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

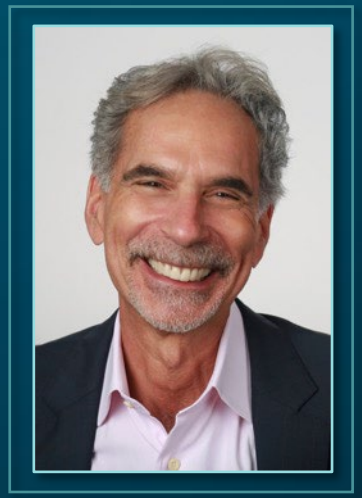
A Multi-Pathway Rationale for the Next Therapeutic Current

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

CMEO Snack

LEARNING OBJECTIVE

Identify obesity as a chronic, relapsing disease process with unmet needs that motivate multi-pathway therapeutic development



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

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1

Framing the Disease

Obesity as a chronic, progressive disease

What is Obesity?

> ***Obesity really is a metabolic disease — the way we would think about hypertension or diabetes.***
>
> — Lee M. Kaplan, MD, PhD

CME OUTFITTERS

The Biology of Regain

> ***Why does the body defend a higher fat mass — and why isn't it a matter of willpower?***
>
> — Dr. Robert Kushner, moderator

Fat Is the Body's Energy “Gas Tank”

Where the body stores fat shifts across the lifespan — that’s normal physiology



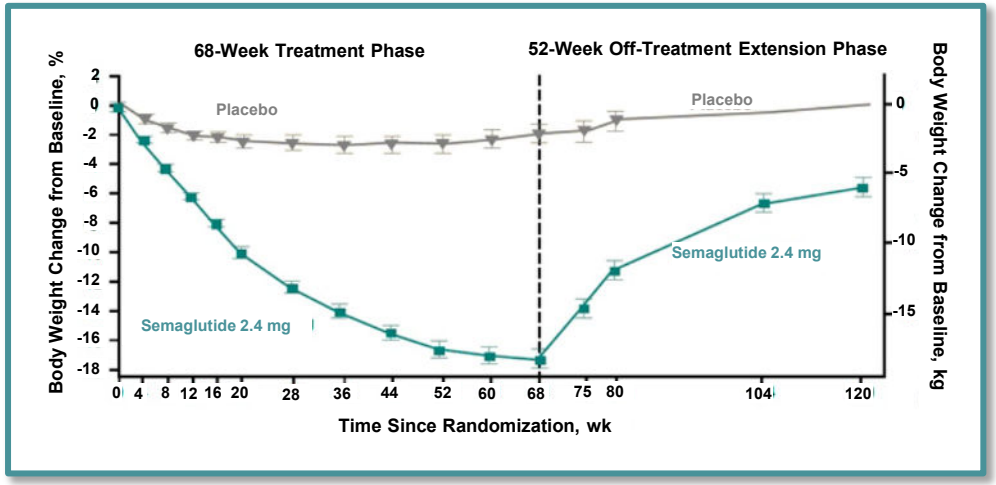
In obesity, both the amount and the location of fat become dysregulated — not just “too much.”

Orsso CE, et al. *Nutrients*. 2020;12(9):2735. Karastergiou K, et al. *Biol Sex Differ*. 2012;3:13. Lovejoy JC, et al. *Int J Obes*. 2008;32:949-958.

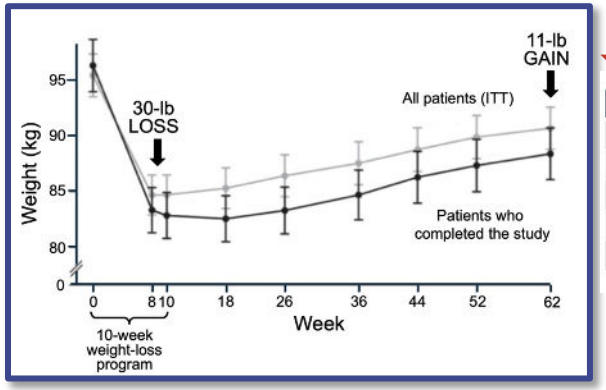
CME OUTFITTERS

After Weight Loss, the Body Defends the Higher "Set Point"

Stop treatment → weight returns



Appetite hormones still favor regain



Satiety signals ↓ Hunger ↑

Reduced:	Increased:
Leptin - 65%	Ghrelin
Peptide YY	
Cholecystokinin	
Insulin	
Amylin	

Sumithran P, et al. *N Engl J Med*. 2011;365(17):1597-1604. Wilding JPH, et al. *Diabetes Obes Metab*. 2022;24(8):1553-1564.

