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MASSACHUSETTS
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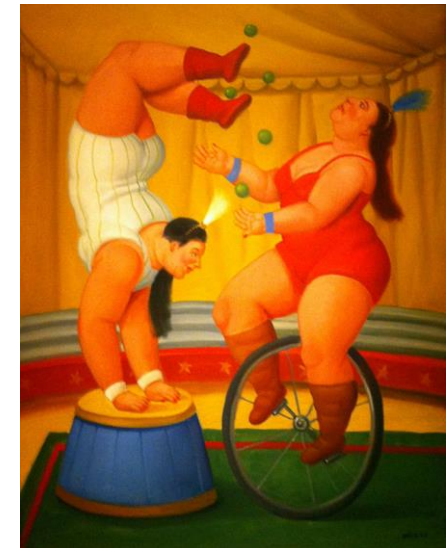
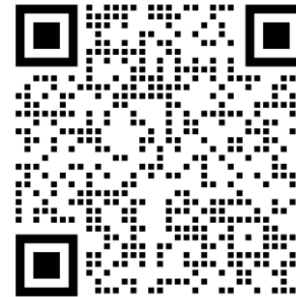
Obesity in 2022: A New Era

Lee M. Kaplan, MD, PhD

The Obesity and Metabolism Institute
Boston, Massachusetts

LMKaplan0@gmail.com

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Fernando Botero, 1932-

Internal Medicine Comprehensive Review and Updates 2022

Disclosures

I am currently or have recently been a paid consultant to the following companies and organizations:

Amgen

Boehringer Ingelheim

Gelesis

Gilead Sciences

Eli Lilly & Company

Novo Nordisk

Optum Health

Pfizer

Rhythm Pharmaceuticals

U.S. National Institutes of Health

The Obesity and Nutrition Institute

Xeno Biosciences

Something to consider ...

In 1984, the first papers from the CDC documented that obesity had become epidemic in the U.S.

In 1984, HIV infection was a death sentence ...

... today, HIV infection barely affects life expectancy in the U.S.

Why haven't we made the same progress in obesity?

Why have we failed to control obesity ...

In the past 40 years, **not a single country** in the world has experienced a reduction in the prevalence of obesity

The data show that **we** have failed miserably

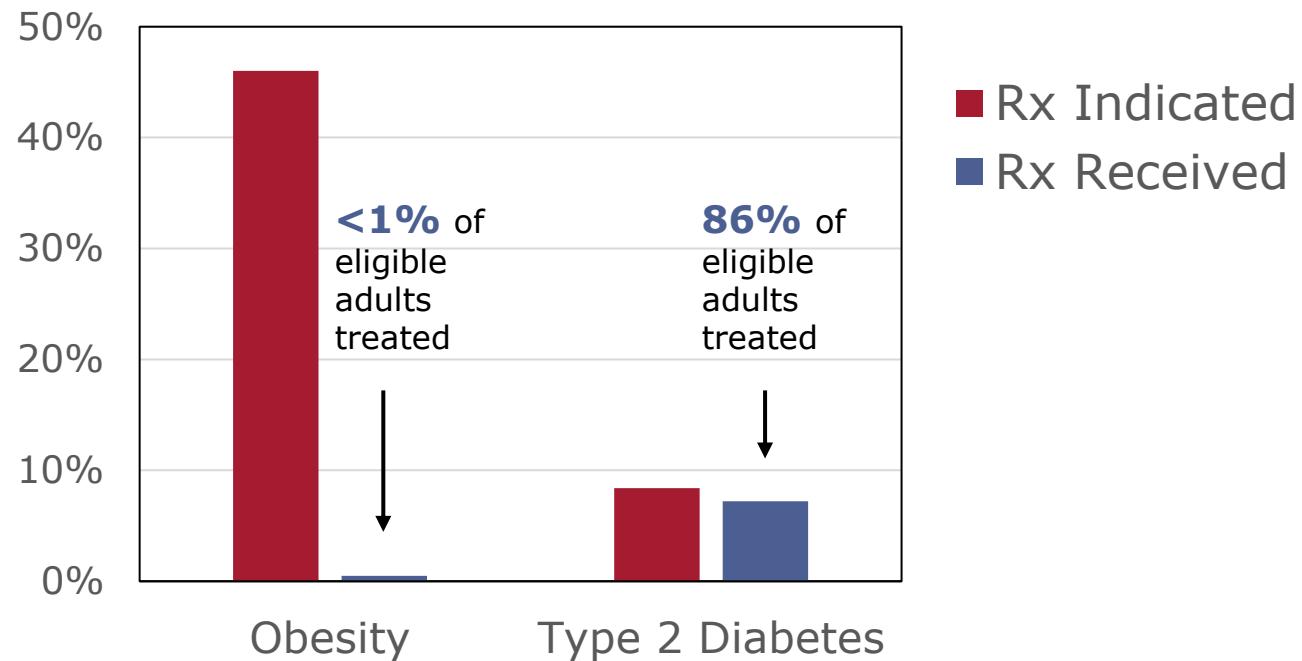
What are we missing?

Is obesity really a behavioral problem?

Is lifestyle-based therapy adequate to solve it?

Obesity is grossly undertreated

- 46% of U.S. adults meet recommendations for anti-obesity pharmacotherapy
- ~0.5% are currently treated with anti-obesity medications



Challenges to recognizing obesity as a disease

- Consideration of obesity only as a **risk factor for other diseases**, rather than as a disease on its own
- **Perception that managing obesity is within the ability** of those who have it and, therefore, that its management is their sole responsibility
- Widespread **weight-related stigma** that ascribes blame to the people with the problem and **induces self-blame** in people with obesity
- **Outward manifestation of obesity** that reinforces bias, stigma and discrimination
- Failure to appreciate the **distinction between obesity and the cultural desire for thinness**, the latter perception undermining recognition of obesity and acceptance of a clinical diagnosis
- Failure to appreciate the normal biology of **body fat mass regulation** that is **disrupted in obesity**

Diseases provoked by the modern environment

Disease	Immunological pathophysiology
Nut allergies	✓
Asthma	✓
Celiac disease	✓
Ulcerative colitis	✓
Crohn's disease	✓
Eosinophilic esophagitis	✓
Rheumatoid arthritis	✓
Psoriatic arthritis	✓

Diseases provoked by the modern environment

Disease	Immunological pathophysiology	Metabolic pathophysiology
Nut allergies	✓	
Asthma	✓	
Celiac disease	✓	
Ulcerative colitis	✓	
Crohn's disease	✓	
Eosinophilic esophagitis	✓	
Rheumatoid arthritis	✓	
Psoriatic arthritis	✓	
NASH	✓	✓
Type 2 diabetes	✓	✓
Obesity		✓

Body fat mass is a physiologically-regulated phenotype

- At multiple stages during development
 - Loss of baby fat
 - Fat changes with puberty
 - Fat changes with aging
 - Fat changes with menopause
- During and after pregnancy

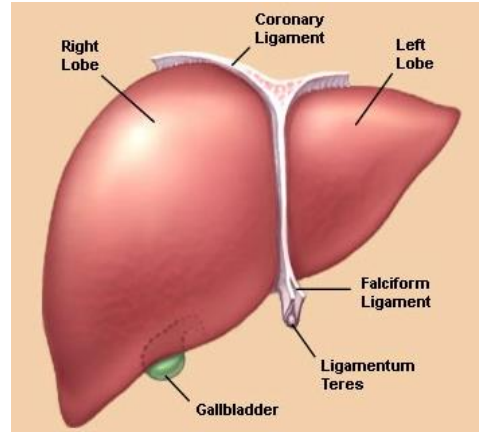
This regulation occurs **without** our conscious or purposeful input

Obesity results from **inappropriate regulation** of body fat mass

For most tissues, the body seeks a target mass



Red blood cells



Liver

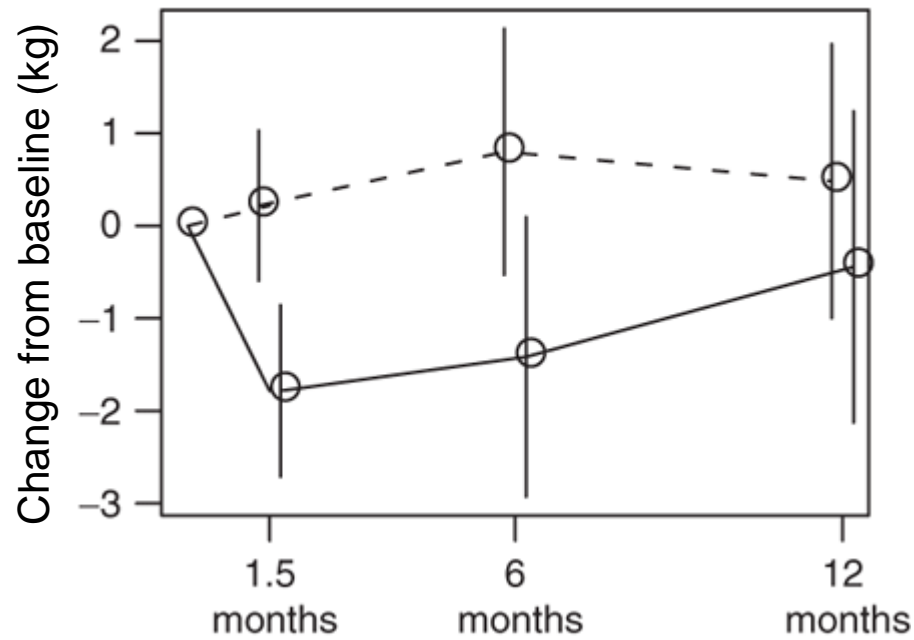
... including fat



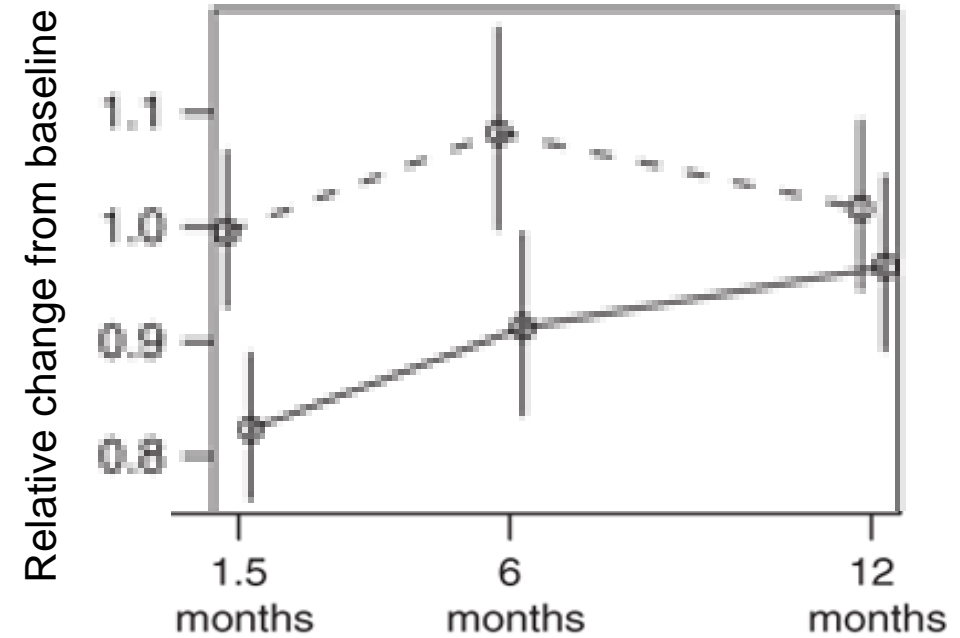
Physical **tissue destruction or removal** leads to **rapid regrowth**

