GLP-1 Medicines: History, Benefits, Long-Term Use, and Emerging Concerns

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Medicines commonly called “GLP-1s” now span several molecules, products, delivery systems, doses, and diseases. The shorthand is convenient but imprecise. Semaglutide is a molecule; Ozempic, Rybelsus, and Wegovy are products containing it; each product has particular approved indications, formulations, and dose schedules. Tirzepatide activates both GIP and GLP-1 receptors and is sold as Mounjaro for type 2 diabetes and Zepbound for chronic weight management and, in specified patients, obstructive sleep apnea. A result for one formulation, dose, or population should not automatically be transferred to another.

These medicines can improve glucose control, produce clinically important weight loss, and—in the right populations—reduce cardiovascular, kidney, liver, or sleep-apnea outcomes. They also commonly cause gastrointestinal symptoms, can cause uncommon serious harms, and usually do not produce a permanent biological “reset” after treatment ends. The decision to start, continue, change, or stop one is individualized. This guide offers general education rather than medication-stopping instructions or a personal treatment plan.

Key Takeaways

• Natural GLP-1 is a short-lived gut hormone released after eating. Medicines prolong or reproduce selected GLP-1 actions; tirzepatide adds GIP activity, and newer candidates combine still more pathways.

• Product names are not interchangeable. Ozempic is not FDA-approved for weight management, even though its molecule, semaglutide, is also used in Wegovy. Doses and instructions differ by product and indication.

• Obesity and type 2 diabetes are usually chronic conditions. Randomized withdrawal evidence shows substantial average weight regain after semaglutide or tirzepatide is withdrawn; this is evidence of biological recurrence, not evidence that the medicine “stopped working.”

• Weight loss includes both fat mass and lean mass. Most measured loss is fat, but lean-tissue loss matters—especially in frail or older adults. Lean mass on a scan is not synonymous with skeletal muscle, strength, or disability.

• Direct evidence about the fat-versus-lean composition of weight regained after stopping is inadequate. Claims that regain is necessarily “mostly fat” or creates a universal body-composition penalty go beyond current evidence.

• “Ozempic face” and “Ozempic butt” are informal appearance labels, not medical diagnoses. Facial or gluteal volume and skin changes can follow substantial or rapid weight loss from many causes; the terms should not be used to shame patients or imply a unique semaglutide disease.

• Nausea, vomiting, diarrhea, constipation, abdominal pain, and indigestion are common. Pancreatitis, gallbladder disease, severe GI reactions, dehydration-related kidney injury, and pulmonary aspiration around anesthesia are important but different risks; labels do not establish that every reported gastroparesis or obstruction case was caused by treatment.

• Diabetic-retinopathy worsening and NAION are distinct. Rapid glucose improvement can transiently worsen diabetic retinopathy in high-risk patients. European regulators concluded that NAION is a very rare semaglutide adverse effect; U.S. product labeling and regulator communications must be checked for each product and revision date.

• Reports of emotional flattening or anhedonia deserve clinical attention, but controlled evidence has not established a class-wide syndrome. FDA and EMA reviews did not find increased suicidality risk; in 2026 FDA requested warning removal from the specific obesity-product labels for Wegovy, Saxenda, and Zepbound.

• Early alcohol-use-disorder trials are promising but small. GLP-1 medicines are not FDA-approved treatments for alcohol, opioid, nicotine, or other substance-use disorders.

• U.S. shortage-related mass compounding has narrowed. Compounded products are not FDA-approved generics, and ordinary 503A/503B “essentially a copy” restrictions apply when shortage exceptions do not.

1. From a natural hormone to a medicine class

What natural GLP-1 does

Glucagon-like peptide-1 is made from the proglucagon precursor and released mainly by intestinal L cells after nutrients enter the gut. It helps coordinate a meal response: insulin secretion rises when glucose is elevated, glucagon secretion falls, gastric emptying slows, and appetite-related signaling changes. The glucose dependence of much of the insulin effect helps explain why a GLP-1 medicine used alone has less hypoglycemia risk than insulin or a sulfonylurea, although combinations can still cause low glucose. Natural active GLP-1 lasts only minutes because enzymes—especially dipeptidyl peptidase-4, or DPP-4—rapidly cleave it. [1]

A drug is not simply “more natural GLP-1.” Medicinal peptides are engineered to resist degradation and remain active for hours or days. Oral peptide semaglutide requires a formulation that helps a small fraction cross the stomach lining, while orforglipron is a nonpeptide small molecule. Tirzepatide engages GIP and GLP-1 receptors. Different receptor profiles, exposures, formulations, and doses can produce different effects.

The hormone’s gastric effect also needs nuance. Slower emptying contributes to post-meal glucose control and early fullness, but its intensity varies over time and among people. The effect does not mean that every user has gastroparesis, which is a clinical disorder requiring symptoms and diagnostic evaluation rather than a medicine name alone.

The incretin path and the Gila monster connection

The “incretin effect”—a larger insulin response to oral glucose than to the same glucose given intravenously—pointed scientists toward gut-derived signals. GIP and then GLP-1 became central candidates. A separate line of research examined peptides in Gila monster venom. John Eng identified exendin-4 in 1990; it activates the human GLP-1 receptor but is naturally more resistant to DPP-4 than human GLP-1. Synthetic exendin-4 became exenatide, approved in the United States as twice-daily Byetta in 2005. [2]

That history is sometimes told as if today’s products are “lizard venom.” They are not. Exenatide is a manufactured version of a peptide first identified in venom; semaglutide and liraglutide are modified analogues of human GLP-1, and tirzepatide is a designed dual agonist. The discovery story is scientifically important, but it does not determine the safety or effectiveness of every later molecule.

