



ISAPS® PATIENT SAFETY

EMERGING GUIDANCE OF THE INTERNATIONAL SOCIETY
OF AESTHETIC PLASTIC SURGERY

WEIGHT LOSS DRUGS: LATEST UPDATES AND EVIDENCE-BASED SAFETY

December 13, 2025

The therapeutic landscape for obesity has expanded rapidly, with incretin-based agents demonstrating unprecedented weight-loss efficacy and cardiometabolic benefits. At the same time, real-world data and pharmacovigilance reports highlight tolerability issues, lean-mass loss concerns and ongoing uncertainties in long-term safety. Clinicians should approach these agents as chronic-disease therapies requiring structured monitoring.

A recent systematic review and network meta-analysis (adults, up to Jan 31, 2025) evaluated many obesity-management medications (OMMs) in randomized controlled trials.

HIGHLIGHTS

- 56 RCTs were included, covering ~60,300 participants (32,598 treated, 27,709 placebos) across drugs such as Orlistat (22 trials), Semaglutide (14), Liraglutide (11), Tirzepatide (6), Naltrexone/Bupropion (5) and Phentermine/Topiramate (2).
- All OMMs achieved significantly greater total body weight loss (TBWL%) versus placebo ($p < 0.0001$).
- For the most efficacious drugs: semaglutide and tirzepatide achieved >10% weight loss on average. For example:
 - Semaglutide: ~11% weight reduction after ~24-68 weeks in RCTs (27,949 participants).
 - Tirzepatide: Up to ~16% weight reduction after 12-18 months in 6,361 participants in 8 RCTs.
- Additional beneficial effects were noted:
 - Both semaglutide and tirzepatide showed remediation of type 2 diabetes (normoglycaemia restoration) and reduced hospitalization for heart-failure.
 - Semaglutide also showed reductions in major adverse cardiovascular events (MACE) and reduction in pain in knee OA.
 - In “real-world” use, outcomes tend to be somewhat lower than RCTs but still substantive in adherent patients.
- *There is a newer oral small-molecule GLP-1 receptor agonist under investigation: **Orforglipron**, with phase 3 data showing encouraging results.*

Table 1: Currently Approved/Widely Used Anti-Obesity Medications

Drug (route)	Main mechanism	Typical average total body weight loss vs. baseline*	Key published data (examples)	Common adverse effects	Important warnings/cautions
Orlistat (oral)	Inhibits pancreatic lipase → ↓ fat absorption	~5-7% at 1 year (modest)	Older RCTs in obesity; included in large network meta-analyses of 50+ trials of obesity meds (tens of thousands of pts).	Oily stools, fecal urgency, flatulence, fat-soluble vitamin deficiency.	Avoid in chronic malabsorption, cholestasis. Need low-fat diet to tolerate.
Liraglutide 3.0 mg (SC daily)	GLP-1 receptor agonist (incretin)	~8% at 56 weeks in RCTs	Phase 3 SCALE trials showed significantly greater weight loss vs. placebo and improved glycemia in T2DM.	Nausea, vomiting, diarrhea, constipation, headache, injection-site reactions.	Boxed warning for thyroid C-cell tumors (rodent data); avoid in personal/family history of MTC or MEN2; caution with pancreatitis, gallbladder disease.
Semaglutide 2.4 mg (SC weekly; Wegovy)	Potent GLP-1 RA	~12-15% at ~68 weeks in STEP trials; >10% in many real-world analyses	Multiple STEP RCTs: large, consistent weight loss and improvements in cardiometabolic markers; also shown to reduce major adverse CV events in high-risk pts.	Very common GI: nausea, vomiting, diarrhea, abdominal pain; sometimes constipation, fatigue.	Same thyroid warning class; rare pancreatitis, gallbladder events; possible worsening of diabetic retinopathy in rapid improvement of glycemia; weight regain common after stopping.
Tirzepatide (SC weekly; Mounjaro/Zepbound)	Dual GIP + GLP-1 RA	~15-20% in obesity trials at higher doses over ~72 weeks	SURMOUNT-1 and related RCTs: some of the largest % losses seen so far; also strong A1c reduction in T2DM and favorable CV risk markers.	Similar GI profile, often more intense with high doses; nausea, vomiting, diarrhea, decreased appetite.	Same thyroid tumor warning; being monitored for pancreatitis, gallbladder disease; emerging signal of rare serious events incl. deaths temporal to use (causality under investigation).
Phentermine / Topiramate ER (oral)	Sympathomimetic + antiepileptic; appetite suppression	~8-10% at 1 year in RCTs	EQUIP & CONQUER trials: significantly greater weight loss vs. placebo with metabolic benefits.	Paresthesia, dry mouth, constipation, insomnia, dizziness, dysgeusia.	Teratogenic (oral clefts) – strict pregnancy prevention; caution with tachycardia, mood changes, cognitive issues; avoid in uncontrolled HTN, heart disease.