Physical removal of body fat leads to rapid regrowth

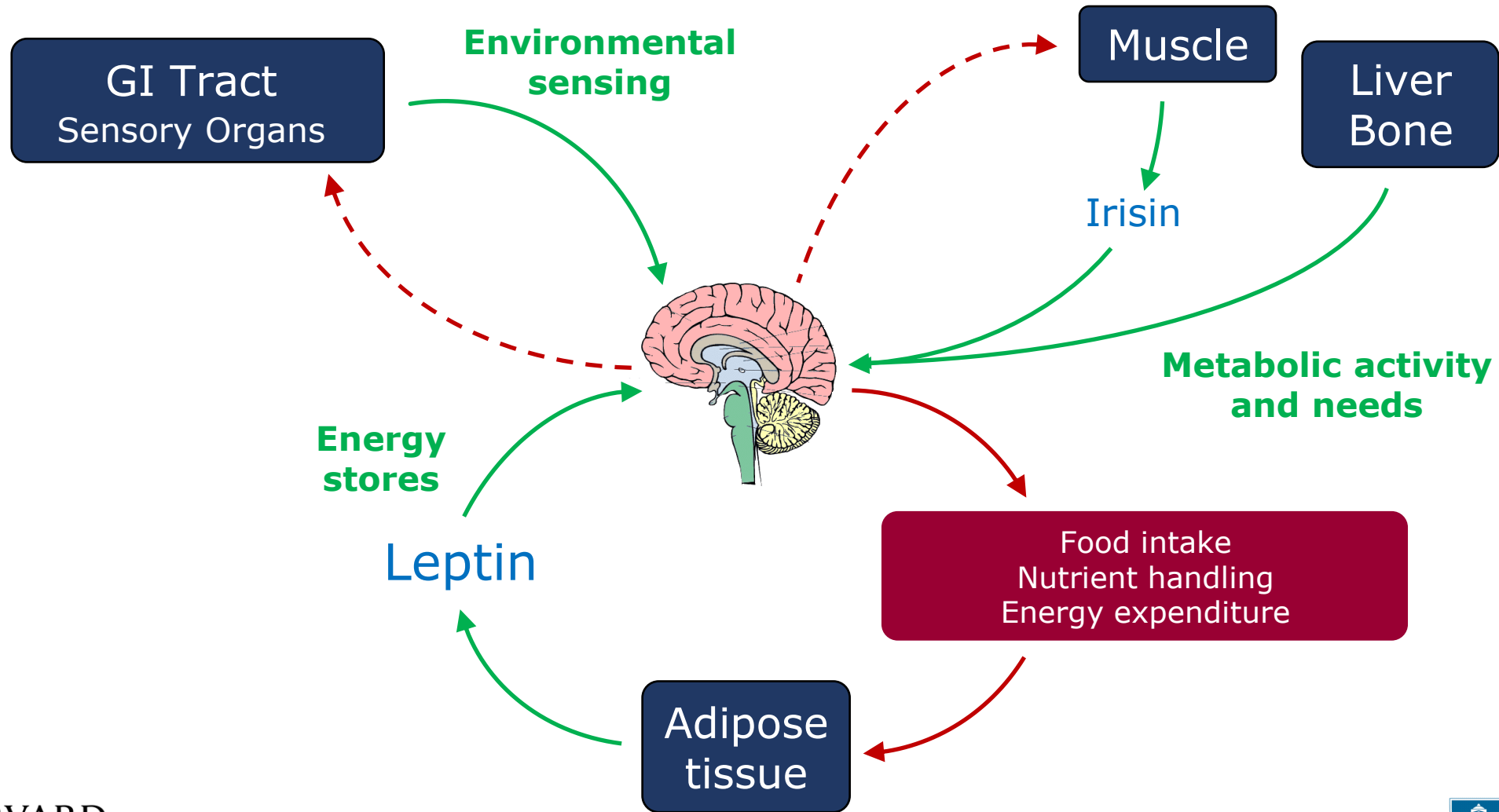
Total body weight



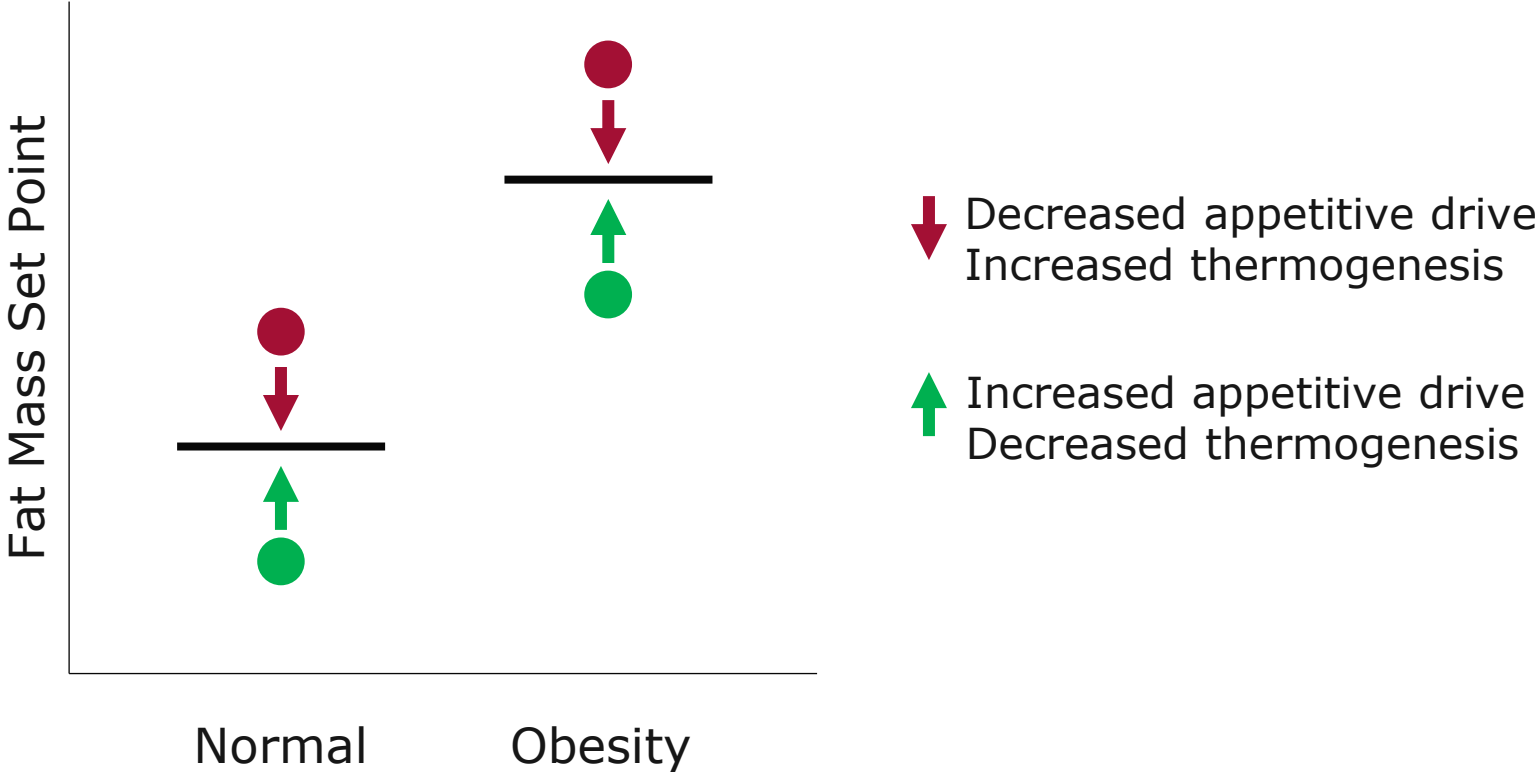
Abdominal fat



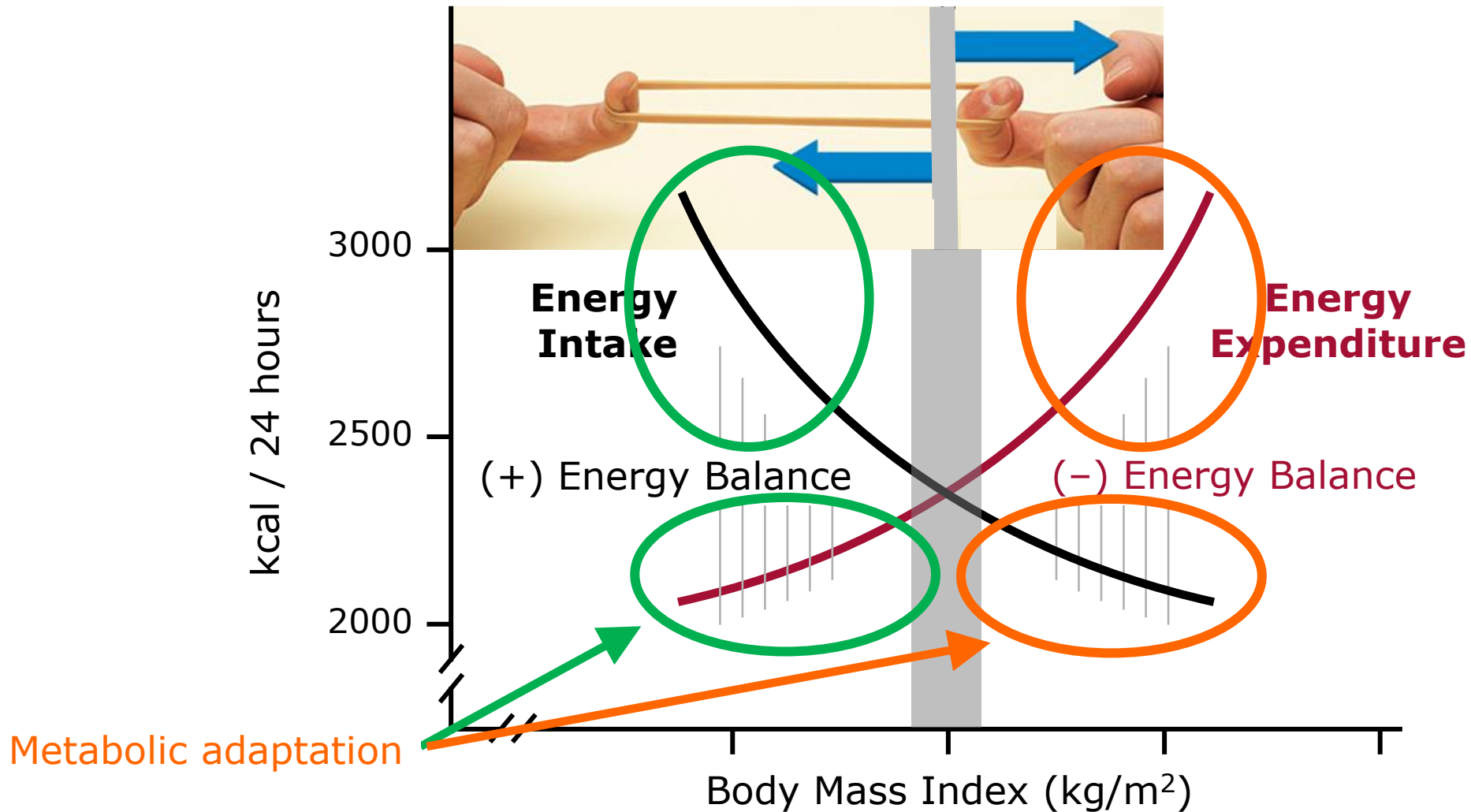
Physiological determination of defended fat mass (set point)



Relationship to set point drives physiological response more than set point itself



During most of adult life, the body defends a fat mass “set point,” a process mediated by metabolic adaptation



What this means ...

Obesity results from a genetic and environmentally driven dysfunction of the normal fat mass regulatory mechanisms ...

... leading to an elevated defended body fat mass

Together, what this implies is that ...

Overeating does not cause obesity ...

... obesity causes overeating

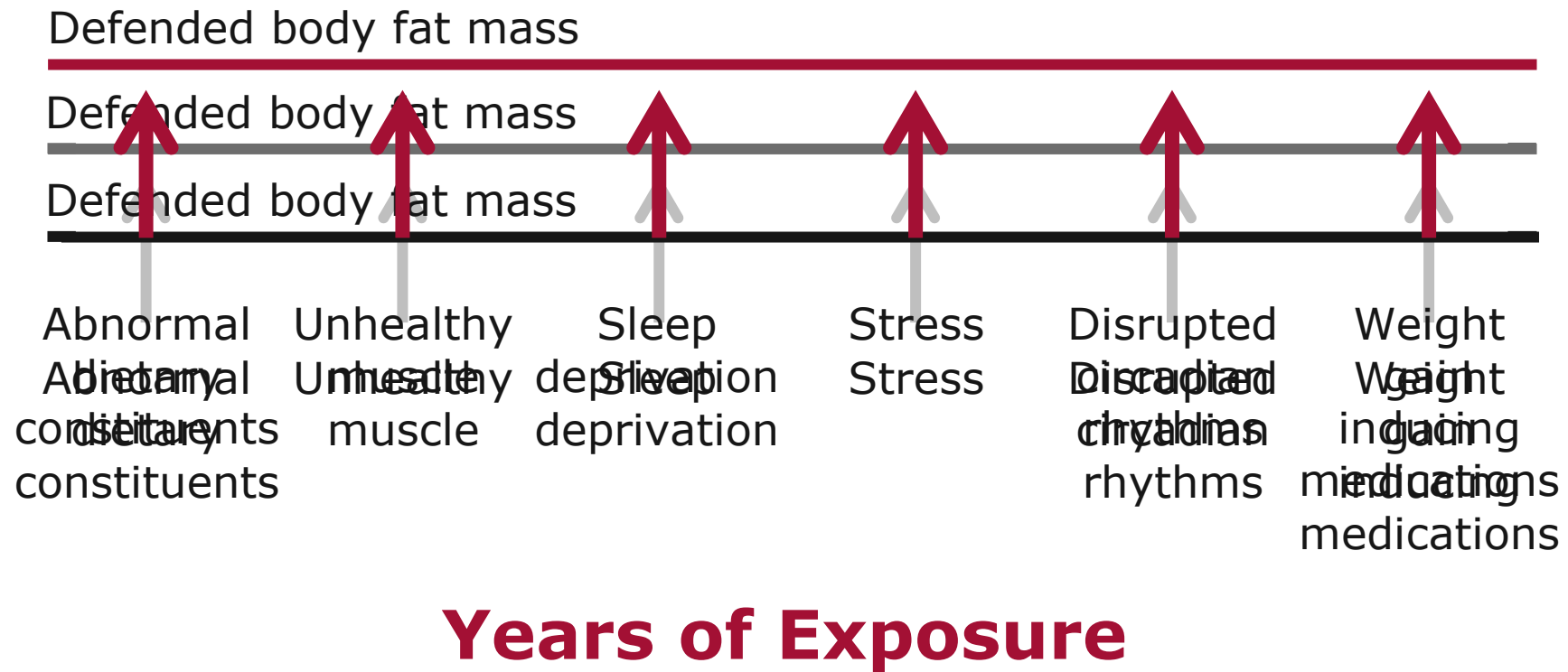
And ...

Undereating does not fix obesity ...

... fixing obesity leads to undereating

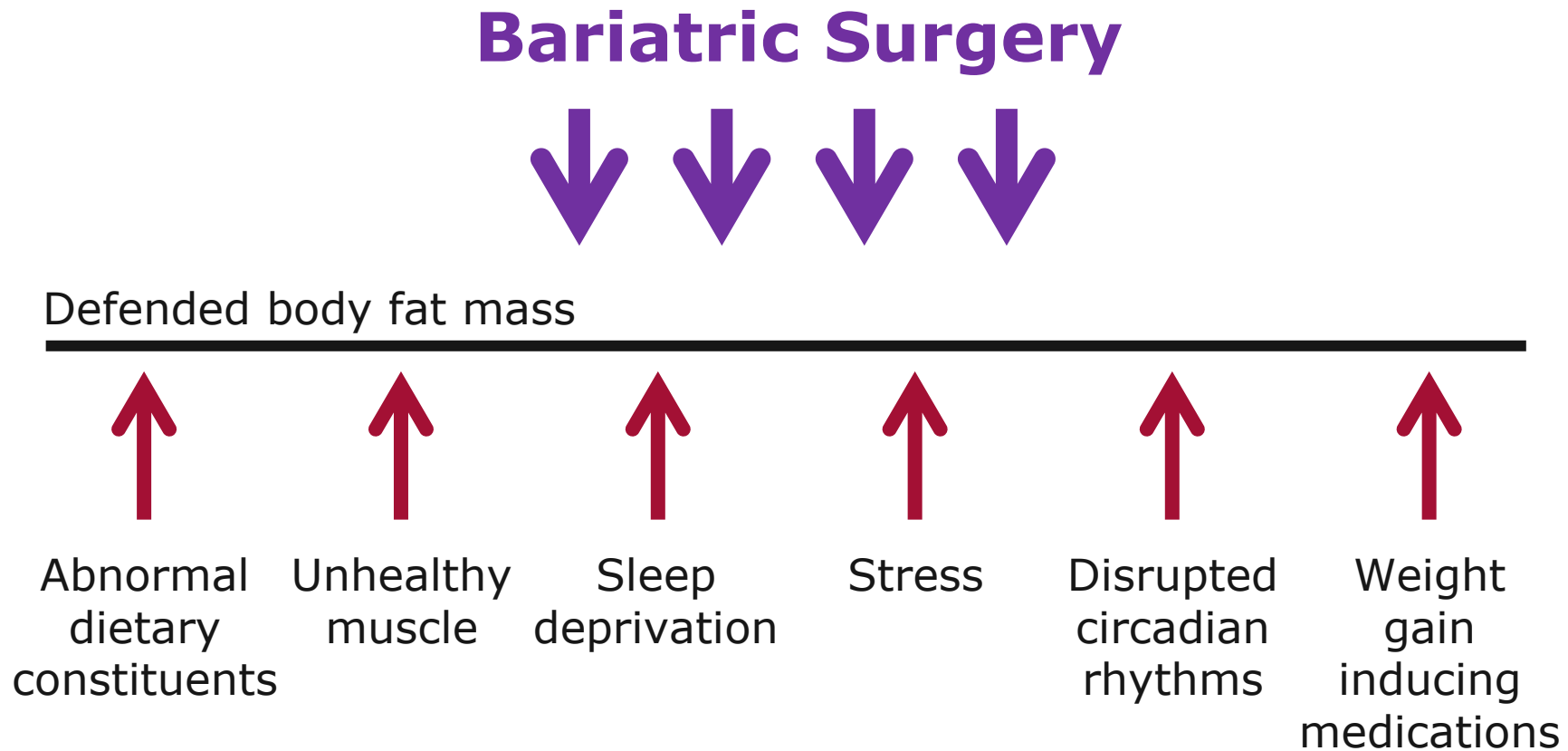
These conclusions have critical implications
for the long-term control of obesity

The modern environment causes obesity by driving up the target (defended) fat mass



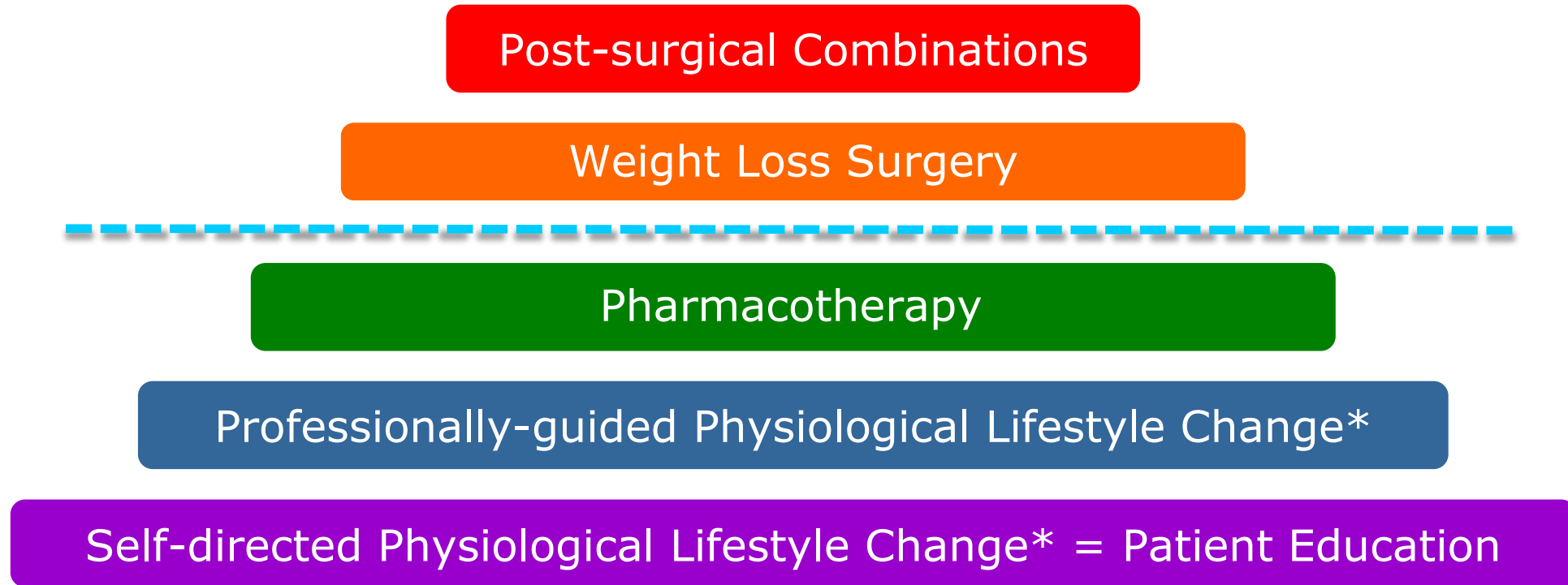
Implications for obesity treatment

Obesity and its care: a battle of forces that influence the target (defended) fat mass



