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

Riding the Waves of Obesity Science

Amylin at a Glance: A Mechanistic Map of a Systems Satiety Signal

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

CMEO Snack

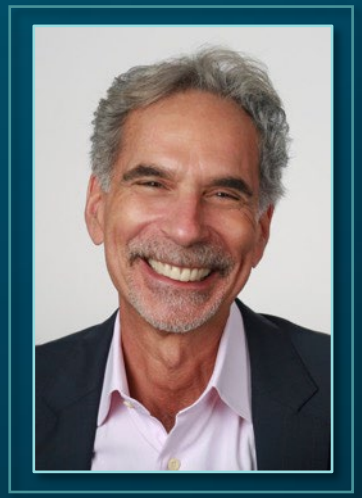
LEARNING OBJECTIVE 1

Evaluate the physiologic role of amylin in energy and glucose regulation

CMEO Snack

LEARNING OBJECTIVE 2

Assess how amylin receptor biology supports complementary therapeutic strategies



Robert F. Kushner, MD, MS, FACP, FTOS, DABOM

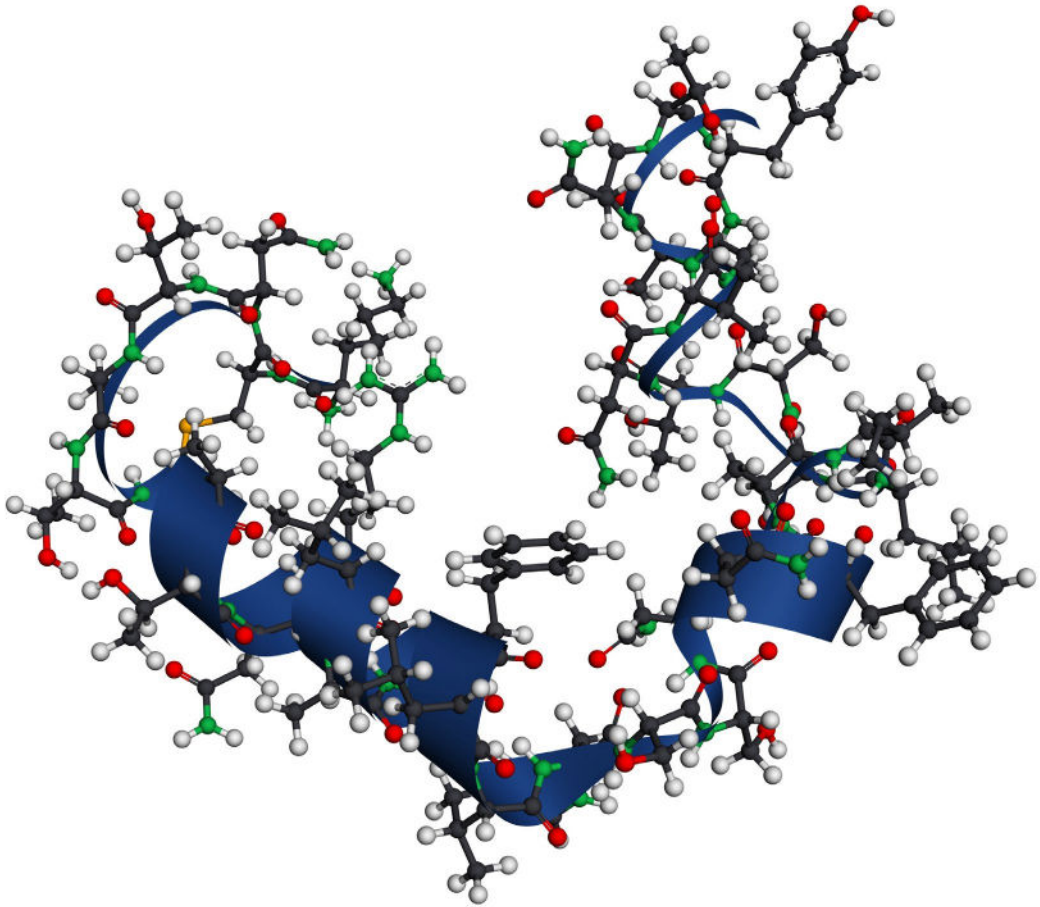
Professor Emeritus
Departments of Medicine and Medical Education
Northwestern University Feinberg School of Medicine
Chicago, IL



Matthew R. Hayes, PhD

Albert J. Stunkard Professor in Psychiatry
Vice Chair of Basic and Translational Neuroscience Research
Director, Molecular and Neural Basis of Psychiatric Disease Section
Department of Psychiatry
Director of the Obesity Unit, Institute for Diabetes, Obesity, and Metabolism (IDOM)
University of Pennsylvania
Philadelphia, PA

Amylin



Amylin is a pancreatic β-cell hormone that produces effects in several different organ systems.

Hay DL, et al. *Pharmacol Rev*. 2015;67(3):564-600.

CME OUTFITTERS

What is amylin?
How is it related to insulin?
What is its role in physiology?

Two Signals From One Cell

	Insulin	Amylin
Source	Pancreatic β-cell	Pancreatic β-cell (co-secreted)
Molar ratio at release	~100	~1
Primary function	Lowers blood glucose (glucose disposal)	Meal-ending satiation; slows nutrient delivery
Key actions	Cellular glucose uptake, hepatic output	Satiation, slowed gastric emptying, postprandial glucagon suppression
Half-life (native)	~5–6 min	~13 min

Arrigoni S, et al. *Eur J Neurosci.* 2021;54(3):4863-4876. Chung CW, et al. *J Obes Metab Syndr*. 2026;35(1):38-48. Erzen S, et al. *Int J Mol Sci.* 2024;25(3):1517.

CME OUTFITTERS

What does amylin do?

