This activity may include discussions of products or devices that are not currently labeled for use by the U.S. Food and Drug Administration (FDA).

The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any uses not approved by the FDA) of products or devices.

CMEO Snack

Module 4 of 4:

Riding the Waves of Obesity Science

Reaching the Shoreline: Emerging Amylin-Based Therapies and Trial Signals

This activity is supported by an independent educational grant from Novo Nordisk, Inc.

CMEO Snack

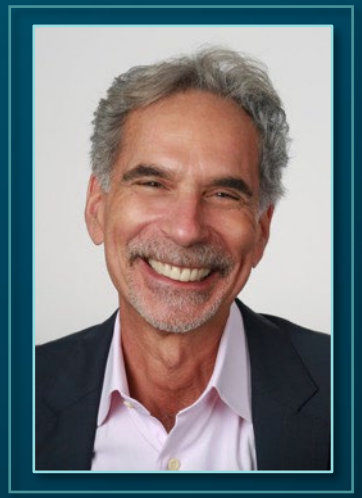
LEARNING OBJECTIVE 1

Assess emerging amylin-based therapeutic strategies in obesity management

CMEO Snack

LEARNING OBJECTIVE 2

Differentiate key trial signals that inform interpretation of investigational data



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CMEO Snack

Riding the Waves of Obesity Science

1. *A Multi-Pathway Rationale for the Next Therapeutic Current*
2. *Amylin at a Glance: A Mechanistic Map of a Systems Satiety Signal*
3. *The Phenotype Breakers: Heterogeneity, Signals, and Who Might Benefit from Which Biology*
4. ***Reaching the Shoreline: Emerging Amylin-Based Therapies and Trial Signals***

We already have effective GLP-1 RAs and GLP-1/GIP combinations. Why do we need another gut hormone?

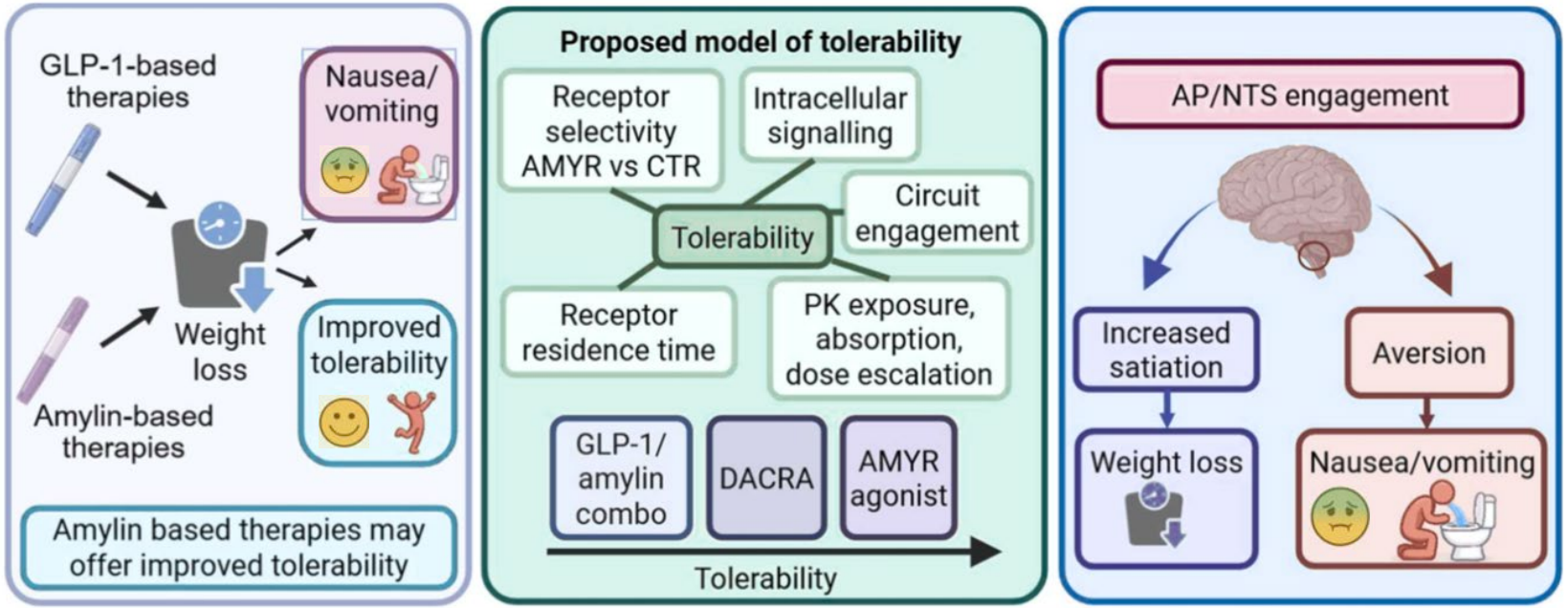


What is the principal unmet need driving development of long-acting amylin analogs, rather than more potent incretin-based agents?

