Turning the Scales: Prioritizing the Evidence in the Treatment of Patients with Obesity

PRE-READ MATERIALS

Learning Objectives

- Compare the safety and efficacy of established and emerging antiobesity medications
- Engage patients in shared decision making when selecting weight reduction strategies

FDA-Approved Anti-Obesity Pharmacotherapy Agents

Drug	Main mechanism of action
Phentermine	Noradrenalin releaser
Phentermine with topiramate	Noradrenalin releaser and anticonvulsant
Diethylpropion	Secondary to CNS effects, including stimulation of hypothalamus to release norepinephrine
Phendimetrazine	Stimulates release of norepinephrine
Benzphetamine	Stimulates release of norepinephrine
Bupropion with naltrexone	Noradrenaline/dopamine reuptake inhibitor and opioid receptor antagonist
Orlistat	Gastric and pancreatic lipase inhibitor
Liraglutide	GLP-1 receptor agonist
Semaglutide	GLP-1 receptor agonist
Tirzepatide	GLP-1/GIP receptor agonist

GLP-1 = glucagon-like peptide 1.

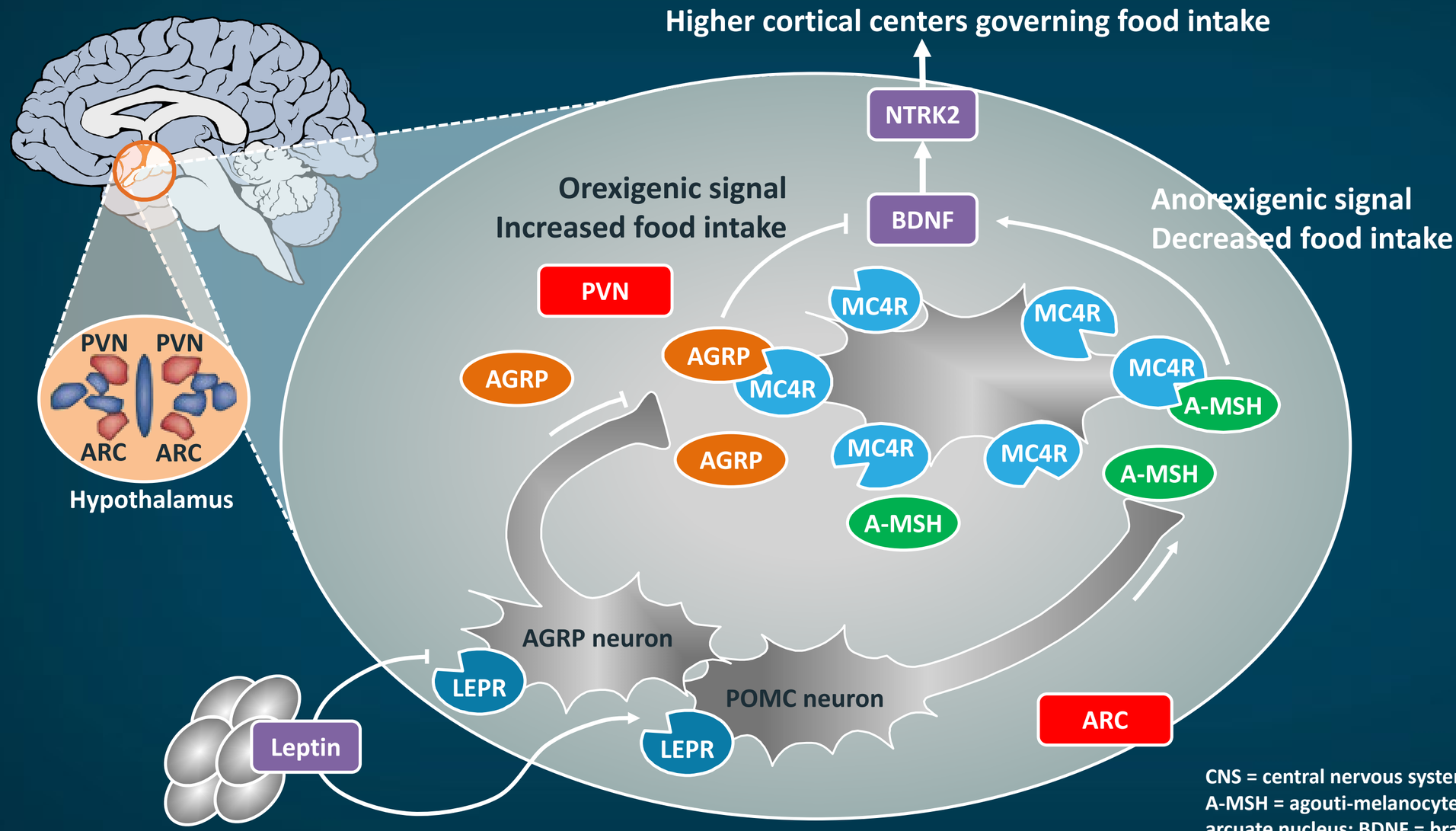
Adan RAH. *Trends Neurosci*. 2013;36:133-140. FDA. Semaglutide for obesity (www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014). Accessed 6/19/2023.

