# From Needles to Tablets: Integrating Oral Treatments Into Obesity Care

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## INTRODUCTION

Obesity is a chronic disease characterized by excess adiposity that impairs health, and current estimates suggest the clinical burden will continue to expand over the coming decades in the United States.[1,2] A recent cross-sectional analysis suggests that approximately 46.9% of US adults will be living with obesity by 2035, compared to 42.5% in 2022 and 19.3% in 1990.[3] The consequences of obesity extend far beyond body weight alone to include cardiometabolic disease, obstructive sleep apnea, steatotic liver disease, osteoarthritis, physical limitations, and impaired quality of life.[2,4]

Framing obesity as a chronic disease is essential when approaching treatment. Diagnostic and treatment algorithms emphasize that body mass index (BMI) remains a screening tool, though used in association with other measures such as waist-to-height ratio. Treatment should be individualized according to complications, health goals, and patient characteristics.[2,5,6] As described in the "Comprehensive Obesity Management" series published in *Hot Topics in Primary Care 2025* (https://www.medscape.com/infosites/432972.3), obesity care is strengthened when clinicians use person-first language, ask permission to discuss weight, and structure management around the 5 As: Ask, Assess, Advise, Agree, and Assist.[7,8]

Historically, oral obesity pharmacotherapy offered convenience but often only modest efficacy. Short-course phentermine, long-term orlistat, naltrexone/bupropion, and phentermine/topiramate remain clinically useful in selected patients, yet most oral options before the incretin era were limited by single-digit mean weight loss, contraindications, or adverse-effect profiles that narrowed long-term use.[9,10]

### Key takeaways

- Oral obesity pharmacotherapy now spans legacy agents that deliver modest weight loss and newer incretin-based therapies that can produce double-digit reductions in body weight.
- Choice of an oral obesity agent should be individualized based on efficacy, complications, route preference, dosing burden, gastrointestinal (GI) tolerability, cost, and expected long-term persistence.
- Successful implementation of oral obesity therapies involves approaching obesity as a chronic disease.
- Primary care clinicians (PCCs) should emphasize shared decision-making, appropriate dose titration, proactive mitigation of GI adverse events, nutrition and exercise, behavioral therapy if indicated, and regular follow-up when managing obesity with oral treatments.

Other oral obesity therapies were withdrawn from the market: sibutramine was removed after cardiovascular safety concerns, and lorcaserin left the market after a postmarketing safety review identified cancer signals.[11,12] The historical landscape of oral obesity therapies can remind PCCs that convenience alone does not outweigh potential risks in some cases.

Today, oral incretin therapy represents a meaningful shift toward increased efficacy and acceptable tolerability for obesity therapy. Oral semaglutide 25 mg is approved as a once-daily treatment for weight management, and orforglipron—also taken once daily—was approved in April 2026 for the same indication.[13,14] These advances present important alternatives to injectable obesity therapies, which were pre-

viously the only incretin-based treatments for obesity.[10] Oral obesity therapy offers another route of administration based on preferences, helping patients access the medication and remain adherent to treatment to maximize potential benefit.[10,15] Considerations for initiating oral obesity therapy are similar to considerations for injectable incretin-based therapies, such as titration dosing, minimizing and managing GI adverse effects, and helping patients access and adhere to the treatment to maximize potential benefit.[10,15] Current and emerging options for oral obesity pharmacotherapy are summarized in **TABLE 1**.[13,16-22]

## CASE STUDY

SB is a 57-year-old woman with obesity (from Part 1 and Part 2 of this series) who has done well on tirzepatide 10 mg once weekly for the past 2 years and reports better sleep, improved function, and more confidence in long-term treatment.

Her 32-year-old daughter, KB, accompanies her and has an appointment to discuss weight management immediately following her mother's appointment. KB's BMI is 33 kg/m$^2$ and she asks about obesity treatment. She is interested in obesity medication but says that injections her mom is taking are not her preference. Using the 5 As, the PCC frames the discussion around whether the daughter meets criteria for pharmacotherapy, what outcomes matter most to her, and whether an oral regimen would improve the likelihood that she can start and persist with treatment.