CME OUTFITTERS

The Body Defends Its “Set Point”

Set the thermostat wrong, and the system defends the wrong setting



Regain is biology defending a set point — not a failure of willpower.

Sumithran P, et al. *N Engl J Med*. 2011;365(17):1597-1604.

CME OUTFITTERS

What You Eat vs How Much You Eat

> ***It's not about calories. What you eat influences the regulatory system — but how much you eat is determined by that system.***
>
> — Lee M. Kaplan, MD, PhD

CME OUTFITTERS

2

Why Obesity Needs Multiple Pathways

Complementary mechanisms and the amylin story

From Monotherapy to Combinations

> ***Why has obesity been treated one drug at a time — when we don't do that for other chronic diseases?***
>
> — Dr. Robert Kushner, moderator

CME OUTFITTERS

Before we continue, please answer the following audience response question.

Audience Response



A patient has an inadequate response to a nutrient-stimulated hormone despite appropriate dosing. What would you do next?

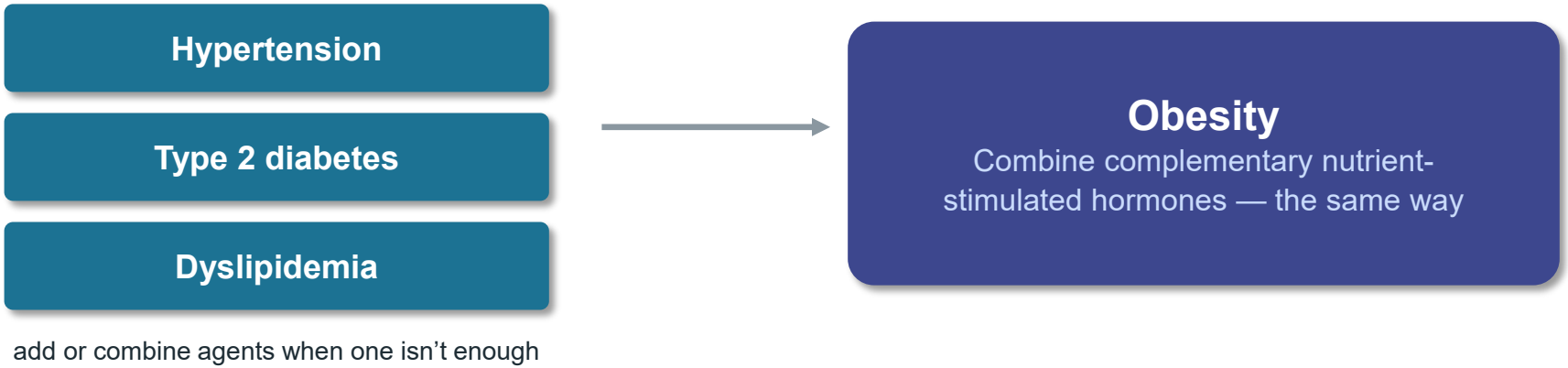
A. Keep the current agent and intensify lifestyle measures before changing pharmacotherapy
B. Switch to another agent in the same class before trying a different mechanism
C. Add or switch to an agent with a different, complementary mechanism
D. Push the current agent to its maximally tolerated dose before considering another mechanism
E. I don't know

Please select your answer now.

CME OUTFITTERS

Obesity: Take the “Road Taken”

In every other chronic disease, we already combine complementary mechanisms



When one agent is insufficient, add or switch to a complementary mechanism

Müller TD, et al. *Nat Rev Drug Discov*. 2022;21(3):201-223.

