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Review Article

Oral GLP-1 Receptor Agonists: The Next Generation of Obesity Pharmacotherapy

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ABSTRACT

Background: Obesity is a chronic, relapsing disease associated with cardiometabolic complications and substantial health-system burden. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have transformed pharmacological weight management, but injectable administration, access, cost, and treatment persistence can limit their use. Oral GLP-1 RAs may expand treatment options by combining incretin-based efficacy with tablet administration.

Objective: To review the pharmacology, clinical evidence, therapeutic applications, safety, and future directions of oral GLP-1 receptor agonists for obesity pharmacotherapy.

Methods: A narrative review was developed from peer-reviewed clinical trials and reviews, regulatory documents, and authoritative prescribing information. Emphasis was placed on oral semaglutide and orforglipron, including phase 3 evidence available through October 2026. This was not a systematic review and no formal risk-of-bias assessment or quantitative synthesis was performed.

Results: In the OASIS 4 randomized trial, oral semaglutide 25 mg daily produced an estimated mean body-weight change of −13.6% at week 64, compared with −2.2% with placebo, among adults with overweight or obesity without diabetes. In the 72-week ATTAIN-1 trial, orforglipron produced mean body-weight changes of −7.5%, −8.4%, and −11.2% at the 6-mg, 12-mg, and 36-mg doses, respectively, compared with −2.1% with placebo. Gastrointestinal adverse events were common with both agents. Oral semaglutide and orforglipron received US approval for chronic weight management in 2025 and 2026, respectively; regulatory status differs by jurisdiction.

Conclusion: Oral GLP-1 RAs represent a major advance in obesity treatment, potentially improving convenience and expanding patient choice. Their benefits must be considered alongside gastrointestinal tolerability, contraindications, medication administration requirements, cost, access, and the need for long-term follow-up. Comparative effectiveness should not be inferred from cross-trial weight-loss percentages.

Keywords: Obesity; GLP-1 receptor agonists; oral semaglutide; orforglipron; pharmacotherapy; weight management; incretin; cardiometabolic risk.

1. Introduction

Obesity is a chronic and multifactorial disease involving biological, behavioural, environmental, and social determinants. It is associated with type 2 diabetes, cardiovascular disease, obstructive sleep apnoea, metabolic dysfunction-associated steatotic liver disease, osteoarthritis, and impaired quality of life. Contemporary treatment therefore extends beyond short-term weight reduction to long-term health improvement and management of weight regain. [1,2]

GLP-1 receptor agonists (GLP-1 RAs) have become important pharmacological options because they influence appetite, satiety, energy intake, gastric emptying, and glucose regulation. Injectable semaglutide and other incretin-based therapies have demonstrated substantial weight reduction in clinical trials. However, injections, supply, affordability, and patient preferences can influence treatment uptake and persistence. [3,4]

Oral formulations represent a new phase in obesity pharmacotherapy. Oral semaglutide is a peptide formulated with an absorption enhancer, whereas orforglipron is a non-peptide small-molecule GLP-1 RA. These distinct molecular approaches have different administration requirements and pharmacological properties. By October 2026, oral semaglutide 25 mg and orforglipron had received US approval for chronic weight management, although availability and approved indications must be checked locally. [5-8]

This review summarizes the rationale for oral GLP-1 therapy, appraises pivotal clinical evidence, discusses clinical selection and safety, and identifies research priorities for integrating these agents into long-term obesity care.

2. Methodology / Literature Search Strategy

A narrative literature review was prepared using peer-reviewed clinical trials, review articles, regulatory decisions, and official prescribing information relevant to oral GLP-1 receptor agonists for weight management. Sources were identified through PubMed-indexed literature and targeted searches of journal and regulatory websites, focusing on oral semaglutide, the OASIS programme, orforglipron, the ATTAIN programme, obesity guidelines, and safety labelling.

Priority was given to randomized controlled trials, major peer-reviewed reviews, and current official product information. The review emphasized efficacy outcomes, study populations, adverse events, dosing and administration, regulatory status, and limitations of cross-trial comparisons. Evidence was considered current through 30 October 2026.

This manuscript is a narrative review rather than a systematic review. No exhaustive reproducible database search, formal screening log, protocol registration, or structured risk-of-bias assessment was performed. The article therefore does not claim comprehensive study capture or provide a PRISMA flow diagram.