A. Achieving greater peak weight loss than currently available agents
B. Tolerability sufficient to support long-term persistence at moderate (~15%) weight loss
C. Availability of an oral formulation for patients who decline injections
D. Elimination of the need for dose escalation during treatment initiation
E. I don’t know

CME OUTFITTERS

Amylin-Based Therapies May Offer Improved Tolerability



AMYR = amylin receptor; AP/NTS = area postrema/nucleus of the solitary tract; CTR = calcitonin receptor; DACRA = dual amylin and calcitonin receptor agonist; GLP-1 = glucagon-like peptide-1; PK = pharmacokinetics.

Fischer SL, et al. *Pharmacol Res*. 2026;232:108382.

CME OUTFITTERS

The Goal Isn’t Just More Weight Loss

- Long-term durability
  - Patients may stop taking weight loss medications because of side effects (20% of patients in some studies)
  - Long-acting amylin medications may offer better tolerability and help patients stay on therapy, so benefits don’t reverse when medications are stopped





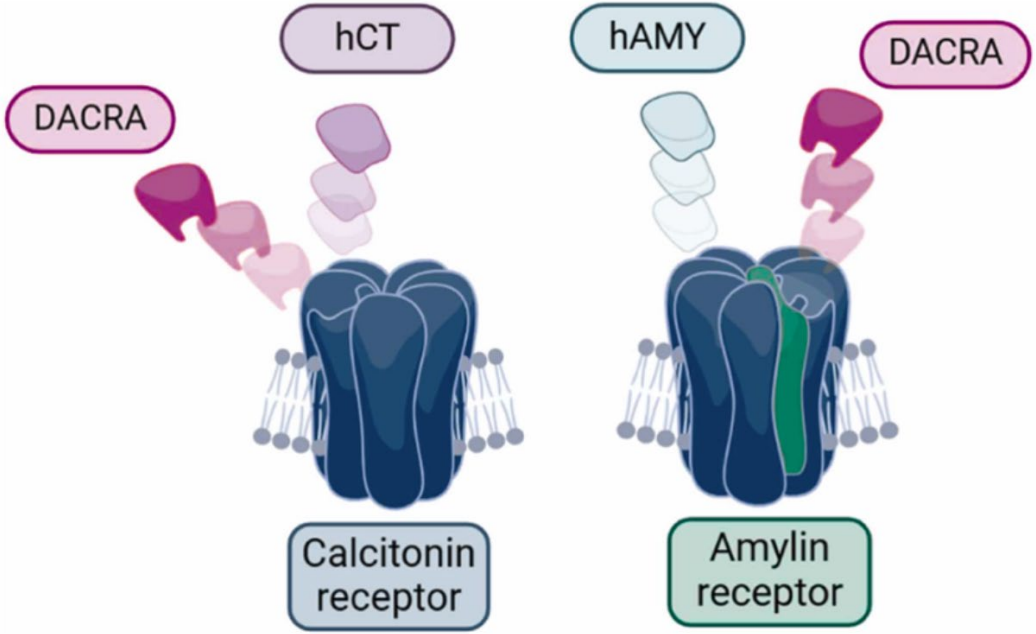
Fischer SL, et al. *Pharmacol Res*. 2026;232:108382. Gasoyan H, et al. *Obesity (Silver Spring)*. 2025;33(12):2296-2303. Van Laren J, et al. *Diabetes Obes Metab*. 2026;28(5):3965-3973.

CME OUTFITTERS

The amylin receptor is not as simple as GLP-1 in that they include DACRA-amylins and selective agonists. How important is it for clinicians to recognize these differences?