A practical approval timeline

After exenatide, progressively longer-acting agents reduced injection frequency and expanded outcomes. Liraglutide arrived for type 2 diabetes as Victoza and later at a higher target dose for chronic weight management as Saxenda. Semaglutide was approved as weekly Ozempic for type 2 diabetes, daily oral Rybelsus for type 2 diabetes, and higher-dose Wegovy for chronic weight management. Tirzepatide entered as weekly Mounjaro for type 2 diabetes and Zepbound for chronic weight management. The same molecule can therefore live in separate labels.

The oral landscape has changed quickly. FDA approved Wegovy tablets in December 2025; their initiation, monthly titration, maintenance dosing, and fasting administration instructions are product-specific. [3] [4] FDA then approved Foundayo, orforglipron, on April 1, 2026, for chronic weight management in eligible adults. Unlike oral semaglutide, it is a small molecule with its own once-daily instructions, dose range, contraindications, and evidence base. [5] [6]

Wegovy injection also gained a 7.2 mg adult maintenance option marketed as Wegovy HD in 2026. That approval did not turn 7.2 mg into a universal semaglutide dose: the current injection label specifies eligible adult use, while other populations and semaglutide products retain their own schedules. [7] [8]

Product, molecule, indication, and dose

Molecule / receptor activity	Selected U.S. product	Selected approved use	Dose distinction that matters
Semaglutide, GLP-1 agonist	Ozempic injection	Type 2 diabetes; cardiovascular and kidney risk reduction in label-defined adults	Weekly diabetes doses; not labeled as a chronic-weight-management product. [9]
Semaglutide, GLP-1 agonist	Rybelsus / Ozempic tablets	Type 2 diabetes, with product-specific outcome indications	Daily oral dosing and fasting administration; not the same tablet or indication as Wegovy tablets. [10]
Semaglutide, GLP-1 agonist	Wegovy injection	Chronic weight management in label-defined adults and adolescents; cardiovascular risk reduction in specified adults; MASH in specified adults	Weekly titration; maintenance dose depends on formulation, age, indication, tolerability, and current label. [8]
Semaglutide, GLP-1 agonist	Wegovy tablets	Chronic weight management and label-defined cardiovascular risk reduction in adults	Daily tablet with a distinct escalation schedule and administration rules. [4]
Tirzepatide, GIP/GLP-1 agonist	Mounjaro	Type 2 diabetes	Weekly diabetes label and doses; not interchangeable with Zepbound labeling.
Tirzepatide, GIP/GLP-1 agonist	Zepbound	Chronic weight management; moderate-to-severe obstructive sleep apnea in adults with obesity	Weekly titration to label-specified maintenance doses; severe gastroparesis is a specific caution. [11]
Orforglipron, nonpeptide GLP-1 agonist	Foundayo	Chronic weight management in eligible adults	Daily small-molecule tablet; no assumption that peptide-label rules transfer. [6]

“Diabetes dose” and “obesity dose” are useful shorthand, not universal categories. A clinician considers the actual label, kidney or liver context, other glucose-lowering medicines, age, indication, adverse effects, access, and response. Dose escalation is designed partly to improve tolerability; racing to the highest dose is not a general goal.

2. Benefits depend on the population and endpoint

Glucose, weight, and outcomes are different endpoints

A reduction in A1c measures average glycemia; a change in body weight measures another outcome; fewer heart attacks or kidney events requires a much larger and longer outcomes trial. A medicine can have evidence for one without yet having evidence—or an approval—for all three.

Ozempic's label includes type 2 diabetes treatment and, for specified adults with type 2 diabetes, cardiovascular and chronic-kidney-disease outcome indications. Wegovy's label covers chronic weight management in defined populations and other product-specific outcomes. These are not cosmetic approvals: eligibility uses body-mass-index and comorbidity criteria, and treatment is an adjunct to reduced-calorie diet and increased physical activity. [12] [8]

In SELECT, adults with cardiovascular disease and overweight or obesity but without diabetes had fewer major adverse cardiovascular events with Wegovy than placebo—6.5% versus 8.0% over the trial period. FDA added a cardiovascular risk-reduction indication in 2024 for that defined population. The result should not be reframed as proof that every person seeking weight loss will receive the same absolute cardiovascular benefit; baseline risk determines absolute benefit. [13]

Zepbound became the first FDA-approved medication for moderate-to-severe obstructive sleep apnea in adults with obesity in 2024. The trials combined treatment with a calorie-reduced diet and increased physical activity and measured apnea-hypopnea changes and remission or mild nonsymptomatic disease. This is not an indication for every person with snoring, nor does it make airway evaluation or positive-airway-pressure decisions irrelevant. [14] [15]

Wegovy also received accelerated approval for metabolic dysfunction-associated steatohepatitis, or MASH, with moderate-to-advanced fibrosis in adults, based on histologic improvement endpoints. Accelerated approval means an important evidentiary threshold was met, but continued approval may depend on confirmation of clinical benefit. It does not mean semaglutide treats every cause or stage of fatty liver disease. [16] [17]

Adolescents

Wegovy injection is approved for chronic weight management in adolescents aged 12 years and older with obesity under label criteria. Pediatric evidence is not simply a scaled-down adult trial; growth, puberty, eating-disorder screening, family context, mental health, and long-term exposure matter. FDA's clinical review assessed the adolescent program separately. [18]

Neither a child's BMI alone nor social pressure should dictate treatment. Potential benefits include weight and cardiometabolic improvement; potential burdens include GI symptoms, injections, cost, stigma, and the possibility of long-duration therapy. Current evidence does not answer every question about decades of use beginning in adolescence.