3. Background

3.1 GLP-1 physiology and obesity

GLP-1 is an incretin hormone released primarily from intestinal enteroendocrine L cells after nutrient exposure. GLP-1 receptor activation enhances glucose-dependent insulin secretion, suppresses inappropriate glucagon secretion, and contributes to appetite and energy-intake regulation through peripheral and central pathways. Pharmacological GLP-1 RAs extend receptor activation beyond the short physiological exposure of endogenous GLP-1. [3,4]

Weight loss with GLP-1 RAs is largely mediated by reduced energy intake and increased satiety, with effects on gastric emptying also contributing, particularly early in treatment. Response varies among individuals, and medication should be integrated with nutritional, behavioural, physical-activity, and clinical support.

3.2 Why oral GLP-1 receptor agonists?

Oral therapy may be attractive to people who prefer tablets, have difficulty with injections, or face practical barriers to injectable administration. However, oral delivery of peptide medicines is challenging because of enzymatic degradation and limited gastrointestinal permeability. Oral semaglutide uses the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) to facilitate gastric absorption. Orforglipron is a non-peptide small molecule designed for oral delivery and does not require the same peptide absorption-enhancer approach.

3.3 Obesity pharmacotherapy as chronic disease management

Guidelines recommend considering anti-obesity medication for eligible patients as an adjunct to lifestyle intervention, based on body mass index, complications, treatment goals, preferences, contraindications, and local regulatory criteria. Weight regain after stopping effective therapy is common, reinforcing the need to discuss chronic treatment, follow-up, and sustainable access from the outset. [1,2,9]

4. Current Evidence

4.1 Oral semaglutide: OASIS 4

OASIS 4 was a 71-week, double-blind, randomized, placebo-controlled trial involving adults without diabetes who had a BMI of at least 30 kg/m², or at least 27 kg/m² with an obesity-related complication. Participants received oral semaglutide 25 mg once daily or placebo, alongside lifestyle intervention. At week 64, the estimated mean body-weight change was −13.6% with oral semaglutide and −2.2% with placebo, a between-group difference of −11.4 percentage points. Gastrointestinal adverse events were reported in 74.0% and 42.2%, respectively. [5]

These results establish clinically meaningful weight-loss efficacy for the studied regimen in the trial population. They should not be interpreted as directly equivalent to outcomes from injectable semaglutide or other agents because trials differ in duration, population, estimand, adherence, and study design.

4.2 Orforglipron: ATTAIN-1

ATTAIN-1 was a phase 3, multinational, randomized, double-blind trial in 3,127 adults with obesity, or overweight with a weight-related complication, without diabetes. At week 72, mean body-weight changes under the treatment-regimen estimand were −7.5% with 6 mg, −8.4% with 12 mg, and −11.2% with 36 mg of orforglipron, compared with −2.1% with placebo. Gastrointestinal events were the most common adverse events, and treatment discontinuation due to adverse events occurred more frequently in active-treatment groups than in the placebo group. [6]

As a non-peptide small molecule, orforglipron may offer practical advantages in administration. The US product information states that it can be taken once daily with or without food. This flexibility may be meaningful for adherence, although real-world persistence and comparative effectiveness require ongoing evaluation. Regulatory status, available strengths, and product labelling vary by jurisdiction.[7]

4.3 Regulatory status and clinical translation

The US FDA approved oral semaglutide tablets for chronic weight management in December 2025 and approved orforglipron for chronic weight management in 2026. These developments mark a shift from oral GLP-1 therapy being primarily associated with diabetes treatment to oral formulations with specific obesity indications. Clinicians must verify the latest local label rather than extrapolate US indications to other countries. [7,8]

Approval does not remove the need for individualized prescribing. Eligibility, contraindications, dosing escalation, product availability, reimbursement, and post-marketing safety requirements are jurisdiction-specific. Oral agents should be used only under appropriate prescribing and follow-up.

4.4 Interpreting efficacy across trials

Observed weight-loss percentages from OASIS 4 and ATTAIN-1 should not be used to rank oral semaglutide against orforglipron directly. These were separate trials with different durations, populations, dose regimens, analysis estimands, and placebo responses. Head-to-head randomized trials and real-world comparative studies are needed to establish relative efficacy, tolerability, persistence, cost-effectiveness, and patient-reported outcomes.

