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DIFFERENCES IN SAFETY PROFILE AND ADVERSE EFFECTS OF ORAL AND SUBCUTANEOUS GLP-1 ANALOGUES: A SYSTEMATIC REVIEW AND REAL-WORLD DATA ANALYSIS (2024–2026)

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ABSTRACT

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a cornerstone of therapy for type 2 diabetes mellitus (T2DM) and obesity, offering effective glycaemic control alongside significant cardiometabolic benefits. The introduction of oral formulations has raised the need for a precise comparison of their safety profile with classical subcutaneous preparations, particularly regarding pharmacokinetic differences and treatment tolerability.
Objective: This review aimed to compare the safety profile and adverse effects of oral and subcutaneous GLP-1 analogues based on available data from 2024–2026, incorporating evidence from clinical trials and real-world studies.
Methods: A systematic literature search was performed using PubMed and PubMed Central. Meta-analyses, randomised controlled trials (RCTs), and observational studies evaluating safety, tolerability, and pharmacokinetics of GLP-1 RAs were included, with emphasis on comparisons between oral and subcutaneous semaglutide.
Results: Both oral and subcutaneous GLP-1 RAs share a broadly similar adverse effect profile, dominated by dose-dependent gastrointestinal (GI) symptoms — nausea, vomiting, and diarrhoea — which are most pronounced during treatment initiation. Subcutaneous formulations offer a more predictable pharmacokinetic profile and stable systemic exposure, translating into more consistent tolerability. Oral semaglutide exhibits greater bioavailability variability, potentially leading to a more heterogeneous clinical response and higher rates of GI events. Real-world evidence indicates a significantly higher treatment discontinuation rate with oral formulations due to adverse effects. Subcutaneous GLP-1 RAs are additionally associated with mild injection-site reactions absent in oral forms. Increased risk of gallbladder disease is observed in both groups, while no conclusive evidence of elevated pancreatitis risk exists.
Conclusions: Despite a broadly similar safety profile, oral and subcutaneous GLP-1 analogues differ in pharmacokinetics, tolerability patterns, and treatment discontinuation rates. Subcutaneous formulations provide a more predictable clinical effect, while oral agents may offer greater patient convenience at the cost of higher interindividual variability. The choice of administration route should be individualised, accounting for patient preferences, adverse effect risk profile, and anticipated impact on adherence. Long-term data and further real-world evidence are needed for a comprehensive safety evaluation.

KEYWORDS

GLP-1 Receptor Agonists; Semaglutide; Real-World Evidence; Treatment Adherence; Treatment Outcomes; Obesity; Type 2 Diabetes Mellitus

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Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a pivotal therapeutic class for the management of type 2 diabetes mellitus (T2DM) and obesity. Their mechanism of action involves mimicking endogenous GLP-1, thereby stimulating glucose-dependent insulin secretion, suppressing glucagon release, and decelerating gastric emptying (Ayoub et al., 2025). Beyond glycaemic control, GLP-1 RAs confer significant cardiometabolic benefits, as demonstrated in landmark randomised trials such as LEADER and SUSTAIN-6 (Leiter et al., 2020).

The recent development of oral GLP-1 formulations — most notably oral semaglutide — represents a significant advance in terms of patient convenience and potential adherence compared to conventional subcutaneous preparations (Hoffmann et al., 2025). However, pharmacokinetic differences inherent to the route of administration may influence the safety and tolerability profiles of these agents (Karedath et al., 2025).

Gastrointestinal (GI) adverse effects, including nausea, vomiting, diarrhoea, and constipation, represent the most frequently reported events across both formulations and constitute the principal cause of treatment discontinuation (Xie et al., 2025). Additional concerns include an increased risk of gallbladder disease and

gastro-oesophageal reflux (Chiang et al., 2025). Importantly, available data do not confirm a significantly elevated risk of acute pancreatitis, although this signal continues to be monitored (Ayoub et al., 2025).

Against this background, a detailed comparison of the adverse effect profiles of oral and subcutaneous GLP-1 analogues is essential for optimising treatment and enabling individualised patient management. The present systematic review synthesises evidence from clinical studies and real-world data published between 2024 and 2026.

Mechanisms of Action and Basis of Adverse Effects

GLP-1 is an incretin gut hormone secreted by intestinal L-cells in response to nutrient intake, playing a central role in glucose homeostasis and energy balance. Physiologically, GLP-1 enhances glucose-dependent insulin secretion, suppresses glucagon secretion, slows gastric emptying, and promotes satiety via central nervous system effects (Nauck et al., 2021). GLP-1 RAs exploit these mechanisms and additionally exert pleiotropic effects, including cardiovascular and renal protection, as confirmed by RCTs (Leiter et al., 2020).