Older adults, frailty, and sarcopenia

Chronological age alone does not decide benefit or risk. An older adult with obesity, type 2 diabetes, cardiovascular disease, and preserved function may have substantial outcome benefits. A frail person with low appetite, unintentional weight loss, swallowing difficulty, recurrent dehydration, or limited muscle reserve may face a different balance.

Trials often enroll fewer very old or frail adults than clinicians see in practice. Reviews raise concern that loss of lean tissue, repeated loss-regain cycles, and inadequate nutrition could worsen sarcopenic obesity in vulnerable people, but direct long-term causal evidence remains limited. [19] Clinical context therefore includes weight trajectory, food intake, strength, falls, function, and goals—not only BMI.

Pregnancy and other boundaries

Current labels warn about fetal risk and generally direct planned discontinuation of long-half-life semaglutide before a planned pregnancy. The exact timing and action belong to the product label and the patient's clinician; this guide does not provide a stopping schedule. GLP-1 medicines are not weight-loss treatment during pregnancy. A person who becomes pregnant, is breastfeeding, or is planning pregnancy needs product-specific medical guidance rather than a class assumption.

3. Why treatment is often long-term—and what happens after withdrawal

Chronic treatment is not the same as dependence

Appetite, satiety, energy expenditure, fat-cell biology, sleep, environment, and many medications influence body weight. After weight loss, biological pressures often favor regain. A medicine that suppresses appetite and improves metabolic control only while present can be effective without being curative. Blood pressure often rises again after an antihypertensive is withdrawn; that does not mean the medicine caused hypertension or created addiction. The same chronic-disease framework is useful here.

Physical dependence and addiction also should not be confused. GLP-1 medicines are not known to produce intoxication, compulsive drug seeking, or a classic withdrawal syndrome. Return of appetite, glucose elevation, or weight after stopping is recurrence of treated physiology, not proof of substance dependence.

What semaglutide withdrawal showed

In the STEP 1 extension, participants without diabetes had received semaglutide 2.4 mg or placebo plus lifestyle intervention for 68 weeks, then all treatment and structured lifestyle intervention stopped. Among the extension participants, the semaglutide group had lost 17.3% on average at week 68 and regained 11.6 percentage points over the following year—about two-thirds of the previous loss. The group remained, on average, 5.6% below baseline. Many cardiometabolic measures moved back toward baseline. [20]

That result has boundaries. The extension included 327 participants from selected STEP 1 sites, not every randomized participant; there was no continued-treatment arm during the extension; and both medication and trial lifestyle support ended. It shows average regain after withdrawal under that design, not an exact prediction for an individual and not a universal deadline for full regain.

What tirzepatide withdrawal showed

SURMOUNT-4 used a randomized-withdrawal design. All 783 enrolled adults with obesity or overweight and a weight-related complication first received open-label tirzepatide for 36 weeks, losing 20.9% on average. The 670 participants who completed that lead-in and were randomized either continued tirzepatide or switched to placebo for 52 weeks. From randomization, continued-treatment participants lost another 5.5%, while those switched to placebo gained 14.0%. At week 88, 89.5% continuing tirzepatide versus 16.6% switched to placebo maintained at least 80% of the initial loss. [21]

This trial strongly supports continued pharmacologic effect, but it is an enriched population: people had to tolerate and complete the lead-in to enter the randomized phase. It does not establish that every patient should remain on a particular drug forever, nor does it test every lower-dose maintenance strategy, switching strategy, pregnancy plan, cost interruption, or adverse-effect scenario.

“Lifelong” is a planning concept, not a prediction

Patients are often told treatment may be long-term or lifelong because the underlying condition is chronic and trial benefits diminish after withdrawal. “May” matters. Over years, indication, response, adverse effects, affordability, pregnancy plans, competing illness, frailty, preferences, and new medicines can change. Long-term care can involve continuing, adjusting, switching, or supervised discontinuation; evidence does not support a single plan for everyone.

No patient should interpret this guide as an instruction to stop abruptly or continue despite concerning symptoms. Medication decisions are safer when the prescriber knows the actual product, current dose, other diabetes medicines, recent symptoms, and the reason a change is being considered.

4. Fat, lean tissue, and the uncertain composition of regain

What “lean mass” means

Body weight is often divided into fat mass and fat-free or lean mass. Dual-energy x-ray absorptiometry estimates compartments; it does not directly weigh individual muscles. Lean mass includes water, organs, connective tissue, glycogen, and muscle. Bioimpedance is even more sensitive to hydration assumptions. A decline in “lean mass” therefore is not identical to loss of contractile muscle, and muscle mass is not identical to strength or physical function.

