

A deep dive into incretin mechanisms of action – a call for a more diverse portfolio of medications.

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Main points

- The approved and coming anti-obesity medications are to a large degree dependent in GLP-1 agonism
- This considerable overlap in mechanism of action affects efficacy AND tolerability
- If the patient does not respond sufficiently and/or has problematic side-effects, switching to a different molecule with similar or overlapping mechanism of action will not help, as shown by recent study (<https://doi.org/10.1002/oby.70179>)

Here follows seven somewhat overlapping mechanistic factors to support the main point that a patient who has poor efficacy and/or does not tolerate one GLP-1–based therapy is unlikely to be rescued by switching to another GLP-1 drug.

1. Shared primary mechanism and receptor

All of the listed mono-agonists in table 1 below act through the GLP-1 receptor (GLP-1R) as their dominant mechanism, and the dual and triple agonists listed in table 2 still include potent GLP-1R activation as a component of efficacy.

If a patient's poor weight-loss "response" reflects fundamental non-responsiveness of their central or peripheral GLP-1R pathways (e.g., limited central satiety signaling, minimal gastric-emptying effect, or low β -cell responsiveness), changing to another drug that still relies on GLP-1R as the key driver is unlikely to transform outcomes, because the same receptor system is being targeted.

2. Class-wide dependence on nausea/anorexia mechanisms

GLP-1-based weight loss is tightly linked to central GLP-1R activation in brainstem and hypothalamus and to delayed gastric emptying, both of which are also central drivers of nausea and other GI symptoms. Because all GLP-1R agonists reduce food intake via the same brainstem circuits that mediate illness-like behaviors, patients who cannot tolerate those circuits being activated (severe nausea, vomiting, aversion) are likely to experience similar problems with any other GLP-1–driven drug, even if the exact incidence differs modestly between molecules.

3. Cross-intolerance of gastrointestinal side-effects

Across the GLP-1 class, nausea, vomiting, diarrhea and constipation are the dominant adverse events; they are dose-dependent and highly prevalent for all currently marketed and investigational GLP-1RAs. Thus, a patient who has already had severe, class-limiting GI tolerability issues despite slow titration is at high risk of cross-intolerance when switching to another GLP-1-centric

drug; mechanistic differences (half-life, bias, route) may tweak the AE profile but rarely eliminate it.

4. Dual/triple agonists still depend on GLP-1 signaling

Even though tirzepatide and HRS9531 add GIP agonism, mazdutide/survodutide add glucagon agonism, and retatrutide adds both GIP and glucagon agonism. their weight-loss efficacy still to varying degrees depends on GLP-1R-mediated appetite suppression and GI motility changes.

Trial data show that GIP or glucagon co-agonism does not remove the GLP-1-driven mechanisms that cause nausea and reduced oral intake. If the patient cannot tolerate any degree of GLP-1-mediated nausea/vomiting then moving to a dual or triple agonist or with equal or greater GLP-1 potency and longer exposure is unlikely to fix this and may exacerbate it.

5. Non-response that is pharmacodynamic, not exposure-related

Some patients have adequate drug exposure but limited clinical effect possibly because of biology (e.g., lower central sensitivity to GLP-1, different hedonic drivers of eating, strong compensatory hunger signals, or limited β -cell reserve). In such pharmacodynamic “non-responders”, switching within the same mechanistic class (different GLP-1 analogue, oral vs injectable, or GLP-1/GIP vs GLP-1 alone) will not overcome the underlying lack of receptor-mediated response; you are essentially re-stimulating the same pathway that already showed insufficient efficacy.

6. Ceiling effects on weight loss set by GLP-1 biology

Even in responders, GLP-1-mediated weight loss typically plateaus as adaptive mechanisms (increased hunger signals, changes in energy expenditure, ...) counteract further weight reduction. Switching to another GLP-1-based drug after a clear plateau at adequate dose and duration does not yield large additional losses, because the physiological ceiling is set by the shared GLP-1 biology rather than any specific molecule.

7. Shared long-term unknowns and class risks

Rare but serious concerns such as severe gastroparesis, intestinal obstruction, and potential gallbladder disease appear to be class phenomena linked to sustained GLP-1R activation and reduced gut motility, not to a single molecule. A patient who has already demonstrated a significant class-level complication (e.g., frank gastroparesis, repeated pancreatitis) with one GLP-1RA is unlikely to be safely managed on another GLP-1-centric agent because the same pathophysiologic trigger remains.

In summary, all of the listed medications below are variations on the incretin theme, with GLP-1R activation at their core; for patients with true GLP-1 class failure, either lack of pharmacodynamic effect or class-limiting adverse effects, switching among them often replays the same mechanisms rather than offering a fundamentally different solution.