The same mechanisms underlying therapeutic efficacy are responsible for the principal adverse effects. Delayed gastric emptying and activation of central chemoreceptor trigger zones and emetic centres give rise to GI symptoms: nausea, vomiting, diarrhoea, and postprandial fullness (Xie et al., 2025; Alhazmi & le Roux, 2026). These symptoms are dose-dependent and most intense during initial titration, typically attenuating with continued treatment as physiological adaptation occurs (Alhazmi & le Roux, 2026).

Alterations in GI motility and lipid metabolism may also predispose to gallstone formation, particularly in patients experiencing rapid weight loss (He et al., 2022). Preclinical studies have identified potential C-cell effects in the thyroid; however, the clinical relevance in humans remains uncertain and unconfirmed in current literature (Espinosa De Ycaza et al., 2024).

Pharmacokinetic Differences Between Oral and Subcutaneous Administration

The pharmacokinetic distinctions between oral and subcutaneous GLP-1 analogues arise primarily from their differing absorption mechanisms and bioavailability characteristics. Subcutaneous semaglutide displays a predictable pharmacokinetic profile with a long half-life, enabling once-weekly dosing (Yang & Yang, 2024). In contrast, the oral formulation employs the absorption enhancer SNAC (sodium N-[8-(2-hydroxybenzoyl)amino]caprylate), which facilitates absorption across the gastric mucosa by transiently increasing mucosal permeability and protecting against enzymatic degradation (Karedath et al., 2025; Niman et al., 2021).

However, oral bioavailability is subject to considerable limitations. Food intake, GI disorders, and variations in dosing schedules may substantially affect absorption and systemic exposure (Yang & Yang, 2024). Subcutaneous administration consequently provides more stable systemic exposure with lower interindividual variability, whereas the oral formulation is characterised by greater variability in drug concentrations (Karedath et al., 2025).

These pharmacokinetic differences translate into differential clinical outcomes. In a 2025 meta-analysis by Drygalski et al. involving 12 RCTs and 6,253 adults with T2DM, both formulations produced significant HbA1c reductions — oral by −1.16 percentage points (95% CI −1.22 to −1.10) and subcutaneous by −1.40 percentage points — with subcutaneous semaglutide achieving significantly greater glycaemic reduction. Subcutaneous semaglutide was also superior in weight and BMI reduction (Drygalski et al., 2025). A parallel meta-analysis by Karedath et al. (2025) confirmed the superiority of subcutaneous semaglutide in HbA1c reduction (SMD: 0.21, 95% CI: 0.04–0.38), while the difference in body weight reduction was not statistically significant (SMD: 0.12, 95% CI: −0.27 to 0.52).

From a practical standpoint, oral semaglutide requires fasting administration and a defined interval before food intake, which may complicate adherence to dosing instructions. Weekly subcutaneous injection is a simpler regimen with fewer external dependencies (Karedath et al., 2025). Nonetheless, a 2025 analysis by Wang et al. suggested that oral GLP-1 agents may be associated with greater patient preference for the route of administration, although this preference did not necessarily translate into superior real-world adherence outcomes.

Methods

A systematic literature search was conducted in PubMed and PubMed Central, supplemented by targeted searches in Google Scholar to capture additional real-world evidence and recent meta-analyses. The search covered the period from January 2024 to April 2026, with seminal earlier publications included where required for mechanistic, pharmacokinetic or historical context. The review is reported as a narrative synthesis informed by a systematic literature search; no formal protocol was registered and no quantitative meta-analysis was performed.

Search Strategy

Searches combined controlled vocabulary (MeSH terms) and free-text keywords using Boolean operators. Core terms included "GLP-1 receptor agonists", "semaglutide", "liraglutide", "tirzepatide", "oral semaglutide", "subcutaneous semaglutide", "adverse effects", "safety", "tolerability", "pharmacokinetics", "real-world evidence", "pharmacovigilance" and "treatment discontinuation". Reference lists of identified meta-analyses and systematic reviews were screened to identify additional relevant publications.

Eligibility Criteria

Eligible publications were peer-reviewed meta-analyses, systematic reviews, randomised controlled trials, cohort and registry studies, pharmacovigilance and FAERS analyses, and prospective observational studies that evaluated the safety, tolerability, pharmacokinetics or treatment-discontinuation outcomes of oral or subcutaneous GLP-1 RAs in adults with T2DM, obesity or both. Studies comparing oral and subcutaneous semaglutide directly or indirectly were prioritised. Non-English publications, conference abstracts without an associated full-text peer-reviewed manuscript, editorials, commentaries and animal-only studies were excluded.

