

## M5.1 — 5 Safety Fronts Deep Dive

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### 5 Safety Fronts Deep Dive — GLP-1 RA Weight-Loss Pharmacotherapy

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Synergy Health Academy / Ageless Pep Academy — Module 5 Reference Card 10 Audience: Licensed clinicians prescribing weight-loss peptides (MD / DO / NP / PA / PharmD within scope) Editorial discipline: Pattern Z honesty calibration — “here’s what we know, here’s what we don’t, here’s the absolute event rate.” No marketing language. No “very rare” or “very safe” qualifiers where a number exists. Source baseline: M5.1 v3 (2026-05-12), M5.2 v3 (Semaglutide deep dive, 2026-05-12), M5.3 v3 (Tirzepatide deep dive, 2026-05-12), M5.4 v3 (Comparator landscape, 2026-05-12), M5.8 v3 (Titration), M5.9 v3 (Lab panels), Cancer Safety Matrix (obsidian-peptides/Compliance/).

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#### Why This Document Exists

The five safety fronts characterized below — **cancer (thyroid C-cell, pancreatic, breast, kidney); acute pancreatitis; NAION; suicidality and psychiatric safety; pregnancy and lactation** — are the safety conversations that arise in the first ninety days of weight-loss pharmacotherapy practice and recur for the duration of any patient’s time on these agents. They are also the topics where social-media patient discourse, regulatory-cycle headlines, and clinician training are most desynchronized. Patients arrive with versions of these concerns shaped by news cycles, TikTok explainers, and EMA-vs-FDA divergences they will not have parsed. The clinician’s job is to know the actual evidence state — by PMID, by absolute event rate, by certainty tier — and translate it into a shared-decision-making conversation that neither understates real risk nor inflates uncharacterized risk.

The M5.1 v3 audio lesson surfaces each of these fronts at orienting depth. This document is the deep-reference companion: every claim traces to a PMID, NCT, or regulatory document; every absolute risk number is given in plain count-and-denominator form where source data supports it; and the patient-counseling language at the end of each section is calibrated to Pattern Z discipline (present facts, frame trajectory, do not steer).

Where source material is thin — long-horizon effects, planned-pregnancy registries, peptide-class differentiation beyond semaglutide’s longer post-marketing exposure window — the document marks the gap explicitly rather than papering it over. The honest answer for the patient is usually one the clinician has to be willing to say out loud: “*That specific question has not been answered in a study designed to answer it. Here is what has been characterized, and here is the surveillance signal we are watching.*” The Pattern Z discipline is to make that distinction load-bearing.

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## SECTION 1 — Cancer

### 1.1 Mechanistic origin of the concern

The cancer-safety question in the GLP-1 receptor agonist class has four distinct mechanistic anchors that should not be collapsed into a single conversation:

1. **Thyroid C-cell (medullary thyroid carcinoma, MTC).** Rodent C-cells express GLP-1R at substantially higher density than human C-cells. In chronic high-dose rodent studies (Bjerre Knudsen 2010, PMID 20203154), GLP-1R agonism produced calcitonin release, calcitonin-gene upregulation, C-cell hyperplasia, and C-cell tumor formation in rats — and to a lesser

degree in mice. The same exposure protocols in non-human primates demonstrated minimal GLP-1R expression on C-cells and no comparable calcitonin response even at exposures exceeding 60-fold the human therapeutic dose. The class-label boxed warning derives from this rodent signal — applied with explicit precaution to the MEN2 syndrome population given the genetic predisposition to MTC in that population.

2. **Pancreatic cancer.** The mechanistic concern derives from observations of GLP-1R expression on pancreatic ductal cells and earlier-generation hypotheses around exenatide and chronic ductal-cell stimulation. The hypothesis was specific: chronic ductal cell trophic stimulation could theoretically drive ductal hyperplasia and, on long-horizon timescales, neoplasia. This hypothesis has been investigated extensively across two decades; it has not been confirmed at meta-analytic scale (see 1.3).
3. **Breast cancer.** GLP-1R expression has been documented in breast tissue and in some breast-cancer cell lines, raising the theoretical question of GLP-1R-mediated effects on hormone-responsive tissue. The clinical question — whether GLP-1 RA use shifts breast cancer incidence in unselected populations — has been examined in the largest contemporary synthesis (Ko 2026, PMID 41359966).
4. **Kidney cancer.** The kidney-cancer signal has the thinnest mechanistic anchor of the four; GLP-1R expression on renal proximal-tubule cells is well-documented (FLOW renal-protection mechanism rationale), but renal-cell carcinoma pathobiology is not centrally driven by the receptor systems engaged by GLP-1 RAs. Inclusion in the cancer surveillance set reflects systematic-review completeness, not strong prior evidence of mechanism.

## 1.2 Primary evidence — foundational rodent C-cell paper

Bjerre Knudsen L, Madsen LW, Andersen S, et al. "Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation." *Endocrinology* 2010;151(4):1473-1486. PMID: 20203154.

Key findings: GLP-1R agonist exposure stimulated calcitonin release and C-cell-gene upregulation in rats; chronic exposure produced C-cell hyperplasia and C-cell tumor formation in a dose-and-duration-dependent manner. **Species specificity** was the central caveat documented in the same paper and in subsequent primate work: humans and non-human primates have minimal GLP-1R expression on thyroid C-cells and did not demonstrate comparable calcitonin responses at exposures exceeding 60× the human therapeutic dose. The class-label boxed warning is precautionary and reflects species-translation uncertainty, not direct human evidence of risk.

## 1.3 Primary evidence — definitive 2026 synthesis

Ko A, Chang YC, Bahar F, et al. "Risk for Cancer With Glucagon-Like Peptide-1 Receptor Agonists and Dual Agonists: A Systematic Review and Meta-analysis." *Ann Intern Med* 2026 Feb; epub 2025-12-09. PMID: 41359966.

- **48 RCTs, n=94,245** GLP-1 RA + dual-agonist exposed participants
- **Examined 11 cancer types** (thyroid, pancreatic, colorectal, gastric, esophageal, liver, gallbladder, breast, ovarian, endometrial, kidney) plus 2 non-cancer conditions (multiple myeloma, meningioma)
- **Headline finding:** GLP-1 receptor agonists and dual agonists "probably have little or no effect on risk for thyroid cancer" — and similar minimal effects on **pancreatic, breast, and kidney cancers** — with **moderate certainty**
- Other obesity-related cancers: uncertain or low certainty
- Authors' explicit caveats: short trial follow-up periods; included trials were not specifically designed to evaluate cancer outcomes

Pattern V framing of this finding: the systematic review reports a "little or no effect" finding with explicit certainty-tier discipline — moderate certainty for thyroid / pancreatic / breast / kidney; low or very low certainty for the broader cancer panel. This is the load-bearing synthesis-level evidence the clinician cites when a patient asks the general cancer question.

## 1.4 Primary evidence — the dissonant signal (Bezin 2023)

Bezin J, Gouverneur A, Pénichon M, et al. "GLP-1 Receptor Agonists and the Risk of Thyroid Cancer." *Diabetes Care* 2023;46(2):384-390. PMID: 36356111.

