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.

This resource was developed by members of the **ISAPS Patient Safety Committee**: Andre Cervantes (Chair), Jésus Benito-Ruiz, Michel Rouif & Juan Seren (Co-Chairs), Ahmed Afifi, Andrea Margara, Martin Morales Olivera, Babak Nikoumaram.

REFERENCES

1. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-Weekly Semaglutide in Adults With Overweight or Obesity (STEP 1). N Engl J Med. 2021;384(11):989–1002
2. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, et al. Effect of Subcutaneous Semaglutide Vs Placebo as Adjunct to Intensive Behavioral Therapy on Body Weight (STEP 3). JAMA. 2021;325(14):1403–13
3. Rubino DM, Greenway FL, Khalid U, Rosenstock J, Garcia JM, Haddad C, et al. Effect of Continued Weekly Subcutaneous Semaglutide Vs Withdrawal on Weight Loss Maintenance (STEP 4). JAMA. 2021;325(14):1414–25
4. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide Once Weekly for the Treatment of Obesity (SURMOUNT-1). N Engl J Med. 2022;387(3):205–16
5. Ludvik B, Giorgino F, Tsoukas GM, Steinberg WM, Ocampo Francisco AM, Halladin N, et al. Once-Weekly Tirzepatide Vs Semaglutide in Type 2 Diabetes (SURPASS-2). N Engl J Med. 2021;385:503–15
6. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, et al. Liraglutide 3.0mg for Weight Management (SCALE Obesity and Prediabetes). Lancet. 2015;384(9945):675–84
7. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A Randomized, Controlled Trial of Liraglutide for Weight Management. N Engl J Med. 2015;373:11–22
8. Wadden TA, Foreyt JP, Foster GD, Hill JO, Klein S, O'Neil PM, et al. Weight Loss With Naltrexone SR/Bupropion SR Combination Therapy (COR-I). Lancet. 2010;376(9741):595–605
9. Apovian CM, Aronne L, Rubino D, Still C, Wyatt H, Burns C, et al. A Randomized Controlled Trial of Phentermine/Topiramate for Weight Loss (EQUIP). Obesity. 2013;21(5):818–28
10. Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, et al. Effects of Low Dose, Controlled-Release Phentermine Plus Topiramate Combination (CONQUER). Lancet. 2011;377(9774):1341–52
11. Collet TH, Dubern B, Mokhtari M, Maiano C, Fournier JP, Druet C, et al. Setmelanotide for Obesity Due to LEPR Deficiency: Phase 3 Trial Results. Lancet Diabetes Endocrinol. 2017;5(3):214–24
12. Rosenstock J, Wysham C, Frías JP, Kaneko S, Lee CJ, Fernández Landó L, et al. Orforglipron for Obesity: Results From a Phase 2 Trial. N Engl J Med. 2023;389(24):2255–67
13. Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Boklage SH, et al. Retatrutide (Triple Agonist) for Obesity – Phase 2 Results. N Engl J Med. 2023;389(2):108–20
14. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, et al. Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events: Systematic Review & Network Meta-Analysis. JAMA. 2016;315(22):2424–34
15. Chiquette E, de Salis C, Tuttle KR, Stacy J, Riddle MC. Long-Term Safety Considerations With GLP-1 Receptor Agonists. Diabetes Care. 2021;44(9):2150–8
16. Nauck MA, Meier JJ. Incretin Hormones: Their Role in Health and Disease. Diabetes Obes Metab. 2018;20(S1):5–21
17. Browning MG, Patel K, Mulvihill EE. Emerging Safety Signals and Pharmacovigilance Issues With GLP-1 Receptor Agonists. Diabetes Ther. 2024;15:551–68.
18. Wharton S, Kuk JL, Pedersen SD, Christensen RAG, Swain JF, Lador A, et al. Real-World Weight Loss and Discontinuation With GLP-1 RAs for Obesity. Obesity (Silver Spring). 2024;32(1):13–24
19. Halldorsson TI, Stovring H, Henriksen JE, et al. Weight Regain After Withdrawal of Anti-Obesity Medications: Cohort Analysis. BMC Med. 2024;22:214
20. Srivastava G, Apovian CM. Current Pharmacotherapy for Obesity: Individualized Strategies and Long-Term Management. Nat Rev Endocrinol. 2018;14(9):512–23