Study Selection and Data Extraction

Titles and abstracts were screened for relevance against the eligibility criteria, after which full texts of potentially relevant articles were retrieved and assessed. Data of interest comprised study design, sample size, formulation and dose of GLP-1 RA, comparator, follow-up duration and reported safety outcomes — in particular GI adverse events, hepatobiliary events, pancreatitis, thyroid-related events, injection-site reactions for subcutaneous formulations, cardiovascular and renal events, and treatment discontinuation due to adverse effects.

Synthesis

Given the heterogeneity of study designs, comparator groups and reported outcomes, results were synthesised narratively rather than through quantitative meta-analysis. Particular emphasis was placed on directly comparative evidence between oral and subcutaneous semaglutide and on real-world evidence to complement the controlled environment of randomised trials. Where appropriate, point estimates with 95% confidence intervals are reproduced from the original sources.

Results

Study Selection and Characteristics

The systematic literature search identified a substantial body of evidence published between 2024 and 2026 evaluating the safety profile and adverse effects of GLP-1 receptor agonists. After title and abstract screening followed by full-text assessment, 23 publications were retained for narrative synthesis. The included evidence comprised recent meta-analyses and systematic reviews (Karedath et al., 2025; Drygalski et al., 2025; Chiang et al., 2025; Xie et al., 2025; Ramírez-Mejía et al., 2025; He et al., 2022; Alhindi & Avery, 2022; Espinosa De Ycaza et al., 2024), randomised controlled trials and cardiovascular or renal outcome trials (Pratley et al., 2019; Husain et al., 2019; Lincoff et al., 2023; Perkovic et al., 2024; Leiter et al., 2020), real-world cohort and pharmacovigilance studies (Thomsen et al., 2025; Hoffmann et al., 2025; Xiong et al., 2024; Sodhi et al., 2023; Wang et al., 2025), and pharmacological, clinical and mechanistic reviews (Nauck et al., 2021; Niman et al., 2021; Yang & Yang, 2024; Kim & Yoo, 2025; Alhazmi & le Roux, 2026; Ayoub et al., 2025). Wherever possible, evidence is reported hierarchically — meta-analytic and randomised data are presented alongside corroborating real-world evidence to permit a balanced appraisal. An overview of the included studies, with their design, population, comparison and principal findings, is provided in Table 1.

Table 1. Summary of the principal clinical trials, meta-analyses and real-world studies included in the synthesis.

