabetic retinopathy lower than anticipated over a mean follow-up of 2.9 years [203]. The ongoing FOCUS trial (NCT03811561), a dedicated post-

authorization safety study utilizing standardized ophthalmic assessments, is expected to provide definitive evidence regarding long-term safety data by 2027.

17. Future Directions and Research Priorities

The rapid evolution of GLP-1 RAs from single-indication diabetes medications to multi-system therapeutic platforms creates unprecedented opportunities for continued innovation and clinical advancement. Future research priorities must address fundamental mechanistic questions, explore novel therapeutic applications, overcome current limitations, and ensure equitable access to these transformative therapies. Strategic research priorities encompass mechanistic insights, expanded clinical applications, technological advances, and implementation strategies, each with distinct timelines and anticipated population health impacts are presented in Table 14.

Table 14. Research Priorities by Category.

Research Area	Priority Objectives	Timeline	Expected Impact
Mechanistic	• Tissue-specific signaling• Multi-receptor optimization• Personalized biomarkers	2–5 years	Enhanced therapeutic targeting
Clinical Development	• Neurological trials completion• Pediatric applications• Combination therapies	3–7 years	Expanded indications
Technology	• Long-acting formulations• Alternative delivery routes• Digital integration	2–5 years	Improved patient experience
Implementation	• Cost-effectiveness studies• Access improvement• Provider education	1–3 years	Population health impact

Mechanistic research priorities focus on elucidating tissue-specific and context-dependent GLP-1 receptor signaling pathways, aiming to facilitate the development of next-generation therapeutics with enhanced efficacy and safety profiles. Understanding how β -arrestin-mediated pathways contribute to therapeutic effects versus adverse events could facilitate the development of biased agonists with enhanced therapeutic windows.

Clinical development priorities encompass expansion into novel therapeutic areas where mechanistic rationale supports potential benefits, with neurological disorders representing a particularly promising frontier. Completion of ongoing Alzheimer’s trials will provide definitive evidence for disease-modifying potential, while future studies should explore applications in multiple sclerosis, amyotrophic lateral sclerosis, and traumatic brain injury.

18. Conclusions

GLP-1 RAs represent a paradigmatic transformation in modern therapeutics, evolving from glucose-lowering agents to comprehensive multi-system interventions that address fundamental pathophysiological processes across diverse medical conditions. This extensive review demonstrates how GLP-1 RAs have transcended traditional therapeutic boundaries by modulating core cellular mechanisms, including mitochondrial enhancement, anti-inflammatory actions, autophagy-mediated quality control, and neuroprotective pathways that underlie multiple disease states.

The clinical evidence establishes unprecedented therapeutic efficacy across established indications, with newer multi-receptor agonists achieving HbA1c reductions exceeding 2.0% in diabetes, weight loss approaching 24% in obesity that rivals bariatric surgery outcomes, and cardiovascular protection demonstrating consistent 14–20% MACE reduction with emerging benefits in heart failure with preserved ejection fraction. The expansion into novel applications spanning neurological disorders, sleep medicine, dermatology, respira-

tory diseases, and substance use disorders reflects the broad therapeutic potential of targeting fundamental biological pathways that contribute to diverse pathological processes.

The mechanistic foundation underlying this therapeutic versatility stems from the widespread distribution of the GLP-1 receptor and its pleiotropic signaling effects, which create a unified framework for understanding clinical benefits across seemingly disparate conditions. The progression from single receptor agonists to dual and triple receptor targeting demonstrates how mechanistic insights can drive therapeutic innovation, with combination approaches achieving synergistic effects that exceed the sum of individual pathway modulation.

The integration of GLP-1 RAs into clinical practice requires systematic approaches that encompass evidence-based patient selection, structured initiation and monitoring protocols, multidisciplinary collaboration across medical specialties, and comprehensive care coordination to optimize therapeutic outcomes while ensuring patient safety. The expanding evidence base necessitates continuous provider education, clinical decision support tools, and adaptations to healthcare delivery models to accommodate the complexity of multi-indication prescribing and monitoring requirements.

Future research priorities encompass mechanistic investigations to enable next-generation therapeutic development, clinical trials exploring novel indications and combination approaches, technological innovations improving drug delivery and patient monitoring, and implementation research addressing real-world effectiveness and healthcare system integration. The success of continued GLP-1 RA development will require coordinated efforts across basic science, clinical research, regulatory science, and health services research to realize the full therapeutic potential while ensuring safe, equitable access for all patients who could benefit.

The evidence reviewed establishes GLP-1 RAs as transformative precision medicine tools that exemplify how mechanistic understanding can drive therapeutic innovation in addressing complex, interconnected diseases through targeted modulation of biological pathways. Their continued evolution promises further advances in an emerging medical paradigm where single interventions address multiple pathophysiological processes, improving outcomes while simplifying treatment complexity.

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