DACRAs Can Bind Both Calcitonin and Amylin Receptors

- Schematic illustration of the amylin and calcitonin receptor
- Each of the human ligands is relatively selective for its target receptor, while DACRAs activate both receptors

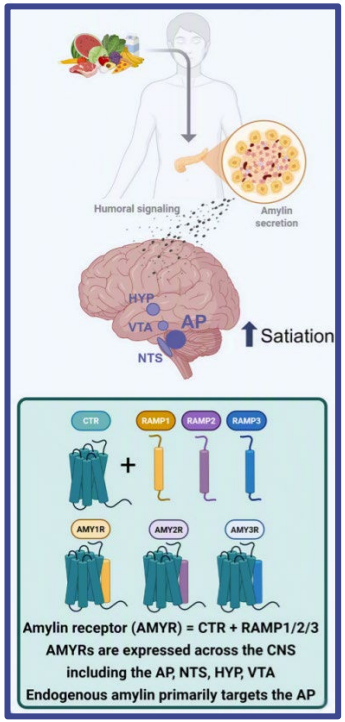


hAMY = human amylin; hCT = human calcitonin.
Larsen AT, et al. *Biomed Pharmacother.* 2025;190:118388.

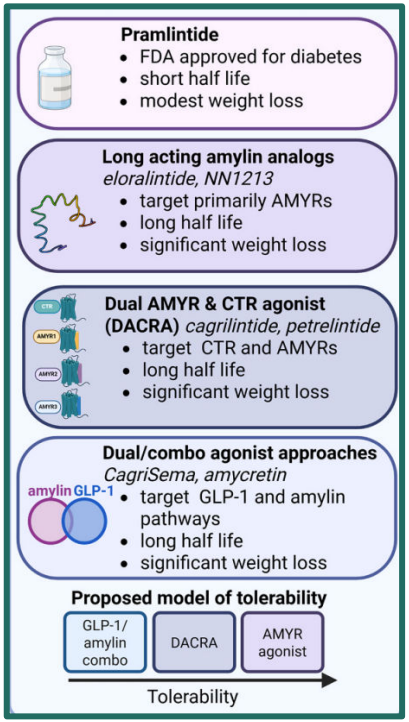
CME OUTFITTERS

Amylin-Based Therapeutics

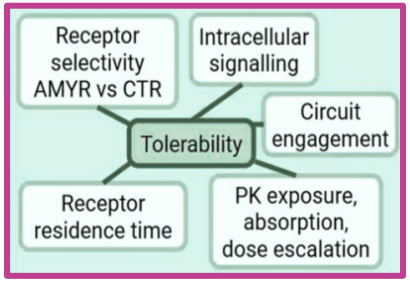
Amylin Biology

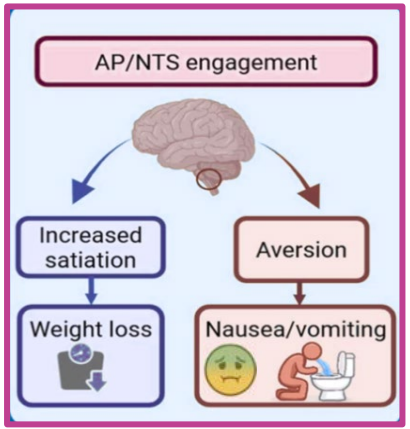


Amylin-Based Drugs



Tolerability Factors





CNS = central nervous system; HYP = hypothalamus; NTS = nucleus tractus solitarius; RAMP = receptor activity-modifying proteins; VTA = ventral tegmental area.

Fischer SL, et al. *Pharmacol Res.* 2026;232:108382

CME OUTFITTERS

Can you walk us through the medications in development (phase 2 and phase 3) and what we are starting to see regarding outcomes?

Amylin Agents in Development

Agent	Class	Stage
Cagrilintide	Long-acting amylin analog / DACRA	Phase 3 program
CagriSema	Amylin + GLP-1 (fixed-dose)	Phase 3 / NDA filed

Not head-to-head: directional, not comparative.

Billings LK, et al. *Lancet.* 2025;406(10520):2631-2643. Dahl K, et al. *Lancet.* 2025;406(10499):149-162. Garvey WT, et al. *N Engl J Med.* 2025;393(7):635-647. ClinicalTrials.gov identifier: NCT06662539.

NDA = new drug application.

CME OUTFITTERS

Amylin Agents in Development

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CagriSema	Amylin + GLP-1 (fixed-dose)	Phase 3 / NDA filed
Eloralintide	Selective amylin receptor agonist	Phase 3 recruiting

Not head-to-head: directional, not comparative.