Study (year)	Design	Population (n)	Comparison	Principal safety / outcome findings
Pratley et al. (2019) — PIONEER 4	Phase 3a randomised, double-blind RCT; 52 weeks	Adults with T2DM (n = 711)	Oral semaglutide 14 mg vs subcutaneous liraglutide 1.8 mg vs placebo	Oral semaglutide non-inferior to liraglutide for HbA1c reduction; superior weight loss; nausea ~20 % vs ~18 %; AE-related discontinuation 11 % vs 9 %.
Husain et al. (2019) — PIONEER 6	Cardiovascular outcomes RCT; median 16 months	T2DM with high CV risk (n = 3,183)	Oral semaglutide 14 mg vs placebo	Non-inferior MACE (HR 0.79, 95 % CI 0.57–1.11); CV death 0.9 % vs 1.9 %; safety profile consistent with class.
Leiter et al. (2020) — SUSTAIN-6 / LEADER synthesis	Pooled analysis of CV outcomes RCTs	T2DM (varied baseline blood pressure)	Subcutaneous semaglutide / liraglutide vs placebo	Cardiovascular and renal benefit consistent across blood-pressure subgroups; class-level CV protection.
Lincoff et al. (2023) — SELECT	Cardiovascular outcomes RCT; mean follow-up 39.8 months	Adults with overweight/obesity and pre-existing CVD without diabetes (n = 17,604)	Subcutaneous semaglutide 2.4 mg vs placebo	20 % relative reduction in MACE (HR 0.80, 95 % CI 0.72–0.90; $p < 0.001$); discontinuation due to GI events more frequent with semaglutide.
Perkovic et al. (2024) — FLOW	Renal outcomes RCT	T2DM with chronic kidney disease (n = 3,533)	Subcutaneous semaglutide 1.0 mg weekly vs placebo	24 % reduction in composite kidney endpoint (HR 0.76, 95 % CI 0.66–0.88); 18 % reduction in MACE; 20 % reduction in all-cause mortality.
Karedath et al. (2025)	Systematic review and meta-analysis	T2DM (4 studies; n = 559)	Oral vs subcutaneous semaglutide	Comparable common GI events; subcutaneous superior in HbA1c reduction; RR for AE-driven discontinuation 1.79 (95 % CI 1.13–2.83) for oral.
Drygalski et al. (2025)	Systematic review and meta-analysis (12 RCTs)	T2DM (n = 6,253)	Oral vs subcutaneous semaglutide	HbA1c reduction −1.16 pp (oral) vs −1.40 pp (subcutaneous); subcutaneous superior in weight and BMI reduction.
Chiang et al. (2025)	Systematic review and meta-analysis	GLP-1 RA users in RCTs	GLP-1 RA vs control	Elevated odds of severe GI adverse events; signal for cholelithiasis; absolute risk modest.
Xie et al. (2025)	Bayesian network meta-analysis	T2DM patients on GLP-1 RAs and multi-target analogues	Cross-comparison across agents	Differential GI tolerability profile across agents; tirzepatide and semaglutide formulations cluster together for GI events.
Xiong et al. (2024)	FAERS pharmacovigilance analysis (2019–2023)	Oral semaglutide tablet recipients (real-world)	Disproportionality vs other drugs	Beyond GI symptoms: signals for acute cholecystitis, dizziness and selected neurological events.
Sodhi et al. (2023)	Retrospective cohort (PharMetrics Plus database)	Adults receiving GLP-1 RA for weight loss (~16 million-record sample)	GLP-1 RA vs bupropion–naltrexone	aHR pancreatitis 9.09 (95 % CI 1.25–66.00); bowel obstruction 4.22 (1.02–17.40); gastroparesis 3.67 (1.15–11.90); biliary disease NS.
Thomsen et al. (2025)	Real-world evidence narrative review	Newer GLP-1 RA-based weight-loss therapy users	Routine clinical use	Real-world treatment discontinuation 20–50 % within first year; predominantly GI intolerance.
Hoffmann et al. (2025)	Prospective observational cohort (Poland)	Adults with obese T2DM	Subcutaneous semaglutide vs liraglutide	Effectiveness in real-world practice attenuated relative to RCT findings; modulated by adherence and comorbidity.

Study (year)	Design	Population (n)	Comparison	Principal safety / outcome findings
Ayoub et al. (2025)	Propensity score-matched analysis	T2DM patients without confounding comorbidity	GLP-1 RA users vs matched non-users	No significantly elevated risk of acute pancreatitis.
He et al. (2022)	Systematic review and meta-analysis of RCTs	GLP-1 RA recipients	GLP-1 RA vs comparator	Increased risk of gallbladder and biliary disease, including cholelithiasis and cholecystitis.
Wang et al. (2025)	Editorial / commentary review	T2DM and obesity populations	Oral vs injectable GLP-1 RA	Patient preference for oral administration noted, although did not consistently translate to superior real-world adherence.

General Adverse Effect Profile of GLP-1 Analogues

GLP-1 RAs have a well-characterised adverse effect profile dominated by GI symptoms. Nausea, vomiting, diarrhoea, and constipation arise mechanistically from delayed gastric emptying and central emetic effects, are typically most pronounced at treatment initiation, and are dose-dependent, with a tendency to diminish over time (Karedath et al., 2025; Kim & Yoo, 2025). Clinical and observational data consistently identify these symptoms as the primary drivers of treatment discontinuation or impaired tolerability.

Beyond GI effects, meta-analyses and systematic reviews indicate an increased risk of gallbladder and biliary diseases, including cholelithiasis and cholecystitis, attributable to GLP-1 RA effects on GI motility and bile metabolism (Ramírez-Mejía et al., 2025; Chiang et al., 2025). No conclusive evidence of a significantly elevated acute pancreatitis risk has been established; however, safety signals continue to be monitored in ongoing pharmacovigilance programmes (Kim & Yoo, 2025).

Real-world data indicate that treatment discontinuation rates for GLP-1 RAs are substantial in routine practice, with estimates of 20–50% within the first year, highlighting the significant clinical burden of adverse effects on long-term adherence (Thomsen et al., 2025).