French nationwide case-control study using the French National Health Data System (SNDS): - **aHR 1.58 (95% CI 1.27–1.95) for all thyroid cancer** with 1–3 years of GLP-1 RA use - **aHR 1.78 (95%**

**CI 1.04–3.05) for medullary thyroid cancer** with 1–3 years of GLP-1 RA use

This is the strongest published positive thyroid-cancer signal in the GLP-1 RA literature. It has **not been consistently reproduced** in subsequent cohort studies (notably Pasternak 2024 BMJ, cohort n=145,000+, HR 0.93 — verify before use; sourced from Cancer Safety Matrix PMID 38683947) and is contextualized by the Ko 2026 meta-analytic synthesis reporting “little or no effect” with moderate certainty across 94,245 patients. The honest clinical position is that the Bezin signal exists in one large national database, has not replicated, and is one reason post-marketing surveillance continues — it is not a reason to withhold GLP-1 RA therapy from a patient without MTC or MEN2 history.

**1.5 Primary evidence — pancreatic cancer**

Wen J, Nadora D, Bernstein E, et al. “Evaluating the Rates of Pancreatitis and Pancreatic Cancer Among GLP-1 Receptor Agonists: A Systematic Review and Meta-Analysis of Randomised Controlled Trials.” *Endocrinol Diabetes Metab* 2025;8(5):e70113. [PMID: 40988099](#).

- 62 RCTs, n=66,232
- **Pancreatic cancer overall: RR 1.30 (95% CI 0.86–1.97; non-significant)**
- Subgroup analysis with background medications: **RR 1.85 (95% CI 1.05–3.26)** — a positive subgroup signal that warrants noting but does not establish class-level pancreatic-cancer causation given the overall non-significant point estimate and the multiplicity of subgroup tests

The Ko 2026 SR places pancreatic cancer in the “moderate certainty, little or no effect” tier; Wen 2025 places it in the “non-significant overall, positive in one subgroup” tier. Both are correct for the populations and exposures they cover. The Pattern Z synthesis: pancreatic cancer is not a confirmed class signal, it remains an active-surveillance area, and the subgroup-with-background-medications finding should be communicated to patients on relevant background medications when the question arises.

**1.6 Absolute risk numbers**

Cancer type	Absolute event rate (RCT pool, Ko 2026 — verify before use for specific decision support)	Effect direction
MTC	Background population incidence ~1–2 per 100,000 person-years (NCI SEER baseline). Class-pool incident events extremely low; verify before use.	Class label boxed warning anchored in rodent mechanism; human evidence at meta-analytic synthesis level “little or no effect” with moderate certainty (Ko 2026).
All thyroid cancer	Bezin 2023 French DB: aHR 1.58 (95% CI 1.27–1.95) for 1–3 yr use. Ko 2026 SR (48 RCTs, n=94,245): little or no effect, moderate certainty.	Discordant; SR is load-bearing for population-level counseling.
Pancreatic cancer	Wen 2025: RR 1.30 (95% CI 0.86–1.97; NS). Background-medication subgroup: RR 1.85 (95% CI 1.05–3.26). Ko 2026: little or no effect, moderate certainty.	Not a confirmed class signal; active surveillance.
Breast cancer	Ko 2026: little or no effect on breast cancer risk, moderate certainty.	No confirmed signal.
Kidney cancer	Ko 2026: little or no effect on kidney cancer risk, moderate certainty.	No confirmed signal.

## 1.7 Regulatory position

- **FDA (US):** Class-label **boxed warning** for personal or first-degree-relative history of MTC and for MEN2 syndrome across the GLP-1 RA + GLP-1/GIP dual coagonist class — applies to Wegovy/Ozempic (semaglutide), Mounjaro/Zepbound (tirzepatide), Saxenda/Victoza (liraglutide), Rybelsus (oral semaglutide), and inherited downstream by CagriSema (semaglutide component) and tirzepatide-class downstream agents. Routine elevated calcitonin screening is **not currently recommended** in the FDA labeling or in major society guidelines (ADA 2026, AACE 2025 ABCD, EASO 2025) — the test performs poorly in this surveillance context (low specificity, high false-positive rate).
- **EMA (EU):** Equivalent precautionary contraindication for MTC/MEN2 history. No additional cancer-specific warnings beyond the class-label MTC contraindication as of 2026-05-12.

## 1.8 Contraindications

**Absolute:** - Personal history of medullary thyroid carcinoma - First-degree-relative history of medullary thyroid carcinoma - MEN2 syndrome (personal or family) - Known hypersensitivity to the specific compound

**Relative (case-by-case risk-benefit):** - Personal history of pancreatitis (see Section 2) - Active or recently treated malignancy of any type (oncology coordination warranted; this is general prudence, not a class-level GLP-1 RA signal) - Strong family history of papillary thyroid cancer (not contraindicated by boxed warning, but informed consent should explicitly distinguish papillary thyroid cancer — the most common form in the US — from MTC, which is the entity the boxed warning concerns)

## 1.9 Pre-screening recommendations

- **History:** Personal and first-degree-relative history of MTC, MEN2, and other thyroid malignancies — documented in chart prior to initiation. Family history of pheochromocytoma or primary hyperparathyroidism should prompt MEN2 evaluation if not already characterized.
- **Physical:** Thyroid examination at intake — palpable thyroid nodules should be evaluated per ATA guidelines independent of the GLP-1 RA initiation decision.
- **Routine calcitonin screening:** Not recommended.
- **Routine thyroid ultrasound screening:** Not recommended for GLP-1 RA initiation in the absence of palpable nodules or other thyroid-specific clinical indication.
- **General cancer screening:** Maintain age-appropriate cancer screening per USPSTF and specialty-society recommendations independent of GLP-1 RA status.

## 1.10 On-treatment monitoring recommendations

- **Symptom surveillance:** Counsel patients to report new neck mass, persistent dysphagia, persistent hoarseness — evaluate clinically; FNA biopsy if indicated per standard otolaryngology / endocrinology pathways.
- **Routine calcitonin testing during treatment:** Not recommended absent specific clinical indication.
- **General oncology surveillance:** Maintain age-appropriate cancer screening (mammography, colonoscopy, low-dose CT for eligible smokers, etc.) per current USPSTF and specialty-society recommendations — GLP-1 RA therapy does not modify these intervals.

## 1.11 Patient conversation (Pattern Z calibration)

**For the patient asking about thyroid cancer:**

*“There’s an FDA boxed warning based on rat studies of a specific rare thyroid cancer called medullary thyroid carcinoma — MTC for short. The warning is precautionary; the effect in rats was driven by very high receptor density on rat thyroid C-cells, which humans don’t have at the same level. If you or any first-degree relative has a history of MTC specifically, or of MEN2 syndrome, this medication is not for you. Outside that history, the strongest current evidence — a 2026 meta-analysis of 48 trials and 94,000 patients in Annals of Internal Medicine — concludes the medications probably have little or no effect on thyroid cancer risk, with moderate certainty. One French database study reported a positive thyroid-cancer signal in 2023, which is part of why surveillance continues. The overall picture for patients without MTC or MEN2 history is reassuring, and we don’t do routine calcitonin screening because the test doesn’t perform well*

in this context. Standard cancer screening — mammogram, colonoscopy, the age-appropriate ones — continues regardless of which medication you're on."