CME OUTFITTERS

In obesity, we want the road taken — the road we use for every other disease.

— Lee M. Kaplan, MD, PhD

Complementary mechanisms

Two therapies acting on different pathways, so a patient who responds poorly to one may respond well to the other.

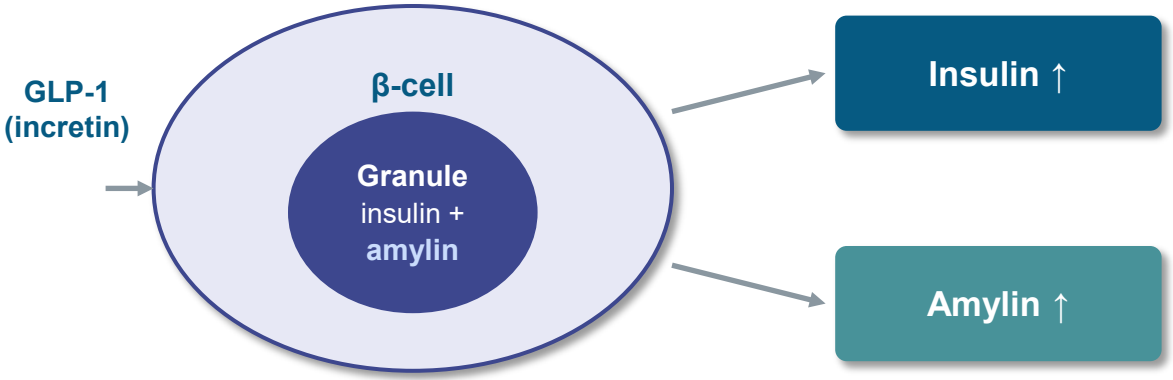
Complementarity and Amylin

> ***Complementary versus simply additive action — and where does amylin fit in the picture?***
>
> — Dr. Robert Kushner, moderator

CME OUTFITTERS

Amylin Rides Along With Insulin

In diabetes, a GLP-1 drives the β-cell — and amylin is co-secreted from the same granule



Same pathway in diabetes.

Stimulating GLP-1 also raises amylin.

In obesity the effects are in the brain — where the wiring may be different, so amylin can be truly complementary.

Whether a second drug just “amplifies” or truly complements depends on the pathway.

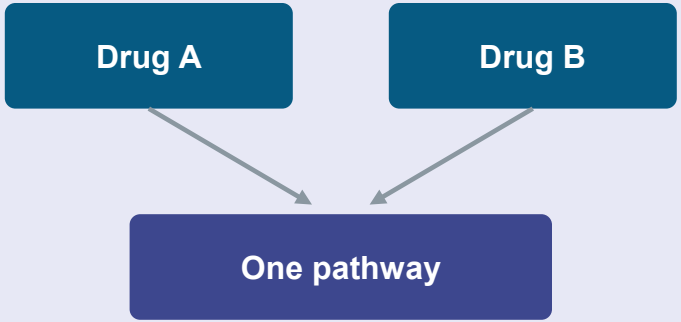
Kahn SE, et al. *Diabetes.* 1990;39(5):634-638.

CME OUTFITTERS

“Goosing Up” vs True Complementarity

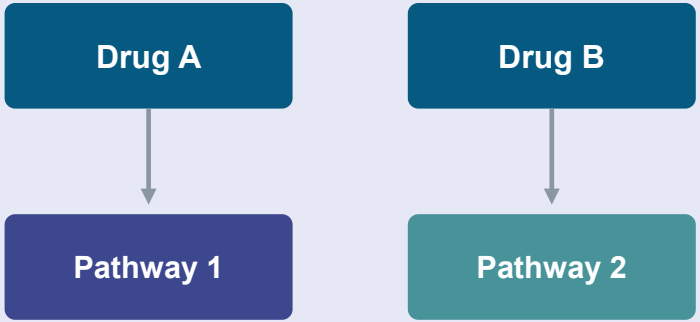
Two drugs, two possibilities — and either way the patient can benefit