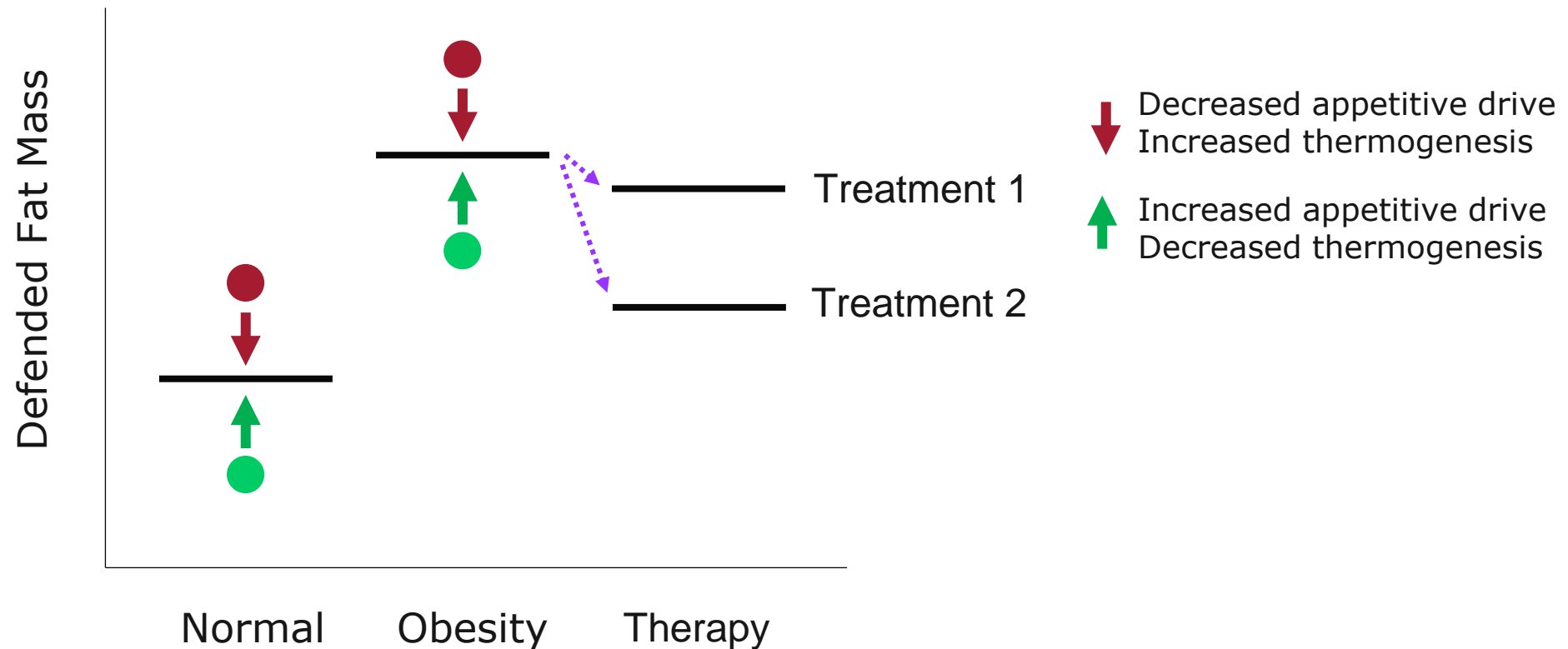
Physiology-based obesity treatment strategy

A stepwise approach – aimed at restoring normal physiology
(progress through algorithm as clinically required)



*NOT based on calorie reduction

Any durably effective therapy will change the set point

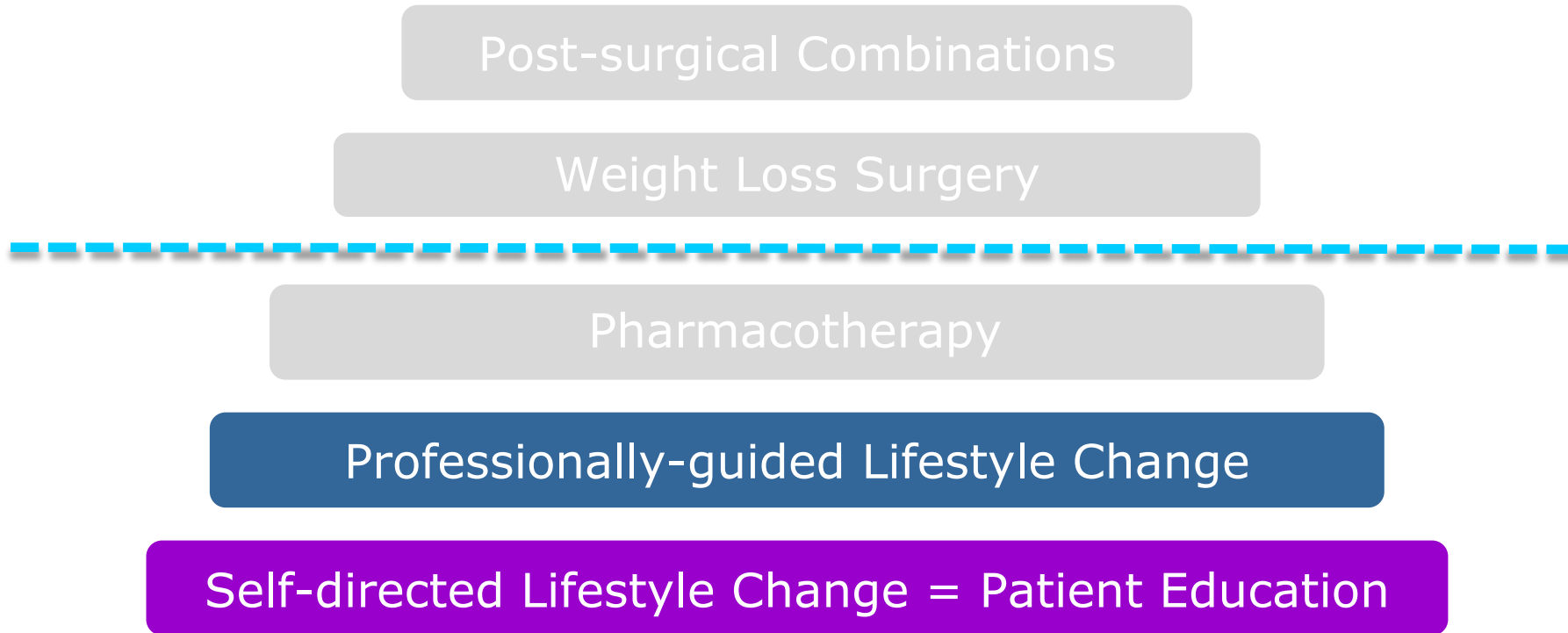


This is the basis of its long-term effectiveness

Obesity treatment strategy

A stepwise approach – aimed at restoring normal physiology

(progress through algorithm as clinically required)

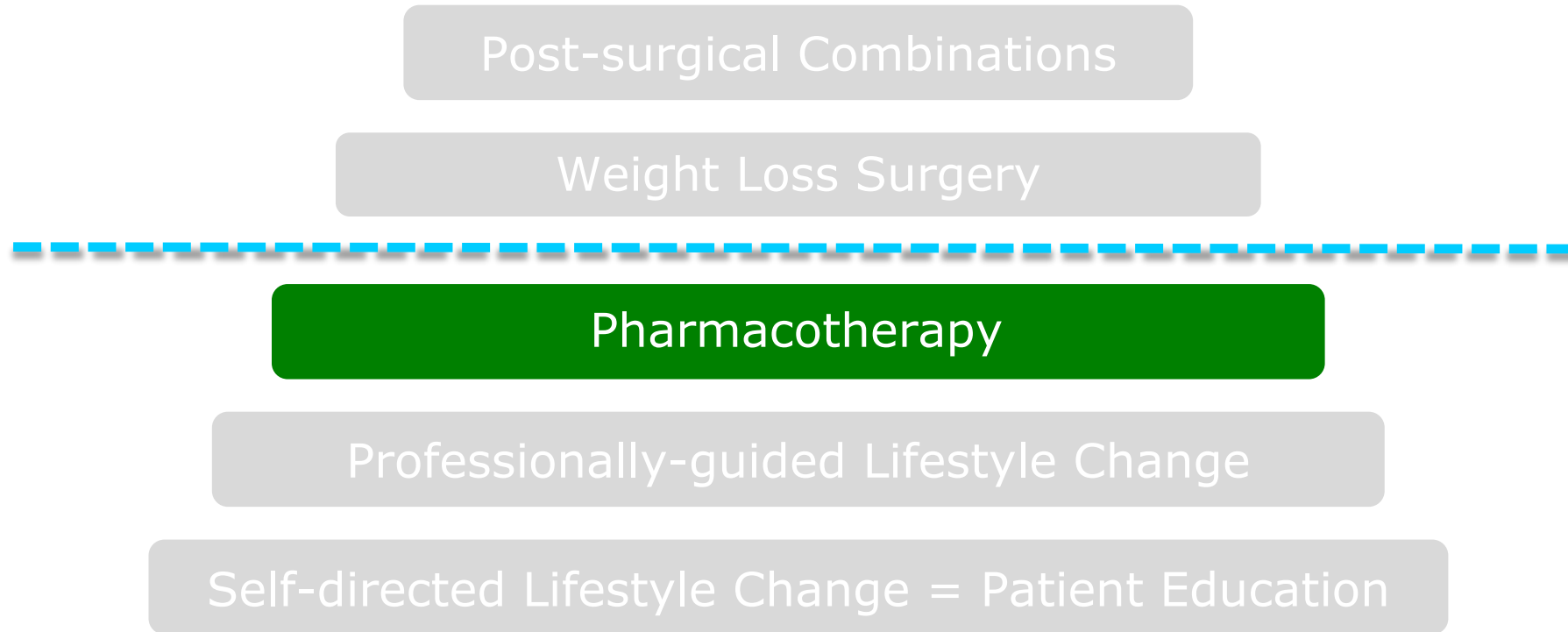


What this means in practice – lifestyle-based treatment

- Take a good **obesity history**, looking for factors associated with periods of greatest weight gain
 - **Don't confuse** increased eating with weight gain
 - **Use the history to identify opportunities** for lifestyle-based intervention
 - This is the essence of **physiologically-driven lifestyle intervention**
 - Using a **checklist** can be helpful
 - ❑ Overall dietary content – e.g., processed, homogeneous, nutrient-biased
 - ❑ Physical activity (looking for minimal activity)
 - ❑ Severe, **chronic** stress – e.g., financial, traumatic, interpersonal, work-related
 - ❑ Sleep deprivation – decrease in quantity or quality
 - ❑ Circadian rhythm disruption (e.g., erratic mealtimes, sleep times, or work shifts)
 - ❑ Obesogenic medications

Obesity treatment strategy

A stepwise approach – aimed at restoring normal physiology
(progress through algorithm as clinically required)



FDA-approved anti-obesity medications (AOMs)

Medication
Phentermine (Adipex®, Ionamin™, Lomaira™)
Orlistat (Xenical®)
Phentermine/topiramate (Qsymia®)
Naltrexone/bupropion (Contrave®)
Liraglutide 3.0 mg/day (Saxenda®)
Semaglutide 2.4 mg/week (Wegovy®)
Setmelanotide* (Imcivree™)

FDA indication for AOMs:

- **BMI >30 kg/m²**
- **BMI >27 kg/m² with co-morbidities**
- In conjunction with diet/lifestyle intervention

* Setmelanotide is indicated for treatment of obesity arising from selected genetic or syndromic disruptions in the melanocortin-4 receptor signaling pathway

AOMs commonly used in clinical practice

Medication	Mechanism
<p>Phentermine* (Adipex®, Ionamin™, Lomaira™)</p>	<p>Norepinephrine (NE)-releasing agent</p>
<p>Orlistat* (Xenical®, Alli®)</p>	<p>Pancreatic lipase inhibitor</p>
<p>Phentermine/topiramate * (Qsymia®)</p>	<p>NE-releasing agent (phentermine) GABA receptor modulator (topiramate)</p>
<p>Naltrexone/bupropion* (Contrave®)</p>	<p>Opiate antagonist (naltrexone) NE and dopamine reuptake inhibitor (bupropion)</p>
<p>Liraglutide* Semaglutide* Dulaglutide (Saxenda®, Victoza®) (Wegovy®, Ozempic®, Rybelsus®) (Trulicity®)</p>	<p>Glucagon-like peptide-1 (GLP-1) receptor agonists</p>
<p>Topiramate Zonisamide (Topamax®) (Zonegran®)</p>	<p>Na⁺ channel and Ca⁺⁺ channel modulators</p>
<p>Metformin (Glucophage®, Glucophage® XR, Fortamet®, Glumetza®, Riomet®)</p>	<p>Insulin sensitizer; inhibitor of hepatic glucose production</p>

*FDA-approved for treatment of obesity; all other drugs FDA approved for other indications

Average AOM weight loss over placebo

Medication	Average weight loss (over placebo) [†]
Phentermine (Adipex [®] , Ionamin [™] , Lomaira [™])	5.0–7.5%
Orlistat (Xenical [®] , Alli [®])	2.5–3.5%
Phentermine/topiramate (Qsymia [®])	7.5–9.0%
Bupropion/naltrexone (Contrave [®])	4.5–6.0%
Liraglutide 3.0 mg/day* (Saxenda [®])	7.0-8.5%
Semaglutide 2.4 mg/week (Wegovy [®])	15-17%
Setmelanotide** (Imcivree [™])	10-25% in patients with genetic POMC or leptin receptor deficiency

* Liraglutide 3.0 mg/day FDA-approved for treatment of obesity in adults and adolescents;
all other drugs FDA-approved for treatment of obesity in adults;

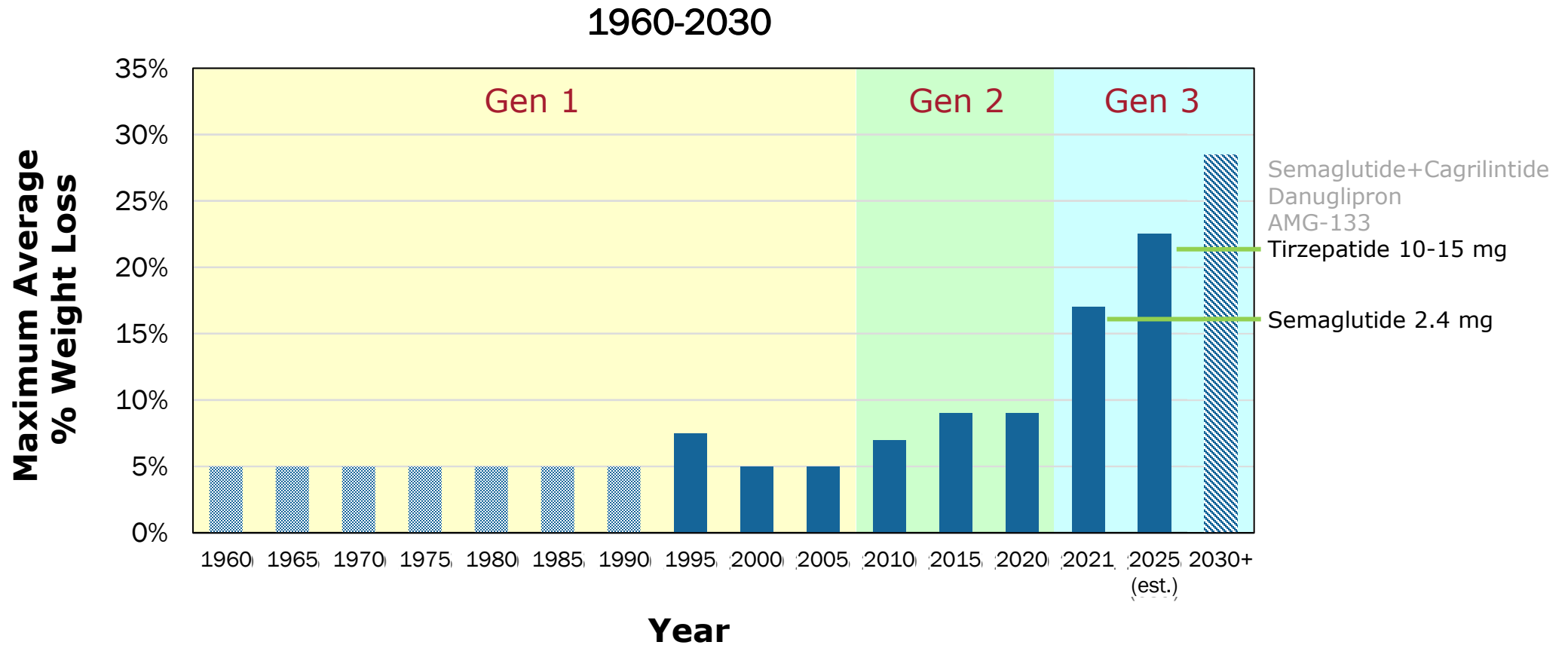
** FDA-approved for treatment of obesity from genetic defects in melanocortin-4 receptor pathway