**For the patient asking about pancreatic, breast, or kidney cancer:**

"The 2026 Annals of Internal Medicine meta-analysis I just mentioned examined those cancers specifically and concluded little or no effect with moderate certainty. There's one subgroup analysis in a different meta-analysis where pancreatic cancer signal became positive in patients on certain background medications — that's a surveillance signal, not a confirmed class effect, and we can talk through whether any of your current medications would put you in that subgroup."

## 1.12 Open questions / what's still being characterized

- **Long-horizon ( $\geq 10$  year) cancer surveillance.** The longest published GLP-1 RA exposure data is approximately 5 years (SELECT extension; FLOW extension; SUSTAIN-6 long-term follow-up). Indefinite-use cancer surveillance requires continued post-marketing follow-up and registry data.
- **Dual-agonist (tirzepatide) and triagonist (retatrutide) class-specific cancer surveillance.** Tirzepatide has substantially shorter post-marketing exposure (FDA-approved 2022 for T2D; 2023 for chronic weight management) than semaglutide (2017 for T2D; 2021 for chronic weight management). Retatrutide is pre-FDA-approval as of 2026-05-12. Class-specific cancer signals will continue to characterize as exposure accumulates.
- **GIPR-mediated mechanisms in C-cells.** Tirzepatide-specific GIPR expression on thyroid C-cells is research-state-incomplete; no established mechanism for C-cell tumorigenesis exists for the GIPR component. The MTC/MEN2 contraindication applies to tirzepatide as a class-level precaution.
- **Bezin 2023 non-reproduction.** Why the French SNDS database produces a positive thyroid signal that other large cohorts (Pasternak BMJ 2024 — verify; PMID 38683947) do not is mechanistically unclear. Database-specific confounding, exposure measurement, detection bias, or true population-specific effect are all hypotheses; none is established.

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## SECTION 2 — Pancreatitis

### 2.1 Mechanistic origin of the concern

The acute pancreatitis concern in the GLP-1 RA class has two converging mechanistic anchors:

1. **Direct receptor pharmacology.** GLP-1R is expressed on pancreatic acinar and ductal cells; chronic GLP-1R agonism produces measurable effects on pancreatic morphology in animal models. Whether this translates into clinically meaningful pancreatitis risk in humans has been the central post-marketing question since the first-generation exenatide signals in the late 2000s.
2. **Indirect — gallbladder events as upstream trigger.** GLP-1 RA therapy increases gallstone incidence (1.5–2.5% per M5.2 v3 Section 5.6) via the combined effects of rapid weight loss (well-characterized cholelithiasis driver) and direct effects on gallbladder motility. Gallstone disease is itself the most common cause of acute pancreatitis in the general population, providing an indirect pathway from GLP-1 RA therapy to pancreatitis even without direct acinar/ductal effects.

### 2.2 Primary evidence

Wen J, Nadora D, Bernstein E, et al. "Evaluating the Rates of Pancreatitis and Pancreatic Cancer Among GLP-1 Receptor Agonists: A Systematic Review and Meta-Analysis of Randomised Controlled Trials." *Endocrinol Diabetes Metab* 2025;8(5):e70113. PMID: 40988099.

- **62 RCTs, n=66,232**
- **Acute pancreatitis: pooled RR 1.44 (95% CI 1.09–1.89, P=0.009)** — statistically significant 44% relative-risk elevation
- Absolute event rates remain low: **<1–2% per year** across the trial pool
- Authors' framing: "slightly increased risk, likely minimal"

This is the load-bearing class-level synthesis evidence. The signal is real, statistically significant, and modest in absolute magnitude.

### 2.3 Absolute risk numbers

- **Absolute pancreatitis event rate on GLP-1 RA therapy:** <1–2% per year (Wen 2025 pooled trial-level data)
- **Background population pancreatitis incidence:** ~13–45 per 100,000 person-years for first-attack acute pancreatitis in unselected adult populations (verify before use for specific risk communication — sourced from epidemiologic literature outside primary M5 corpus)
- **Number-needed-to-harm framing:** with a baseline annual pancreatitis incidence of ~0.5–1% in obesity + T2D populations (somewhat elevated above the unselected adult population), an RR 1.44 translates to approximately 0.2–0.5 additional pancreatitis events per 100 patient-years. Most patients on GLP-1 RAs will never develop pancreatitis; the small minority who do will typically present in the first 6–12 months of therapy.

### 2.4 Regulatory position

- **FDA (US):** Class-label warning for acute pancreatitis. Discontinuation if pancreatitis is suspected. The label does not require pancreatic-enzyme screening at baseline or during routine monitoring.
- **EMA (EU):** Equivalent class warning for acute pancreatitis. No additional pre-screening requirements.

### 2.5 Contraindications

**Relative (case-by-case risk-benefit; no absolute contraindication exists at class label):** - **History of prior acute pancreatitis** (idiopathic, alcohol-related, gallstone-related, post-ERCP, hypertriglyceridemia-related, autoimmune, hereditary) — case-by-case evaluation; the threshold for proceeding should be higher than in patients without this history, and informed consent should explicitly document the additional risk dimension - **Chronic pancreatitis** — most clinicians would not initiate; risk-benefit overwhelmingly unfavorable - **Hypertriglyceridemia  $\geq 500$  mg/dL** — independent pancreatitis risk factor; addressing triglyceride elevation first is preferable - **Active or recent symptomatic gallbladder disease** — case-by-case; consider cholecystectomy timing relative to GLP-1 RA initiation

**Permanent discontinuation indication:** - **Confirmed acute pancreatitis during GLP-1 RA therapy** — permanent discontinuation; avoid class rechallenge

### 2.6 Pre-screening recommendations

- **History:** Document prior pancreatitis episodes (etiology, severity, residual structural change), prior cholecystectomy, alcohol use history, fasting triglyceride level, family history of hereditary pancreatitis.
- **Routine baseline lipase / amylase:** Not required by FDA label. M5.9 v3 Section 1 lists pancreatic surveillance enzymes (fasting lipase + amylase) as a class-context extension to the standard metabolic core panel for clinicians who wish to establish a baseline reference for future symptom-triggered evaluation. Not all clinicians order this routinely; some do.
- **Fasting triglycerides:** Part of standard baseline lipid panel;  $\geq 500$  mg/dL warrants triglyceride-directed intervention before initiating GLP-1 RA.

### 2.7 On-treatment monitoring recommendations

- **Symptom surveillance:** Counsel patients to report severe, persistent mid-epigastric pain — particularly pain radiating to the back, often associated with nausea and vomiting that exceeds the expected GI-tolerability profile of titration.
- **Lipase / amylase:** Obtain when pancreatitis is clinically suspected (severe persistent epigastric pain, abnormal vital signs, peritoneal findings). Lipase elevation  $>3\times$  ULN supports the pancreatitis diagnosis per M5.9 v3 Section 1 threshold; correlate with imaging (CT or MRI) and clinical context.
- **Routine surveillance lipase / amylase during treatment:** Not currently recommended in the absence of symptoms. The negative predictive value of asymptomatic lipase monitoring is poor in this context.



- **Discontinuation threshold:** Suspected acute pancreatitis → discontinue; confirmed acute pancreatitis → permanent discontinuation, avoid class rechallenge per M5.2 v3 Section 5.2.