Across GLP-1–based weight-loss studies, fat mass generally falls more than lean mass, so body-fat percentage and the fat-to-lean ratio often improve. A 2026 systematic review and meta-analysis nevertheless found measurable decreases in both compartments and substantial variation across drugs, populations, durations, and methods. [22] The medically important question is not whether the lean-mass number is exactly zero; some lean loss accompanies many forms of weight reduction. It is whether a person preserves adequate protein intake, strength, mobility, and function.

The issue is most consequential for older adults, people with frailty, chronic kidney or liver disease, cancer, low baseline muscle, very low intake, or rapid unplanned loss. Persistent vomiting or aversion to food can compound risk. Resistance exercise, adequate nutrition, and clinical assessment may help, but a generic protein target or exercise prescription is not safe for every kidney, heart, mobility, or eating-disorder context.

What is known about regain composition

Randomized withdrawal trials measured body weight and cardiometabolic markers much better than they measured the tissue composition of regain. STEP 1’s extension did not provide definitive serial imaging that could establish what proportion of regained weight was fat versus lean tissue. SURMOUNT-4 likewise does not settle a universal composition rule. Reviews discuss the possibility of adverse body-composition cycling, but that concern is not the same as direct proof. [23]

It is therefore accurate to say:

• Weight loss on these medicines usually contains both fat and lean mass, with fat the larger component on average.

• Substantial regain is common after withdrawal in trial populations.

• Direct evidence is insufficient to state that regained weight is always or predominantly fat, that all lost lean tissue stays lost, or that every stop-restart cycle causes sarcopenic obesity.

Future studies need serial imaging, muscle strength and function, diet and activity measurement, and follow-up after discontinuation. Until then, dramatic “fat comes back but muscle never does” statements should be treated as hypotheses rather than established patient facts.

5. Persistence and the “80% stop by two years” claim

Real-world discontinuation estimates are not one number. They depend on why the drug was used, which products were included, insurance, calendar year, the length of the allowed prescription gap, whether cash purchases were visible, and whether switching counted as stopping.

A 2024 claims study of 195,544 adults who newly filled dulaglutide, exenatide, liraglutide, or semaglutide in 2021 defined discontinuation as a 60-day gap after the expected end of supply. At six months, 26.2% were classified as discontinued; at twelve months, 45.2% were. People with obesity but not type 2 diabetes had higher discontinuation than those with diabetes. The study could observe fills, not whether every dose was taken or the patient’s full reason. [24]

A separate 2025 electronic-health-record cohort began with 125,474 U.S. adults with overweight or obesity who initiated injectable semaglutide, liraglutide, or tirzepatide products labeled for diabetes or obesity during 2018–2023. It estimated 53.6% discontinuation by one year and 72.2% by two years overall. At two years, the Kaplan-Meier estimate was 84.4% (95% CI, 84.0%–84.8%) among participants without type 2 diabetes, compared with 64.1% (95% CI, 63.7%–64.5%) among those with it. These estimates describe one retrospective U.S. cohort and its subgroups, rather than all users or a global population. They do not establish that adverse effects caused every discontinuation. [25]

The denominator was eligible initiators captured in the study data, and discontinuation was inferred from medication records using a gap definition. Among discontinuers with follow-up, some later restarted. Observed associations included weight response, GI adverse events, and income in the diabetes subgroup; the authors discussed access and insurance coverage as possible contributors. Records did not provide a complete, adjudicated reason for each person, so these findings do not establish how often declining effectiveness, side effects, or access barriers caused discontinuation. [25]

Trial discontinuation is different again. A randomized trial actively supplies medicine, schedules visits, and records reasons; routine care does not. Claims persistence also is not clinical success: filling a prescription does not prove benefit, while stopping does not prove treatment failure.

6. Common gastrointestinal effects and uncommon serious risks

Expected symptoms

Nausea, diarrhea, vomiting, constipation, abdominal pain, dyspepsia, belching, and reflux-type symptoms are common across current labels, often most noticeable during escalation. Frequency depends on molecule, dose, population, ascertainment, and trial design; a percentage from one product should not be pasted onto another.

Symptoms can matter even when not “serious” by a regulatory definition. Repeated vomiting can cause dehydration, electrolyte disturbance, inability to take other medicines, and kidney injury. Persistent constipation can be disabling. A tolerability plan is product- and patient-specific.

Gastroparesis, ileus, and obstruction

GLP-1 receptor activity slows gastric emptying, especially early in treatment. Current Wegovy and Zepbound labeling warns about severe gastrointestinal adverse reactions and says use is not recommended in severe gastroparesis. [26] [11] This label language is stronger evidence than a social-media anecdote but still requires careful interpretation: “not recommended in severe gastroparesis” is not a claim that every treated person develops gastroparesis.

Postmarketing reports can reveal rare problems not detectable in trials, but reporting systems generally cannot determine incidence or prove causality by themselves. Ileus means impaired intestinal propulsion; mechanical obstruction means a physical blockage; severe constipation, gastroparesis, and functional bowel disorders are not interchangeable diagnoses. Symptoms such as persistent vomiting, marked abdominal distension, severe or continuing abdominal pain, inability to keep fluids down, or inability to pass stool or gas warrant prompt medical assessment rather than online self-diagnosis.