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Petrelintide	Long-acting amylin analog	Phase 3 starting 2nd half 2026

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CME OUTFITTERS

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Eloralintide	Selective amylin receptor agonist	Phase 3 recruiting
Petrelintide	Long-acting amylin analog	Phase 3 starting 2nd half 2026
Zenagamtide [amycretin]	Unimolecular GLP-1/amylin	Phase 3 underway

Not head-to-head: directional, not comparative.

Billings LK, et al. *Lancet.* 2025;406(10520):2631-2643. Dahl K, et al. *Lancet.* 2025;406(10499):149-162. Garvey WT, et al. *N Engl J Med.* 2025;393(7):635-647. ClinicalTrials.gov identifier: NCT06662539.

CME OUTFITTERS

What magnitude of weight loss are we seeing – monoagonist versus dual agonist – versus the GLP-1 and GLP-1/GIP agents we use now?

Across phase 2 data, mean weight loss is ~11-12% with cagrilintide and petrelintide and up to ~20% with eloralintide. What is the most important limitation to consider before concluding that eloralintide is more effective?

A. Figures are from separate trials that were not head-to-head
B. Weight loss was measured by bioimpedance rather than calibrated scales
C. None of the trials included a placebo comparator
D. All 3 agents were studied only in participants with type 2 diabetes
E. I don't know

CME OUTFITTERS

Amylin Agents in Development

Agent	Class	Stage	Weight Loss
Cagrilintide	Long-acting amylin analog / DACRA	Phase 3 program	11.5% at 68 wk vs 3.0% placebo (Phase 3) [P value not provided.]
CagriSema	Amylin + GLP-1 (fixed-dose)	Phase 3 / NDA filed	20.4% at 68 wk vs 3.0% placebo; estimated difference –17.3 percentage points (95% CI –18.1 to –16.6), P<.001 (treatment policy); efficacy estimand: 22.7% vs 2.3% placebo, estimated difference –20.4 percentage points (–21.1 to –19.7); no P value reported.
Eloralintide	Selective amylin receptor agonist	Phase 3 recruiting	20% at 48 wk (95% CI –22.7 to –17.5) vs. 0.4% placebo (Phase 2)
Petrelintide	Long-acting amylin analog	Phase 3 starting 2nd half 2026	10.7% at 42 wk vs 1.7% placebo (Phase 2); P<.001 Conference-reported (ADA 2026); primary endpoint was week 28.
Zenagamtide [amycretin]	Unimolecular GLP-1/amylin	Phase 3 underway	24.3% at 36 wk vs 1.1% placebo (Phase 1b/2a) [P<.0001] Body weight was a secondary endpoint in safety-primary phase 1b/2a trial.

Not head-to-head: directional, not comparative. P values are within-trial vs placebo only and are not comparable across rows.

Billings LK, et al. *Lancet.* 2025;406(10520):2631-2643. Dahl K, et al. *Lancet.* 2025;406(10499):149-162. Garvey WT, et al. *N Engl J Med.* 2025;393(7):635-647. ClinicalTrials.gov identifier: NCT06662539.

CME OUTFITTERS

How do you see clinicians actually using these medications? What should we be looking for as the trials read out?

Dr. Garvey's Hypothesized Approach to Care

BMI ≥ 40 ± Mobility Limits	Complication-Driven	Everyone Else (Most Patients)
• Go for magnitude with dual or triple agonists • Some patients will be surgical candidates	• CV secondary prevention (MASH, OSA, T2D) • Use the GLP-1-based agent with outcomes data for the complication(s)	• No GLP-1-responsive complication: a well-tolerated long-acting amylin first line is reasonable • Add a GLP-1 RA if goals are not met

Hypothesis – NOT a guideline recommendation. Amylin agents are investigational.

CV = cardiovascular; MASH = metabolic dysfunction-associated steatohepatitis; OSA = obstructive sleep apnea; T2D = type 2 diabetes; RA = receptor agonist.