Beyond Glucose, Amylin Acts as a Systems Signal

1. **Glucagon suppression**
   Glucose-dependent — dampens inappropriate post-meal glucagon

2. **Slowed gastric emptying**
   Flattens the post-meal glucose curve; prolongs fullness

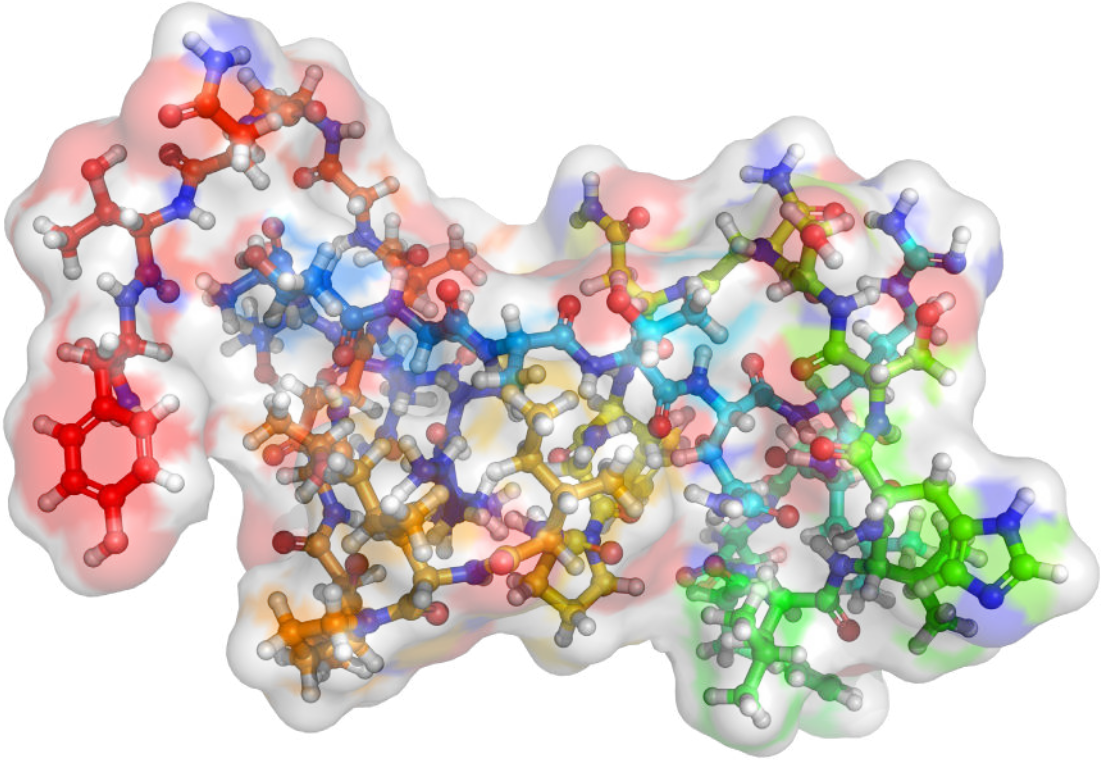
3. **Meal-ending satiation**
   Signals the brain that the meal is over

4. **Motivation & reward**
   Modulates food-directed and reward-based behavior (preclinical)

Chung CW, et al. *J Obes Metab Syndr*. 2026;35(1):38-48. Walker CS, et al. *Nat Rev Endocrinol*. 2025;21(8):482-494.

CME OUTFITTERS

Pramlintide: The First Amylin Mimetic



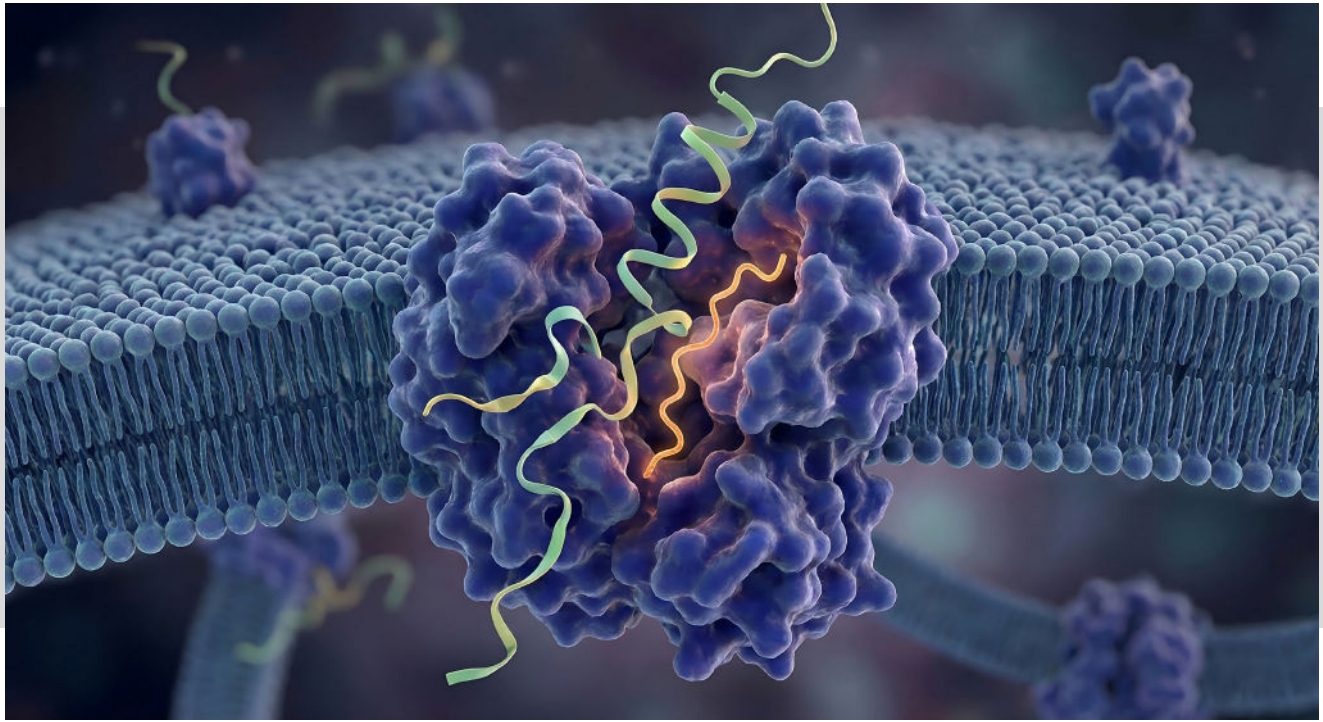
Pramlintide is a synthetic analogue of the human hormone amylin.