Same pathway → “goosing up”



Amplifies the same signal — ≈ doubles efficacy for everyone

Different pathways → complementary



A poor responder to one may respond well to the other

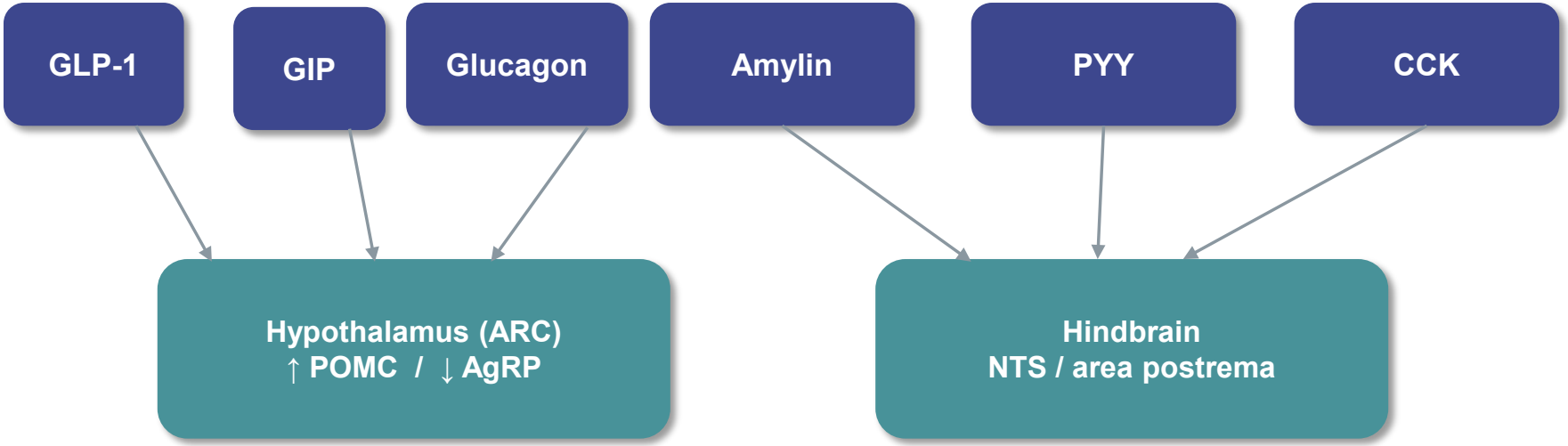
In obesity we don’t yet know which — but either way, combining mechanisms benefits patients.

Müller TD, et al. *Nat Rev Drug Discov*. 2022;21(3):201-223.

CME OUTFITTERS

Why Obesity Needs Multiple Pathways

Many gut and pancreatic signals → overlapping brain circuits that counter-regulate