Table 1. Key randomized evidence for oral GLP-1 receptor agonists in obesity

Study / agent	Design and population	Regimen and duration	Mean body-weight change	Important interpretation
OASIS 4: oral semaglutide	Randomized, double-blind, placebo-controlled; adults with overweight/obesity without diabetes; n=307	25 mg once daily; 71-week trial; primary weight endpoint at week 64	−13.6% semaglutide vs −2.2% placebo at week 64	GI adverse events: 74.0% vs 42.2%; trial-specific estimate
ATTAIN-1: orforglipron	Phase 3 randomized, double-blind; adults with obesity/overweight complication without diabetes; n=3,127	6, 12, or 36 mg once daily; 72 weeks	−7.5%, −8.4%, −11.2% vs −2.1% placebo	GI events most common; discontinuation due to adverse events 5.3–10.3% vs 2.7% placebo

Abbreviations: GI, gastrointestinal; GLP-1, glucagon-like peptide-1. Values are taken from the cited trials and are not a head-to-head comparison.

5. Clinical Applications

5.1 Patient selection

Oral GLP-1 RAs may be considered for adults who meet the locally approved criteria for chronic weight management and for whom pharmacotherapy is appropriate alongside lifestyle intervention. Selection should account for BMI and complications, prior treatment, goals, preferences, comorbidities, pregnancy plans, contraindications, affordability, and capacity for long-term follow-up.

5.2 Shared decision-making

Patients should be counselled that response varies, titration is generally used to improve tolerability, and nausea or other gastrointestinal symptoms can occur. Discussion should include expected benefits, realistic treatment goals, the possibility of long-term use, cost and access, missed-dose instructions from the product label, and what to do if adverse effects persist.

5.3 Integration with lifestyle and comorbidity care

Medication is not a replacement for nutrition support, physical activity, sleep assessment, behavioural care, or management of obesity-related complications. Follow-up can include weight trajectory, waist circumference where appropriate, blood pressure, glycaemic status, lipid profile, functional status, quality of life, and symptoms of adverse effects. Treatment goals should include health and function rather than weight alone.

5.4 Potential role in cardiometabolic risk reduction

Weight reduction can improve several cardiometabolic risk factors, but outcome claims must be tied to the particular molecule, formulation, population, and indication supported by evidence and labelling. Cardiovascular outcome evidence from one semaglutide formulation or trial should not automatically be attributed to every oral GLP-1 RA. Product-specific indications and supporting evidence must be reviewed.

5.5 Practical clinical pathway

- Assess obesity-related health risks, prior treatment, goals, and eligibility under the local product label.
- Review contraindications, pregnancy status or plans, relevant comorbidities, and concomitant medicines.
- Explain expected benefits, gastrointestinal tolerability, administration instructions, cost, and long-term treatment considerations.
- Initiate the locally approved starting dose and titrate according to the product label and tolerability.
- Monitor weight trajectory, symptoms, hydration, relevant metabolic measures, and treatment persistence.
- Reassess benefit-risk balance, adherence, affordability, and the need for continued or alternative treatment.

6. Safety & Limitations

6.1 Gastrointestinal effects and tolerability

Nausea, vomiting, diarrhoea, constipation, and abdominal discomfort are common adverse effects of GLP-1 RAs, particularly during initiation and dose escalation. Gradual titration according to the approved label, smaller meals, hydration, and clinical review of persistent symptoms may help. Severe or prolonged symptoms require assessment for dehydration, renal consequences, or another diagnosis.

6.2 Important warnings and precautions

Current US prescribing information for semaglutide and orforglipron includes a boxed warning concerning thyroid C-cell tumours observed in rodents; the relevance to humans is unknown. These products are contraindicated in people with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Product-specific warnings also address issues such as pancreatitis, gallbladder disease, severe gastrointestinal reactions, and other risks; the complete current label must be consulted. [7,8]

GLP-1 RAs are not appropriate for weight loss during pregnancy. Patients who become pregnant or are planning pregnancy should receive product-specific medical advice. Before procedures requiring anaesthesia or deep sedation, clinicians should follow current peri-procedural guidance and assess individual risk because delayed gastric emptying may be relevant.

6.3 Drug interactions and oral administration

Oral semaglutide has product-specific administration instructions designed to support absorption, including taking the tablet on an empty stomach with a small amount of water and waiting before food, beverages, or other oral medicines as specified in the label. Orforglipron has different administration instructions and can be taken with or without food under US labelling. These regimens are not interchangeable. Clinicians and pharmacists should review concomitant medicines, potential effects of delayed gastric emptying, and product-specific interaction information.

6.4 Treatment discontinuation and weight regain

Obesity is a chronic disease, and discontinuation of effective pharmacotherapy may be followed by weight regain. Decisions to stop or switch treatment should consider adverse effects, patient preferences, pregnancy, cost, availability, clinical response, and alternative treatment options. Follow-up and a plan for ongoing weight management are important regardless of whether medication continues.