## 2.8 Patient conversation (Pattern Z calibration)

### At initiation:

*“There’s a class signal for acute pancreatitis — the inflammation of the pancreas — across this group of medications. The 2025 meta-analysis of 62 trials shows about a 44% relative increase in pancreatitis risk, but the absolute rate is still low — well under 2% per year, and most patients will never develop it. We’re going to set you up so that if it does happen, we catch it early. The symptom you need to know is severe persistent pain in the upper middle of the abdomen, often radiating to the back, often with nausea and vomiting that’s worse than typical GI side effects you might get from the medication. If you experience that, stop the injections and contact me the same day — that’s the safety net for this risk. We don’t routinely check pancreas blood tests unless you have symptoms because the test isn’t useful as a screen when you feel fine. If you ever do develop a confirmed pancreatitis episode on this class, we don’t restart it — we’d transition to a different mechanism.”*

### For the patient with prior pancreatitis asking whether GLP-1 RA is still possible:

*“Your prior pancreatitis history doesn’t categorically rule this out, but it does change the math. Let’s look at the specifics — what caused the prior episode, how severe it was, whether there’s residual structural change on imaging, and what your current triglycerides and gallbladder status look like. The relative-risk number from the meta-analysis is 1.44; your baseline risk is higher than someone without that history. We need a higher bar of benefit to take that on, and explicit documentation of the discussion. There are mechanisms — for example, the GH-axis adjuncts in lesson M5.5 / M5.6, or weight-management approaches outside the GLP-1 class — that may be more appropriate first-line for your situation.”*

## 2.9 Open questions / what’s still being characterized

- **Dose-response relationship.** Whether higher GLP-1 RA doses (Wegovy HD 7.2 mg, tirzepatide 15 mg, retatrutide 12 mg) produce dose-dependent pancreatitis incidence above the class-level Wen 2025 RR 1.44 is not characterized at meta-analytic precision.
- **Recurrence after rechallenge.** Class rechallenge after a confirmed acute pancreatitis episode is generally avoided; rechallenge data is sparse and the threshold for clinical exploration would be very high.
- **Cross-class differentiation.** Whether dual incretin (tirzepatide), GLP-1/glucagon (survodutide), or triagonist (retatrutide) compounds carry the same pancreatitis class-level RR as single GLP-1 RAs is not yet characterized at the precision Wen 2025 achieves for the broader class.
- **Compounded preparations.** Quality variability across 503A compounding pharmacies introduces a pancreatitis-relevant question (potency consistency, residual solvents, endotoxin) that is not addressed by the FDA-approved-product evidence base.

## SECTION 3 — NAION (non-arteritic anterior ischemic optic neuropathy)

### 3.1 Mechanistic origin of the concern

NAION is a sudden, painless, typically monocular vision loss caused by ischemic injury to the anterior optic nerve head. Established risk factors include “disc at risk” anatomy (small crowded optic disc with reduced cup-to-disc ratio), hypertension, diabetes, obstructive sleep apnea, hypotension (particularly nocturnal), and hyperlipidemia. The mechanistic question for GLP-1 RAs is whether rapid changes in glycemia, blood pressure, intravascular volume, or direct vascular effects on the optic nerve microcirculation could shift the ischemic threshold in susceptible individuals. The mechanism remains hypothesis-level; the signal has been characterized observationally before any mechanistic explanation has been definitively established.

### 3.2 Primary evidence — the original signal

Hathaway JT, Shah R, Hyman MJ, et al. "Risk of Nonarteritic Anterior Ischemic Optic Neuropathy in Patients Prescribed Semaglutide." *JAMA Ophthalmol* 2024;142(8):732-739. PMID: 38958939.

Retrospective matched cohort study, Mass Eye and Ear, propensity-score matched: - **T2D cohort: HR 4.28 (95% CI 1.62–11.29; P<0.001)** - **Overweight/obesity cohort: HR 7.64 (95% CI 2.21–26.36; P<0.001)** - 36-month cumulative NAION incidence: - Semaglutide T2D group: **8.9%** vs control 1.8% - Semaglutide overweight/obese group: **6.7%** vs control 0.8%

This was the first published signal and the one that triggered the subsequent regulatory cycle. Note that the absolute incidence figures from the Mass Eye and Ear cohort are substantially higher than the population-level "approximately 1 per 10,000 person-years" framing the EMA subsequently adopted — reflecting the eye-clinic referral population captured by this single-center cohort, not the general semaglutide-prescribed population.

### 3.3 Primary evidence — Danish national cohort

Grauslund J, Sabbah N, Hansen TW, et al. "Once-weekly semaglutide doubles the five-year risk of nonarteritic anterior ischemic optic neuropathy in a Danish cohort of 424,152 persons with type 2 diabetes." *Int J Retina Vitreous* 2024;10(1):97. PMID: 39696569.

- **HR 2.19 (95% CI 1.54–3.12) at 5 years**
- n=424,152 T2D patients — the largest cohort to date
- Effect size attenuated relative to Hathaway but directionally confirmatory at nationwide scale

### 3.4 Primary evidence — 180-country pharmacovigilance

Lakhani M, Kosiborod MN, McGuire DK, et al. "Association of Glucagon-Like Peptide-1 Receptor Agonists With Optic Nerve and Retinal Adverse Events: A Population-Based Observational Study Across 180 Countries." *Am J Ophthalmol* 2025;277:148-168. PMID: 40383360.

FAERS + VigiBase pharmacovigilance analysis: - **Semaglutide ischemic optic neuropathy: ROR 11.12 (FAERS); ROR 68.58 (VigiBase)** — substantial reporting-odds-ratio signal - Semaglutide diabetic retinopathy: ROR 17.28 (FAERS); ROR 7.81 (VigiBase) - Semaglutide retinal/vitreous detachment and hemorrhage: ROR 2.44–20.91 - **Tirzepatide: significant findings limited to diabetic retinopathy in FAERS; no significant NAION signal at the same threshold**

**Class-differentiation caveat (Pattern V + exposure-window asymmetry).** Tirzepatide has substantially shorter post-marketing exposure than semaglutide. The absence of a same-magnitude tirzepatide NAION signal at the same surveillance threshold may reflect lower cumulative person-year exposure rather than true mechanism-level class differentiation. Surveillance continues.

### 3.5 Absolute risk numbers

- **EMA PRAC (June 2025) classification: "very rare"** by EU definition (may affect up to 1 in 10,000 patients)
- **EMA risk estimate:** approximately two-fold increase vs non-users — **approximately one additional case of NAION per 10,000 person-years of treatment**
- **Mass Eye and Ear cohort absolute incidence:** 36-month cumulative 6.7–8.9% in semaglutide-exposed; 0.8–1.8% in matched controls — this absolute incidence reflects the referral-clinic population and should not be extrapolated to unselected populations
- **Background population NAION incidence:** ~2.3–10.2 per 100,000 person-years in adults >50 years old (verify before use; sourced from ophthalmologic epidemiologic literature outside the M5 primary corpus)

### 3.6 Regulatory position — the central divergence

- **EMA (EU): June 2025** — PRAC formally classified NAION as a **"very rare" side effect** of semaglutide medicines (Ozempic, Rybelsus, Wegovy). EU product information updated accordingly. EASO 2025 framework formally incorporates this classification and advises patient counseling.
- **FDA (US): NOT updated as of 2026-05-12.** The US/EU labeling divergence on NAION is the most clinically material regulatory-cycle item in the 2025–2026 window. ADA 2026 Standards



of Care integrate the EMA “very rare” classification for clinician awareness even though the FDA label has not adopted equivalent language.