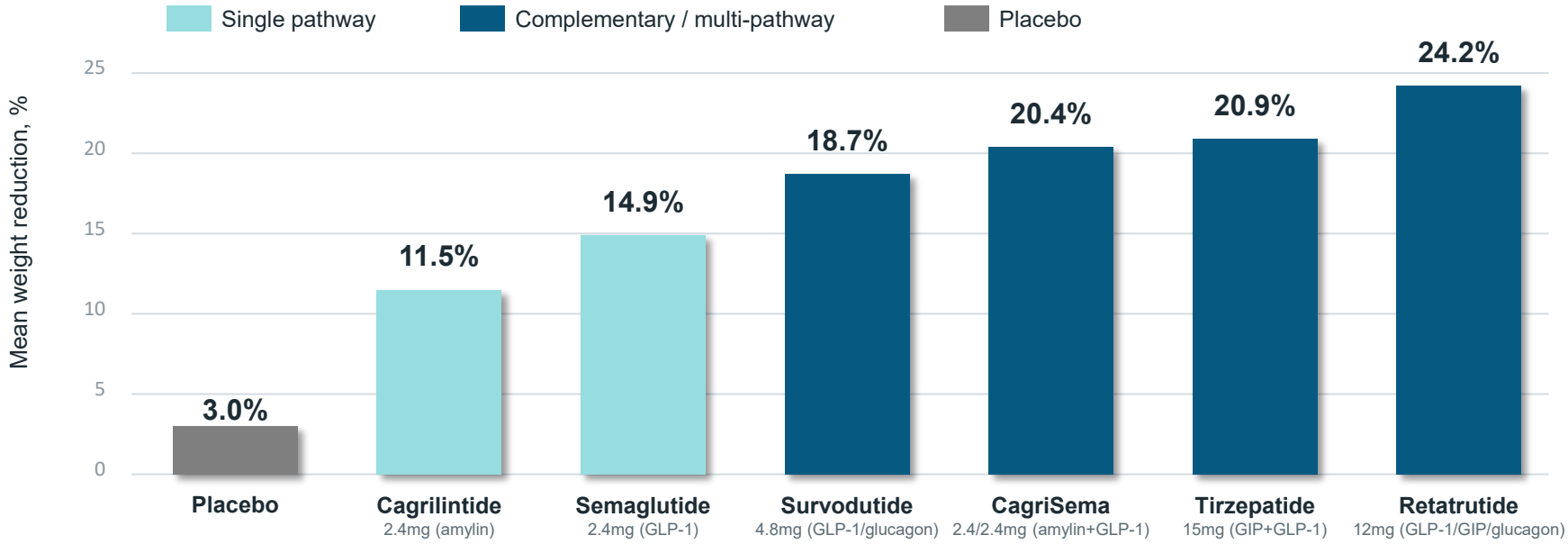
Redundant, overlapping circuits → push one node and the system counter-regulates.
Engaging complementary pathways is what overcomes that built-in redundancy.

AgRP = agouti-related peptide; ARC = arcuate nucleus; CCK = cholecystokinin; GIP = glucose-dependent insulinotropic polypeptide; GLP = glucagon-like peptid; NTS = nucleus tractus solitarius; POMC = pro-opiomelanocortin; PYY = peptide YY. Müller TD, et al. *Nat Rev Drug Discov*. 2022;21(3):201-223.

CME OUTFITTERS

Complementary vs Single Pathway

Engaging complementary pathways → more than pushing one harder



REDEFINE 1 / SURMOUNT-1 at week 68 (treatment-policy estimand); survodutide (46 wk) and retatrutide (48 wk) are phase-2, cross-trial benchmarks — not head-to-head. Garvey WT, et al. *N Engl J Med*. 2025;393(7):635-647. Jastreboff AM, et al. *N Engl J Med*. and 2023;389(6):514-526. Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216. le Roux CW, et al. *Lancet Diabetes Endocrinol*. 2024;12(3):162-173.