Safety Profile of Subcutaneous GLP-1 Analogues

Subcutaneous GLP-1 RAs, including semaglutide and liraglutide, are characterised by a well-documented and relatively predictable safety profile, derived from their stable pharmacokinetics and controlled systemic exposure. Pharmacokinetic data confirm that subcutaneous administration produces consistent drug concentrations with lower interindividual variability, resulting in more predictable treatment tolerability (Yang & Yang, 2024).

Evidence from RCTs and meta-analyses demonstrates that the incidence of serious adverse events with subcutaneous GLP-1 RAs is low and comparable to other antidiabetic therapies, with most adverse events not resulting in permanent treatment discontinuation (Drygalski et al., 2025). A distinguishing feature of subcutaneous formulations is the occurrence of mild local injection-site reactions — erythema, pruritus, and mild oedema — which are absent with oral preparations and are generally transient (Nauck et al., 2021).

Importantly, the Karedath et al. (2025) meta-analysis demonstrated that patients receiving oral semaglutide had a significantly higher risk of treatment discontinuation due to adverse effects compared to subcutaneous semaglutide (RR: 1.79, 95% CI: 1.13–2.83), suggesting that subcutaneous administration may confer an advantage in long-term treatment maintenance attributable to fewer treatment-limiting adverse effects. RWE analyses corroborate that the safety profile of subcutaneous GLP-1 RAs in clinical practice is broadly consistent with RCT findings, albeit modifiable by patient age, comorbidities, and polypharmacy (Thomsen et al., 2025).

Safety Profile of Oral GLP-1 Analogues

Oral GLP-1 analogues, principally oral semaglutide, have a well-established safety profile that is broadly comparable to subcutaneous formulations and similarly dominated by GI adverse effects of mild to moderate severity (Niman et al., 2021). Phase III clinical trials and systematic analyses have shown that adverse events occur in a substantial proportion of patients (exceeding 50–70%), though most are transient and rarely lead to serious complications; the incidence of serious adverse events remains comparable to placebo or other GLP-1 RAs (Karedath et al., 2025).

Treatment discontinuation with oral semaglutide increases with dose escalation, with GI adverse effects being the principal reason for cessation, confirming a dose-dependent pattern (Niman et al., 2021). While comparative meta-analyses report similar rates of nausea, diarrhoea, and vomiting between oral and

subcutaneous formulations, oral semaglutide may exhibit a higher frequency of GI events compared to placebo and some other GLP-1 RAs (Alhindi & Avery, 2022). The Karedath et al. (2025) meta-analysis confirmed the significantly higher treatment discontinuation risk with oral versus subcutaneous semaglutide.

Pharmacovigilance analyses based on real-world databases (FAERS, 2019–2023) report a broad spectrum of adverse events with oral semaglutide, extending beyond GI effects to include acute cholecystitis, dizziness, and neurological disturbances, underscoring the importance of safety monitoring in routine clinical practice (Xiong et al., 2024). RWE further demonstrates that real-world adverse event profiles may diverge from RCT findings due to greater patient heterogeneity, comorbidities, and polypharmacy (Karedath et al., 2025).

Direct Comparative Evidence Between Oral and Subcutaneous Formulations

Direct head-to-head comparisons between oral and subcutaneous GLP-1 RAs remain limited, but the available data permit an informed appraisal of differential safety. The PIONEER 4 trial (Pratley et al., 2019) constitutes the largest direct comparison: 711 adults with T2DM were randomised in a 2:2:1 ratio to once-daily oral semaglutide 14 mg, once-daily subcutaneous liraglutide 1.8 mg, or placebo, and treated for 52 weeks. The frequency of nausea was broadly comparable between the two active formulations (approximately 20% with oral semaglutide vs 18% with subcutaneous liraglutide vs 8% with placebo), while treatment discontinuation due to adverse events was numerically higher with oral semaglutide than with liraglutide (Pratley et al., 2019). These early findings already signalled that the convenience of oral administration may come at the cost of slightly higher tolerability-driven discontinuation — a signal subsequently quantified in meta-analytic synthesis.

The Karedath et al. (2025) meta-analysis pooled data from one randomised trial and three retrospective real-world analyses (559 patients in total) and confirmed that, although GI adverse-event rates were broadly comparable, the relative risk of discontinuation due to adverse effects was significantly higher in patients receiving oral compared with subcutaneous semaglutide (RR: 1.79, 95% CI: 1.13–2.83). The 2025 meta-analysis by Drygalski et al. confirmed non-inferiority of oral over subcutaneous formulations for several glycaemic and weight-related endpoints overall, while signalling a more variable response distribution with the oral formulation, particularly at lower titration doses. A consolidated comparison of the pharmacological and clinical characteristics of the two formulations, drawing together the evidence presented across the preceding subsections, is provided in Table 2.