McQueen J. *Am J Health Pharm.* 2005;62(22):2363-2372.

CME OUTFITTERS

What happened to pramlintide, which was introduced more than 20 years ago?

Acylation Changes the Half-Life of a Peptide-Based Therapeutic



Molecular structure of ghrelin O-acyltransferase (GOAT) enzyme embedded in lipid bilayer acylating ghrelin peptide (active site mechanism for obesity drug targets).

Abizaid A, et al. *Trends Endocrinol Metab.* 2020;31(2):107-117.

CME OUTFITTERS

How is amylin more complex than glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) in terms of the receptor?

Audience Response 1 of 2



What has to happen for the calcitonin receptor to act as an amylin receptor?

A. Nothing – the calcitonin receptor binds amylin on its own with full effect
B. It must bind to the GLP-1 receptor
C. It must pair with a receptor activity-modifying protein (RAMP) to form an amylin (AMY) receptor
D. It must first be cleaved into calcitonin
E. I don't know

Please select your answer now.

CME OUTFITTERS

Audience Response 2 of 2



Several different “amylin” molecules are now in clinical development. Which statement is most accurate when describing these agents?

A. They are all selective amylin analogs, so calling any of them an “amylin agent” is always precise
B. Some agents referred to as “amylin” drugs are actually DACRAs – dual amylin and calcitonin receptor agonists that also activate the naked calcitonin receptor
C. “Amylin” and “DACRA” describe the same single molecule under two different names
D. DACRAs do not act on any amylin receptor complex
E. I don’t know

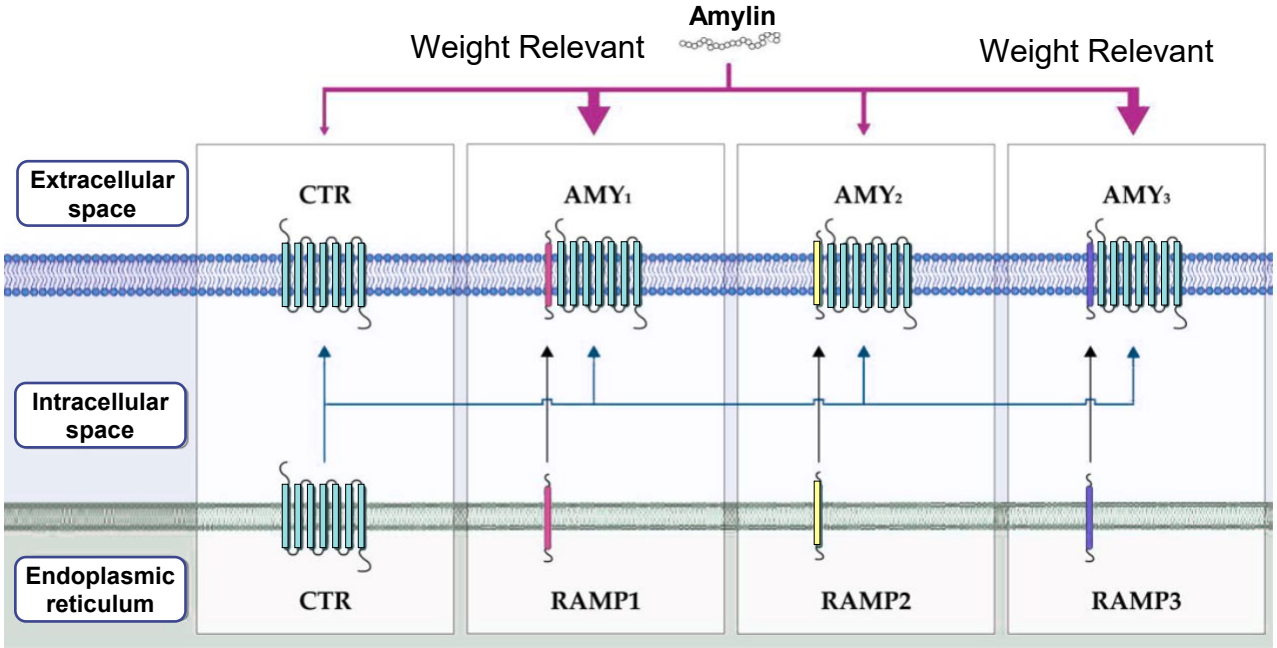
Please select your answer now.

CME OUTFITTERS

Three Main Amylin Receptors: Relationship With Calcitonin Receptor (CTR) and Receptor Activity-Modifying Proteins (RAMP)

The active amylin receptor is the calcitonin receptor (CTR) – but only once it pairs with a RAMP

- CTR + RAMP1/2/3 → AMY_1, AMY_2, AMY_3
- RAMP raises CTR's susceptibility to amylin
- **AMY_1 and AMY_3 carry the strongest weight relevance**