Pancreatitis and gallbladder disease

Acute pancreatitis is a labeled warning for semaglutide and tirzepatide products. Severe persistent abdominal pain, sometimes radiating to the back and with or without vomiting, is a classic warning symptom described in labels. Labels direct clinicians to discontinue when pancreatitis is suspected; a patient with symptoms needs urgent professional advice rather than applying a guide’s instruction independently. [12] [27]

Gallstones and gallbladder inflammation are separate risks. They can accompany substantial or rapid weight loss from many methods, while trials also report gallbladder events with these medicines. The absolute frequency is far lower than that of ordinary nausea or diarrhea, but the consequences can be serious. Right-upper-abdominal pain, fever, or jaundice requires clinical evaluation.

Evidence about pancreatic cancer is different from evidence about acute pancreatitis. Current labels do not establish that these medicines cause pancreatic cancer. A mechanistic concern, spontaneous report, pancreatitis warning, and proven cancer risk are different evidentiary categories.

Kidney injury, low glucose, and aspiration

The medicines are not typically directly toxic to kidneys; acute kidney injury reports often occur with nausea, vomiting, diarrhea, and volume depletion. This can be especially important in people taking diuretics or other medicines affecting kidney perfusion. Conversely, Ozempic has an approved kidney-outcome indication for specified adults with type 2 diabetes and chronic kidney disease. A product can provide kidney benefit in one context while dehydration creates acute risk in another. [9]

Hypoglycemia risk rises when a GLP-1–based medicine is combined with insulin or an insulin secretagogue. Dose adjustment of the companion medicine may be considered by the prescriber. “Low risk alone” does not mean “no risk in every regimen.”

Delayed stomach emptying also creates a procedural issue. Rare postmarketing reports describe pulmonary aspiration during general anesthesia or deep sedation despite standard fasting. Current labels tell patients to inform procedural teams. The anesthesia team—not a general internet rule—should decide peri-procedural management because aspiration risk, procedure urgency, symptoms, dose escalation, diabetes control, and anesthesia technique differ.

Thyroid tumor warning

Semaglutide, tirzepatide, liraglutide, and orforglipron labels carry boxed thyroid C-cell-tumor warnings and contraindicate use with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. The basis is not identical for every molecule. Foundayo’s label states that orforglipron is not pharmacologically active in rats or mice and did not produce tumors in rodents; its warning refers to GLP-1 receptor-dependent rodent tumors observed with other pharmacologically active products and says the human relevance is unknown. [6] This warning concerns a specific rare thyroid-cancer pathway; it should not be broadened to mean these medicines are proven to cause every thyroid nodule or thyroid cancer.

7. “Ozempic face,” “Ozempic butt,” and hair or skin concerns

“Ozempic face” describes a public perception of facial hollowing, skin laxity, or an aged appearance after substantial weight loss. “Ozempic butt” similarly describes reduced gluteal volume or loose skin. Neither is a diagnosis in FDA labeling. The names also over-attribute a general effect of losing subcutaneous fat to one brand, sometimes when the person used a different medicine.

Facial and gluteal fat are part of total fat stores. How appearance changes depends on amount and speed of loss, age, genetics, baseline fat distribution, smoking and sun exposure, skin elasticity, hydration, and muscle. Comparable changes can follow bariatric surgery, illness, or non-drug weight loss. UCLA Health’s clinical explainer similarly frames “Ozempic face” as an informal term related to rapid weight loss rather than a unique disease. [28]

Research is beginning to quantify facial volume, but current studies are small and vulnerable to selection and imaging limitations. They do not justify predicting that everyone will develop a recognizable face or buttock change. Cosmetic distress can still be real. A neutral conversation can consider weight trajectory, nutrition, resistance training, skin health, expectations, and—if desired—appropriately qualified cosmetic care without moralizing about body size or treatment.

Hair shedding after major weight loss may reflect telogen effluvium, nutritional issues, endocrine disease, stress, or another cause. It is not automatically proof of direct follicle toxicity. Evaluation should look beyond the medicine name.

8. Vision: retinopathy is not NAION

Diabetic retinopathy and rapid improvement

Diabetic retinopathy is retinal microvascular damage caused by diabetes. Rapid improvement in longstanding high glucose can temporarily worsen retinopathy—a phenomenon known from insulin intensification and other contexts. In SUSTAIN-6, diabetic-retinopathy complications occurred in 3.0% of semaglutide participants and 1.8% of placebo participants. The excess was concentrated in people with pre-existing retinopathy, poor baseline glucose control, insulin use, and large early A1c reductions. [29]

A post hoc mediation analysis found that much of the excess could be attributed to the magnitude and rapidity of early A1c reduction, supporting an “early worsening” interpretation rather than proof of a direct toxic effect on the retina. [30] Current Ozempic labeling therefore warns that patients with a history of diabetic retinopathy should be monitored. This does not mean semaglutide uniformly worsens long-term eye health; sustained glucose control generally protects against diabetic microvascular disease, while high-risk transitions need monitoring.

Sudden vision loss is not expected retinopathy monitoring territory. It requires urgent assessment.

NAION

Non-arteritic anterior ischemic optic neuropathy is sudden injury to the optic nerve thought to involve inadequate blood supply. It is distinct from diabetic retinopathy. Diabetes, hypertension, sleep apnea, age, and optic-disc anatomy are among background risk factors, which makes observational drug studies vulnerable to confounding by indication and comorbidity.