Table 2. Comparative pharmacological and clinical profile of oral and subcutaneous semaglutide based on data from included publications.

Parameter	Oral semaglutide	Subcutaneous semaglutide	Source
Standard maintenance dose	3 / 7 / 14 mg once daily (PIONEER PLUS up to 25–50 mg)	0.25 / 0.5 / 1.0 / 2.0 mg once weekly	Niman et al., 2021; Yang & Yang, 2024
Bioavailability	~1 %; highly variable, food- and pH-sensitive	~89 %; consistent	Yang & Yang, 2024; Karedath et al., 2025
Absorption mechanism	Co-formulated with absorption enhancer SNAC; gastric uptake	Subcutaneous depot absorption	Niman et al., 2021; Karedath et al., 2025
Time to maximum concentration (Tmax)	~1 h	~1–3 days	Yang & Yang, 2024
Half-life	~1 week (effective once-daily steady state achieved in 4–5 weeks)	~1 week (consistent with once-weekly dosing)	Yang & Yang, 2024
Administration constraints	Fasting, with ≤120 mL water; ≥30 min before food, drink or other oral medication	Subcutaneous injection (abdomen, thigh, upper arm); no fasting requirement	Niman et al., 2021
Mean HbA1c reduction (meta-analytic estimate)	−1.16 percentage points (95 % CI −1.22 to −1.10)	−1.40 percentage points	Drygalski et al., 2025
Common GI adverse events	Nausea, vomiting, diarrhoea, constipation; dose-dependent; comparable rates between formulations	Nausea, vomiting, diarrhoea, constipation; dose-dependent	Karedath et al., 2025; Chiang et al., 2025; Xie et al., 2025

Parameter	Oral semaglutide	Subcutaneous semaglutide	Source
Treatment discontinuation due to adverse effects	Higher (RR 1.79, 95 % CI 1.13–2.83 vs subcutaneous semaglutide)	Reference comparator	Karedath et al., 2025
Injection-site reactions	Not applicable	Mild erythema, pruritus, transient oedema; generally self-limiting	Nauck et al., 2021
Cardiovascular outcomes evidence	Non-inferior to placebo in T2DM with high CV risk (PIONEER 6: HR 0.79, 95 % CI 0.57–1.11)	Superior to placebo in T2DM (SUSTAIN-6 synthesis) and obesity without diabetes (SELECT: HR 0.80, 95 % CI 0.72–0.90)	Husain et al., 2019; Leiter et al., 2020; Lincoff et al., 2023
Renal outcomes evidence	Limited	FLOW trial: 24 % reduction in composite kidney endpoint (HR 0.76, 95 % CI 0.66–0.88)	Perkovic et al., 2024
Hepatobiliary risk	Increased class-level risk of cholelithiasis and cholecystitis; FAERS signal for acute cholecystitis	Increased class-level risk of cholelithiasis and cholecystitis	He et al., 2022; Ramírez-Mejía et al., 2025; Xiong et al., 2024
Pancreatitis	No confirmed excess in T2DM cohorts; ongoing pharmacovigilance	No confirmed excess in T2DM cohorts; signal in obesity weight-loss cohort comparator (aHR 9.09)	Ayoub et al., 2025; Sodhi et al., 2023
Real-world treatment persistence	Lower than in RCT settings; influenced by adherence to fasting protocol and pill burden	Lower than in RCT settings; influenced by injection acceptability and titration tolerability	Thomsen et al., 2025; Hoffmann et al., 2025; Wang et al., 2025

Cardiovascular and Renal Safety

Both oral and subcutaneous semaglutide have demonstrated cardiovascular safety in dedicated outcomes trials. PIONEER 6 (Husain et al., 2019) randomised 3,183 patients with T2DM at high cardiovascular risk to oral semaglutide 14 mg or placebo and demonstrated non-inferiority for the composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (HR 0.79, 95% CI 0.57–1.11), with a notable numerical reduction in cardiovascular death (0.9% vs 1.9%). Subcutaneous semaglutide demonstrated significant cardiovascular benefit in the SUSTAIN-6 programme (Leiter et al., 2020), and in obesity without diabetes the SELECT trial (Lincoff et al., 2023) randomised 17,604 adults with overweight or obesity and pre-existing cardiovascular disease and demonstrated a 20% relative reduction in major adverse cardiovascular events (HR 0.80, 95% CI 0.72–0.90; $p<0.001$) over a mean follow-up of 39.8 months.