### 3.7 Contraindications

**Absolute:** None specifically for NAION risk.

**Relative considerations / heightened counseling load:** - Personal history of NAION in the fellow eye (NAION is recurrent in the contralateral eye in approximately 15–25% of patients; addition of any potentially contributing exposure warrants explicit shared decision-making) - Known “disc at risk” anatomy (small crowded optic disc, reduced cup-to-disc ratio) documented on prior ophthalmologic evaluation - Severe uncontrolled hypertension, untreated obstructive sleep apnea, severe dyslipidemia — concurrent NAION risk factors that compound the GLP-1 RA-associated incremental risk

### 3.8 Pre-screening recommendations

- **History:** Personal or family history of NAION; known “disc at risk” anatomy; OSA history and CPAP-adherence pattern; baseline visual acuity; current ophthalmology relationships.
- **Routine ophthalmologic examination at GLP-1 RA initiation:** Not currently required by FDA or EMA labels. M5.9 v3 lists ophthalmologic baseline considerations as part of the class-context extension panel; not all clinicians order routine baseline ophthalmologic evaluation. For patients with diabetic retinopathy, baseline ophthalmology coordination is independent good practice (see Section 3.10 on retinopathy below).
- **STEP-2 / SUSTAIN-6 context — diabetic retinopathy:** Rapid glycemic improvement in T2D patients with pre-existing diabetic retinopathy can transiently worsen retinopathy independent of the NAION signal. Coordinate ophthalmology surveillance at semaglutide initiation in T2D patients with established retinopathy.

### 3.9 On-treatment monitoring recommendations

- **Symptom surveillance:** The load-bearing intervention. Counsel patients to seek **same-day ophthalmologic evaluation** for any sudden change in vision, painless monocular vision loss, visual field defect, or “curtain”/altitudinal scotoma.
- **Routine on-treatment ophthalmology surveillance:** Not required by FDA or EMA labels in the absence of symptoms.
- **Discontinuation threshold:** Discontinue semaglutide if NAION occurs; the recurrence risk in the fellow eye is the primary downstream concern.

### 3.10 Patient conversation (Pattern Z calibration)

*“European regulators classified a rare eye condition called NAION — a type of optic nerve stroke that causes sudden vision loss — as a ‘very rare’ possible side effect of semaglutide in June 2025. ‘Very rare’ in their definition means about one extra case per 10,000 people treated per year, roughly double the background rate. U.S. regulators have not yet updated U.S. labels, but you should know about it regardless of which country’s label you’re reading. The risk is small in absolute terms; it matters most for people who have known eye anatomy that’s already prone to this — small crowded optic disc, prior NAION in one eye, uncontrolled high blood pressure, untreated sleep apnea. If you notice sudden vision change in either eye, especially painless vision loss or a ‘curtain’ that comes down across part of your vision, stop the medication and get to an ophthalmologist the same day. The class-pattern observation so far is that the signal is documented for semaglutide and not for tirzepatide in the same surveillance data, with the caveat that tirzepatide has been on the market for less time.”*

**For the patient with prior NAION in one eye asking about GLP-1 RA initiation:**

*“Your history changes the conversation. The recurrence risk in the second eye for NAION is in the 15-to-25% range over time independent of any medication, and adding a potential contributing exposure puts that into a ‘we need to think carefully’ tier. Let’s get ophthalmology involved before any decision — the conversation needs to include them. We may proceed; we may decide a different mechanism class is the better fit for your situation.”*

### 3.11 Open questions / what's still being characterized

- **Mechanism.** No established mechanism connects GLP-1R agonism to optic nerve head ischemia. Rapid glycemic correction, blood-pressure changes, intravascular volume shifts, and direct vascular effects are all candidates; none has been definitively characterized.
  - **Class differentiation.** Tirzepatide's absence of a same-threshold NAION signal in Lakhani 2025 is exposure-window-asymmetric; characterization will mature as tirzepatide post-marketing exposure accumulates.
  - **Dose-response.** Whether Wegovy HD 7.2 mg carries higher NAION risk than Wegovy 2.4 mg is not characterized.
  - **FDA label-update trajectory.** Whether and when FDA will harmonize with EMA on NAION labeling is a regulatory-cycle question; current US-EU divergence is the operative clinical reality.
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## SECTION 4 — Suicidality / Psychiatric Safety

### 4.1 Mechanistic origin of the concern

The psychiatric-safety concern for GLP-1 RAs has two distinct origins, frequently conflated in patient-facing discourse:

1. **2023 Iceland Medicines Agency signal:** Three case reports of suicidal ideation in patients on liraglutide and semaglutide, reported to the European pharmacovigilance system in mid-2023, triggered EMA review and a global cycle of regulatory inquiry. The Iceland cases were the proximate cause of the 2023–2024 black-box concern wave.
2. **Mechanistic plausibility argument:** GLP-1R is expressed in central reward and mood circuits (ventral tegmental area, nucleus accumbens, hippocampus, amygdala, prefrontal cortex). Modulation of central reward signaling — the same mechanism that produces appetite suppression and may produce therapeutic effects in substance use disorders — could in principle affect mood and suicidality. The mechanism is bidirectional: receptor pharmacology could produce protective effects in mood disorders as easily as harmful ones.

### 4.2 Primary evidence — FDA preliminary evaluation (2024)

**FDA Drug Safety Communication, January 11, 2024.** FDA preliminary evaluation of the suicidality signal concluded that available evidence “did not find evidence” that GLP-1 RA medications cause suicidal thoughts or actions. The supporting analyses included: - Meta-analysis of 91 placebo-controlled trials, n=107,910 — no increased psychiatric-AE risk - Retrospective cohort comparing GLP-1 vs SGLT2i users — no increased intentional self-harm risk

**Subsequent FDA action (2025):** FDA requested removal of suicidal-ideation-and-behavior warnings from GLP-1 RA labels for Saxenda (liraglutide), Wegovy (semaglutide), and Zepbound (tirzepatide). The regulatory action confirms the 2024 preliminary null finding at label level.

### 4.3 Primary evidence — the strongest design (Bezin 2024, protective)

Bezin J, Bénard-Larivière A, Hucteau E, et al. “Suicide and suicide attempt in users of GLP-1 receptor agonists: a nationwide case-time-control study.” *EClinicalMedicine* 2024;80:103029. PMID: 39844933.

- French National Health Data System case-time-control study
- n=1,102 cases + 5,494 controls
- **OR 0.62 (95% CI 0.51–0.75) — a protective association**
- Results held across psychiatric-history and obesity subgroups
- DPP-4 inhibitor negative control: OR 0.75 (similar protective direction in negative control)
- Authors’ own framing: the study “provides reassurance about the short-term psychiatric safety of GLP-1 RA”

Pattern V framing: this is a **protective signal**, not a “weak signal of concern” and not a “null finding.” The authors’ wording is the appropriate citation register.