[†] Patients with type 2 diabetes generally experience diminished weight loss

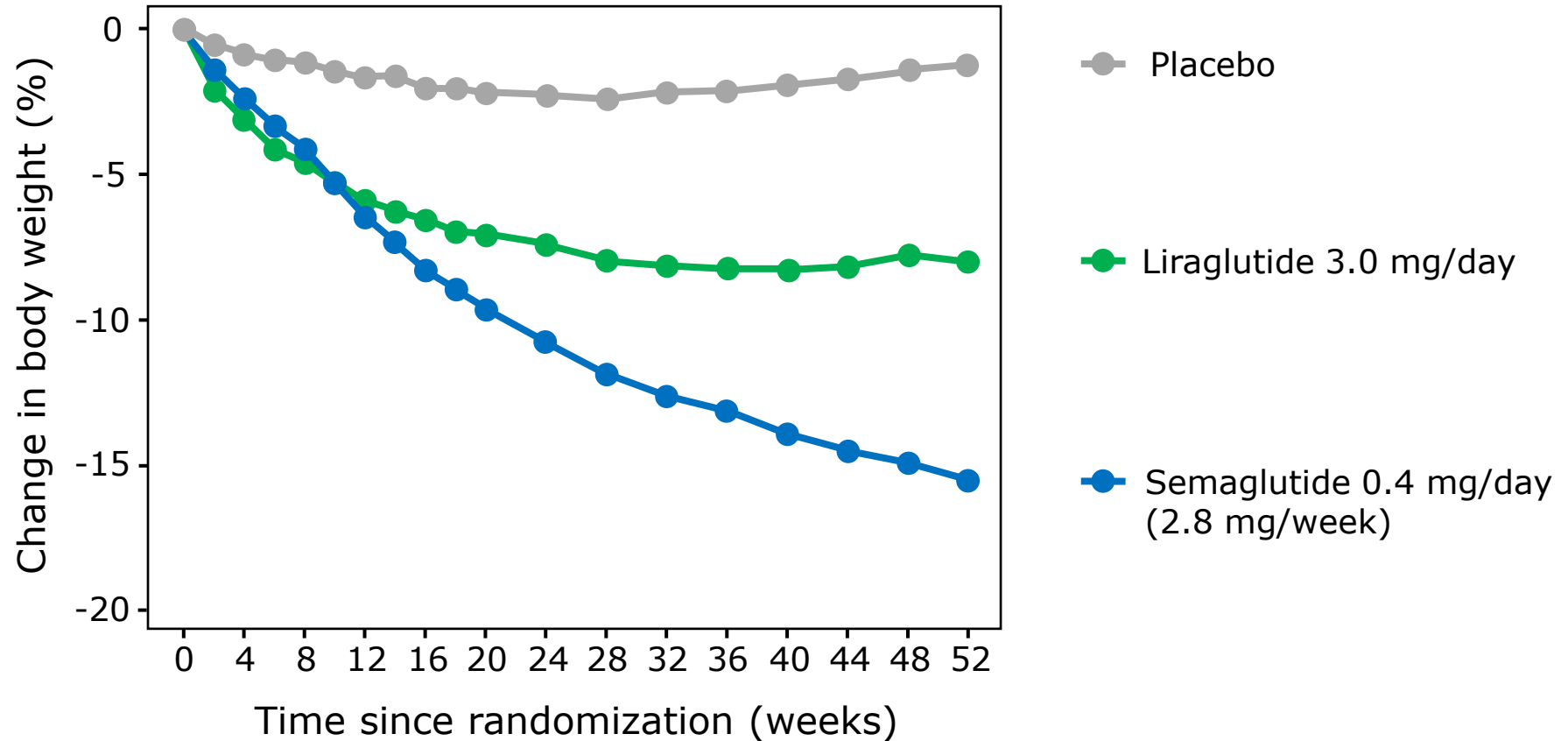
Estimated weight loss required for substantial improvement of obesity complications

Obesity complication	Weight loss for substantial improvement (%)	Benefits increase with increasing weight loss
Type 2 diabetes	5-15	✓
Hypertension	15	✓
Dyslipidemia	10-15	✓
Fatty liver disease (NAFLD)	10	✓
Sleep apnea	10	✓
Osteoarthritis	5-15	✓
Stress incontinence	5-10	✓
Gastroesophageal reflux	10-15	✓
Polycystic ovary syndrome	10-15	✓

We have entered the 3rd generation of anti-obesity medications

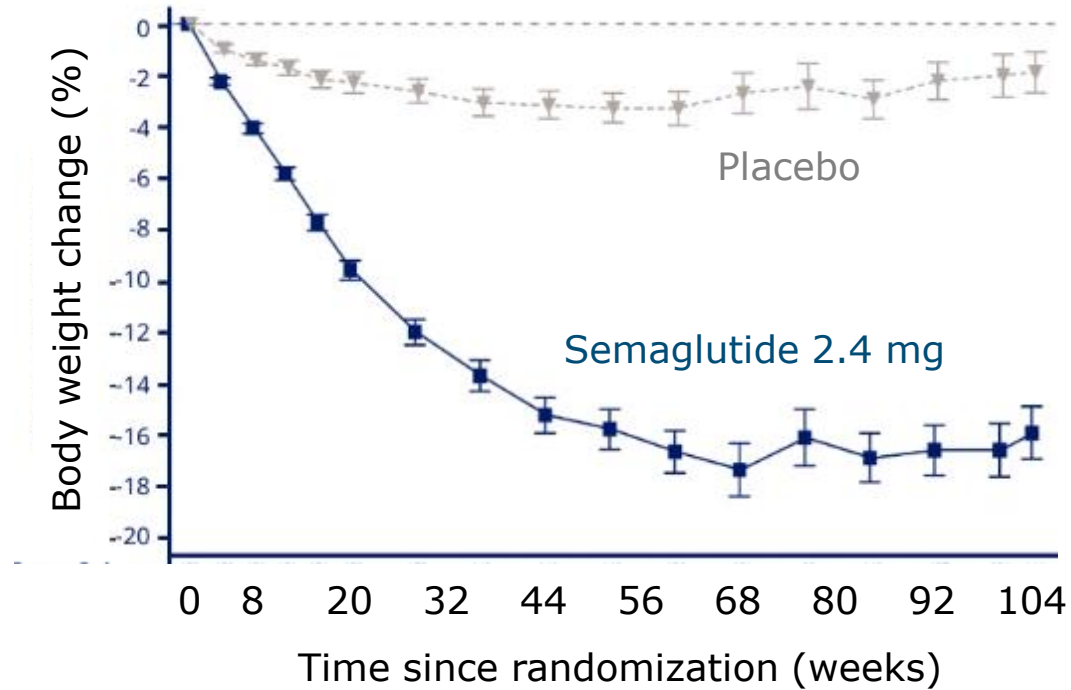


With a similar mechanism (GLP-1 receptor agonism), semaglutide is twice as effective as liraglutide



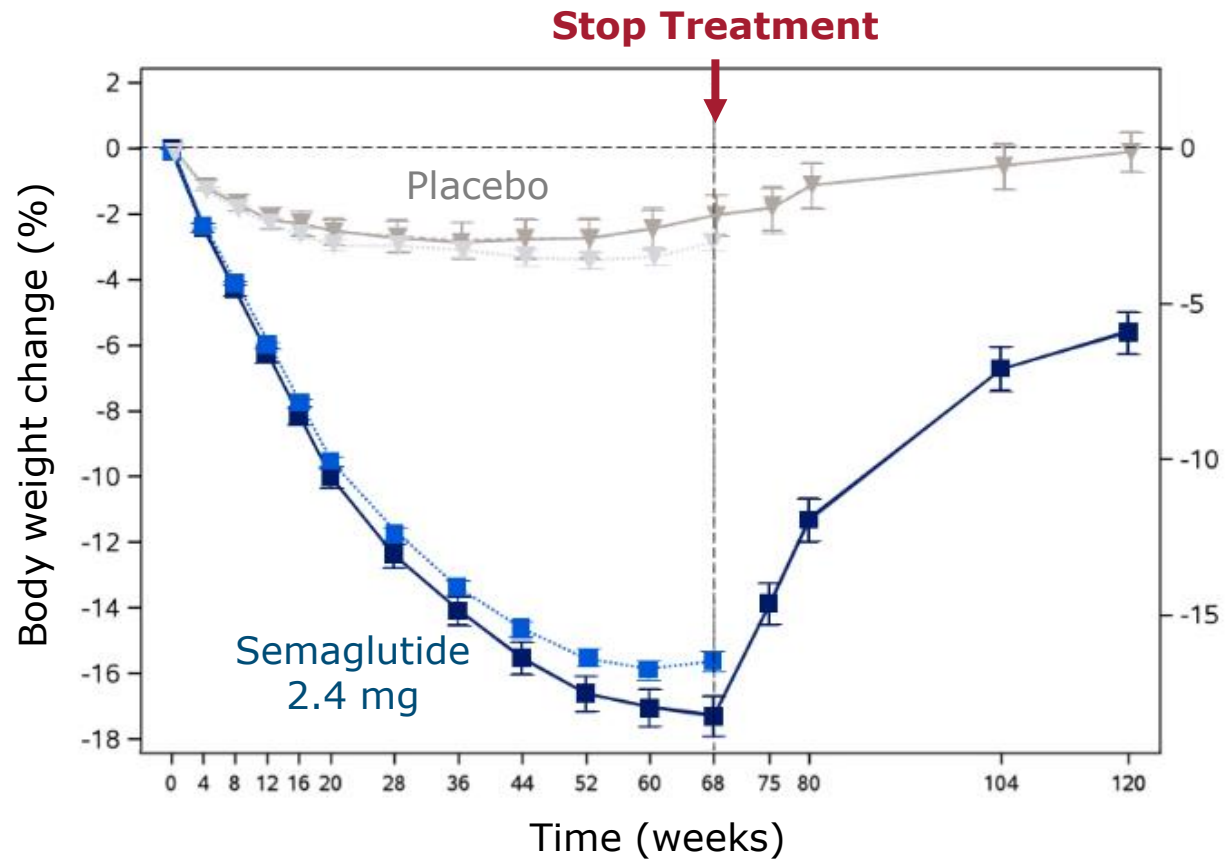
Maintenance of semaglutide-induced weight loss at two years

STEP 5 Trial Subjects without Diabetes



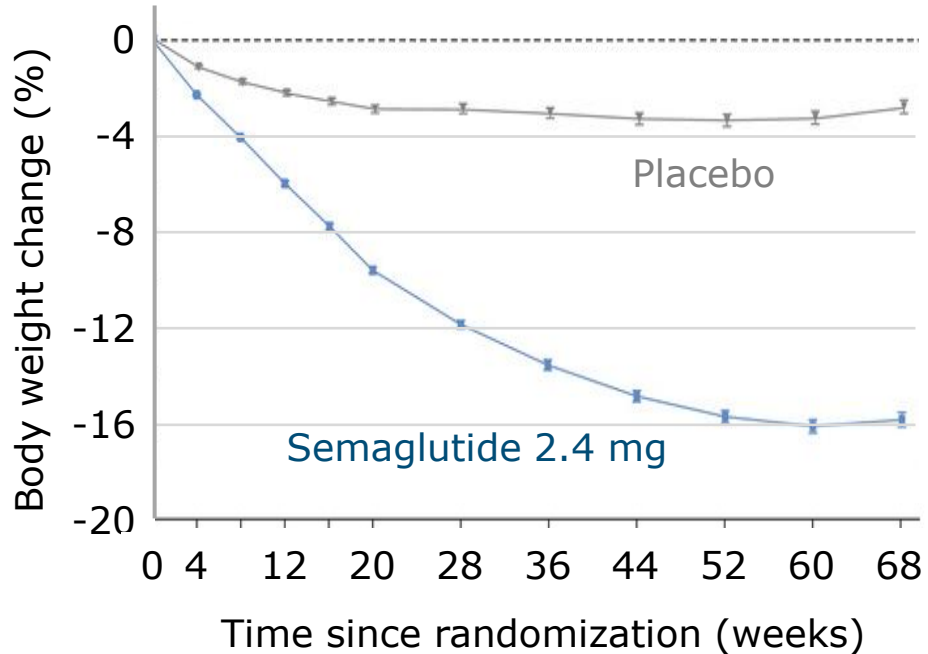
Long-term benefit of AOMs requires continued treatment

STEP 1 Trial Subjects without Diabetes

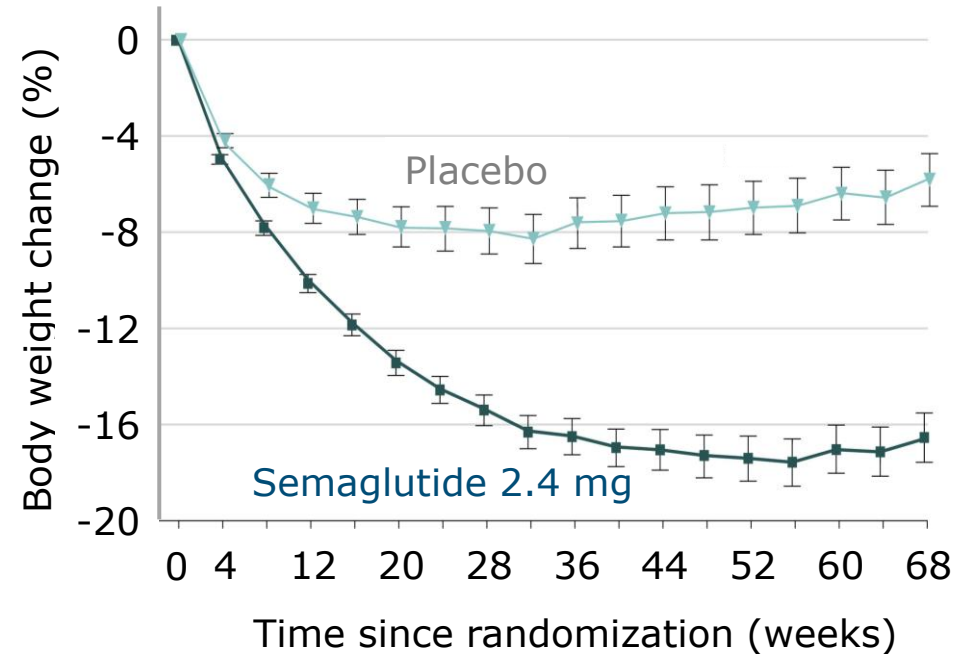


Limited effect of IBT on semaglutide-induced weight loss

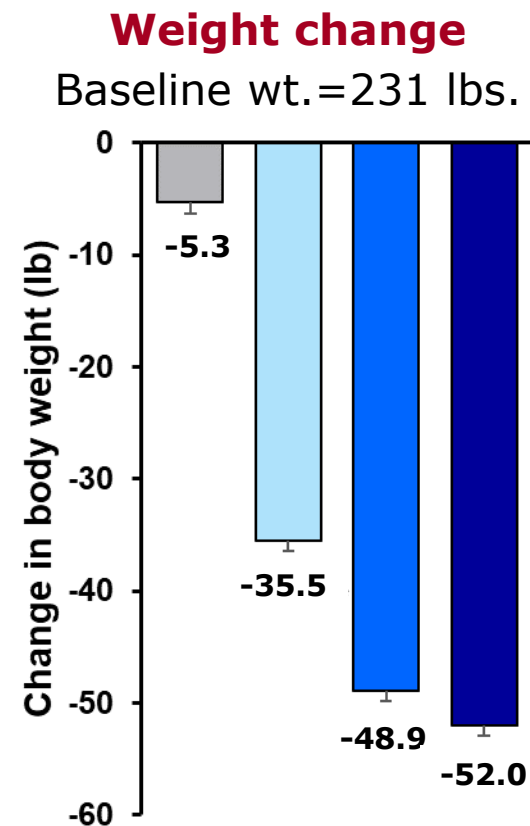
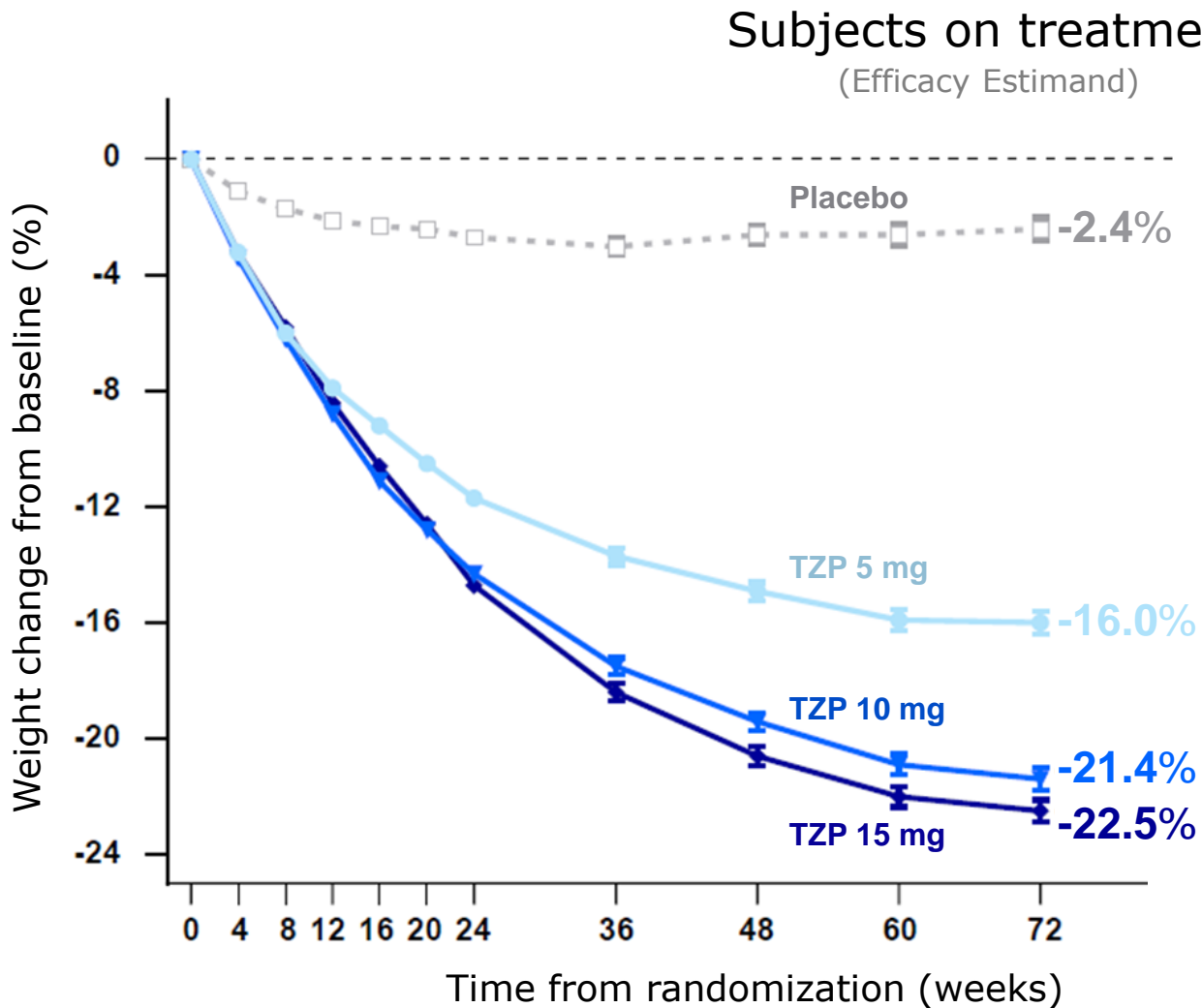
STEP 1 Trial
Subjects without Diabetes