The standard treatment paradigm in hypertension, hyperlipidemia and diabetes is to start of with one medication and if the treatment effect is insufficient or side-effects concerning, you add or

switch to a medication with a different mechanism of action. Amylin agonists are a step in the right direction, but still somewhat related [Will be covered in a different text].

How to mechanistically interpret differences between molecules (how to read the tables)

- Note, this is not a complete listing, more to illustrate a point.
- Within GLP-1 **mono-agonists**, practical differences arise from: receptor residency (fatty-acid acylation or Fc-fusion vs short-acting native GLP-1), signaling bias (orforglipron's cAMP-favored partial agonism vs full unbiased peptides), and tissue distribution (e.g., oral small molecules vs injectables), which together shape appetite suppression intensity, duration of gastric-emptying delay, and β -cell cAMP exposure.
- Dual GIP/GLP-1 agonists overlay GLP-1R anorectic/incretin actions with strong GIPR activation, amplifying β -cell cAMP while modulating adipocyte metabolism and potentially improving tolerability of high GLP-1 exposure through GIP-dominant bias. Molecules may differ regarding degree of GLP1 vs GIP agonism.
- Dual GLP-1/glucagon agonists deliberately accept some glucagon-driven gluconeogenesis in exchange for markedly higher energy expenditure; the GLP-1 arm reins in hyperglycemia and appetite, while GCGR activation shifts substrate use toward fat oxidation and may improve hepatic steatosis.
- Triple agonist GLP-1/glucagon agonists try to balance the three targets, but as of now limited information regarding this class of agonist, so not included in the table.

Table 1 Examples of mono-agonists (GLP-1 receptor only)

Drug	Structural / PK features	Mechanism details relevant to obesity	Distinguishing points vs other GLP-1 RAs
Liraglutide	Acylated GLP-1 analog (97% homology to human GLP-1), C16 fatty acid side chain enabling albumin binding and once-daily dosing.	Activates GLP-1R (Gs-coupled) $\rightarrow$ $\uparrow$ cAMP/PKA in β -cells, $\uparrow$ glucose-dependent insulin secretion, $\downarrow$ glucagon, slowed gastric emptying, hypothalamic appetite suppression and modest $\uparrow$ energy expenditure.	Long-acting but still "first-generation" potency; full GLP-1R agonism with classical GLP-1 signaling, no intentional bias; central appetite and gastric-emptying effects are well characterized and moderate compared with newer agents.

Beinaglutide	Recombinant human GLP-1 (identical sequence to native GLP-1); very short half-life, administered 2–3 times daily to mimic physiologic post-prandial GLP-1 pulses.	Rapid GLP-1R activation with sharp cAMP peaks in β -cells, strong acute effects on insulin secretion, glucagon suppression, gastric emptying and appetite around meals.	“Physiologic mimetic”: same sequence and very short Tmax (~5 minutes) gives a profile closest to endogenous GLP-1, with high post-meal satiety/GE effects but less continuous 24-h receptor engagement than acylated once-daily or weekly GLP-1RAs.
Bofanglutide	Long-acting peptide GLP-1RA, once-monthly or once-every-2-weeks formulations under development for chronic weight management.	Prolonged GLP-1R stimulation drives sustained $\downarrow$ food intake and improved glycemia; mechanistically similar GLP-1–mediated cAMP/PKA signaling, gut-brain appetite effects and delayed gastric emptying.	Distinct in very long dosing interval (monthly/bi-weekly), aiming to maintain GLP-1-class effects with improved adherence; mechanistically still a classical GLP-1 mono-agonist rather than biased or dual.
Orforglipron	First-in-class non-peptide, oral small-molecule GLP-1RA; partial agonist with biased signaling toward cAMP over β -arrestin recruitment.	Binds the GLP-1R orthosteric pocket and stabilizes an active conformation favoring G-protein coupling $\rightarrow$ robust cAMP, limited β -arrestin-mediated internalization; leads to $\uparrow$ insulin, $\downarrow$ glucagon, delayed GE and appetite suppression similar to injectables.	Key differentiator is biased partial agonism and oral, non-peptide structure: persistent cAMP signaling with relatively less receptor desensitization/internalization may modulate GI tolerability and weight-loss/AE balance compared with full peptide agonists.