## OVERVIEW OF CURRENT ORAL OBESITY THERAPIES

Current guidelines continue to position pharmacotherapy as an adjunct to nutrition, physical activity, sleep, stress management, and behavioral support for adults with obesity or overweight plus at least 1 weight-related complication.[5,10,23] Within that framework, oral therapies encompass 2 broad roles in practice: established nonincretin agents that are indicated in certain clinical scenarios and newer incretin-based tablets that may offer much greater compliance by patients who prefer not to use injectable therapies.[5,9]

Cost, coverage, and financial durability remain central to treatment selection. Oral therapy may be less expensive or easier to access than injectable therapy, though the practical success of any medication depends on whether the patient can obtain it consistently after the initial prescription and through titration to maintenance dosing.[10,15] For many patients, the best obesity medication is selected based on a combination of factors such as efficacy, tolerability, accessibility, dosing, persistence, and patient preference.[5,6]

**TABLE 1. Current and emerging oral obesity agents.**

| Agent | FDA approval | Mechanism | Efficacy | Key practical considerations |
|---|---|---|---|---|
| Phentermine[17] | 1959 (short-term use) | Sympathomimetic appetite suppression | Modest, generally single-digit mean weight loss | Low cost in some settings; avoid where stimulatory effects or misuse risk are problematic |
| Orlistat[18] | 1999 | Gastrointestinal lipase inhibition | Modest mean weight loss | Noncentral mechanism; counsel on oily stools, meal fat content, and fat-soluble vitamin use |
| Phentermine/topiramate ER[19] | 2012 | Sympathomimetic plus central appetite effects | Upper single-digit to near-double-digit mean weight loss | More effective than older oral monotherapies; consider teratogenicity, paresthesia, and contraindications |
| Naltrexone/bupropion ER[20] | 2014 | Opioid antagonism plus norepinephrine/dopamine reuptake inhibition | Modest-to-moderate mean weight loss | Can help patients with hedonic eating concerns; avoid when seizure risk or uncontrolled hypertension is present |
| Oral semaglutide 25 mg[13] | 2025 | Peptide GLP-1 receptor agonist | Double-digit mean weight loss demonstrated in phase 3 obesity trial | Once daily but must be taken fasting with up to 4 oz water and 30-minute wait before food, drink, or other oral medications |
| Orforglipron[16] | 2026 | Small-molecule, nonpeptide GLP-1 receptor agonist | Double-digit mean weight loss demonstrated in phase 3 obesity trial | Once daily without fasting or water restrictions |
| Zenagamtide (amycretin)[21] | Investigational; early phase | GLP-1 and amylin receptor agonist | Positive data from early trials | Additional clinical trials ongoing |

**Abbreviations:** ER, extended release; FDA, US Food and Drug Administration; GLP-1, glucagon-like peptide 1.

Legacy oral agents may remain an option for certain patients even though newer incretin therapies are more effective on average. Phentermine/topiramate can provide greater efficacy than older single agents when the risk-benefit profile is acceptable. Naltrexone/bupropion can be useful when food cravings or depression history shape treatment goals. Orlistat may fit patients who prefer a noncentral mechanism and are willing to accept GI tradeoffs.[5,9] These agents rarely produce the magnitude of weight loss seen with newer incretins, but they remain relevant if cost is lower, coverage is better, large amounts of weight reduction are not needed, and/or the patient values a noninjectable option with a long clinical track record.

Oral semaglutide and orforglipron have shown double-digit weight loss in clinical trials, as described below. Selecting between the 2 therapies involves matching the right drug to the right patient by aligning attributes of medications with preferences. For example, a key difference between oral semaglutide and orforglipron is administration. Oral semaglutide is a peptide GLP-1 receptor agonist formulated for once-daily use, but it must be taken on an empty stomach with no more than 4 oz of plain water, followed by a wait of at least 30 minutes before food, beverages, or other oral medications.[13] Orforglipron is a nonpeptide small-molecule GLP-1 receptor agonist with once-daily dosing that does not require fasting or water-volume restrictions. This may reduce dosing complexity and align with patient preferences, especially for those who take multiple medications in the morning or have strict dietary requirements.[24] Characteristics of oral semaglutide and orforglipron are discussed in **TABLE 2**.