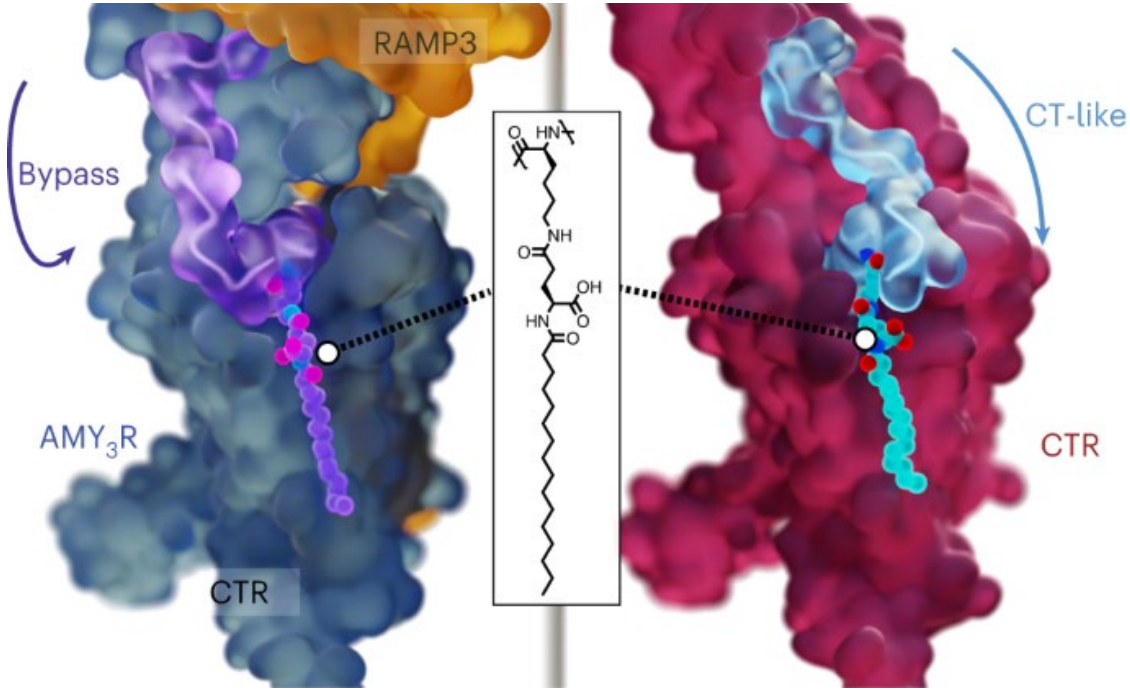


AMY = amylin receptor; RAMP = receptor activity-modifying protein.

Erzen S, et al. *Int J Mol Sci.* 2024;25(3):1517. Gu Y-M, et al. *Acta Pharmacol Sin.* 2026;47(1):162-172.

CME OUTFITTERS

DACRAs Can Hit Both the Naked Calcitonin Receptor or an Amylin Receptor Complex



Dual Amylin and Calcitonin Receptor Agonists (DACRAs)

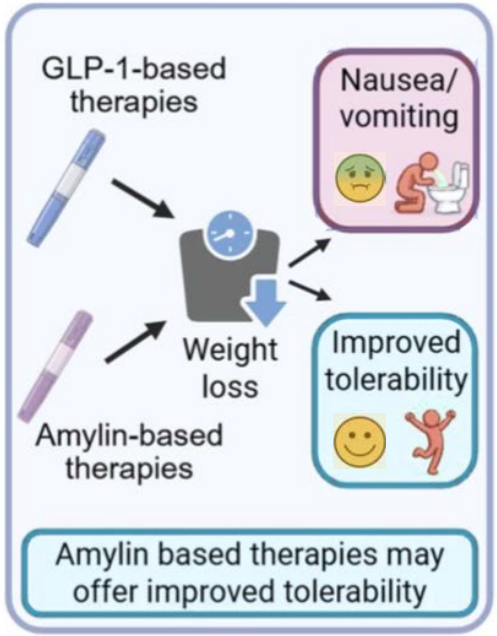
AMY_3R = amylin receptor 3; CT-like = calcitonin-like.
Cao J, et al. *Nat Chem Biol.* 2024;20(2):162-169.

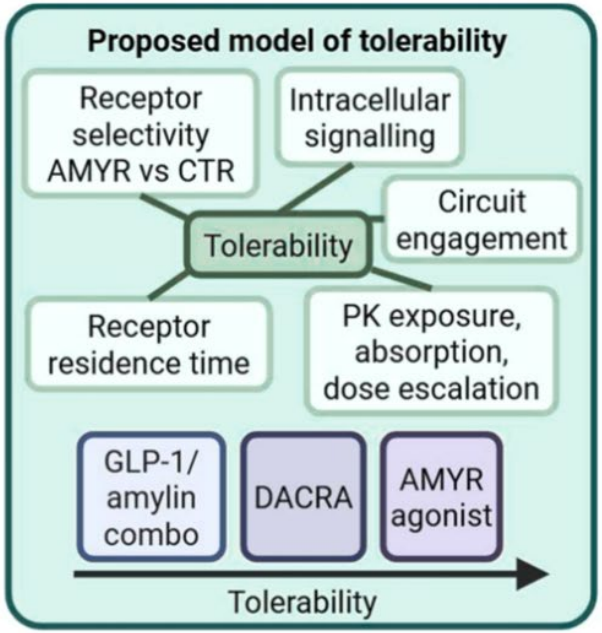
CME OUTFITTERS

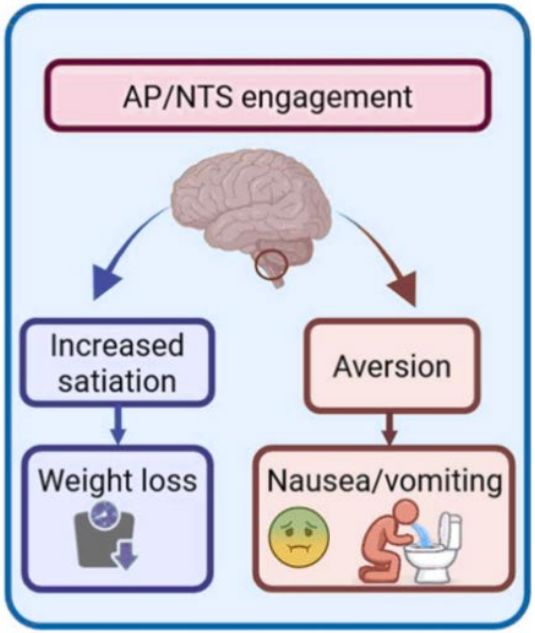
How do researchers decide which receptor complex to target?