STEP 3 Trial
Subjects without Diabetes
Intensive Behavioral Therapy



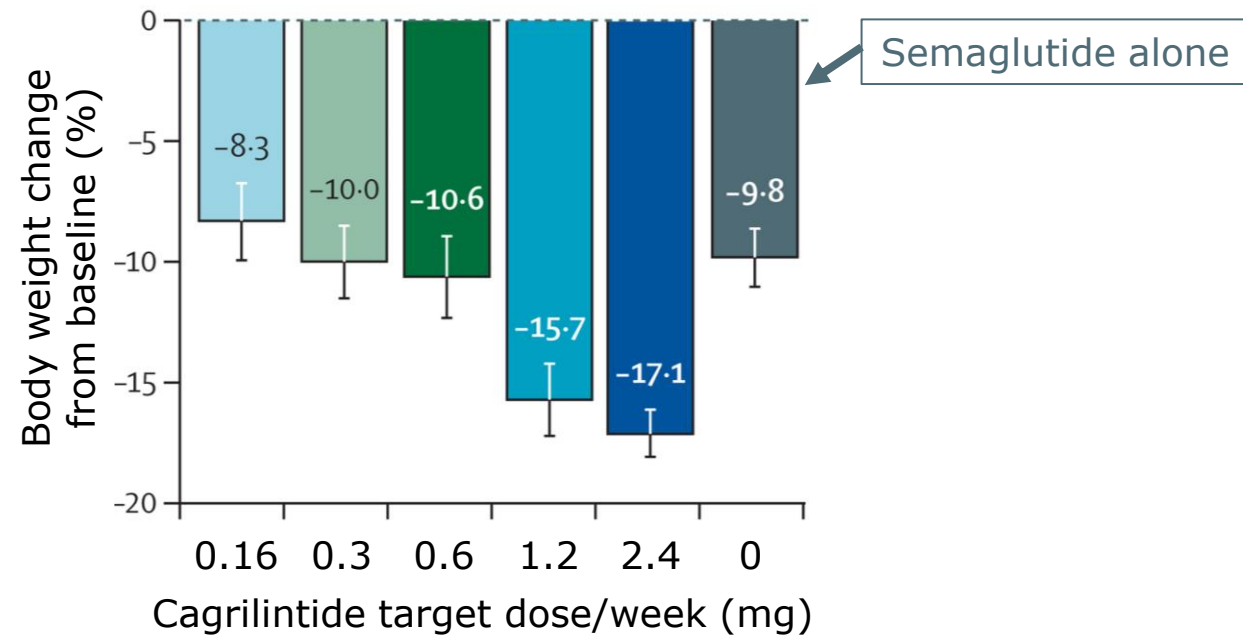
Weight reduction on tirzepatide – subjects without diabetes



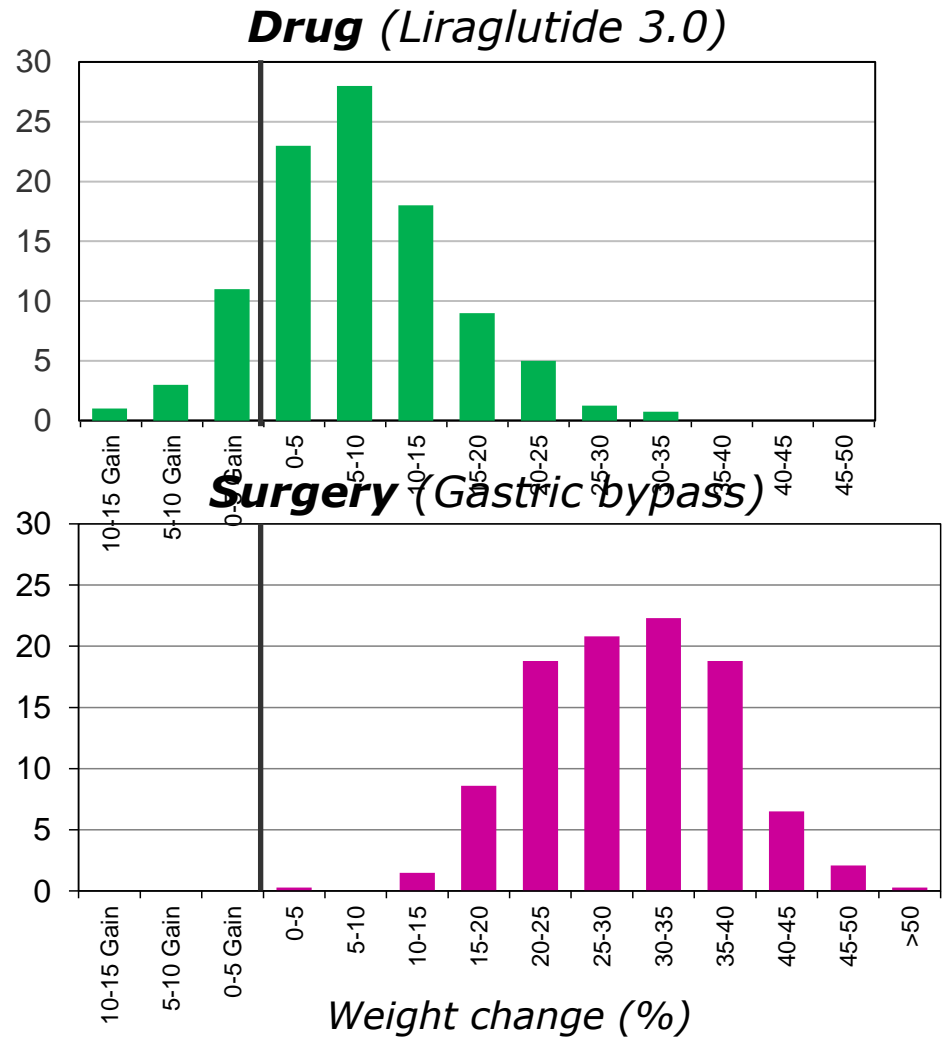
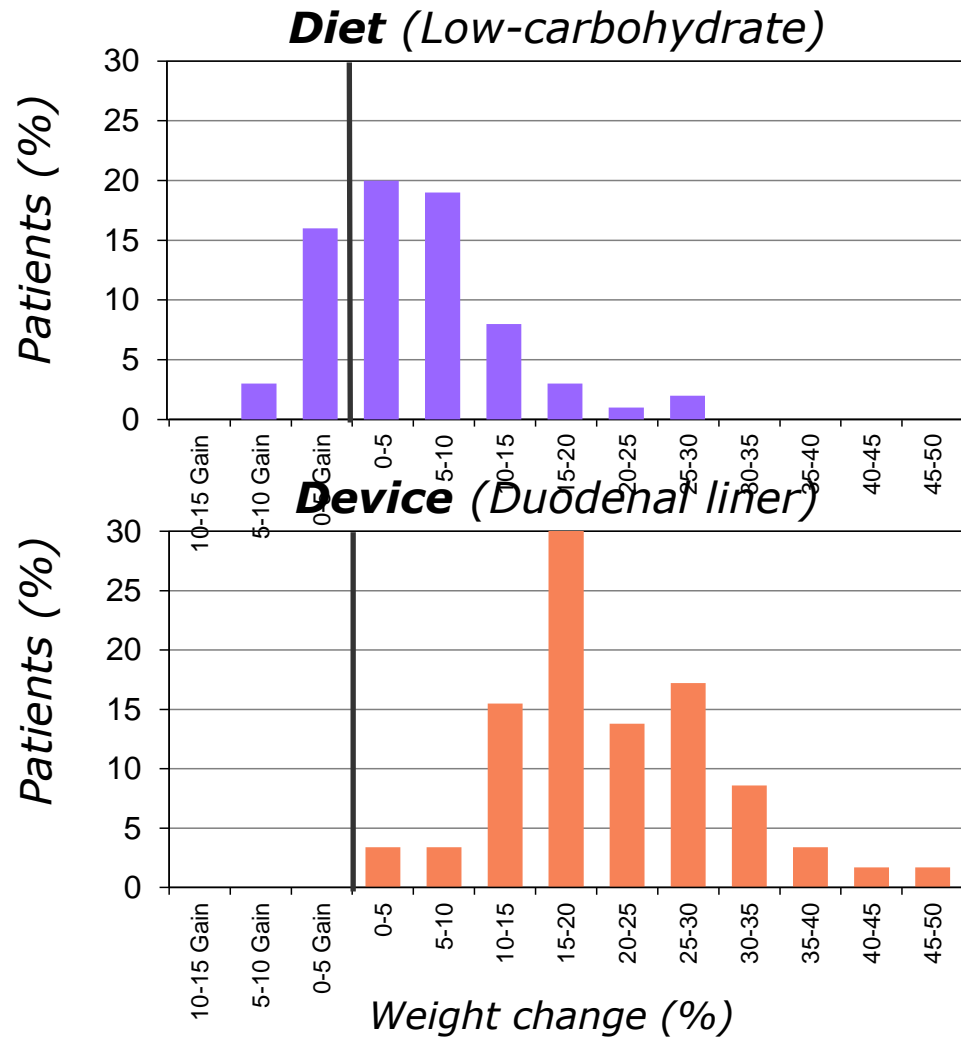
Average weight reduction 35-52 lbs.

Combination therapy with semaglutide and cagrilintide

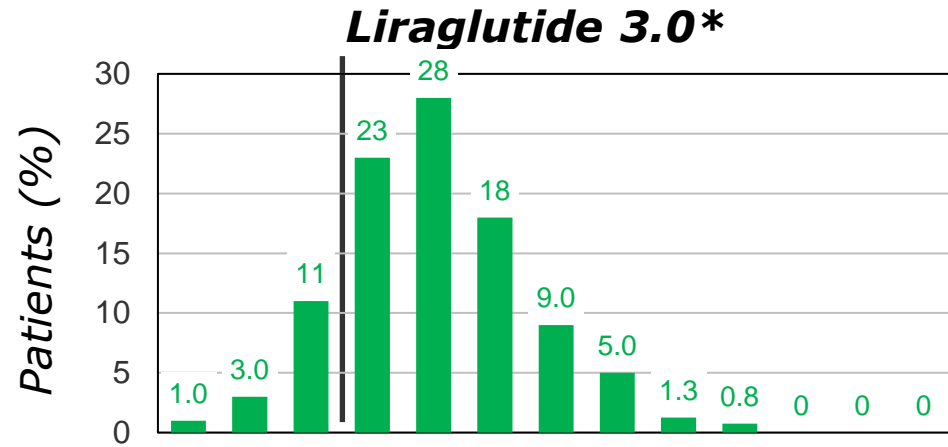
Phase 1B trial – **20 weeks** (4 weeks at target dose)
Semaglutide target dose 2.4 mg/week in all groups
NO lifestyle intervention in any group



Weight loss varies widely among patients

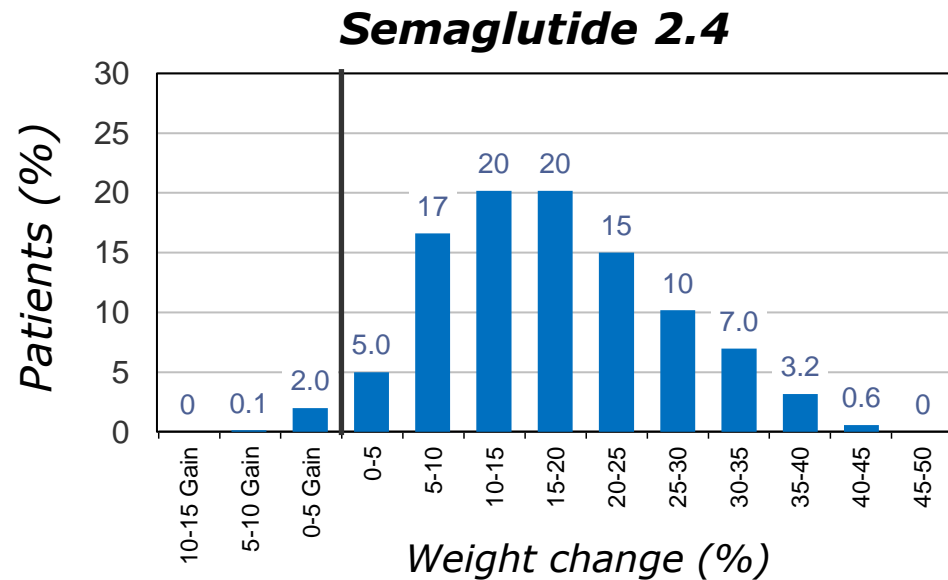


Semaglutide 2.4 shows similar patient-to-patient variability



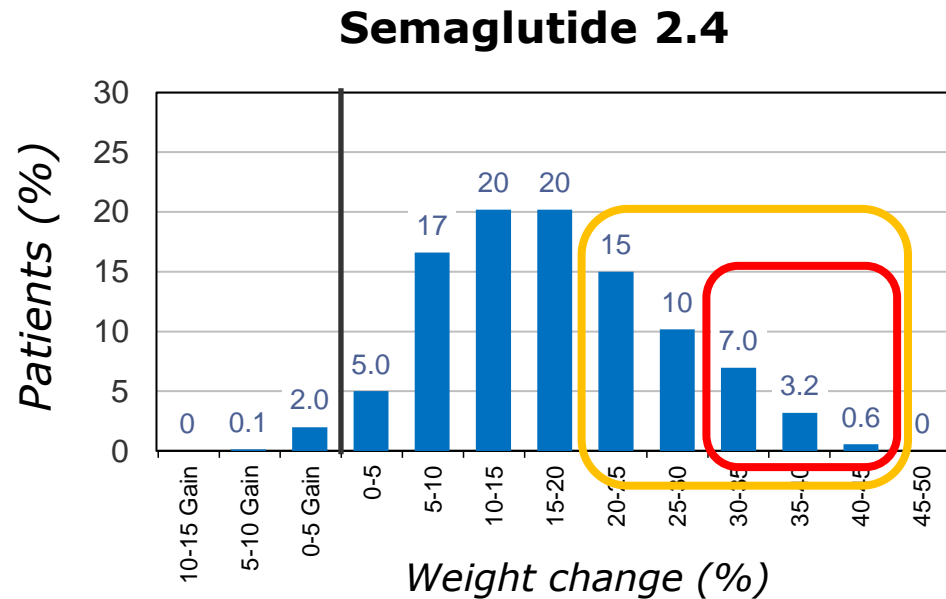
*FDA-approved for the treatment of obesity

Adapted from Pi-Sunyer X *et al.*, *NEJM* 2015
SCALE - Obesity and Prediabetes Trial



Adapted from Wilding JPH *et al.*, *NEJM* 2021
STEP 1 Obesity Trial

Implications of profound weight loss with semaglutide 2.4



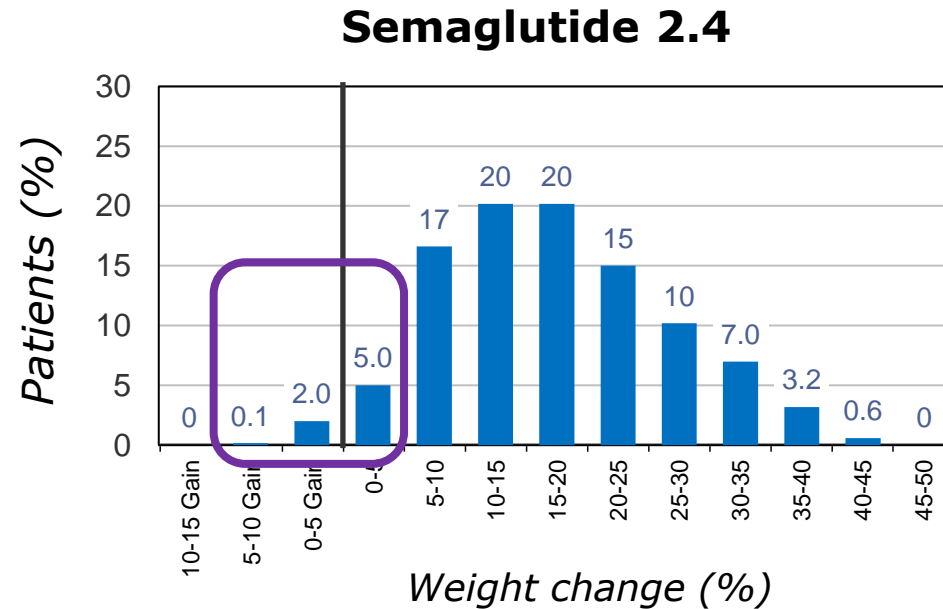
35% of patients lose more than 20% body weight