CME OUTFITTERS

Heterogeneity of Response

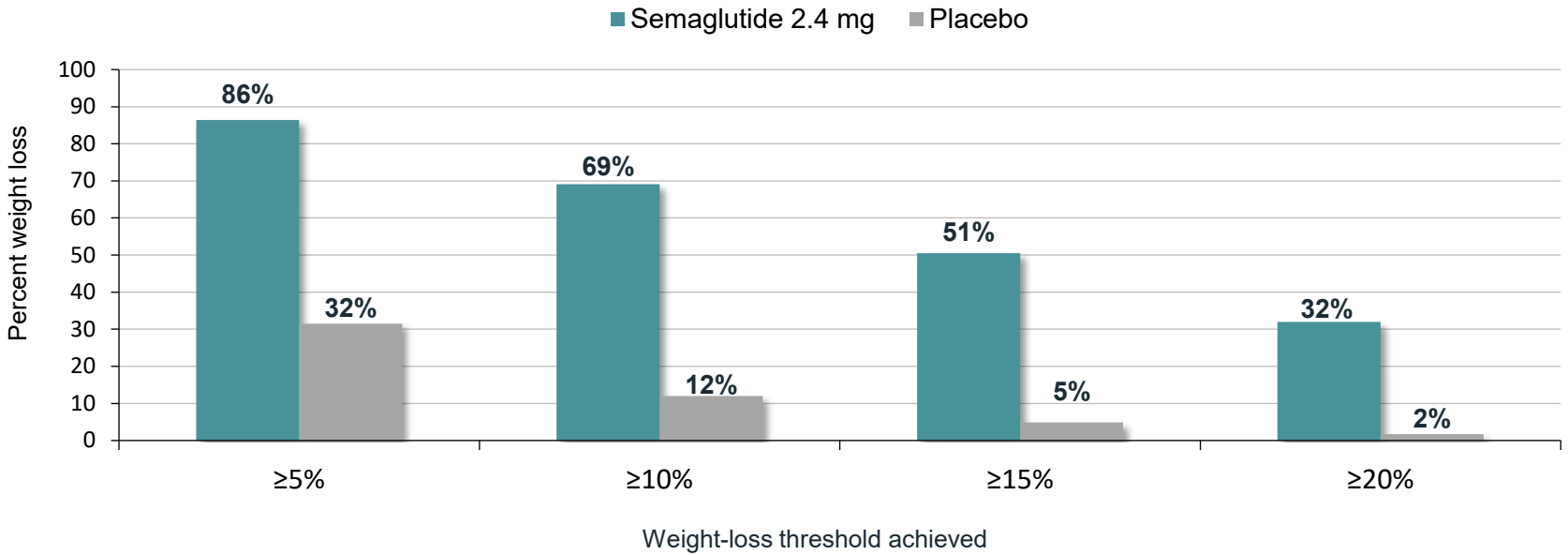
> ***What's behind the super-responders and the frustrating non-responders — and what are phenotypes?***
>
> — Dr. Robert Kushner, moderator

CME OUTFITTERS

Is Variability in Response Due to Phenotypes?

The “mean” (−14.9%) hides a wide responder distribution

Same drug: some patients lose >20%, others <5% — that spread is the “phenotype”