#### 4.4 Primary evidence — supporting synthesis

- **Bushi 2025 systematic review** (PMID: 39945396, *Diabetes Metab Res Rev*): 4 pooled observational studies; pooled RR 0.568 (95% CI 0.077–4.205); not statistically significant; high heterogeneity ( $I^2=98\%$ ). Authors conclude no significant association between GLP-1 RA use and increased suicidal ideation/behavior.
- **Sa 2026 broader psychiatric-effects SR** (PMID: 41126551, *Diabetes Obes Metab*): scope includes depression, suicidality, eating disorders, substance use disorders, schizophrenia-spectrum disorders. Findings: **modest antidepressant effects**; inconsistent suicidality associations; **potentially therapeutic signals in eating disorders and substance use disorders** (pending RCT confirmation).
- **Hendershot 2025 Phase 2 RCT on alcohol use disorder** (PMID 39937469): n=48; 9 weeks; semaglutide reduced grams of alcohol consumed and reduced craving. The therapeutic-direction signal in reward-regulation disorders is real and being actively investigated.

#### 4.5 Absolute risk numbers

- **Bezin 2024 OR 0.62**: translates to a 38% lower odds of suicide / suicide attempt during GLP-1 RA exposure relative to non-exposure in the case-time-control design
- **FDA meta-analysis (91 RCTs, n=107,910)**: no increased psychiatric AE incidence in GLP-1 RA arms vs placebo arms
- **Base-rate context**: suicide rates in adults with obesity and adults with T2D are elevated above the general adult population; any absolute-risk discussion with a patient should anchor to their individual baseline psychiatric profile rather than to a population number

#### 4.6 Regulatory position

- **FDA (US)**: Suicidal-ideation-and-behavior warnings **removed** from GLP-1 RA labels for Saxenda, Wegovy, and Zepbound (2025 action). No active labeling concern.
- **EMA (EU)**: Equivalent removal of suicidal-ideation warnings (2024–2025 timing).

#### 4.7 Contraindications

**Absolute:** None for the psychiatric-safety axis.

**Relative considerations:** – Active untreated severe psychiatric illness (acute psychosis, severe untreated mood disorder, recent suicide attempt or psychiatric hospitalization) — initiation warrants coordination with mental-health providers, not because GLP-1 RAs are psychiatrically harmful, but because any new chronic-disease management initiation in this population benefits from coordinated care – Active eating disorder (anorexia nervosa, severe restrictive ED) — appetite-suppressant pharmacotherapy is generally contraindicated; bulimia-spectrum and binge-eating-disorder presentations may be considerations for which GLP-1 RAs could be therapeutically appropriate but the decision belongs in an integrated psychiatric/eating-disorder care pathway

#### 4.8 Pre-screening recommendations

- **Validated screening tools at intake:** PHQ-9 (depression), GAD-7 (anxiety), and Columbia-Suicide Severity Rating Scale components when indicated. Appropriate practice for any obesity-care initiation — not specific to GLP-1 RA risk surveillance.
- **Mental-health history:** Document history of depression, anxiety, prior suicide attempts, current and prior psychotropic medications, current psychiatric care relationships.
- **Eating-disorder screening:** SCOFF or equivalent brief screen; positive screen warrants further evaluation before initiation.

#### 4.9 On-treatment monitoring recommendations

- **Mood and suicidality re-screening:** At each titration step and at standard follow-up intervals. Document.
- **Specific surveillance for GLP-1 RA-induced psychiatric AEs:** Not labeled or recommended by guidelines beyond the standard chronic-disease-management mental-health attention any longitudinal patient relationship warrants.
- **Communication discipline:** Do not cite a suicidality causal link in patient counseling or educational materials — FDA has formally concluded the available evidence does not support

one.

#### 4.10 Patient conversation (Pattern Z calibration)

##### For the patient asking about the 2023–2024 suicidality concern:

*“You may have seen news in 2023 and 2024 about GLP-1 medications and suicidal thoughts. Here’s where that landed: the FDA reviewed the data in early 2024 and concluded that the evidence did not support a causal link. In 2025, the FDA removed the suicidal-ideation warning from the labels of Wegovy, Saxenda, and Zepbound — that’s the regulatory confirmation of the safety review. The strongest study published since then — a French nationwide case-time-control study of over a thousand suicide cases, published in *EClinicalMedicine* in 2024 — actually found a protective association, with patients on GLP-1 medications having about 38% lower odds of suicide attempt during exposure. That doesn’t mean the medication treats depression — what it means is that the early concern that emerged from a handful of case reports has not held up in larger, better-designed studies. We still screen for mood and suicidality at the start and at follow-ups because that’s good practice for any long-term care relationship, not because of a specific GLP-1 concern.”*

##### For the patient with depression history asking about GLP-1 RA initiation:

*“Your depression history isn’t a contraindication. The data we just discussed shows no excess psychiatric harm signal — and arguably a small protective signal — across the GLP-1 class. We’ll coordinate with your mental-health provider so they know you’re starting therapy, and we’ll do the standard mood and anxiety screening at intake and follow-ups. Some preliminary research is actually looking at GLP-1 medications as potential adjuncts in depression, eating disorders, and substance-use disorders, but those are research-state-incomplete and we’re not initiating treatment with those as the indication.”*

#### 4.11 Open questions / what’s still being characterized

- **Long-horizon mood and cognition effects.** Most published psychiatric-safety data covers exposures of <2 years. Indefinite-duration psychiatric surveillance requires continued post-marketing follow-up.
- **Therapeutic indications.** Whether GLP-1 RAs will become FDA-approved for depression, binge eating disorder, alcohol use disorder, or other psychiatric indications is research-active. Hendershot 2025 Phase 2 RCT on alcohol use disorder is the most-developed adjacent evidence; multiple Phase 2 / Phase 3 programs in adjacent indications are enrolling.
- **Discontinuation-context psychiatric effects.** Whether weight regain after GLP-1 RA discontinuation produces measurable mood effects (a regain-driven body-image-and-mood signal) is hypothesized but not well characterized.

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## SECTION 5 — Pregnancy and Lactation

### 5.1 Mechanistic origin of the concern

The pregnancy concern for GLP-1 RAs has three converging anchors:

1. **Animal teratogenicity data.** Reproductive toxicity studies in animals — at exposures exceeding human therapeutic doses — demonstrated developmental effects sufficient to support Category X-equivalent pregnancy contraindication in product labels for the class. Animal teratogenicity data does not always translate to human teratogenic risk; the load-bearing question is what human exposure data shows.
2. **Caloric restriction in pregnancy.** GLP-1 RA-driven appetite suppression during pregnancy could in principle produce maternal caloric restriction at a developmental phase where appropriate maternal nutritional intake is critical. The mechanistic concern is not exclusively receptor-pharmacologic — it includes the downstream caloric-balance effect.
3. **Long half-life and substantial fetal exposure window.** Semaglutide elimination half-life is approximately 7 days; tirzepatide approximately 5 days. Five half-lives — the standard substantial-clearance window — translates to approximately 35 days for semaglutide and 25 days for tirzepatide. A patient who discovers pregnancy at 4–6 weeks gestational age has had substantial active-drug fetal exposure during the critical organogenesis window even if she discontinues immediately on pregnancy awareness.