11% of patients lose more than 30% body weight

Adapted from Wilding JPH *et al.*, *NEJM* 2021
STEP 1 Obesity Trial

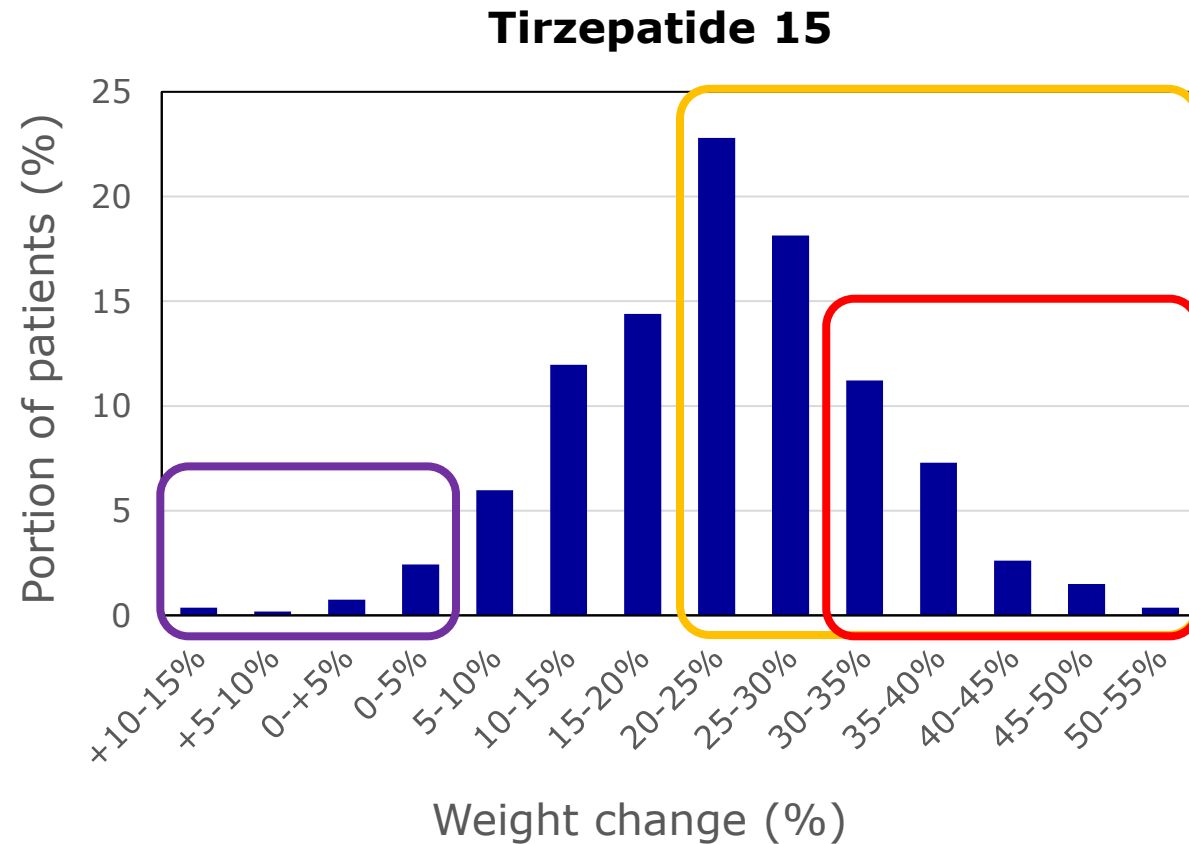
Implications of variable responses to semaglutide 2.4

7-13% of patients lose less than 5% body weight (31% if have T2D)



Adapted from Wilding JPH *et al.*, *NEJM* 2021 STEP 1 Obesity Trial

Variable weight loss response to tirzepatide 15 mg/week

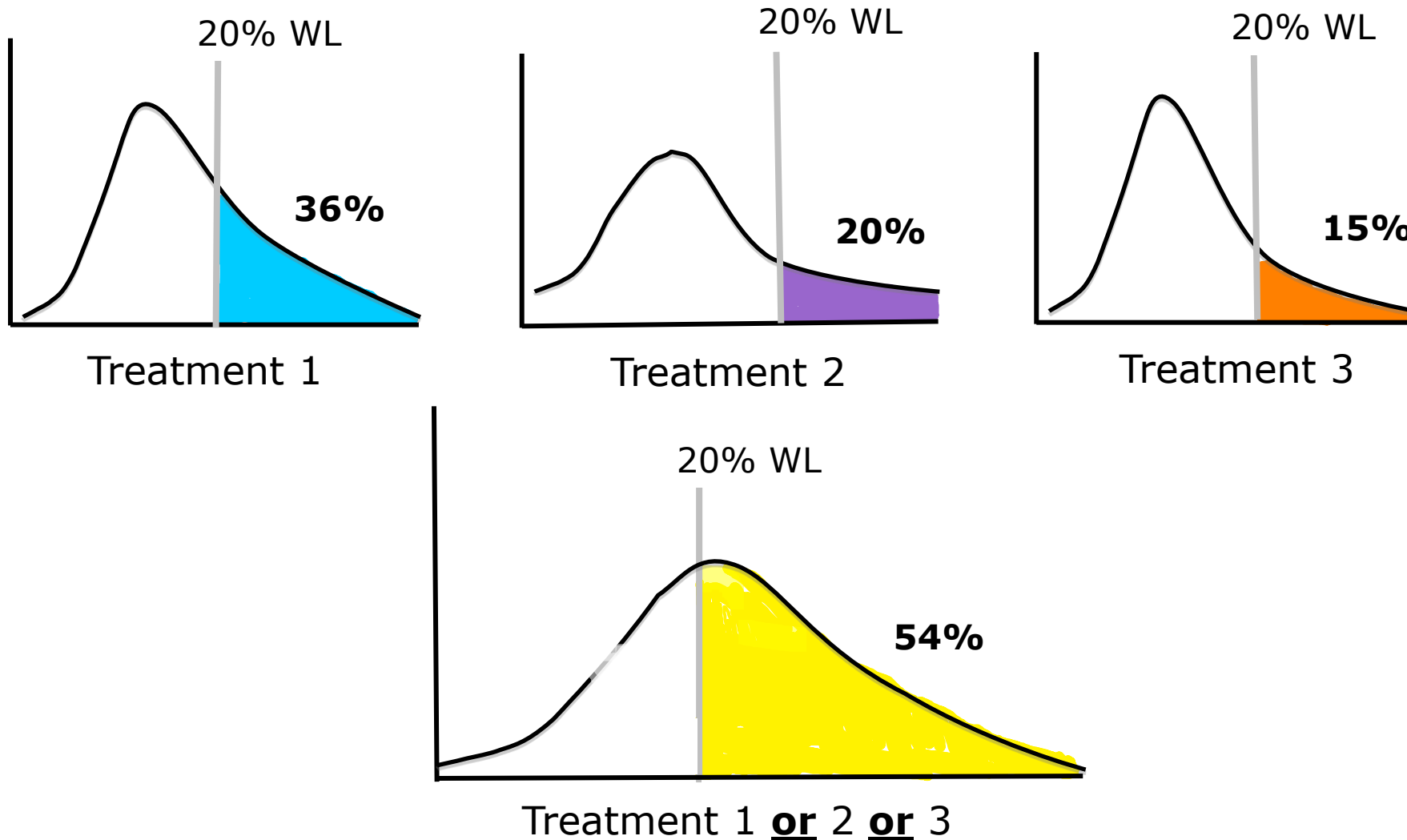


3.7% lost <5% body weight

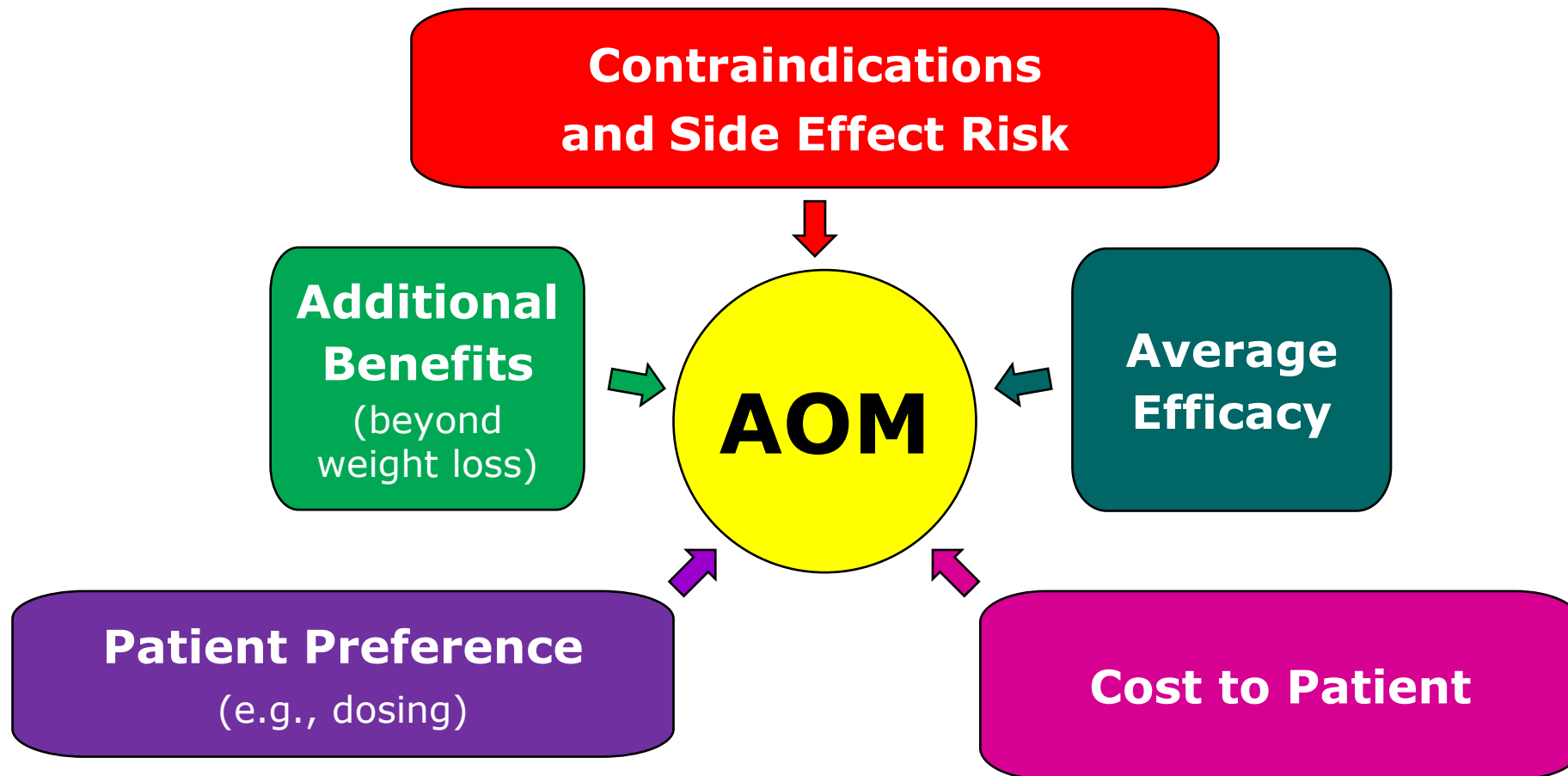
64% lost >20% body weight

23% lost >30% body weight

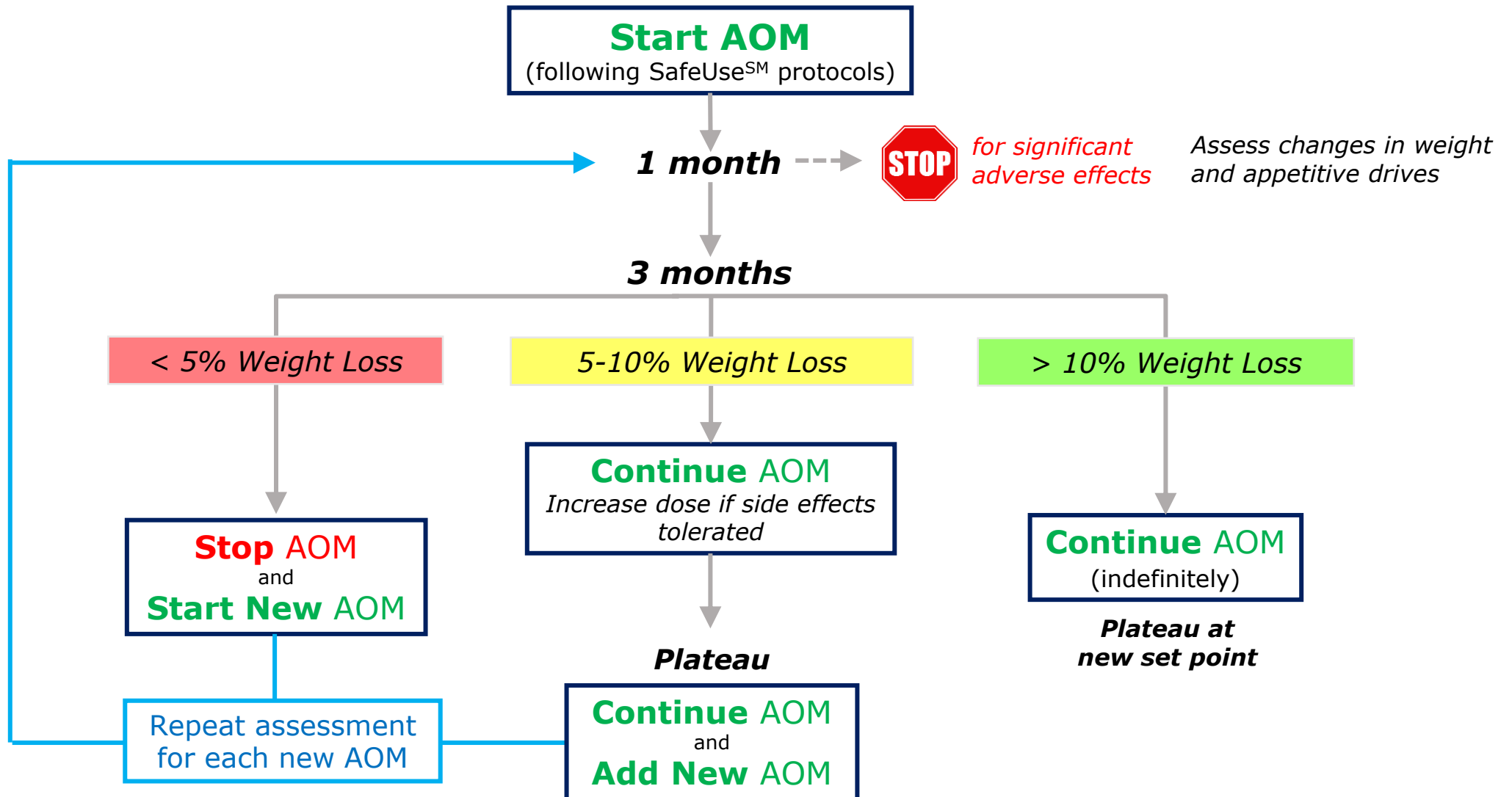
Incorporating heterogeneity of response into treatment plans