Drug (route)	Main mechanism	Typical average total body weight loss vs. baseline*	Key published data (examples)	Common adverse effects	Important warnings/cautions
Naltrexone / Bupropion ER (oral)	Opioid antagonist + antidepressant affecting reward pathways	~5-8% at 1 year	COR-I, COR-II, COR-BMOD trials: modest but significant weight loss vs. placebo.	Nausea, constipation, headache, dizziness, insomnia, dry mouth.	Boxed warning (bupropion) for suicidality in young adults; ↑ BP/HR; avoid in seizure disorder, uncontrolled HTN, chronic opioid use, eating disorders.
Setmelanotide (SC)	MC4R agonist	Can be very large in certain rare genetic forms of obesity	RCTs and open-label studies in monogenic obesity (POMC, LEPR, etc.) show dramatic weight loss in many responders.	Injection-site reactions, hyperpigmentation, nausea, headache.	Indicated only for specific genetic obesity syndromes; requires genetic confirmation and specialist care.

Table 2: Newer GLP-1 / Incretin-Based Agents & Key Concerns

These are either newly approved in some regions or in late-stage development.

Drug	Status/route	Key published efficacy data (high-level)	Notable adverse effects/concerns
Oral semaglutide (higher-dose formulations)	Approved for T2DM; higher doses studied for obesity	Phase 3 trials show clinically meaningful % weight loss, though generally slightly less than injectable 2.4 mg; real-world data show good A1c drop and notable GI side-effects.	Similar GLP-1 GI profile; nausea in ~20-30%, vomiting/diarrhea smaller but significant; long-term safety in obesity indication still building.
Orforglipron (oral small-molecule GLP-1 RA)	In phase 3 for obesity	NEJM and other reports show weight loss in range approaching injectable GLP-1s over ~36-52 weeks, with improved cardiometabolic markers.	GI side effects prominent (nausea, vomiting); long-term data and rare events still unknown; as small molecule, may differ in PK and possibly off-target effects – under study.
Retatrutide (triple agonist: GIP/ GLP-1/Glucagon)	Phase 2/3 trials	Early published trials show very high mean weight loss (approaching or exceeding 20% in some dose cohorts at ~48 weeks).	Strong GI AEs, potential increased HR; glucagon activity raises theoretical concerns around CV safety and hepatic effects; long-term and post-marketing data needed.
Other dual/triple incretin agonists	Development pipeline	Multiple candidates show double-digit weight loss in 6-12 month trials.	Safety profile broadly similar (GI + class warnings), but each molecule may have unique risks; evidence base still immature.

CROSS-CUTTING ADVERSE-EFFECTS

GI Intolerance Is Very Common:

- Nausea, vomiting, diarrhea, constipation, abdominal pain are the leading reasons for discontinuation of GLP-1-based and related incretin therapies.
- Slow dose titration and dietary adjustments help but do not eliminate symptoms.