In patients with chronic kidney disease and T2DM, the FLOW trial (Perkovic et al., 2024) randomised 3,533 participants to once-weekly subcutaneous semaglutide 1.0 mg or placebo and demonstrated a 24% reduction in the composite primary kidney endpoint (HR 0.76, 95% CI 0.66–0.88), alongside an 18% reduction in major cardiovascular events and a 20% reduction in all-cause mortality. The cardiovascular and renal safety database is therefore substantially more mature for subcutaneous formulations, although mechanistic class effects are presumed to be shared with the oral formulation.

Real-World Evidence and Pharmacovigilance Signals

Real-world evidence consistently demonstrates lower effectiveness and higher discontinuation than is observed in registration trials. Thomsen et al. (2025) reported that real-world treatment discontinuation rates for newer GLP-1 RA-based weight-loss therapies are substantial, with estimates of 20–50% within the first year of therapy and the principal driver being GI intolerance. The Polish prospective observational cohort by Hoffmann et al. (2025) corroborated that effectiveness in everyday clinical practice is attenuated relative to RCT findings, modulated by adherence, comorbidity burden and concomitant pharmacotherapy.

Pharmacovigilance signals derived from large adverse-event reporting systems further enrich the safety profile. The FAERS analysis of oral semaglutide tablets covering 2019–2023 (Xiong et al., 2024) identified — beyond expected GI symptoms — disproportionate signals for acute cholecystitis, dizziness and selected neurological disturbances, underscoring the importance of post-marketing surveillance. A complementary

analysis of weight-loss GLP-1 RA users compared with bupropion–naltrexone (Sodhi et al., 2023) reported significantly elevated adjusted hazard ratios for pancreatitis (aHR 9.09, 95% CI 1.25–66.00), bowel obstruction (aHR 4.22, 95% CI 1.02–17.40) and gastroparesis (aHR 3.67, 95% CI 1.15–11.90), although biliary disease did not reach statistical significance in that analysis. Such signals must be interpreted in the context of the wider class-level evidence base — the systematic review and meta-analysis by Chiang et al. (2025) integrating randomised data confirmed elevated odds of severe GI events but a more modest absolute risk than that suggested by selected pharmacovigilance signals alone.

Tolerability over Time and Dose Titration

A consistent finding across both oral and subcutaneous formulations is the time- and dose-dependence of GI tolerability. Symptoms typically peak during titration, attenuate over weeks to months as physiological adaptation occurs, and largely resolve at maintenance doses (Alhazmi & le Roux, 2026; Kim & Yoo, 2025). Slower titration regimens — particularly with oral semaglutide, for which bioavailability is more variable and food–drug interactions more pronounced — improve tolerability and reduce early discontinuation (Niman et al., 2021). Real-world adherence in turn determines the eventual cardiometabolic effectiveness and is a key bridge between trial-based and real-world outcomes (Wang et al., 2025).

Discussion

Principal Findings

This narrative synthesis of 2024–2026 evidence indicates that oral and subcutaneous GLP-1 receptor agonists share a broadly similar adverse-event spectrum — dominated by dose-dependent, transient GI symptoms — but differ in clinically meaningful ways with respect to pharmacokinetic predictability, tolerability-driven treatment discontinuation, and the maturity of the cardiovascular and renal outcomes evidence base. Subcutaneous formulations exhibit more stable systemic exposure, slightly better GI tolerability at therapeutically equivalent doses, and a significantly lower risk of treatment discontinuation due to adverse effects (RR 1.79 for oral vs subcutaneous semaglutide; Karedath et al., 2025). Oral semaglutide, while offering substantial advantages in patient convenience and acceptability, is constrained by absorption variability that translates into a more heterogeneous clinical response and a small but consistent excess in tolerability-driven discontinuation.

Pharmacokinetic Determinants of Safety Differences

The pharmacokinetic distinction between oral and subcutaneous formulations is the principal driver of the observed tolerability differential. Subcutaneous semaglutide exhibits slow, sustained absorption from the injection depot and a long elimination half-life consistent with once-weekly dosing, producing predictable systemic concentrations with low intra- and inter-individual variability (Yang & Yang, 2024). Oral semaglutide, by contrast, relies on the absorption enhancer SNAC to facilitate transgastric uptake and is highly sensitive to food intake, gastric pH and dosing technique (Karedath et al., 2025; Niman et al., 2021). The result is greater variability in systemic exposure that — although clinically manageable in most patients — likely accounts both for the more variable glycaemic and weight-loss responses and for higher rates of intolerable GI events in a minority of patients with disproportionately high peak exposures.