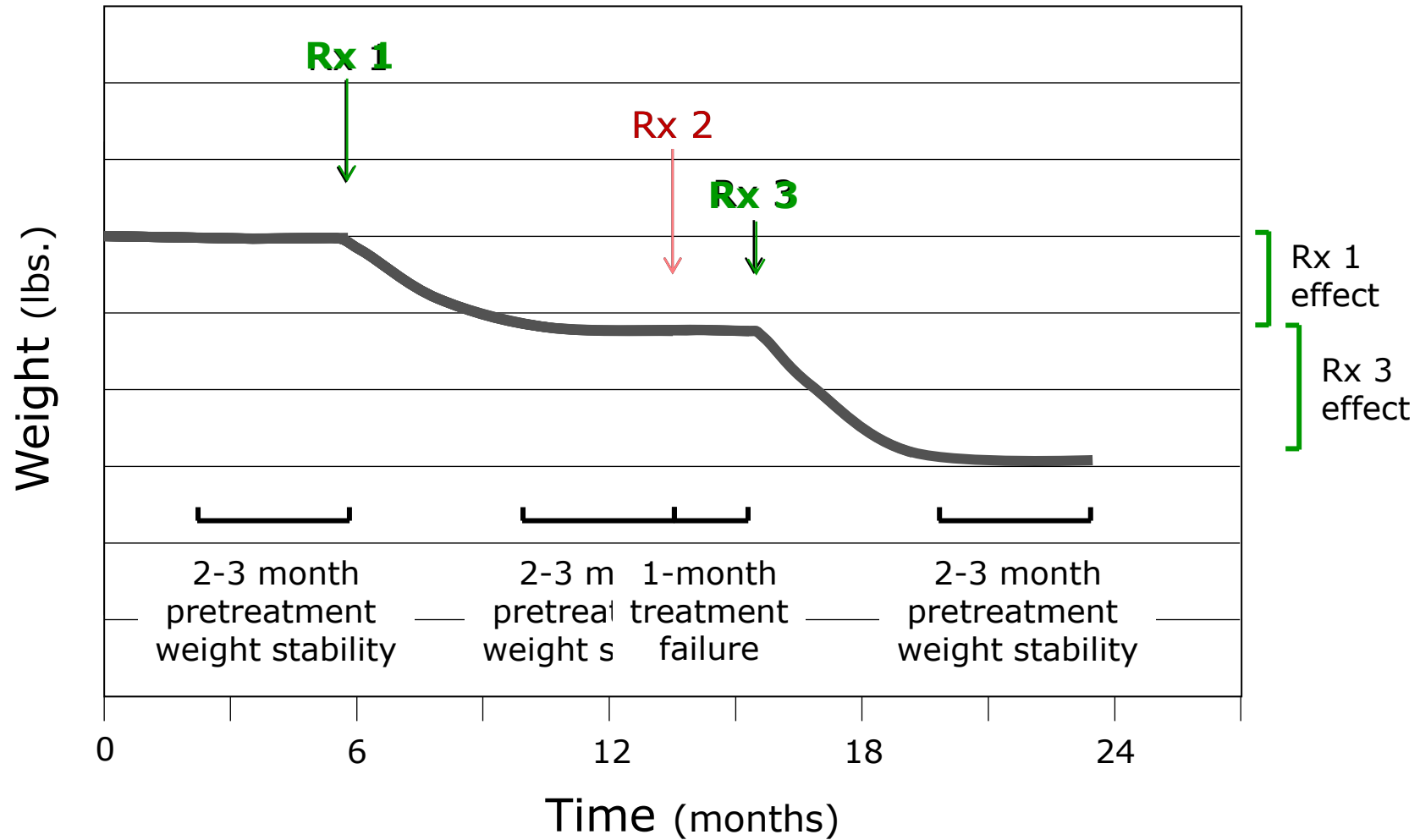
Choosing an anti-obesity medication (AOM)



Pharmacology algorithm



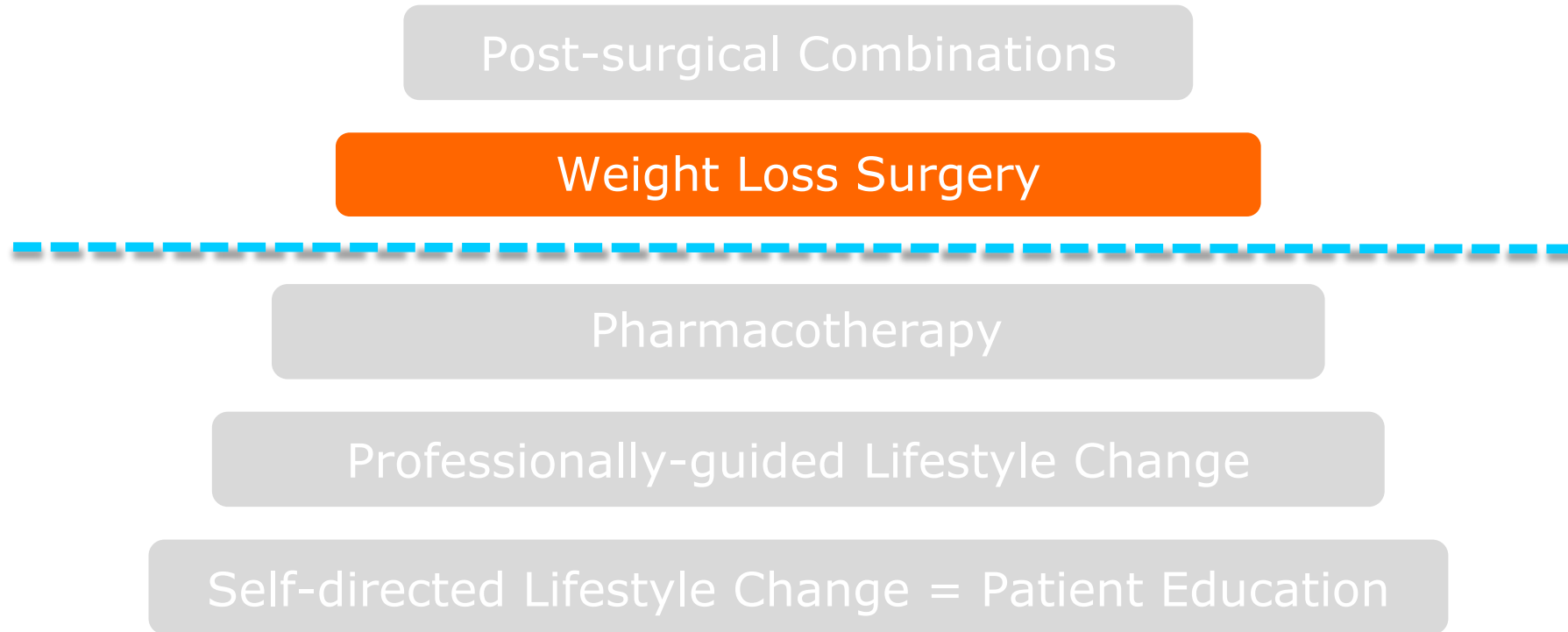
AOM implementation strategy



Obesity treatment strategy

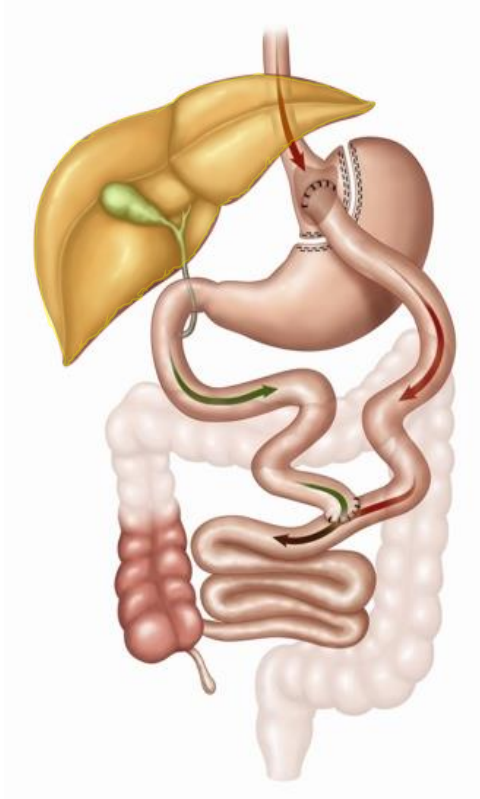
A stepwise approach – aimed at restoring normal physiology

(progress through algorithm as clinically required)

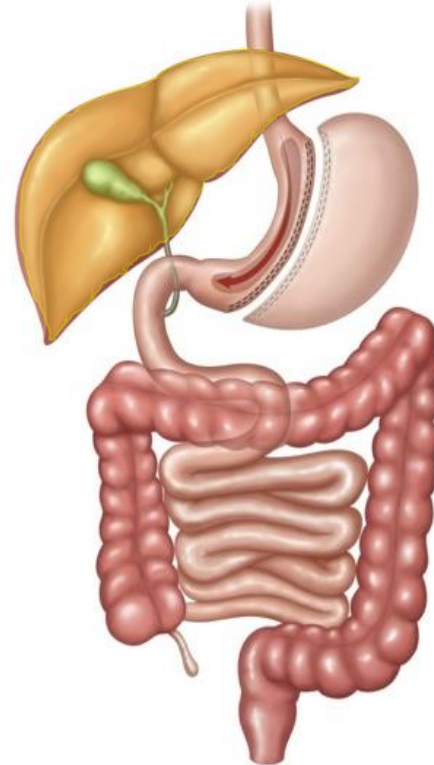


Bariatric/metabolic surgery

Gastric Bypass



Sleeve Gastrectomy

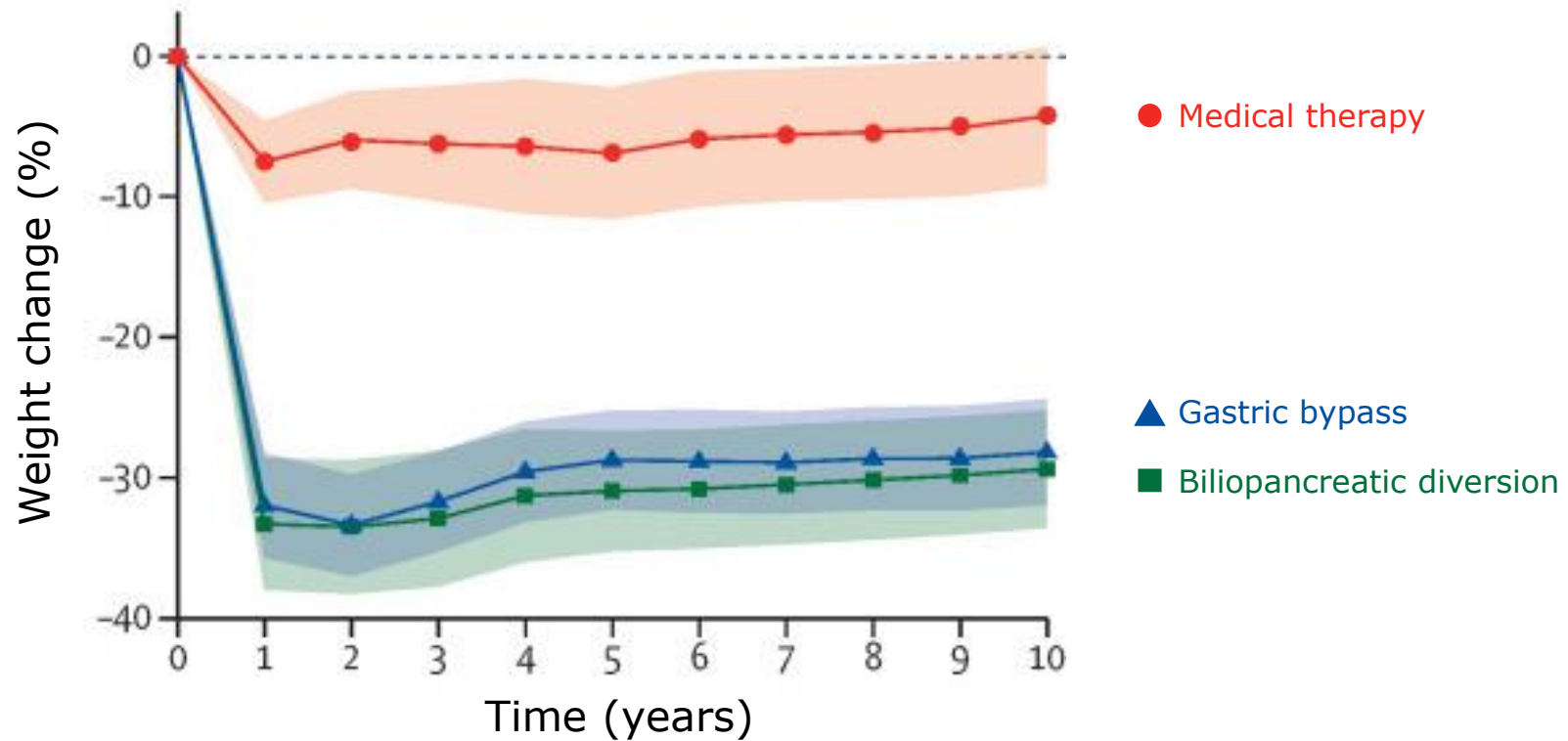


- Currently recommended for patients with BMI ≥ 40 and those with a BMI ≥ 35 with a major obesity complication
- Substantially improves type 2 diabetes, with equal effects in patients with BMI \geq or < 35

Long-term weight loss after bariatric surgery

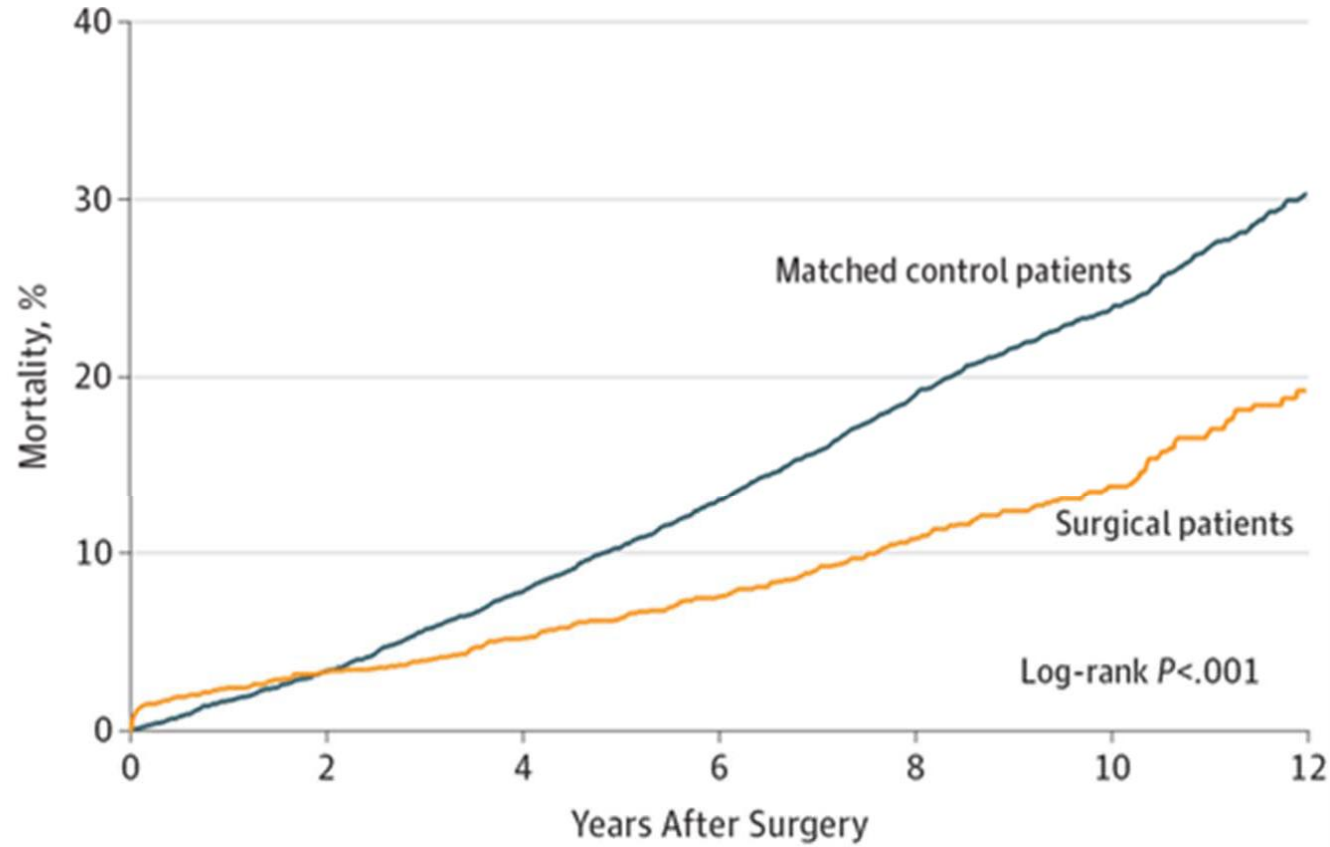
Randomized, controlled trial – medical vs. surgical therapy

Subjects with type 2 diabetes



Bariatric surgery reduces mortality

US Veterans Administration Experience



Arterburn D, *JAMA* 2015

Why is bariatric surgery so effective?