## 5.2 Primary evidence — the load-bearing human dataset

Parker CH, Bachu A, Stevens H, et al. "Pregnancy outcomes with the use of GLP-1 receptor agonists and dual agonists: A pooled analysis." *Diabetes Obes Metab* 2025;27(8):4102-4108. PMID: 40329607.

- Pooled review of unplanned pregnancies from FDA- and EMA-submitted GLP-1 RA regulatory clinical trials
- Compounds included: semaglutide, liraglutide, dulaglutide, tirzepatide, and class-related compounds
- **Headline finding: Incidence of congenital abnormalities appears relatively low** in this pooled dataset
- Sample size is limited
- Exposures are from **unplanned-pregnancy contexts** — patient discovered pregnancy while on therapy, typically discontinued upon discovery
- Authors call for **prospective pregnancy registries**

Pattern Z framing: this is the strongest contemporary human-exposure dataset and the load-bearing reassurance signal for clinicians counseling patients on unplanned-pregnancy contexts. It is **not** evidence of safety for planned pregnancy on GLP-1 RAs (no patient in this dataset intended continued exposure through pregnancy) and **does not** support a position of "GLP-1 RAs are safe in pregnancy." The honest framing is: in the unplanned-pregnancy population where exposure has occurred and discontinuation has followed, the human signal so far is reassuring; the prospective registries needed to characterize planned-exposure outcomes do not yet exist.

## 5.3 Absolute risk numbers

- **Background congenital anomaly rate (US population):** approximately 3% of live births (CDC; verify before use for patient communication)
- **Parker 2025 pooled dataset:** congenital abnormality incidence "appears relatively low" — the publication does not provide a single pooled point estimate suitable for direct citation; verify the specific number against the published paper before using in patient counseling
- **Effective washout windows by compound** (from M5.2 v3, M5.3 v3, M5.4 v3):
  - **Liraglutide:** half-life ~13 hours; substantial clearance ~2–3 days; **shortest washout in the class** — the pre-conception agent of choice when pregnancy is on a near-term horizon
  - **Tirzepatide:** half-life ~5 days; substantial clearance ~25 days; complete clearance ~35 days; ≥2-month washout before planned conception
  - **Semaglutide:** half-life ~7 days; substantial clearance ~35 days; complete clearance up to ~7 weeks; ≥2-month washout before planned conception
  - **Survodutide / cagrilintide / retatrutide:** weekly compounds; analogous ~35-day washout framework; verify per compound-specific PK
  - **Orforglipron (oral non-peptide):** PK distinct from peptide weekly compounds; washout ~5 days per typical small-molecule oral kinetics; verify per Lilly product information at time of FDA approval

## 5.4 Regulatory position

- **FDA (US):** Class contraindication in pregnancy (Category X-equivalent labeling for semaglutide, tirzepatide, liraglutide, and pre-approval compounds). Lactation: not recommended; clinical exposure data is incomplete.
- **EMA (EU):** Equivalent class contraindication in pregnancy and lactation.

## 5.5 Contraindications

**Absolute:** - Active pregnancy — discontinue upon pregnancy awareness - Active attempts at conception within the washout window of the specific compound

**Relative considerations:** - Reproductive-age women without effective contraception — initiation appropriate with explicit contraception counseling - Women planning pregnancy within the next 3–6 months — liraglutide may be the preferred class agent given the shorter washout window (M5.4 v3 Section discussion of liraglutide pre-conception use case) - Postpartum lactating women — not recommended; coordinate with the patient's broader postpartum care plan if weight-management indication arises

## 5.6 Pre-screening recommendations

- **Pregnancy test at baseline:** Standard urine or serum hCG for reproductive-age women prior to initiation. Document.
- **Contraception status and counseling:** Document current contraceptive method, counsel on the need for effective contraception during treatment. For women on oral contraceptives — see Section 5.10 below on the gastric-emptying-delay interaction.
- **Reproductive-life-plan conversation:** Document the patient's pregnancy-intent timeline. A patient planning pregnancy within 6–12 months should be counseled on which compound's washout aligns with that timeline (liraglutide is the short-washout option; weekly compounds require longer pre-conception discontinuation).
- **Folate supplementation:** Folate 400 mcg daily through the washout window for any reproductive-age patient discontinuing GLP-1 RA in anticipation of pregnancy (M5.8 script v3 reference) — independent of GLP-1 RA-specific risk; standard pre-conception care.

## 5.7 On-treatment monitoring recommendations

- **Pregnancy testing during treatment:** Symptom-driven (missed menses, unexplained nausea/fatigue inconsistent with expected GI titration tolerability profile, breast tenderness, etc.). Not routine.
- **Contraception adherence check:** At each follow-up appointment for reproductive-age women. Document.
- **Oral contraceptive backup:** Counsel patients on oral contraception about the gastric-emptying-delay interaction (Section 5.10) and the value of backup non-oral methods during titration, particularly during the first months when GI effects are most prominent.

## 5.8 Pregnancy occurring during treatment — clinical workflow

1. **Discontinue the GLP-1 RA immediately upon pregnancy awareness.** Do not “taper” — discontinuation is the appropriate action.
2. **Document exposure window** — date of last dose, dose at time of last dose, gestational age at last dose, estimated gestational age at pregnancy recognition.
3. **Folate 400 mcg daily through the washout window** if not already on prenatal vitamin.
4. **Coordinate with obstetrics/maternal-fetal medicine** — explicit transfer of relevant exposure history; document. The MFM team may recommend additional anatomy-scan surveillance based on exposure timing relative to organogenesis.
5. **Patient counseling:** Pattern Z framing of the Parker 2025 data — the existing human evidence is reassuring; sample size is limited; the recommendation is standard prenatal care with the documented exposure communicated to obstetric and pediatric providers.
6. **Resume postpartum decision:** Discuss with patient at the postpartum visit. The decision to resume during lactation is contraindicated by current labels; the decision to resume after lactation concludes is a shared-decision-making conversation aligned with the patient's reproductive-life plan.

## 5.9 Patient conversation (Pattern Z calibration)

### At initiation for a reproductive-age woman:

*“This medication is contraindicated in pregnancy. If you become pregnant, we discontinue immediately. The medication stays in your system for about 35 days after the last dose for the weekly versions and about 2–3 days for the daily version, so if you’re actively planning pregnancy in the next few months, we should talk about that now and decide whether to start this medication, start a different one with a shorter washout, or hold off entirely. We’ll do a baseline pregnancy test before your first dose. You’ll need effective contraception throughout treatment — and if you’re on the pill, the medication can slow stomach emptying enough to reduce pill absorption, especially during the early months when GI side effects are at their peak. We can talk through backup contraception options.”*

### For the patient who became pregnant on therapy:

*“We stop the medication today — that’s the most important first step. Here’s the current evidence: a 2025 review pooled the pregnancy outcomes from clinical trials where patients discovered pregnancy while on these medications. The reassuring finding was that congenital abnormality rates appeared relatively low — meaning the existing human data does not show a*



strong teratogenic signal at the population level the trials captured. Sample size is limited and we don't yet have planned-pregnancy exposure data. The plan: continue your standard prenatal care, start folate if you're not already on prenatal vitamins, and we'll let your obstetrician know about the exposure window so they can decide whether any additional surveillance scans are appropriate."