Weight Regain After Stopping:

- Many trials and real-world cohorts show that **stopping** anti-obesity meds leads to **partial or substantial weight regain** over 6–12 months.
- Clinically, these are best thought of as **chronic disease treatments**, not short-term “courses”.

Potential Loss of Lean Mass:

- Rapid, large weight loss often includes loss of **muscle and lean mass** along with fat.
- Early experimental and observational data suggest that GLP-1-based therapies may reduce muscle size and strength if weight loss is not accompanied by resistance training and adequate protein.
- This raises concerns for frailty in older adults or in those with sarcopenia-risk.

Rare but Serious Risks (Signals, not Always Proven Causality):

- **Pancreatitis** and **gallbladder disease** (cholelithiasis, cholecystitis).
- Potential worsening of **diabetic retinopathy** with rapid glucose improvement.
- **Thyroid C-cell tumors** in rodents → boxed warnings; human relevance still uncertain but drives contraindications.
- Emerging reports of **alopecia (hair loss)** with GLP-1 RAs in pharmacovigilance and scoping reviews.
- Regulatory agencies are monitoring reports of **serious adverse events and deaths** temporally associated with these drugs; current labels already include many of these risks, but the full long-term picture is still evolving.

Mental Health and Eating Disorder-Related Issues:

- Concerns that powerful weight-loss drugs might worsen body image preoccupation or disordered eating in susceptible individuals.
- Some patients report mood changes or altered relationship with food; careful screening and follow-up are recommended, particularly in younger patients or those with psychiatric history.

Compounded/Non-Approved Products:

- Reports of serious adverse events with **compounded semaglutide or tirzepatide** (and “research” or online products) highlight the danger of formulations **outside normal regulatory oversight**.
- Professional bodies and regulators advise using **only approved products from reputable sources**.

SUMMARY

1. Efficacy:

- Modern incretin-based drugs (semaglutide, tirzepatide and emerging triple agonists) routinely deliver **double-digit percentage weight** loss in RCTs, far exceeding legacy agents like orlistat or older sympathomimetics.
- Many show **additional benefits**: improved glycemic control, reduced need for diabetes meds and, in some cases, reduced cardiovascular events.

2. Safety and Tolerability:

- GI side-effects are **expected, common and dose-related**.
- Most serious risks are **rare**, but the class now has **boxed warnings** and multiple ongoing safety investigations → clinicians must take a structured risk assessment (thyroid history, pancreatitis/gallbladder history, psychiatric history, pregnancy status).

3. Long-Term Uncertainty:

- Data beyond **2-3 years** (especially in non-diabetic obesity populations and with newer molecules) remain limited.
- Chronic use is likely required for weight maintenance, but we still lack robust, long-horizon data on **hard outcomes**, rare adverse events and impact on frailty/muscle.

4. Clinical Use Should Be Individualized:

- These drugs should be used with lifestyle interventions, not as stand-alone fixes.
- Shared decision-making is crucial: patients should understand the balance of **benefits (weight, glycemia, CV risk)** vs. **risks (GI, rare serious events, need for long-term treatment, cost)**.

ADVERSE EFFECTS & IMPORTANT SAFETY CONSIDERATIONS

While the efficacy is exciting, there are several caveats and adverse-effect profiles to keep in mind.

Common Adverse Effects:

- Gastrointestinal side-effects (nausea, vomiting, diarrhea, constipation) are consistently the most frequent across the GLP-1 based therapies. For example: in a real-world study of oral semaglutide (14mg dose), nausea was reported by ~23% and vomiting/diarrhoea by ~12% of participants.
- Real-world data show high discontinuation rates: 20-50% of patients on GLP-1RAs for weight management discontinue within the first year.
- Emerging/less common adverse signals:
 - Alopecia (hair loss) has been reported as a potential adverse effect associated with GLP-1 receptor agonists.
 - Muscle mass/lean mass loss: A study in mice on Ozempic (semaglutide) suggests that while fat loss is high, lean mass (including muscle) may also decline (~10% reduction in lean mass measured, ~6% muscle loss) and muscle strength may decline.
 - With compounded (non-approved) versions of semaglutide/tirzepatide, there are higher risks because of less regulatory oversight. (e.g., FDA reported 392 adverse events with compounded semaglutide, 215 with compounded tirzepatide as of Nov 2024).