Amylin-Based Therapies in Development

Balancing weight and tolerability







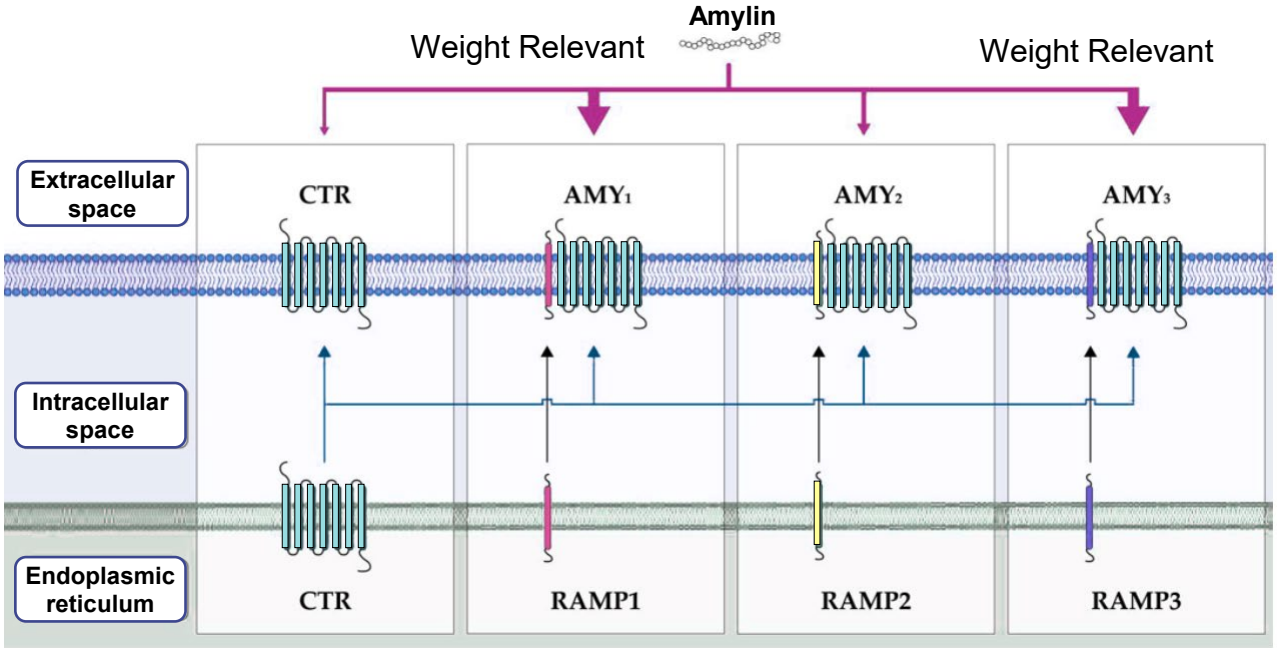
Fischer SL, et al. *Pharmacol Res.* 2026;108382.

CME OUTFITTERS

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AMY = amylin receptor; RAMP = receptor activity-modifying protein.

Erzen S, et al. *Int J Mol Sci.* 2024;25(3):1517. Gu Y-M, et al. *Acta Pharmacol Sin.* 2026;47(1):162-172.

CME OUTFITTERS

Returning to DACRAs, will reduced calcium or changes in bone health be problematic?

Dual Amylin and Calcitonin Receptor Agonists as Multifaceted Disease-Modifying Osteoarthritis (OA) Drugs

DACRAs induce weight loss by activating the amylin receptor, thereby improving patients' QoL and reducing OA pain intensity

DACRAs also activate the calcitonin receptor, known for its skeletal pain-relieving effects and for slowing down bone remodeling, potentially preserving the joint's cartilage and bone

With their dual action on metabolic and skeletal pathways, DACRAs may offer a unique combination of weight loss, pain relief, and a positive influence on joint structures

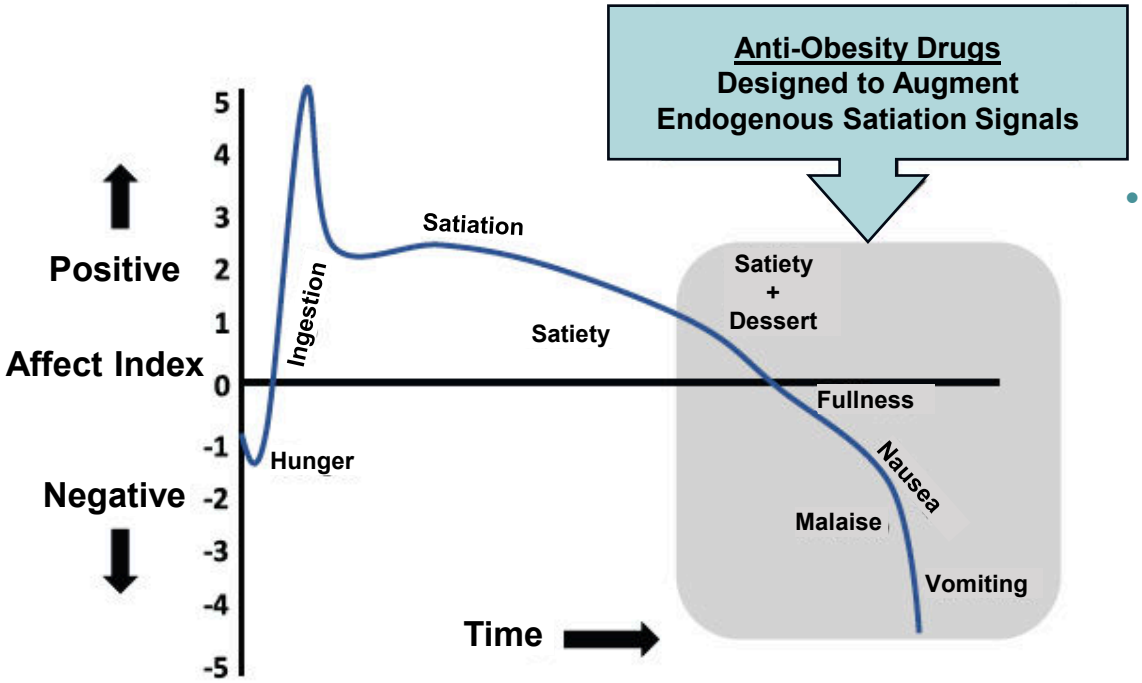
QoL = quality of life.

Mohamed KE, et al. *Int J Obes (Lond)*. 2026;50(7):1415-1425.

CME OUTFITTERS

Should clinicians focus on whether a potential therapeutic is a DACRA or a selective amylin receptor drug?