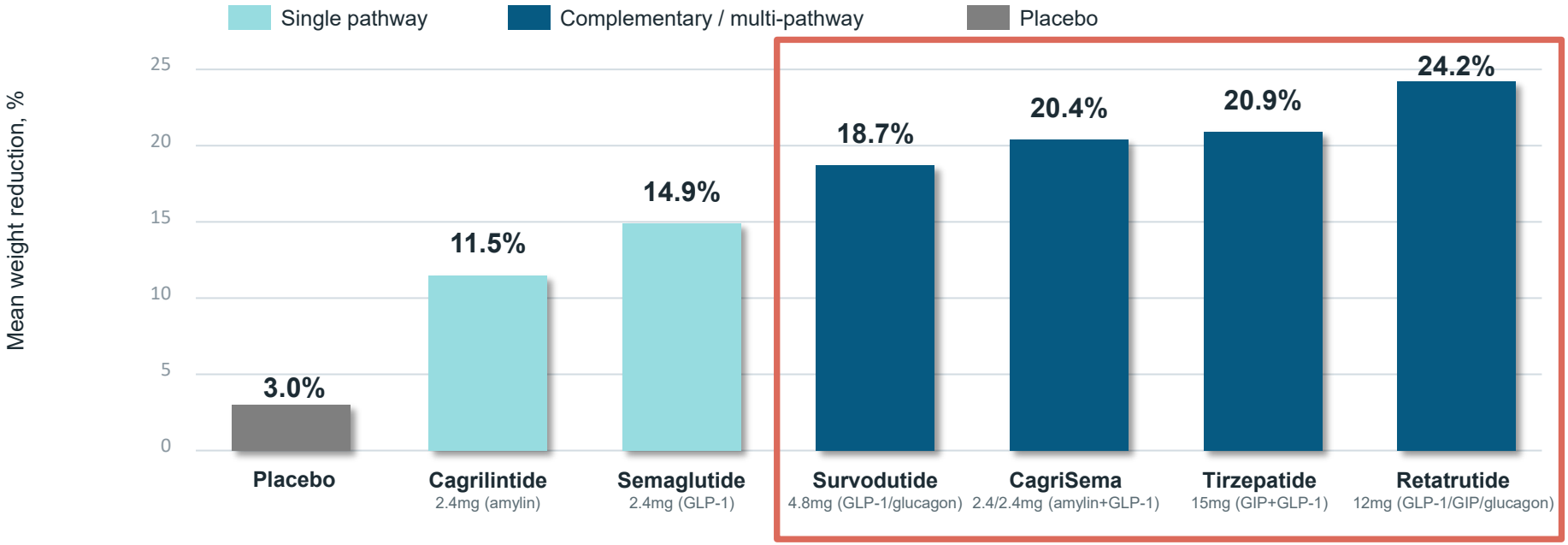


Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989-1002.

CME OUTFITTERS

Complementary vs Single Pathway

Engaging complementary pathways → more than pushing one harder



REDEFINE 1 / SURMOUNT-1 at week 68 (treatment-policy estimand); survodutide (46 wk) and retatrutide (48 wk) are phase-2, cross-trial benchmarks — not head-to-head. Garvey WT, et al. *N Engl J Med*. 2025;393(7):635-647. Jastreboff AM, et al. *N Engl J Med*. and 2023;389(6):514-526. Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216. le Roux CW, et al. *Lancet Diabetes Endocrinol*. 2024;12(3):162-173.

CME OUTFITTERS

Where Amylin Fits: A Distinct Satiety Signal That Complements Incretins

Amylin
(β-cell, co-secreted w/ insulin)

↓

Hindbrain
area postrema

→ promotes satiation
→ slows gastric emptying
→ restores leptin signaling
→ **complements GLP-1**

Amylin is one of the satiety hormones that falls after weight loss
(Sumithran 2011) — a rationale for restoring the signal.

Early signal
cagrilintide (amylin analog)
−10.8%
vs liraglutide −9.0%
vs placebo −3.0%
weight loss at 26 wks

Lau DCW, et al. *Lancet.* 2021;398(10317):2160-2172. Müller TD, et al. *Nat Rev Drug Discov*. 2022;21(3):201-223. Sumithran P, et al. *N Engl J Med*. 2011;365(17):1597-1604.

CME OUTFITTERS

Before we continue, please answer the following audience response question.

Audience Response



Which treatment approach is most appropriate for a patient who is prone to dose-related adverse effects?

A. Combine two complementary agents at lower doses for comparable benefit with fewer adverse effects
B. Titrate one agent to its maximally tolerated dose first, adding a second only if that fails
C. Use the single most most effective agent and accept its side effects as necessary to reach goal
D. Start both agents at full dose dose to reach target quickly, then taper to goal
E. I don't know

Please select your answer now.