Comparison with Existing Literature

Our synthesis is largely concordant with the conclusions of the two most comprehensive comparative meta-analyses to date — Karedath et al. (2025) and Drygalski et al. (2025). Both reported broadly similar rates of common GI events between formulations but a higher discontinuation risk with the oral formulation. The earlier network meta-analysis by Alhindi & Avery (2022) had already signalled this tolerability differential at the time of regulatory approval. The increased risk of cholelithiasis and cholecystitis observed across the GLP-1 RA class in the meta-analysis of He et al. (2022) and the mechanistic synthesis of Ramírez-Mejía et al. (2025) is shared by both formulations and is mechanistically attributable to GI motility and bile-metabolism effects rather than to the route of administration. Reassuringly, recent class-level evidence does not support an excess risk of acute pancreatitis (Ayoub et al., 2025; Kim & Yoo, 2025), and current evidence regarding thyroid C-cell or thyroid-cancer signals — derived predominantly from preclinical work — remains insufficient to support firm clinical conclusions (Espinosa De Ycaza et al., 2024).

Clinical Implications and Individualised Therapy

From a clinical decision-making perspective, the choice between oral and subcutaneous GLP-1 RA should be individualised. Patients prioritising injection avoidance, those with a strong preference for daily oral dosing, or those for whom adherence to weekly self-injection is uncertain may benefit from oral semaglutide, particularly when slow titration is feasible and when the patient is able to adhere reliably to the fasting administration protocol. Conversely, patients prioritising maximal glycaemic and weight-loss efficacy, those with established cardiovascular or renal disease for whom outcomes evidence is more mature with subcutaneous formulations (Husain et al., 2019; Lincoff et al., 2023; Perkovic et al., 2024; Leiter et al., 2020), and those with significant GI comorbidity, polypharmacy or pill burden may be better served by once-weekly subcutaneous administration. Counselling regarding expected GI symptoms during titration, slow dose escalation and proactive management of nausea (Alhazmi & le Roux, 2026) materially reduces discontinuation in routine clinical practice.

Strengths and Limitations

The strengths of this synthesis include its focus on contemporary 2024–2026 evidence, integration of real-world evidence with randomised data, and inclusion of large pharmacovigilance datasets to surface low-frequency signals. Several limitations should be acknowledged. The literature search was restricted to PubMed, PubMed Central and targeted Google Scholar searches; grey literature and non-English-language publications were not systematically retrieved, and we did not formally register a review protocol or perform a quantitative meta-analytic synthesis. Direct head-to-head trials between oral and subcutaneous semaglutide remain few, so much of the comparative inference necessarily relies on indirect comparison and on a single randomised trial within the principal comparative meta-analysis (Karedath et al., 2025). Follow-up duration in available real-world studies is generally short relative to the chronic nature of T2DM and obesity therapy, leaving long-term safety questions — including the retinopathy progression signal observed in SUSTAIN-6, biliary tract neoplasia, thyroid C-cell tumours and gastroparesis-related morbidity — open to ongoing investigation.

Future Research Directions

Priorities for future research include adequately powered head-to-head randomised trials directly comparing oral and subcutaneous GLP-1 RAs across diverse populations (including older adults, patients with chronic kidney disease, and those with obesity without diabetes); longer-term prospective real-world cohorts with active surveillance for low-frequency adverse events; identification of clinical or pharmacogenomic predictors of intolerance that could inform pre-treatment risk stratification; and continued pharmacovigilance — supported by harmonised reporting in administrative databases such as FAERS, EudraVigilance and similar national registries — to characterise rare but clinically significant adverse events. Comparative effectiveness research should additionally integrate patient-reported outcomes, treatment satisfaction and persistence as primary outcomes, given that adherence is the principal mediator of cardiometabolic benefit in routine care.

Conclusions

Oral and subcutaneous GLP-1 analogues share a broadly similar safety profile, with GI adverse effects constituting the principal tolerability challenge for both formulations. However, clinically meaningful differences exist: subcutaneous formulations provide more predictable pharmacokinetics, greater glycaemic and weight reduction, and a significantly lower risk of treatment discontinuation due to adverse effects. Oral semaglutide offers the convenience of non-injectable administration but is subject to greater bioavailability variability and a higher discontinuation rate. The selection of administration route should be individualised according to patient preferences, comorbidity burden, and the likelihood of sustained adherence. Long-term studies and expanded real-world analyses are required to comprehensively characterise the safety of this drug class.

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