Hunger, Satiety, Nausea: Points on the Same Curve of Ingestive Behavior



- Conceptual graph illustrating that hunger, satiety, and nausea can all be viewed as interconnected points on the same curve of positive/negative affect during a meal

Hayes MR, et al. *Diabetes.* 2021;70(9):1956-1961.

CME OUTFITTERS

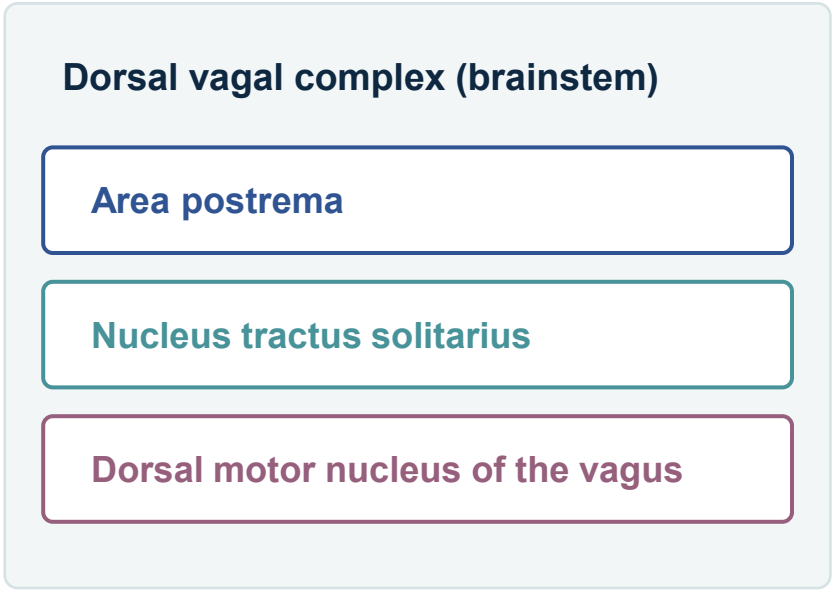
Is the nausea associated with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and other drugs coming from reduced gastric emptying or from "hitting the receptors" in the central nervous system (CNS)?

Where the Side Effects Come From

Nausea is largely central — not just slowed gastric emptying.

Amylin, DACRA, and GLP-1 agents all act on the **dorsal vagal complex** in the brainstem — the same region oncology calls the chemoreceptor trigger zone.

Because it is both the therapeutic site and the output pathway for nausea and vomiting, tolerability travels with efficacy.



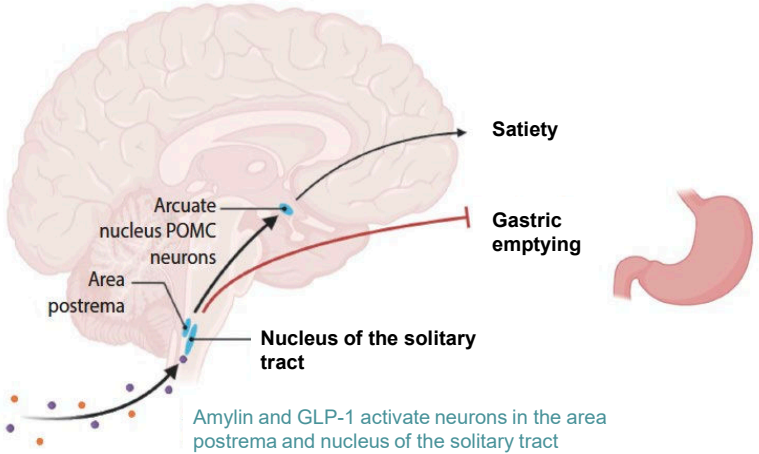
Hayes MR, et al. *Diabetes.* 2021;70(9):1956-1961. Hayes MR, et al. *Physiol Behav*. 2010;100(5):503-510.

CME OUTFITTERS

How do you envision amylin evolving? As a mono-agonist or as part of a multi-receptor agonist?

Amylin: Monotherapy & Combination

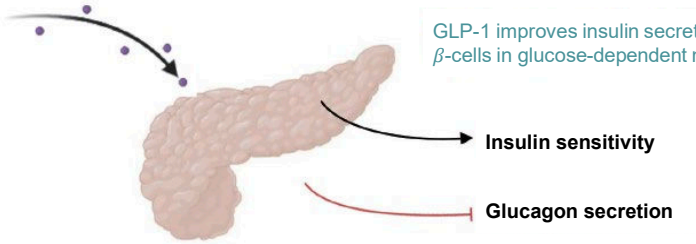
Brain — area postrema & NTS



Amylin and GLP-1 activate neurons in the area postrema and nucleus of the solitary tract

Leptin activates POMC neurons
Amylin improves leptin sensitivity in obesity

Pancreas — glucagon & insulin



GLP-1 improves insulin secretion from pancreas β-cells in glucose-dependent manner