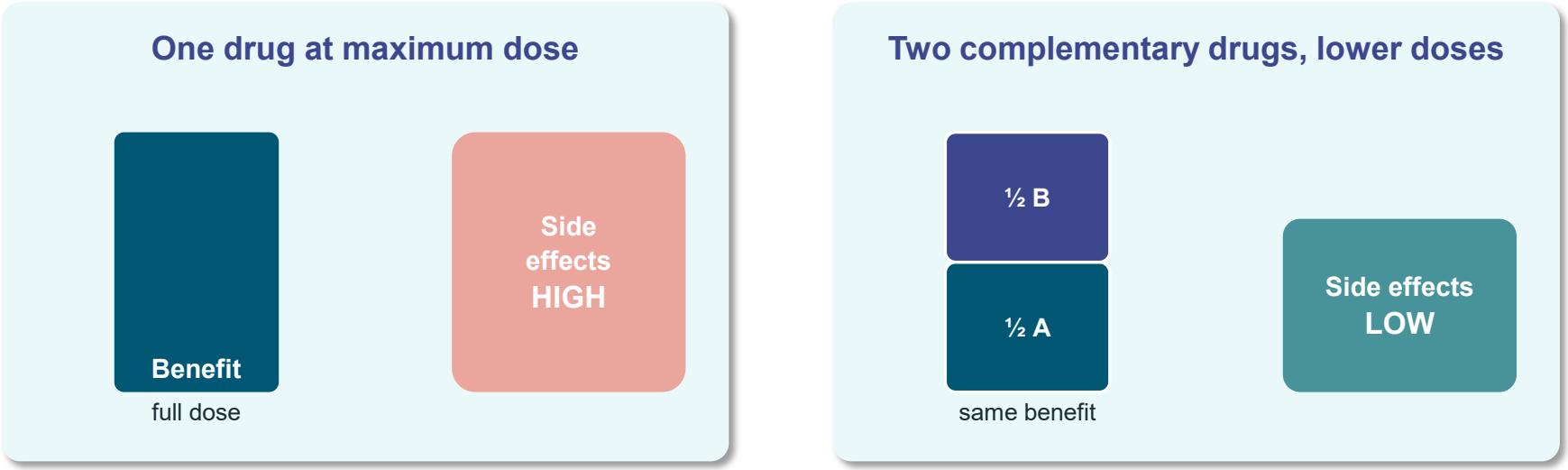
CME OUTFITTERS

Maximize Dose or Combine?

> ***Push one drug to its maximum, or combine complementary mechanisms at lower doses?***
>
> — Dr. Robert Kushner, moderator

Two Lower Doses, Same Benefit

Combining at lower doses can match a single maximal dose — with fewer side effects



Same benefit, better tolerability — the rationale for combining at lower doses.

Coutinho W, Halpern B. *Diabetol Metab Syndr*. 2024;16(1):6. Law MR, et al. *BMJ*. 2003;326(7404):1427. Wald DS, et al. *Am J Med*. 2009;122(3):290-300.

CME OUTFITTERS

Lowest Effective Dose vs Maximum Dose

We push to the maximum only when the goal is to kill something

Most chronic diseases — incl. obesity

Start at the lowest effective dose

→ titrate up, or

→ add a complementary drug

Goal: control the disease over time

Infection & cancer

Start at the maximally tolerated dose

→ hit hard, early

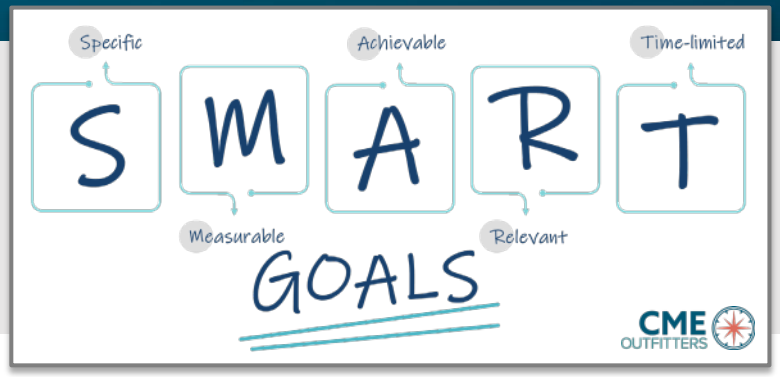
Goal: kill the organism or cell

Obesity belongs with the chronic diseases — start low, then complement.

American Diabetes Association Professional Practice Committee for Obesity. *BMJ Open Diabetes Res Care*. 2026;13(Suppl 1):e005729. Chabner BA, Roberts TG Jr. *Nat Rev Cancer*. 2005;5(1):65-72. Kumar A, et al. *Crit Care Med*. 2006;34(6):1589-1596. McCormack JP, et al. *CMAJ*. 2011;183(1):65-69.

CME OUTFITTERS

> ***You do whatever the patient needs, and you use the therapy that's right for that patient.***
>
> — Lee M. Kaplan, MD, PhD



Put information into action!

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

- *Stay current with the myriad of new therapeutics in development for obesity* including different kinds of GLP1s, GIP agonists, amylins, glucagons, and others
- *Remember that obesity is a disease* and as with most diseases, a diversity of drugs should be employed
  - Complementary approaches with agents that don't overlap is an emerging strategy/pathway that has the potential to improve quality of care and outcomes for patients with obesity

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:

2. The Satiety Current: Amylin Biology as a Systems Signal

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

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