Conveglipron (HDM1002)	Non-peptide, oral small-molecule GLP-1RA	“cAMP-biased” GLP-1R agonist (strong G-protein/cAMP activation; less emphasis on β -arrestin), but detailed arrestin/internalization data are limited	May differ from orforglipron in degree of bias, but data is limited regarding more detailed mechanisms.
Noiiglutide (SHR20004, HS-20004)	Limited public data. Synthetic GLP-1 peptide modulator	Classical GLP-1R-mediated incretin and anorectic actions; detailed bias or receptor-kinetic data not publicly described.	Currently appears as a “me-too” long-acting GLP-1 analog; without published bias/affinity data, it is best thought of as seems similar to other second-generation GLP-1 mono-agonists rather than mechanistically distinct.
Efsubaglutide	Long-acting GLP-1RA (once-weekly) peptide; dose-proportional PK with prolonged receptor engagement.	Sustained GLP-1R activation produces robust $\downarrow$ energy intake, improved insulin secretion and glucagon suppression, with documented large reductions in fat mass and improved lean-to-fat mass ratio in early obesity trials.	Mechanistically resembles other weekly GLP-1RAs but appears optimized for strong weight loss with acceptable GI tolerability; no published evidence of intentional G-protein/ β -arrestin bias, so differences vs semaglutide are more quantitative (potency/PK) than qualitative.

Dual agonists (GIP/GLP-1 or GLP-1/glucagon)

Drug	Dual agonism profile	Mechanistic nuances vs pure GLP-1	How it differs from other duals
Tirzepatide	Dual GIPR/GLP-1R; single peptide with “imbalanced” potency, full agonist at GIPR, partial agonist (~50% efficacy) at GLP-1R.	At β -cells, combined GIPR and GLP-1R activation produces supra-additive cAMP and insulin secretion; in adipose tissue GIPR activation enhances insulin-mediated lipogenesis acutely but, under caloric deficit and high GLP-1 tone, appears to facilitate fat mobilization and possibly brown-fat thermogenesis. Central GIPR plus GLP-1R signaling amplifies satiety and may improve nausea tolerance vs equivalent GLP-1 drive alone.	Distinguished by GIP-favored bias: tirzepatide has GIP-like affinity/kinetics at GIPR but weaker, partially biased activation of GLP-1R with less receptor desensitization; this allows higher dosing to maximize GIP-driven metabolic benefits while keeping GLP-1-related GI AEs manageable.

HRS9531 (KAI-9531, “ribupatide”)	Dual GLP-1R/GIPR injectable peptide; described as GLP-1/GIP receptor dual agonist for obesity and T2D.	Mechanistically similar to tirzepatide: dual activation enhances insulin secretion, glucagon suppression, and weight loss via integrated incretin signaling; trial data show very large weight-loss (≈ 19 – 23% at higher doses), indicating strong and sustained central and peripheral incretin engagement.	Detailed bias data are not public, but guess is “GLP-1-based” safety profile; relative balance between GIP and GLP-1 may be closer to tirzepatide or somewhat more GLP-1-dominant.
Mazdutide	Dual GLP-1R/GCGR agonist, with measurable affinity for both receptors ($K_i \approx$ 28.6 nM at GLP-1R and 17.7 nM at GCGR in vitro).	GLP-1R arm provides classical incretin and anorectic effects; GCGR activation increases hepatic glucose output and, critically for obesity, raises energy expenditure via enhanced lipid oxidation and possible BAT/WAT browning, while GLP-1R suppresses appetite and counters hyperglycemia. Balanced co-agonism yields large weight loss with preserved glycemic control despite some glucagon-driven gluconeogenesis	Compared with tirzepatide-like GIP/GLP duals, mazdutide trades GIP’s primarily insulinotropic/adipose actions for glucagon’s thermogenic drive, typically producing higher energy-expenditure contribution to weight loss

Survodutide (BI 456906)	Dual GCGR/GLP-1R agonist, long-acting oxyntomodulin-derived peptide, once-weekly.	Simultaneous GLP-1R activation (↓food intake, ↑insulin, ↓gastric emptying) and GCGR activation (↑energy expenditure, enhanced lipid oxidation, potential NAFLD/MASH benefit) yields weight loss via both reduced intake and increased output. Biomarker work shows “balanced” GCGR/GLP-1R pharmacology chosen to exceed weight-loss of pure GLP-1 with similar antidiabetic efficacy.	Survodutide is more explicitly balanced between GCGR and GLP-1R than some earlier glucagon co-agonists; compared with mazdutide, its selection was driven by biomarker-guided optimization for weight loss and MASH, so subtle differences in receptor potency ratio and tissue disposition may yield different glycemic and hepatic profiles.
Olatorepatide	Dual GIP/GLP-1 receptor. Very limited public data	No public data yet specify whether it is GIP-dominant, GLP-1-dominant, or approximately balanced in potency/efficacy at the two receptors (see tirzepatide)	May be similar to tirzepatide, or more of a 50/50 GLP1/GIP agonist.
Poterepatide	Dual GIP/GLP-1 receptor. Very limited public data	Full agonist at both GLP-1R and GIPR	Differ from tirzepatide as it is described as full agonist for both GLP1 and GIP.

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