Amylin and GLP-1 inhibit glucagon secretion from pancreas α-cells

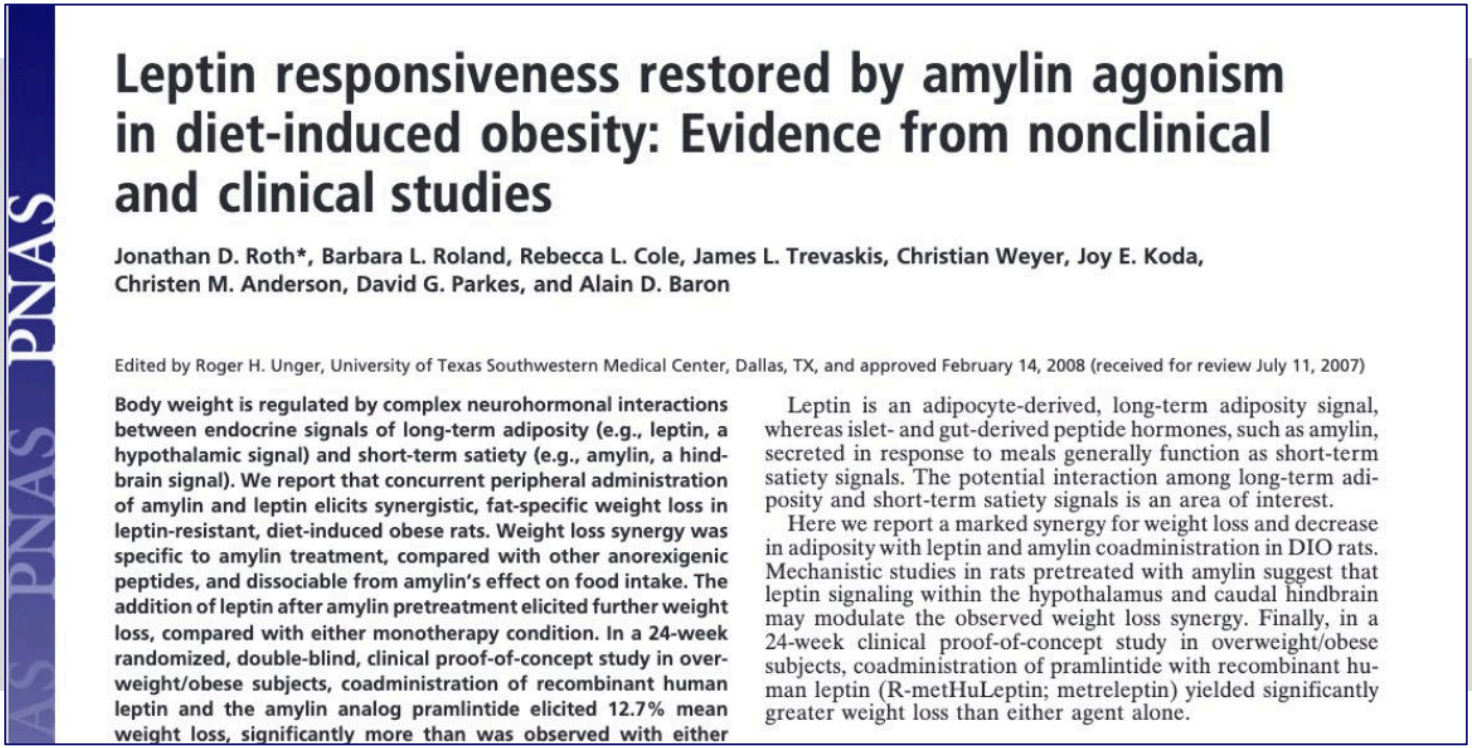
Monotherapy: amylin activates area postrema / NTS — suppresses appetite, slows gastric emptying
Combination: with a GLP-1 or leptin analog, it adds leptin sensitivity, glucagon suppression, and improved insulin action — the systems are not the same, so effects can be combinatorial

NTS = nucleus of the solitary tract/neurotensin; POMC = pro-opiomelanocortin.
Chung CW, et al. *J Obes Metab Syndr.* 2026;35(1):38-48.

CME OUTFITTERS

Preclinical studies of amylin have shown leptin sensitization. Do you think this will also play out in clinical studies?

Leptin Sensitization



PNAS PNAS PNAS

Leptin responsiveness restored by amylin agonism in diet-induced obesity: Evidence from nonclinical and clinical studies

Jonathan D. Roth*, Barbara L. Roland, Rebecca L. Cole, James L. Trevaskis, Christian Weyer, Joy E. Koda, Christen M. Anderson, David G. Parkes, and Alain D. Baron

Edited by Roger H. Unger, University of Texas Southwestern Medical Center, Dallas, TX, and approved February 14, 2008 (received for review July 11, 2007)

Body weight is regulated by complex neurohormonal interactions between endocrine signals of long-term adiposity (e.g., leptin, a hypothalamic signal) and short-term satiety (e.g., amylin, a hindbrain signal). We report that concurrent peripheral administration of amylin and leptin elicits synergistic, fat-specific weight loss in leptin-resistant, diet-induced obese rats. Weight loss synergy was specific to amylin treatment, compared with other anorexigenic peptides, and dissociable from amylin's effect on food intake. The addition of leptin after amylin pretreatment elicited further weight loss, compared with either monotherapy condition. In a 24-week randomized, double-blind, clinical proof-of-concept study in overweight/obese subjects, coadministration of recombinant human leptin and the amylin analog pramlintide elicited 12.7% mean weight loss, significantly more than was observed with either

Leptin is an adipocyte-derived, long-term adiposity signal, whereas islet- and gut-derived peptide hormones, such as amylin, secreted in response to meals generally function as short-term satiety signals. The potential interaction among long-term adiposity and short-term satiety signals is an area of interest.

Here we report a marked synergy for weight loss and decrease in adiposity with leptin and amylin coadministration in DIO rats. Mechanistic studies in rats pretreated with amylin suggest that leptin signaling within the hypothalamus and caudal hindbrain may modulate the observed weight loss synergy. Finally, in a 24-week clinical proof-of-concept study in overweight/obese subjects, coadministration of pramlintide with recombinant human leptin (R-metHuLeptin; metreleptin) yielded significantly greater weight loss than either agent alone.

Roth JD, et al. *Proc Natl Acad Sci USA*. 2008;105(20):7257-7262.