Serious/Rare but Important Risks:

- Deaths: There are reports linking GLP-1 based weight-loss usage and deaths. For example, the UK BMJ reports that 18 deaths have been linked to tirzepatide (10 linked to its use for weight-loss indication, 8 for diabetes indication).
- Long-term safety and long-duration data are still limited. A recent article highlighted that although GLP-1 drugs show promise, “evidence on longer-term outcomes, side effects and potential conflicts of interest remains limited or uncertain.”
- Weight regain: Discontinuation of these medications frequently leads to weight regain. A study showed that after stopping anti-obesity medications (AOMs) people often regain a substantial proportion of lost weight.
- Mental health/eating disorders: There is concern that “widespread” use of these drugs could influence body image, size stigma and potentially eating disorders. The mental-health effects of GLP-1s are mixed.
- Rare but serious events (though causality not firmly established): pancreatitis, thyroid C-cell tumors (in rodents), gallbladder disease, acute gallstones, acute renal impairment, retinopathy worsening - these are warned about in prescribing information for GLP-1/dual-agonist therapies. The real-world signal for many remains under investigation.

Practical Safety Tips and Things to Monitor:

- Titration: Many GI side-effects can be mitigated by starting at lower doses and gradually increasing the dose.
- Monitoring for signs of pancreatitis (abdominal pain) or gallbladder disease if patients develop associated symptoms.
- If patients stop therapy, there must be planning for maintaining lifestyle/behavioral changes because weight regain is common.

- Patients with a personal or family history of medullary thyroid carcinoma or MEN2 (multiple endocrine neoplasia type 2) are typically **contraindicated** for GLP-1 RAs that carry boxed warnings (e.g., tirzepatide has such a contraindication per its label).
- Because muscle/lean mass loss may occur, especially in heavier weight-loss contexts, practitioners may consider assessing muscle strength or recommend concomitant resistance training.
- Given limited long-term evidence, shared decision-making is key: discuss with patients real expectations (not just weight loss, but metabolic outcomes, maintenance), adverse effects, cost/access, off-label use risk (especially compounded/unregulated formulations).
- Avoid unapproved compounding or purchasing “copycat” injections online – these may carry significantly higher risk.

WHAT THIS MEANS AND WHERE WE ARE HEADING

- The pharmacologic landscape for obesity is rapidly advancing. The level of weight loss achievable now (10–20%) is far greater than older medications or lifestyle alone in many cases.
- However, the achieving and maintaining of that weight loss is conditional on **continuation of therapy**, adherence and integration with lifestyle (diet, exercise, behavior). Without continuation, weight regain is frequent.
- Longterm data (beyond 2–3 years) remain somewhat scarce, especially for newer agents and for diverse real-world populations.
- Safety surveillance remains critical – wide uptake means rare adverse events may become more visible.
- Newer therapies (dual agonists, triple agonists, oral small molecules) are in the pipeline which may further enhance efficacy and convenience – e.g., oral GLP-1 (orforglipron), triple-agonist (retatrutide) etc.
- From a clinical practice standpoint, obesity is to be viewed as a **chronic disease** needing long-term plan, not just a short-term “weight loss” sprint. The drug therapy may be one component.

BOTTOM LINE

There has been meaningful progress in the pharmacotherapy of obesity – some medications now deliver double-digit body-weight loss, along with beneficial metabolic outcomes. But they are **not without risk**: gastrointestinal side-effects are common; muscle/lean mass loss and weight regain after cessation are concerns; and longer-term safety data are still evolving. They should be used **with** lifestyle interventions, under medical supervision and in the context of shared decision-making.

ISAPS Patient Safety Committee

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