6.5 Evidence limitations

Pivotal studies differ in population, trial duration, dose, estimand, and lifestyle co-interventions. Trial participants may not represent all patients seen in routine practice, and long-term comparative effectiveness, persistence, rare adverse events, cost-effectiveness, and outcomes in diverse populations remain important areas for study. Manufacturer funding of pivotal trials should be transparently reported and considered alongside the strength and consistency of the evidence.

Table 2. Practical comparison of oral GLP-1 receptor agonists

Feature	Oral semaglutide 25 mg	Orforglipron
Molecular type	Peptide GLP-1 receptor agonist	Non-peptide small-molecule GLP-1 receptor agonist
Oral delivery	Uses SNAC absorption enhancer; label-specific fasting administration	Small-molecule oral delivery; US label permits administration with or without food
Pivotal obesity trial	OASIS 4	ATTAIN-1
Trial duration / main endpoint	71-week trial; weight change assessed at week 64	72 weeks; weight change at week 72
Mean weight change vs placebo	−13.6% vs −2.2% at week 64	−7.5%, −8.4%, −11.2% vs −2.1% at week 72 across trial doses
Common tolerability issue	Gastrointestinal adverse events	Gastrointestinal adverse events
Key caveat	Follow the exact product label; not equivalent to diabetes-dose oral semaglutide	Follow current product label; trial percentages should not be compared directly with OASIS 4

Note: The table summarizes selected trial and label characteristics, not a prescribing recommendation. Verify current local authorisation, strengths, instructions, warnings, and reimbursement

7. Emerging Advances

7.1 New oral incretin molecules

The oral pipeline includes small-molecule GLP-1 receptor agonists and other incretin-based compounds designed to improve efficacy, administration flexibility, stability, and scalability. Clinical development should be judged by randomized evidence, tolerability, persistence, clinically meaningful outcomes, and comparative effectiveness rather than mechanistic novelty alone.

7.2 Beyond body weight

Future studies should examine physical function, obesity-related complications, quality of life, sleep apnoea, liver disease, cardiovascular outcomes, and maintenance of weight loss. Benefits may differ by baseline disease, degree of weight reduction, duration of exposure, and the specific molecule.

7.3 Personalised obesity pharmacotherapy

Treatment choice may increasingly incorporate comorbidities, previous medication response, adverse-effect susceptibility, patient preference, and affordability. Biomarkers and clinical prediction tools remain investigational for selecting one GLP-1 RA over another and should not be presented as established routine practice without validation.

7.4 Formulation and adherence innovation

Simplified administration could reduce practical barriers, but actual adherence depends on cost, availability, tolerability, health literacy, expectations, and continuity of care. Real-world studies are needed to determine whether oral administration improves persistence compared with injectable therapy.

8. Pharmacist's Role

Pharmacists can support safe and effective use of oral GLP-1 RAs through medication reconciliation, counselling, adherence support, monitoring, and collaboration with prescribers.

- Verify the exact product, indication, dose, titration schedule, administration instructions, and locally approved label.
- Counsel on gastrointestinal effects, hydration, missed doses, and when symptoms warrant urgent clinical review.
- Review concomitant medicines, relevant interactions, and potential effects of delayed gastric emptying.
- Identify contraindications and precautions, including personal or family history of medullary thyroid

carcinoma or MEN2 where specified by the label, pregnancy, and relevant comorbidities.
- Monitor treatment response, tolerability, weight trajectory, metabolic parameters, and treatment persistence.
- Discuss affordability, supply continuity, and the risk of unregulated or counterfeit products; do not endorse compounded or non-approved products as equivalent to approved medicines.
- Coordinate with dietitians, physicians, and obesity-care teams to support sustainable lifestyle changes and long-term follow-up

9. Research Gaps

- Head-to-head trials comparing oral semaglutide, orforglipron, and injectable incretin therapies using harmonized endpoints.
- Long-term safety and effectiveness beyond pivotal trial follow-up, including rare events and real-world persistence.
- Evidence in older adults, people with complex multimorbidity, diverse ethnic populations, and underrepresented health systems.
- Cost-effectiveness, affordability, access, and effects of reimbursement policy on treatment continuation.
- Maintenance strategies after dose reduction, treatment interruption, or discontinuation.
- Comparative effects on physical function, quality of life, obesity-related complications, and cardiovascular outcomes.
- Pregnancy-related evidence and practical management around planned pregnancy, procedures, and complex medication regimens.
- Independent post-marketing studies to complement industry-sponsored pivotal trials.