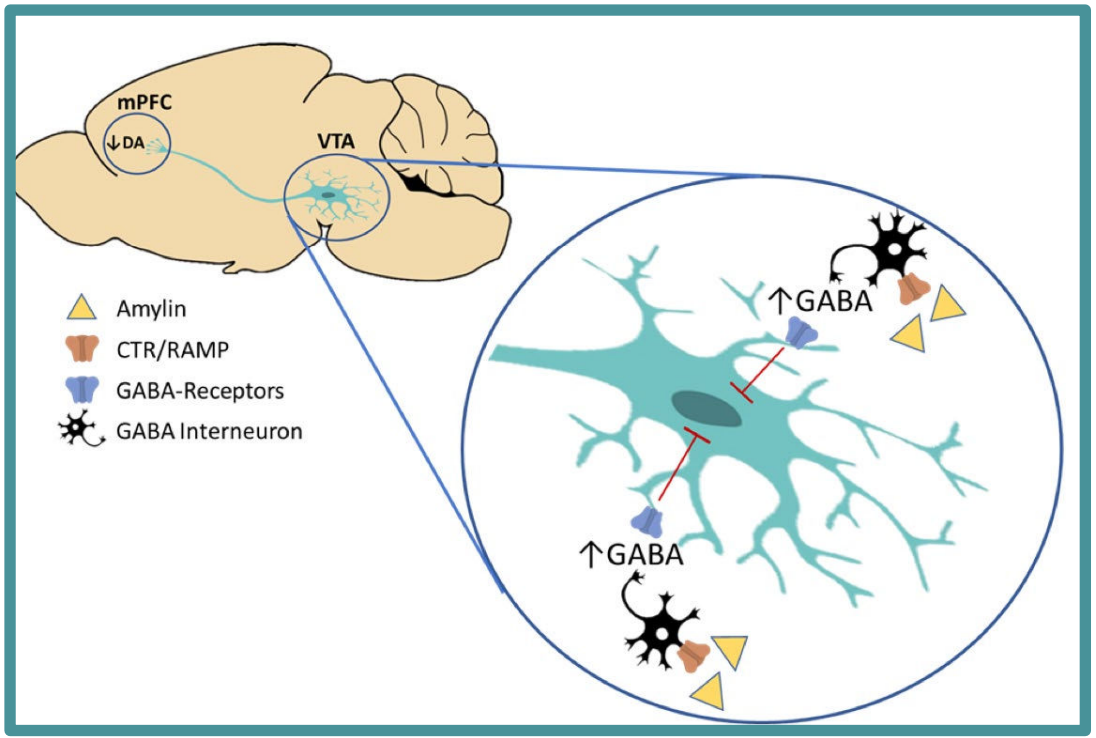
CME OUTFITTERS

Is there anything else you envision amylin would bring to the table that we're not already seeing with GLP-1 or GLP-1/GIP agonists?

How does amylin affect the reward pathway?

The Amylin Reward Angle (Preclinical)

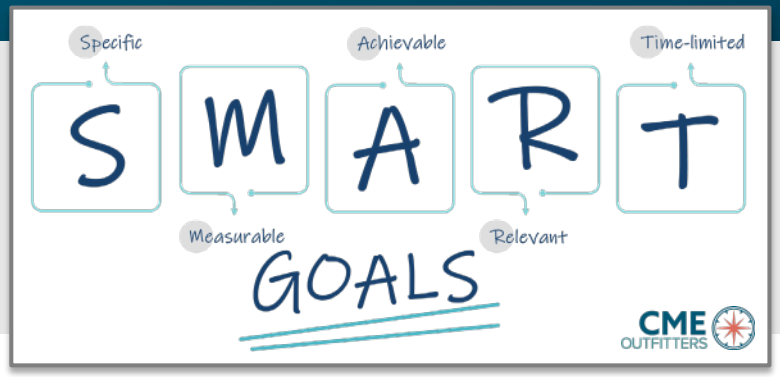
- Amylin modulates a ventral tegmental area-to-medial prefrontal cortex circuit to suppress food intake and impulsive food-directed behavior



DA = dopamine; GABA = gamma-aminobutyric acid; mPFC = medial prefrontal cortex; VTA = ventral tegmental area.

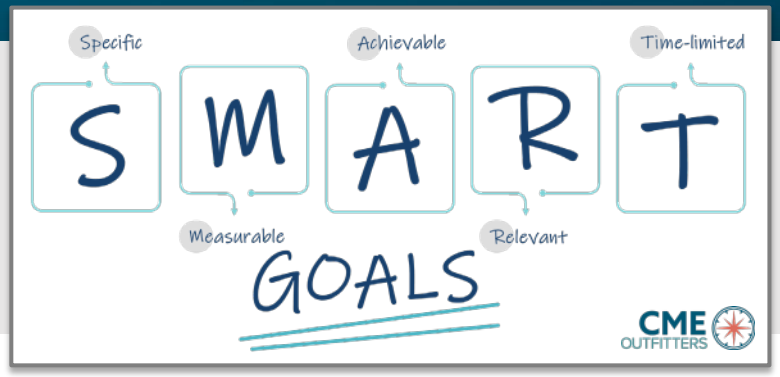
Geisler CE, et al. *Biol Psychiatry.* 2024;95(10):938-950. Hayes Lab. Hayes-lab.com Website. 2024. https://www.hayes-lab.com/research/corrination-of-a-glp-1-receptor-agonist-for-glycemic-control-without-emesis-3ghmy-n6gf2-rjd5w

CME OUTFITTERS



Put information into action!

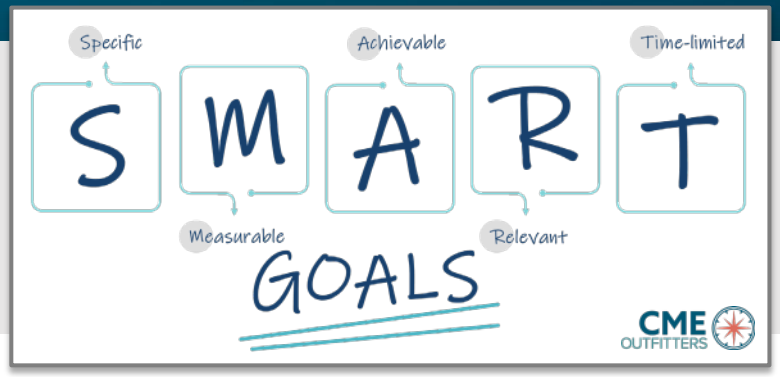
Takeaways from this program can be implemented into your practice to improve patient care.



Put information into action!

Takeaways from this program can be implemented into your practice to improve patient care.

- *Stay current with amylin and DACRA development as they may offer significant weight loss and metabolic control with manageable side effects*



Put information into action!

Takeaways from this program can be implemented into your practice to improve patient care.

- *Stay current with amylin and DACRA-targeted development as they may offer significant weight loss and metabolic control with manageable side effects*
- *Monitor and await completion of clinical trials of combination amylin mimetics with GLP1-RAs as potentially potent therapeutics*

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:

1. A Multi-Pathway Rationale for the Next Therapeutic Current

3. The Phenotype Breakers: Heterogeneity, Signals, and Who Might Benefit from Which Biology

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