#### For the patient planning pregnancy and asking about timing:

"For weekly compounds — semaglutide, tirzepatide, the others — we plan a washout of at least 2 months before active conception attempts. That's because the drug takes about 35 days to clear substantially after the last dose. For liraglutide, the daily compound, the washout is much shorter — about 2 to 3 days for substantial clearance, so 1 week is comfortably above that threshold. If your pregnancy timeline is tight, liraglutide is the version of this class that fits a near-term conception plan most easily. We'll plan the transition off the medication, your folate, and the timeline together."

### 5.10 Oral contraceptive interaction

GLP-1 RA-driven gastric emptying delay can reduce oral contraceptive absorption efficacy. Patient counseling at initiation includes backup contraception recommendation for women of reproductive potential, particularly during titration when GI effects are most prominent. Tirzepatide labeling specifically addresses this interaction (M5.3 v3 Section 6.6). Patients on combined oral contraceptives should consider non-oral methods during titration; some manufacturer labeling specifies a window during which backup contraception is recommended (verify per compound-specific label).

### 5.11 Lactation

- **Current product labels:** GLP-1 RAs are not used during breastfeeding per current Novo Nordisk (semaglutide, liraglutide), Lilly (tirzepatide), and other manufacturer product information.
- **Human lactation-exposure data:** Research-state-incomplete. The molecular size and pharmacokinetic profile of peptide GLP-1 RAs suggest limited expected transfer into breast milk and limited oral bioavailability in the breastfed infant, but this is mechanistic reasoning rather than measured human data.
- **Clinical position:** Discontinue or do not initiate during lactation. The postpartum resumption decision (post-weaning) is shared decision-making aligned with the patient's reproductive-life plan and weight-management priorities.

### 5.12 Open questions / what's still being characterized

- **Prospective planned-pregnancy registries.** The Parker 2025 pooled dataset captures unplanned-pregnancy contexts only. Prospective registries that capture intentional-exposure pregnancy outcomes are needed; authors of multiple papers in the surveillance literature explicitly call for them.
- **Class-specific differences in pregnancy outcomes.** Whether tirzepatide, retatrutide, survodutide, CagriSema, orforglipron carry the same pregnancy-outcome profile as semaglutide is not characterized at meta-analytic precision. Pooled regulatory-trial data includes representation from multiple compounds; per-compound parsing is limited.
- **Long-term offspring outcomes.** Even where congenital abnormality rates are reassuring, long-term metabolic, neurodevelopmental, and cardiovascular outcomes in offspring of exposed pregnancies require multi-decade follow-up that is only just beginning.
- **Effect of compound choice on fertility.** GLP-1 RA-driven weight loss in obesity and PCOS may improve fertility (M5.2 v3 Section 4 reproductive-outcomes discussion; Chen 2025 PMID 40713699 metformin + semaglutide PCOS trial — natural pregnancy rate improvement). This is a beneficial effect but creates an operational tension: the patients most likely to benefit from GLP-1 RA-driven fertility improvement are precisely those most likely to conceive on therapy and require unplanned-pregnancy management.

## Cross-Reference Footer

- **[[M5.1 - Obesity Pathophysiology — Hormonal, Metabolic & Neural Drivers - v3]]** — Section 6.6 (NAION); Section 6.7 (cancer surveillance class-level synthesis); Section 5.5 (psychiatric safety); class-level safety synthesis sweep (PMIDs 41359966, 40988099, 40383360, 39844933, 40329607, 20203154, 36356111)
  - **[[M5.2 - GLP-1 Receptor Agonists — Semaglutide Deep Dive - v3]]** — Section 5 (full five-anchor safety triangulation: pancreatitis, MTC/MEN2, NAION class-differentiation, psychiatric protective signal, pregnancy); Section 5.8 contraindications table; Section 6 US/EU regulatory divergence
  - **[[M5.3 - Tirzepatide (Mounjaro-Zepbound) — Dual GIP-GLP-1 Mechanism - v3]]** — Section 6 (eight-domain safety profile including the class-differentiation NAION finding); Section 6.6 pregnancy / lactation / oral contraceptive interaction
  - **[[M5.4 - Liraglutide, Triagonists & Combo-Products — Module 5 Comparator Landscape - v3]]** — pre-conception washout comparator table; liraglutide as pre-conception agent of choice
  - **[[M5.8 - Patient Titration Schedules, Side Effect Management & Dose Optimization - v3]]** — symptom-management workflows; pancreatitis-symptom counseling at initiation
  - **[[M5.9 - Lab Panels — HbA1c, Lipids, Insulin, Leptin, Body Composition - v3]]** — pre-treatment baseline panel; pancreatic surveillance enzymes; NAION ophthalmologic baseline considerations
  - **Doc 1 (Baseline Labs)** — baseline lab panel that operationalizes the pre-screening recommendations in each section above
  - **Doc 6 (Informed Consent Template)** — patient-facing informed consent language drawing on the five-section evidence anchors
  - **Doc 11 (CME Knowledge Check)** — formative-assessment items keyed to the PMID anchors and absolute-risk numbers in each section
  - **[[Cancer Safety Matrix]]** ( [obsidian-peptides/Compliance/Cancer Safety Matrix.md](#) ) — peptide-by-peptide cancer-context tier classification across the full Synergy peptide pharmacopeia
  - **[[Module 5 - Master Protocol Index]]** — navigation hub for all Module 5 clinical protocols
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## Doc Status

**Draft v1, 2026-05-26.**

**Reviewers needed:** Dr. Jeffrey Gross MD (medical authority — clinical content review and Pattern Z calibration on patient-counseling language).

**Open verification items flagged inline with “verify before use”:** - Section 1.4 — Pasternak 2024 BMJ cohort (HR 0.93, n=145,000+) sourced from Cancer Safety Matrix; PMID 38683947 reference cited but specific cohort number and HR should be verified against the primary publication before patient-facing use - Section 1.6 — MTC and pancreatitis background population incidence figures sourced from NCI SEER / general epidemiologic literature, not primary M5 corpus; verify against authoritative source before patient-facing use - Section 3.5 — Background population NAION incidence (2.3–10.2 per 100,000 person-years in adults >50) sourced from ophthalmologic epidemiologic literature outside the M5 primary corpus; verify before patient-facing use - Section 5.3 — Parker 2025 pooled dataset’s specific congenital abnormality incidence number not extracted in the M5 source material; the publication should be consulted directly before citing a point estimate in patient counseling

**Editorial calibration applied:** Pattern Z honesty discipline (present facts, frame trajectory, do not steer); Pattern V direction-of-effect precision on each safety signal; Pattern AA-precise framing on pre-FDA-approval class members; Pattern AB.4 publication-type discipline on each cited source.

**Scope boundary:** This document covers the five class-level safety fronts most clinically active in 2026. Compound-specific safety items beyond these five (e.g., GHK-Cu hair-color changes per M5.7; tesamorelin IGF-1 surveillance per M5.5; lean-mass-loss preservation discipline per M5.6) are addressed in the corresponding M5.x lesson and are not duplicated here.

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*Doc 10 of the Module 5 reference-card set. Editorial baseline: Synergy Editorial Framework v1.1 (Pattern R/R.1/R.2 + Pattern V/W/Z/AA/AB.1–AB.4 standing scans applied). Source verification per Synergy verification-report methodology — companion verification pass to be ordered as the reference-card set ships.*