10. Future Perspectives

Oral GLP-1 RAs may broaden treatment choice and lower practical barriers for some patients, but their impact will depend on affordability, availability, tolerability, appropriate prescribing, and long-term continuity. Research should prioritise direct comparisons, patient-centred outcomes, real-world effectiveness, and equitable access. Obesity services will need systems for structured follow-up, dose escalation, adverse-effect management, and support for sustained behavioural change.

Future guidance should clarify how oral agents fit alongside injectable GLP-1 RAs, dual incretin agonists, other anti-obesity medicines, metabolic surgery, and multidisciplinary care. Product-specific cardiovascular and other outcome claims should be based on dedicated evidence and approved labelling. The goal is not simply to make treatment oral, but to make long-term obesity care more effective, acceptable, and accessible.

11. Conclusion

Oral GLP-1 receptor agonists represent an important development in obesity pharmacotherapy. Phase 3 evidence shows that oral semaglutide 25 mg and orforglipron can produce clinically meaningful weight reduction compared with placebo in studied populations. Their molecular and administration differences may broaden patient choice, but gastrointestinal adverse effects, contraindications, administration requirements, cost, and long-term treatment needs remain central to safe use. Cross-trial comparisons cannot establish which agent is superior. Individualized prescribing, pharmacist counselling, lifestyle support, local-label adherence, and prospective real-world evaluation will be essential to realizing the potential of this next generation of obesity treatment.

12. Declarations

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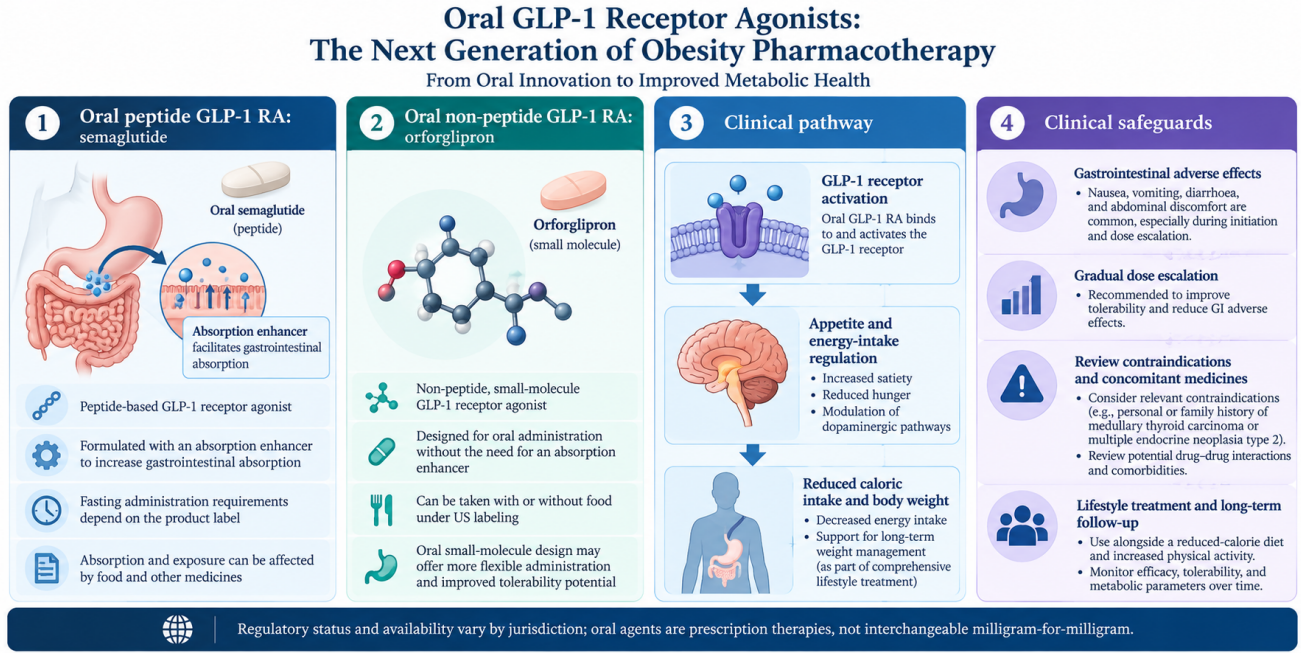
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14. Figures

Figure 1. Oral GLP-1 receptor agonists: molecular approaches, clinical pathway, and safeguards.



Note: This conceptual figure is for educational synthesis. Administration instructions and regulatory status must be confirmed against the current local product label.