After reviewing clinical trials, postmarketing data, nonclinical evidence, and epidemiology, the European Medicines Agency’s safety committee concluded in June 2025 that NAION is a very rare adverse effect of semaglutide—up to 1 in 10,000 treated people—and recommended updating product information for Ozempic, Rybelsus, and Wegovy in Europe. [31]

Regulatory conclusions are jurisdiction- and date-specific. The EMA decision should not be described as an FDA class-wide warning for all GLP-1 medicines, and an observational association with semaglutide should not automatically be transferred to tirzepatide, liraglutide, or orforglipron. Current U.S. labeling should be checked by product and revision date.

Anyone with sudden painless vision loss, a new dark or blank area, or abrupt major visual change needs urgent eye evaluation. This is symptom triage, not an instruction to make an unsupervised medication change.

9. Mood, anhedonia, and suicidality

Emotional flattening reports

Informal patient accounts use terms such as “food noise reduction,” “emotional flattening,” “anhedonia,” or “Ozempic personality,” but those descriptions are not interchangeable and do not establish a diagnosis or drug effect. A 2025 systematic review noted reports of emotional blunting while finding that clinical evidence on psychiatric effects was limited and inconsistent. The review described preclinical reward-circuit findings as biological rationale, not proof that treatment causes generalized loss of pleasure in people. [32]

Available controlled studies have mainly measured broad psychiatric events, depressive symptoms, eating behavior, or quality of life—not the incidence of a specifically defined class-wide emotional-blunting syndrome. Consequently, its frequency, causality, risk factors, and dose relationship remain unknown. Reduced intrusive food thoughts can be welcome, while a persistent loss of pleasure or motivation may reflect depression or another medical, psychiatric, nutritional, substance-related, or medication-related problem and warrants assessment.

A new loss of pleasure, persistent low mood, marked behavioral change, or functional decline deserves assessment. Immediate help is appropriate for suicidal thoughts or inability to stay safe, regardless of whether a medicine is suspected.

What regulators found about suicidality

EMA's Pharmacovigilance Risk Assessment Committee reviewed nonclinical, clinical-trial, postmarketing, and observational data and in April 2024 concluded that available evidence did not support a causal association between GLP-1 receptor agonists and suicidal or self-injurious thoughts or actions. [33]

FDA initially reported in 2024 that a preliminary review had not found evidence of causation but could not exclude a small risk because events were uncommon. After a broader review that included 91 placebo-controlled trials and observational analyses, FDA announced in January 2026 that it found no increased risk and requested removal of suicidal-behavior and ideation warnings from the labels of Wegovy, Saxenda, and Zepbound. [34]

That update does not mean mood symptoms should be dismissed. It means the best available regulatory analysis did not support a medication-caused suicidality signal at the class level. Population findings cannot rule out every individual reaction, while an individual temporal association cannot by itself prove class causation.

10. Alcohol and other addictions: promising, investigational

Animal studies and human observations suggest GLP-1 signaling may reduce reward-driven consumption. The strongest early human experimental evidence is in alcohol use disorder, but the literature remains small.

In a 2025 phase 2 randomized trial, 48 adults with alcohol use disorder received low-dose semaglutide or placebo for nine weeks. Semaglutide reduced alcohol consumed during a laboratory self-administration task, drinks per drinking day, and weekly alcohol craving; it did not significantly change the trial's measure of average drinking days or all prespecified outcomes. The sample was small, treatment was brief, and doses were below common obesity maintenance doses. [35]

A later randomized study of oral semaglutide adds evidence, but it still does not create an FDA-approved addiction indication. [36] Larger trials are registered and ongoing. Results will need to address abstinence, heavy-drinking days, function, safety, retention, interactions with established treatments, and which patients benefit.

For opioid use disorder, an electronic-health-record study found lower recorded overdose risk associated with semaglutide among patients with type 2 diabetes and opioid use disorder. The design was observational; residual confounding, treatment selection, coding, and healthcare-contact differences prevent a causal treatment claim. [37] Small or ongoing studies in opioid and nicotine use should be considered hypothesis testing.

GLP-1 medicines should not replace evidence-based addiction care. For alcohol use disorder, established behavioral treatments and approved medicines exist; for opioid use disorder, buprenorphine, methadone, and extended-release naltrexone have established roles; for tobacco use, counseling and approved cessation medications are available. An investigational adjunct is not a substitute.

11. The next generation: approved versus still experimental

The field now includes peptide and nonpeptide oral drugs, dual and triple agonists, and GLP-1 combinations with amylin analogues. Pipeline tables age quickly; approval status must be attached to a date.

Agent	Mechanism / form	U.S. status on September 23, 2026	What is known—and not known
Wegovy tablet	Oral peptide semaglutide	FDA approved for label-defined adult chronic weight management and cardiovascular risk reduction	Requires product-specific fasting administration and titration; not interchangeable milligram-for-milligram with injections. [4]
Foundayo (orforglipron)	Oral nonpeptide GLP-1 agonist	FDA approved for chronic weight management in eligible adults	Convenient oral small molecule, but its label—not assumptions from semaglutide—governs dose and safety. [6]
Retatrutide	GIP/GLP-1/glucagon triple agonist injection	Investigational; phase 3 results reported, no FDA approval identified at cutoff	Large reported weight effects do not equal authorization; full peer review, safety review, and FDA action remain separate steps. [38] [39]
CagriSema	Cagrilintide (amylin analogue) plus semaglutide	Investigational / phase 3 development at cutoff	Combination evidence cannot be represented as an approved product until FDA acts. [40]
Survodutide	Glucagon/GLP-1 dual agonist	Investigational / phase 3 development	Being studied for obesity and related outcomes; no U.S. approval at cutoff. [41]
Pemvidutide	Glucagon/GLP-1 dual agonist	Investigational / phase 3 MASH study	Trial registration is not proof of efficacy or approval. [42]

Some failed or discontinued small-molecule programs remain visible in old reviews. A molecule's appearance in a paper, press release, or trial registry does not mean it remains active. Likewise, a positive company announcement is not equivalent to a peer-reviewed report or label.