These distinctions between older and newer oral obesity therapies underscore an important principle of obesity care: matching drug attributes to patient preferences can improve persistence. Route of administration, timing restrictions, GI tolerability, work and travel patterns, privacy concerns, and coexisting diabetes or other comorbidities all shape whether an oral therapy is a practical long-term option for a particular patient.[25,26]

## CLINICAL EVIDENCE FOR NEWER ORAL OBESITY THERAPIES

### *Orforglipron*

Orforglipron is a small-molecule GLP-1 receptor agonist taken orally once daily. Of note, this article presents efficacy and safety data from the investigational orforglipron capsule formulation (1 mg, 3 mg, 6 mg, 12 mg, 24 mg, and 36 mg) shown as equivalent doses of once daily orforglipron tablets (0.8 mg, 2.5 mg, 5.5 mg, 9 mg, 14.5 mg, and 17.2 mg) approved in the United States.[14] In the phase 3 ATTAIN-1 trial in adults with obesity or overweight with at least 1 obesity-related complication except diabetes, the mean change in body weight at 72 weeks was –7.5%, –8.4%, and –11.2% with 5.5, 9, and 17.2 mg, respectively, vs –2.1% with placebo.[16] At the 17.2 mg dose, 54.6% of participants achieved at least 10% weight loss, 36.0% achieved at least 15% loss, and 18.4% achieved at least 20% loss. Discontinuation due to adverse events ranged from 5.3% to 10.3% vs 2.7% with placebo. The most common adverse events with orforglipron were GI related: nausea, constipation, diarrhea, vomiting, and dyspepsia.[16]

In ATTAIN-2, which enrolled adults with obesity or overweight plus type 2 diabetes, efficacy was smaller than in the nondiabetes population but still clinically relevant. Mean body-weight change at week 72 was –5.1%, –7.0%, and –9.6% with 5.5, 9, and 17.2 mg, respectively, vs –2.5% with placebo, with parallel improvements in glycemia and cardiometabolic risk markers.[27] GI symptoms were the most common adverse event observed, and discontinuation because of adverse events ranged from 6.1% to 10.6% with orforglipron vs 4.6% with placebo.[27]

### *Oral semaglutide*

For oral semaglutide, FDA approval was based on pivotal obesity data from the OASIS 4 trial. In adults with overweight or obesity, once-daily oral semaglutide 25 mg produced a mean body weight change of –13.6% at 64 weeks compared with –2.2% for placebo, for an estimated treatment difference of –11.4 percentage points. GI adverse events (nausea, vomiting, constipation, dyspepsia, and diarrhea) were the most common adverse events reported in those taking oral semaglutide, and discontinuation due to adverse events was 6.9% with oral semaglutide and 5.9% with placebo.[28]

### *Emerging agents*

Several earlier-stage investigational oral obesity therapies are currently being studied. Oral zenagamtide (amycretin), a GLP-1 and amylin receptor agonist, has shown significant weight loss and acceptable safety and tolerability in a phase 1b/2a trial, supporting continued development.[21,29]

## PRACTICAL STRATEGIES TO IMPLEMENT ORAL OBESITY THERAPIES

Patients most likely to benefit from oral obesity therapy are those who meet standard criteria for pharmacotherapy but decline injections; those who may have stopped an injectable primarily because of route burden rather than lack of effect; and those whose work, travel, privacy, or caregiving constraints make oral dosing more acceptable.[10,15] Oral therapy also may be attractive in patients with obesity and type 2 diabetes when the clinician recommends a drug with an incretin-based mechanism of action but the patient strongly prefers a tablet.[10]

How oral therapy is introduced matters; PCCs should

**TABLE 2. Characteristics of oral semaglutide and oral orforglipron for obesity treatment.**

| Feature | Oral semaglutide 25 mg[13] | Orforglipron[14] |
|---|---|---|
| Molecule/class | Peptide GLP-1 receptor agonist | Small-molecule nonpeptide GLP-1 receptor agonist |
| FDA approval | December 2025 | April 2026 |
| Indication | In combination with a reduced calorie diet and increased physical activity:<br>• Reduce the risk of major adverse events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in adults with established cardiovascular disease and either obesity or overweight<br>• Reduce excess body weight and maintain weight reduction long term in adults with obesity, or in adults with overweight in the presence of at least one weight-related comorbid condition | In combination with a reduced-calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition |
| Administration | Morning dose on empty stomach with up to 4 oz plain water only; wait at least 30 minutes before food, beverages, or other oral medications | Once-daily oral dosing without fasting, water-volume, or timing restrictions |
| Dosing and titration | • Starting dosage: 1.5 mg orally once daily<br>• After 30 days on the 1.5 mg dosage, increase the dosage to 4 mg once daily<br>• After 30 days on the 4 mg dosage, increase the dosage to 9 mg once daily<br>• After 30 days on the 9 mg dosage, increase to the maintenance dosage of 25 mg once daily | • Starting dosage: 0.8 mg orally once daily<br>• After at least 30 days on the 0.8 mg dosage, increase the dosage to 2.5 mg once daily<br>• After at least 30 days on the 2.5 mg dosage, increase the dosage to 5.5 mg once daily<br>• The dosage may be increased to the next dosage level (9 mg, 14.5 mg, or 17.2 mg once daily) after at least 30 days on the current dosage, based on treatment response and tolerability |
| Evidence base in obesity | Positive phase 3 obesity trial with double-digit mean weight loss (OASIS 4)[28] | Positive phase 3 obesity trial data with dose-related weight loss (ATTAIN-1)[16]<br>Positive phase 3 obesity plus type 2 diabetes data (ATTAIN-2)[27] |
| Common adverse effects | Mainly gastrointestinal: nausea, diarrhea, vomiting, constipation | Mainly gastrointestinal: nausea, diarrhea, vomiting, constipation |
| Likely best-fit patient | Patient who prefers an oral tablet and can reliably follow fasting/timing rules | Patient who prefers an oral tablet without requirements for meal timing administration |