Mechanisms of bariatric surgery

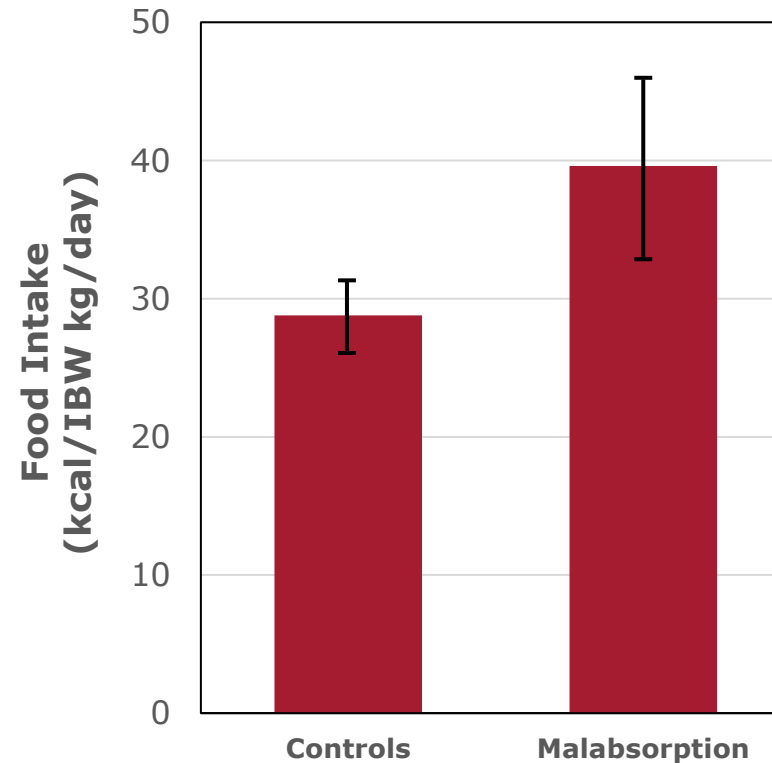
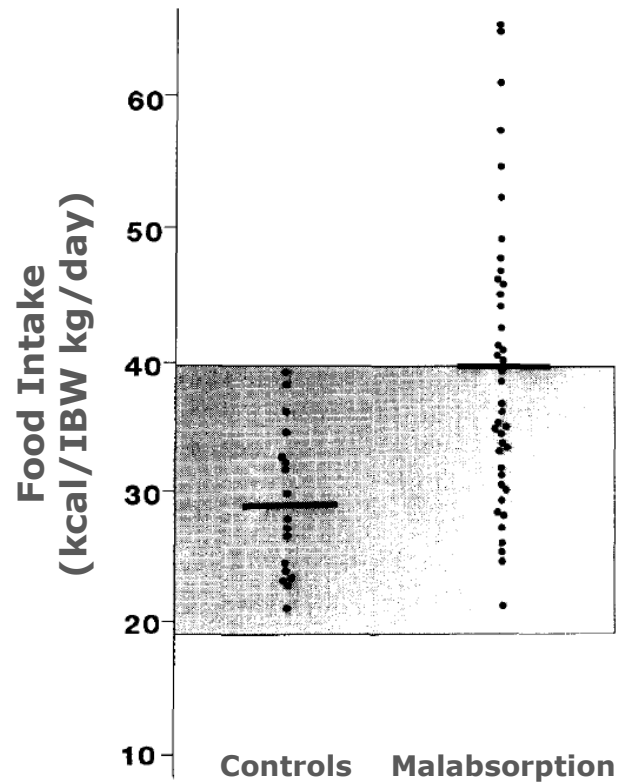
Intended effect:
Mechanical

Restricted food intake

Malabsorption of ingested
nutrients

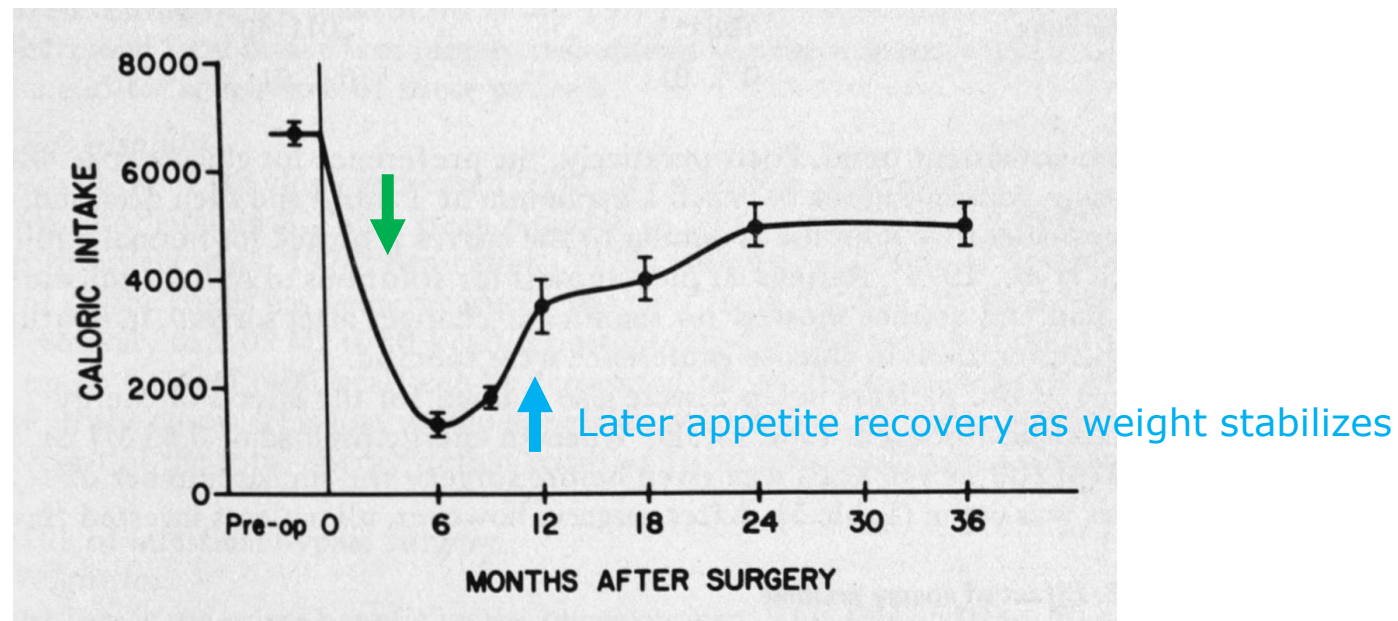
Malabsorption is associated with hyperphagia

Extensive small bowel resection



Food intake after **intestinal bypass**

Intestinal bypass is a truly malabsorptive procedure ...
but different from short bowel syndrome,
spontaneous food intake **decreases** after this operation



Bray et al., *Intl J Obes* **1976**

RYGB effects are opposite to those of restrictive dieting

	Calorie restriction	Metabolic surgery
Energy expenditure	↓	↑
Appetite	↑	↓
Hunger	↑	↓
Satiety	↓	↑
Reward-based eating	↑	↓
Stress response	↑	↓
Gut peptides		
Ghrelin	↑	↓
GLP-1, PYY, CCK, amylin	↓	↑

Mechanisms of bariatric surgery

Intended effect: Mechanical

Restricted food intake

Malabsorption of ingested nutrients

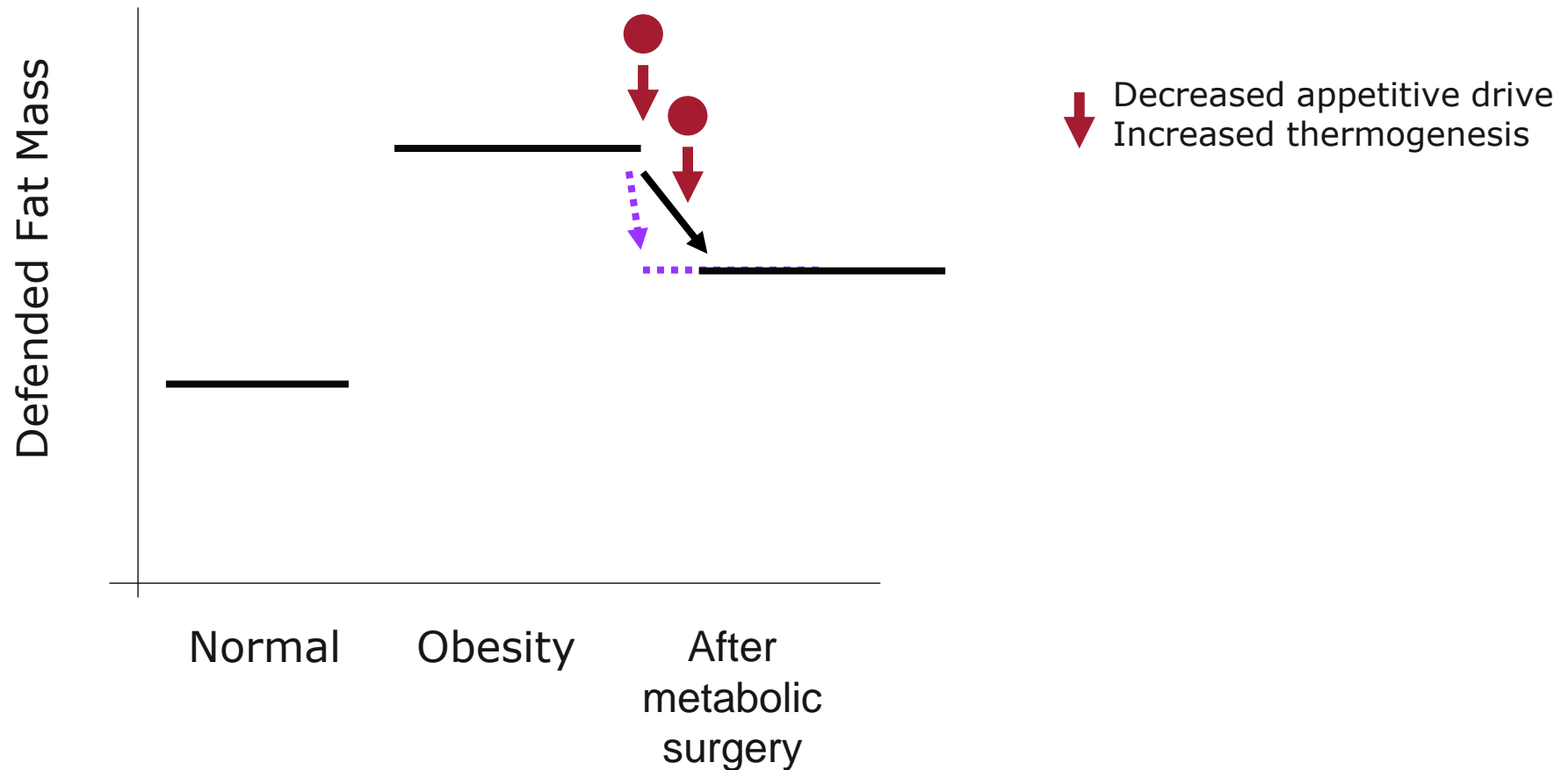
Current understanding: Physiological

Altered GI signals to brain

- Endocrine
- Neuronal
- Immune cell-mediated

Altered GI signals to other tissues
(pancreas, liver)

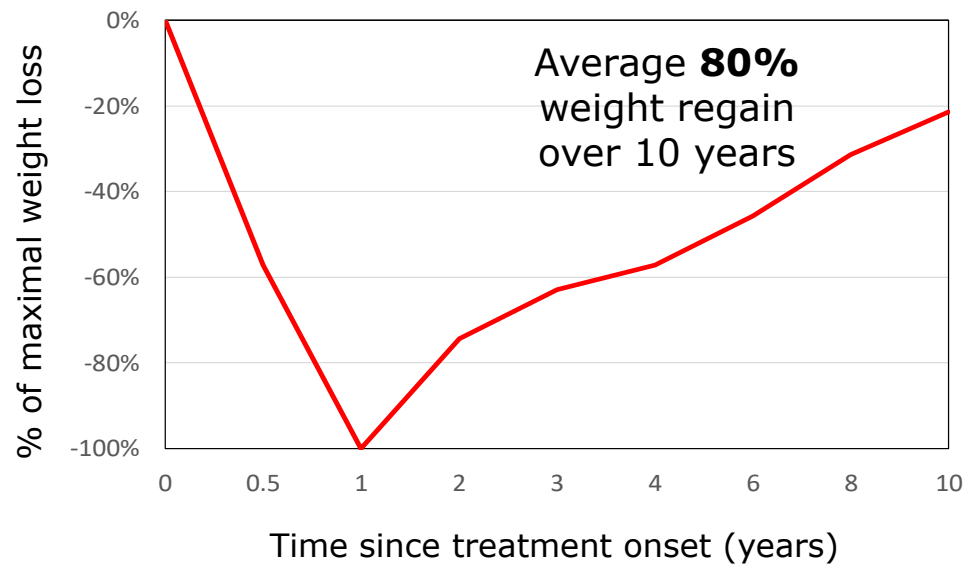
Bariatric/metabolic surgery alters the defended fat mass



Weight regain with different anti-obesity therapies

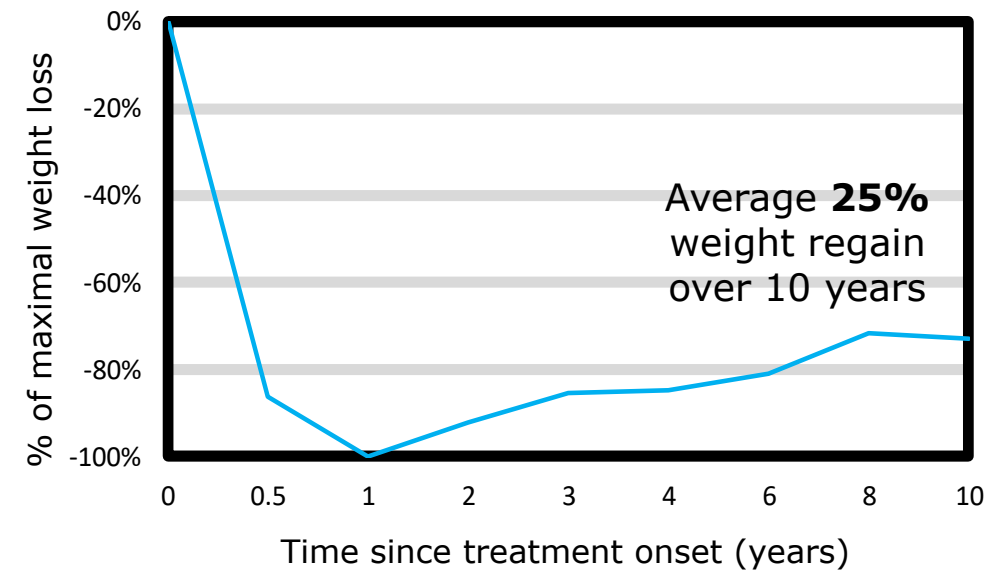
Calorie reduction-based lifestyle therapy

Average maximum weight loss **7-8%**



Bariatric surgery

Average maximum weight loss **28-35%**



Choosing an obesity treatment strategy for your patient

- **Assess his/her clinical need** – not merely their size, shape and BMI
 - **Severity** of obesity – we need a **more clinically predictive** means of assessing severity
 - Already-established **complications**
 - **Risk** of additional complications
- **Understand the long-term benefits and risks of each therapy**
 - Consider the **magnitude** of benefits and risks
 - Focus exclusively on **well-designed, well-executed, long-term** studies
 - Recognize that **interventions can differentially affect individual patients**

Choosing an obesity treatment strategy

- **Favor therapies that target the underlying pathophysiology of obesity**
 - That lower the body's desired – and defended – fat mass
 - **Not** ones that cause **short-term weight loss without altering physiology**
 - **Lifestyle changes** that alter fat mass regulation (not merely calorie reduction)
 - **Drugs** that alter physiological regulation (nearly all do this)
 - **Metabolic (physiologically altering) surgery** when clinically necessary
- **Use trial-and-error to find the therapies appropriate for each patient**
- **Combine therapies** to maximize benefit and limit risk
- **Anticipate life-long treatment** (as for any other chronic disease)

If we want to treat obesity more effectively ...

- We have to **fully understand** why it is a disease and how that disease differs from the cultural desire for thinness
- We have to understand what being a disease means for the effective care of obesity (this is the one thing that we can learn from other diseases)
- We have to **fully understand** the barriers to effective obesity care and the forces working against such care
- And most of all, we have to keep **the needs and goals of all people living with obesity** foremost in our minds, even if many have been previously misled by the bias, stigma, blame and discrimination that surrounds them

Changing our thinking about obesity

When considering the challenges of obesity ...

... ask yourself:

if it were diabetes, cancer, HIV or Alzheimer's, how would you

... discuss it

... approach it

... assess it

... treat it

... and then do it for obesity – using the full spectrum of tools at our disposal



Never doubt that a small group of thoughtful, committed citizens can change the world; indeed, it's the only thing that ever has.

Margaret Mead, 1901-1978
Cultural Anthropologist

It's now **time to join** that "small group" committed to reversing the epidemic of obesity and its many adverse medical, social and economic effects



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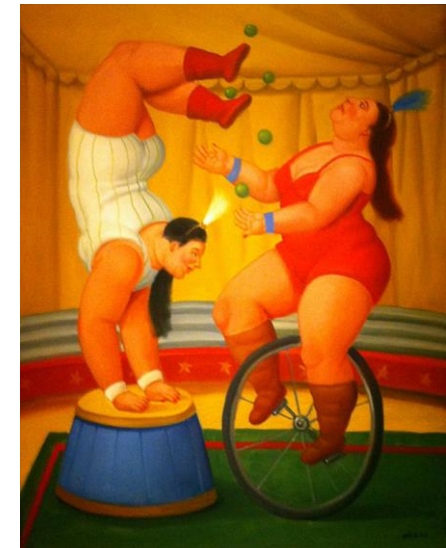
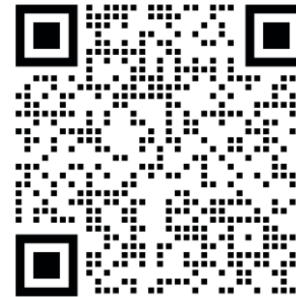
Obesity in 2022: A New Era

Lee M. Kaplan, MD, PhD

The Obesity and Metabolism Institute
Boston, Massachusetts

LMKaplan0@gmail.com

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Fernando Botero, 1932-

Internal Medicine Comprehensive Review and Updates 2022