Multi-agonism may increase weight loss or target liver fat and energy expenditure, but it can also produce new dose-limiting effects. Comparisons across separate trials are unreliable when populations, estimands, lifestyle programs, missing-data methods, and duration differ. Head-to-head randomized evidence is more informative.

12. Compounding, shortages, and the tightening U.S. landscape

Compounded is not generic

An FDA-approved generic must demonstrate regulatory requirements for sameness, quality, manufacturing, and bioequivalence where applicable. A compounded semaglutide or tirzepatide preparation is not an FDA-approved generic and is not reviewed before marketing for safety, effectiveness, or manufacturing quality in the same way.

Federal law creates two main pathways. Section 503A generally concerns patient-specific pharmacy compounding under qualifying prescriptions. Section 503B concerns registered outsourcing facilities that can supply office stock under specified conditions. Both pathways restrict making products that are "essentially copies" of commercially available or approved drugs, with different statutory wording and exceptions. [43] [44] [45]

Shortage status can change how copy restrictions apply. It is an exception framework, not blanket permission for mass marketing, and it does not convert a compounded preparation into an approved product. FDA's shortage list—not a social-media claim that a pharmacy cannot obtain one strength—controls the federal shortage status. [46]

From shortage discretion to enforcement

FDA determined the shortage of semaglutide injection products resolved on February 21, 2025, after finding supply could meet current and projected demand, while allowing transition periods under stated enforcement discretion. [47] Litigation and later policy changes affected timing, so a historical deadline should not be quoted as if it governs all compounders today.

In April 2026 FDA issued updated clarification as national GLP-1 supply stabilized, emphasizing that compounders generally may not make copies of approved products outside applicable statutory conditions and describing current enforcement policy. [48] FDA also proposed excluding semaglutide, tirzepatide, and liraglutide from the 503B bulks list because it found no clinical need for outsourcing facilities to compound them from bulk substances; a proposal should be identified as a proposal until finalized. [49]

There can still be patient-specific compounding when a prescriber determines that a change produces a significant difference for an identified patient and all legal conditions are met. That is not the same as routine lower-price copying or changing a trivial ingredient for mass distribution.

Salt forms, dosing errors, and counterfeits

FDA has warned that some products use semaglutide sodium or semaglutide acetate rather than the base form in approved drugs; the agency says it is not aware of a lawful basis for using those salts in compounding under the cited conditions. It has also received adverse-event reports involving unapproved GLP-1 products and raised concerns about fraudulent labels and ingredients. [50]

Multi-dose vials can create unit conversions unfamiliar to patients. FDA documented compounded injectable semaglutide dosing errors—sometimes five to twenty times the intended dose—arising from concentration differences, syringe units, and instructions, with some hospitalizations. [51]

Counterfeit is a separate category from legally compounded. FDA has identified counterfeit Ozempic in the legitimate U.S. supply chain and published specific lot information. A counterfeit may contain wrong, missing, contaminated, or mislabelled ingredients. [52] Product source, licensed dispensing, packaging, lot information, and suspiciously low prices matter.

13. Lawsuits, class actions, and multidistrict litigation

A lawsuit alleges facts; it does not establish them. A warning in a complaint is not an FDA warning, and the number of filed cases is not an incidence rate.

An individual lawsuit is one plaintiff's case. A class action lets representatives litigate common claims for a defined group after class-certification requirements are met; many pharmaceutical personal-injury claims are not handled as a single damages class because injuries and causation differ. Multidistrict litigation, or MDL, is different: a federal judicial panel transfers cases with shared factual questions to one judge for coordinated pretrial proceedings. Each case generally retains its individual identity, and unresolved cases can later return to their original courts for trial.

In February 2024 the Judicial Panel on Multidistrict Litigation created MDL 3094 for federal GLP-1 receptor-agonist product-liability cases alleging gastrointestinal injuries and inadequate warnings. The transfer order describes allegations and efficiency grounds; it does not decide whether a product caused a plaintiff's injury or whether a warning was legally inadequate. [53] The Eastern District of Pennsylvania maintains the official docket and case-management materials. [54]

Separate federal proceedings now centralize allegations involving NAION in MDL 3163. The existence of a distinct NAION MDL should not be conflated with the GI MDL, and neither should be called a scientific verdict. [55]

Some consumer, pricing, securities, or advertising disputes may be styled as class actions; personal-injury dockets may use MDL. The terms are not interchangeable. Current case counts move rapidly and depend on filing and dismissal rules, so this guide does not freeze a promotional law-firm count into a medical statistic.