present oral options not as a shortcut, but as part of chronic disease care that still requires a long-term plan, realistic expectations, and ongoing follow-up.[5,6] It may be useful to frame the conversation by discussing average weight response in percentage terms, emphasize that early GI symptoms are common but often improve, and explain that the goal is not to "try a pill" briefly but to identify a safe and effective therapy that can be sustained long-term.[15]

Counseling about dose titration should also be presented to patients clearly. They should know in advance that nausea, early satiety, constipation, diarrhea, and occasional vomiting are usually most prominent during initiation and dose escalation, that slower eating and smaller meals can help, and that temporary dose holds or slower escalation may be appropriate when symptoms interfere with adherence.[30,31] Monitoring should include body weight, appetite, adverse effects, blood pressure, glycemia when relevant, and adequacy of nutrition and hydration.[30,32]

Because appetite suppression can substantially reduce overall caloric intake, nutrition counseling remains essential even with oral therapy. Patients should be encouraged to preserve diet quality, emphasize protein and fiber, maintain hydration, and incorporate resistance exercise to reduce loss of lean mass during weight reduction.[30,33] Referral to a

registered dietitian can be especially helpful when reduced intake, persistent constipation, or uncertainty about protein intake threatens long-term success.[32]

Additionally, clinicians should revisit oral therapy in the same way as with any chronic therapy. When response is suboptimal, consider steps that could facilitate the patient's health goals. Options include medication administration technique, continued titration, more intensive nutrition support, reassessment of access (if relevant), or transition to an injectable agent or another medication class.[5,10]

Maintenance therapy expectations should also be discussed before treatment begins. As with injectable obesity medications, stopping an effective oral therapy is likely to be followed by partial or substantial weight regain, so continuation should be communicated as long-term treatment for a chronic disease rather than a finite course intended only to reach a target weight.[5,6] That conversation can improve adherence by aligning the patient's expectations with the biology of relapse and by normalizing dose adjustment or therapy changes over time rather than treating them as failure.[2,32]

## CASE STUDY (CONTINUED)

KB's daughter elects to start oral therapy for obesity. After reviewing her access options, the administration requirements for various treatments, and average weight loss efficacy, she notes that oral orforglipron would be most convenient considering her busy schedule and other medications she takes in the morning. She titrates to the maintenance dose and reports that early nausea was manageable after she slowed meal pace, reduced portion size, and paid more attention to hydration.

At follow-up, the PCC again uses the 5 As: (Ask, Assess, Advise, Agree, and Assist) to confirm that treatment goals remain centered on health improvement, reinforce that maintenance therapy will likely be ongoing, and discuss what would prompt a change in strategy if weight loss plateaus or regimen complexity becomes a barrier.

## SUMMARY

Advancements in oral pharmacotherapy in recent years now offer patients the option of highly effective weight management therapy without injections. While older, established oral agents still have a role, newer oral incretin therapies have changed what is realistically achievable with a tablet by moving expected weight loss from the modest range toward double-digit reductions in selected patients. Clinicians can facilitate improved obesity outcomes by matching the right oral therapy to the right patient through accurate diagnosis, stigma-sensitive communication, setting realistic expectations, and careful attention to dosing burden, tolerability, access, nutrition, and follow-up. When oral therapy is integrated into comprehensive chronic obesity care, it can expand options for patients who might otherwise never start or stay on treatment. ●

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