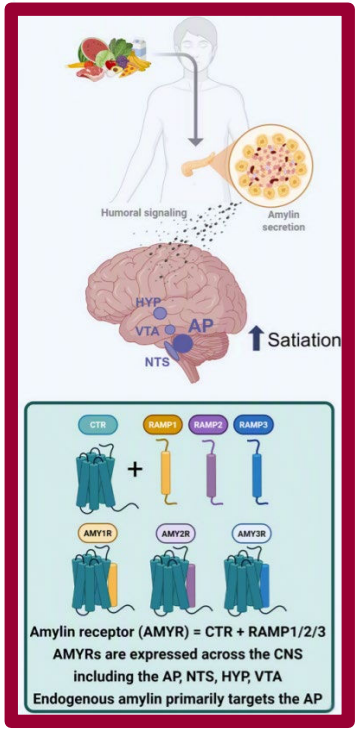
Garvey WT. *Diabetes Spectr.* 2024;37(4):325-334.

CME OUTFITTERS

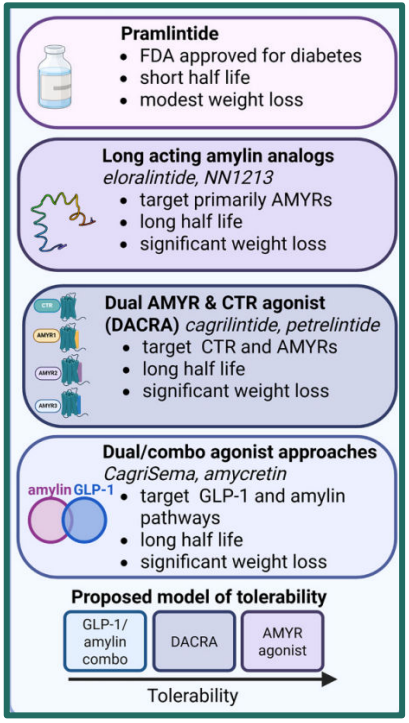
Petrelintide and others show better tolerability, which seems opposite to the biology. How do you square the preclinical picture with the clinical data?

Amylin-Based Therapeutics

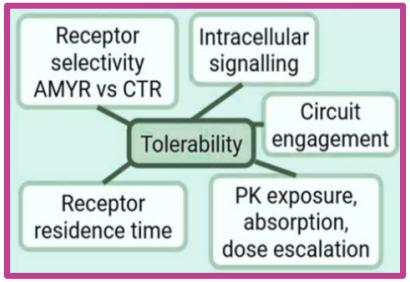
Amylin Biology

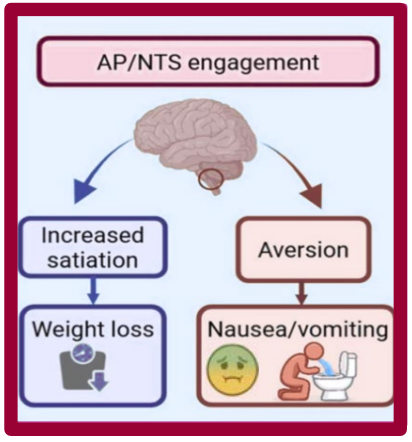


Amylin-Based Drugs



Tolerability Factors





Fischer SL, et al. *Pharmacol Res*. 2026;232:108382

CME OUTFITTERS

Tolerability (Agent vs Placebo)

Agent	Nausea	Vomiting	Discontinue for AE
Petrelintide	19.6% vs 6.2%	3.0% vs. 6.2%	4.5% vs. 4.9%
Cagrilintide	23.8% vs. 12.6%	7.0% vs. 4.1%	2.6% vs. 3.5%
Eloralintide	32.7% vs. 13.5%	8.2% vs. 0%	10% vs. 8%

Not head-to-head: directional, not comparative.

Billings LK, et al. *Lancet.* 2025;406(10520):2631-2643. Braendholt Olsen M, et al. *Diabetes Obes Metab*. 2026;28(7):5915-5925. Garvey WT, et al. *Diabetes*. 2026;75(Suppl 1):3083-LB. Garvey WT, et al. *N Engl J Med*. 2025;393(7):635-647.

CME OUTFITTERS

GLP-1 RAs and GLP-1/GIP dual receptor agonists include cardiometabolic outcomes as part of their trials. Would you expect different outcomes if you're looking at an amylin receptor agonist?

In closing, how should clinicians be thinking about the next two to five years as amylin-based medications potentially become available?

To Receive Credit

To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online.

Participants will be able to download and print their certificate immediately upon completion.

CMEO Snack

Riding the Waves of Obesity Science

Other programs in this series include:

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