14. Putting benefits and risks into perspective

The most useful question is not “Are GLP-1 drugs good or bad?” It is “What product, for which person and indication, compared with what realistic alternative, over what period?”

For a patient with type 2 diabetes, chronic kidney disease, and high cardiovascular risk, glucose, kidney, and cardiovascular outcomes may dominate. For an adolescent with severe obesity, developmental context and long-term access matter. For an older adult with obesity and preserved strength, cardiovascular benefit may coexist with a need to monitor intake and function. For a frail adult losing weight unintentionally, appetite suppression may be harmful. For a person with previous gallstones, retinopathy, or severe GI disease, the relevant precautions differ.

Average trial weight loss is not a promise. People vary in response and tolerability; trials also use eligibility rules, support, and follow-up that routine care may not reproduce. Conversely, sensational rare-event stories should not erase established outcome benefits in indicated high-risk populations.

Useful shared-decision questions include:

1. What exact product, formulation, dose, and approved indication are being considered?
2. What outcome matters most—A1c, weight, cardiovascular risk, kidney disease, OSA, MASH, or another goal?
3. What is the expected absolute benefit at this person’s baseline risk?
4. Which GI, gallbladder, pancreatic, eye, nutritional, frailty, pregnancy, or medication-interaction issues change the plan?
5. How will response, intake, hydration, glucose, eye status when relevant, strength, and function be monitored?
6. Is long-term access realistic, and what is the plan if supply or coverage changes?
7. Is the product FDA-approved, legally compounded for a specific need, unapproved, or counterfeit?

Frequently Asked Questions

Is Ozempic the same as Wegovy?

They contain the same active molecule, semaglutide, but they are different FDA-approved products with different indications and dose schedules. Ozempic is a type 2 diabetes product with specified cardiovascular and kidney outcome indications; Wegovy is a chronic-weight-management product with additional label-defined indications. They should not be treated as interchangeable names.

Are these medicines always lifelong?

They often require long-term treatment because obesity and type 2 diabetes are chronic and randomized withdrawal trials show substantial average weight regain after stopping. “Often long-term” is not a universal mandate. Benefits, harms, goals, access, pregnancy plans, frailty, and alternatives can change; decisions belong in individualized care.

Does stopping guarantee that all weight returns?

No. Trials show substantial average regain, not the same result in every participant. In the STEP 1 extension, the semaglutide group regained about two-thirds of its prior mean loss over one off-treatment year and remained below baseline on average. Different support, duration, drugs, and individuals can produce different trajectories. [20]

Does the regained weight come back only as fat?

That has not been established. Studies measure loss composition better than regain composition. Both fat and lean mass usually decline during treatment, with greater fat loss on average, but direct serial evidence after withdrawal is insufficient for a universal claim about what returns.

Are “Ozempic face” and “Ozempic butt” diseases?

No. They are informal cosmetic labels for volume loss or loose skin after substantial weight loss. Similar changes can occur after weight loss from other medicines, surgery, illness, or lifestyle change. They are not diagnoses unique to Ozempic.

Do GLP-1 medicines cause gastroparesis or bowel obstruction?

They slow gastric emptying and current labels warn about severe GI reactions; some labels say use is not recommended in severe gastroparesis. Postmarketing reports include serious motility problems, but a report alone cannot establish incidence or causation. Persistent vomiting, distension, severe pain, inability to hydrate, or inability to pass stool or gas warrants prompt assessment.

What is the difference between diabetic retinopathy and NAION?

Diabetic retinopathy damages retinal blood vessels over time and can transiently worsen when very high glucose improves rapidly. NAION is an acute optic-nerve injury involving impaired blood supply. EMA concluded NAION is a very rare semaglutide adverse effect; that finding is not the same as diabetic-retinopathy early worsening and is not automatically a class effect.

Do these medicines cause depression or suicide?

Some individuals report mood or reward changes, but regulators’ broad reviews did not find an increased suicidality risk. In 2026 FDA requested removal of the suicidality warning from certain obesity-product labels. New anhedonia, major mood change, or suicidal thoughts still deserve prompt care regardless of cause.

Can semaglutide treat alcohol or opioid addiction?

Not as an approved treatment. Small randomized alcohol studies show a signal worth testing, and observational opioid data are hypothesis-generating. GLP-1 medicines remain investigational for substance-use disorders and should not replace established medications and behavioral care.

Is compounded semaglutide the same as an FDA-approved generic?

No. A compounded product is not an FDA-approved generic and is not reviewed premarket in the same way. Shortage exceptions have narrowed, federal copy restrictions apply, and FDA has warned about salt forms, dosing errors, fraudulent labeling, and counterfeits.

Limitations and evidence gaps

This guide is a snapshot through September 23, 2026. Labels, shortage policy, litigation, and investigational pipelines can change quickly. Regulatory conclusions differ by jurisdiction. Several pivotal trials were industry-funded, and trial populations underrepresent some very old, frail, pregnant, or medically complex patients.

The evidence is particularly thin on decades-long use beginning in adolescence, functional muscle outcomes in frail adults, the body composition of post-withdrawal regain, validated measurement of emotional blunting, and GLP-1 medicines as addiction treatment. Real-world discontinuation data identify prescription gaps more reliably than personal reasons. Litigation allegations are not clinical evidence. This guide has not undergone clinician review and does not replace individualized diagnosis, monitoring, or treatment advice.

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