Peripheral Messengers Regulating Food Intake

Substance	Production site	Effect (relevant for feeding)
Ghrelin **Growth hormone**	Stomach Neurons in hypothalamus	Appetite (orexigenic)
Anandamide **Endocannabinoid** **Ananda: Bliss, delight + amide**	Small intestine	Appetite (orexigenic)
Insulin **Insula** **Island or islet**	Pancreas (β-cells in islets of Langerhans)	Satiety (anorexigenic) Glycogen and lipid storage
Leptin **Leptos, thin**	Adipocytes—long term Stomach—short term	Satiety (anorexigenic)
Cholecystokinin (CCK) **“move the bile-sac”**	Small intestine	Early satiety (anorexigenic) Release of digestive enzymes
Glucagon-like peptide 1 (GLP-1)	Ileum Colon	Satiety (anorexigenic) Slowed gastric emptying
Peptide tyrosine tyrosine (PYY)	Ileum Colon	Satiety (anorexigenic)

Authesserre N, et al. *Cell Biology Promotion*. Updated 9/1/2015 (www.cellbiol.net/ste/alpobesity2.php). Accessed 6/19/2023.

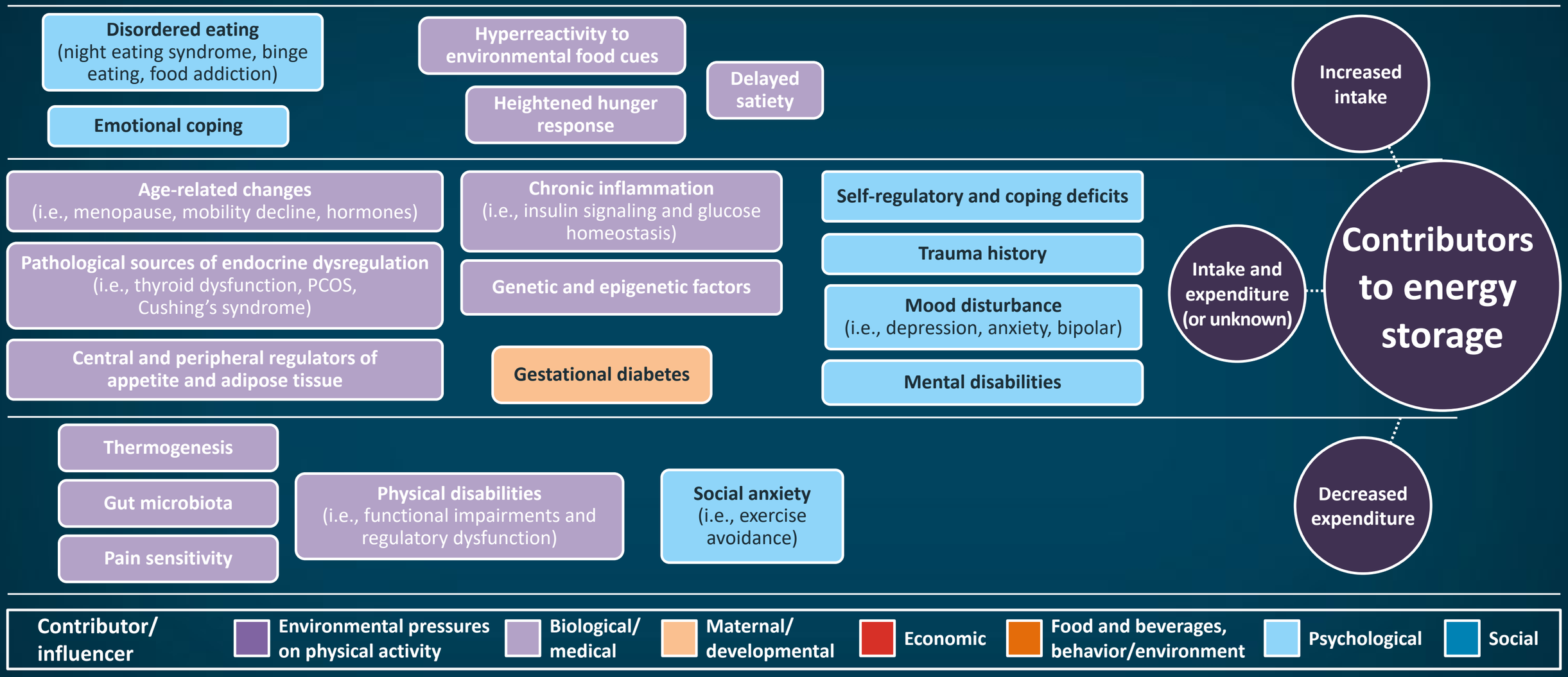
Central Nervous System in Regulation of Food Intake



CNS = central nervous system; AGRP = agouti-related protein; A-MSH = agouti-melanocyte-stimulating hormone; ARC = arcuate nucleus; BDNF = brain-derived neurotrophic factor; LEPR = leptin receptor; MC4R = melanocortin 4 receptor; NTRK2 = neurotrophic tyrosine kinase receptor type 2; POMC = proopionomelanocortin; PVN = paraventricular nucleus.

Walley AJ, et al. *Nat Rev Genet*. 2009;10:431-442.

Potential* Contributors to Obesity: Inside the Person

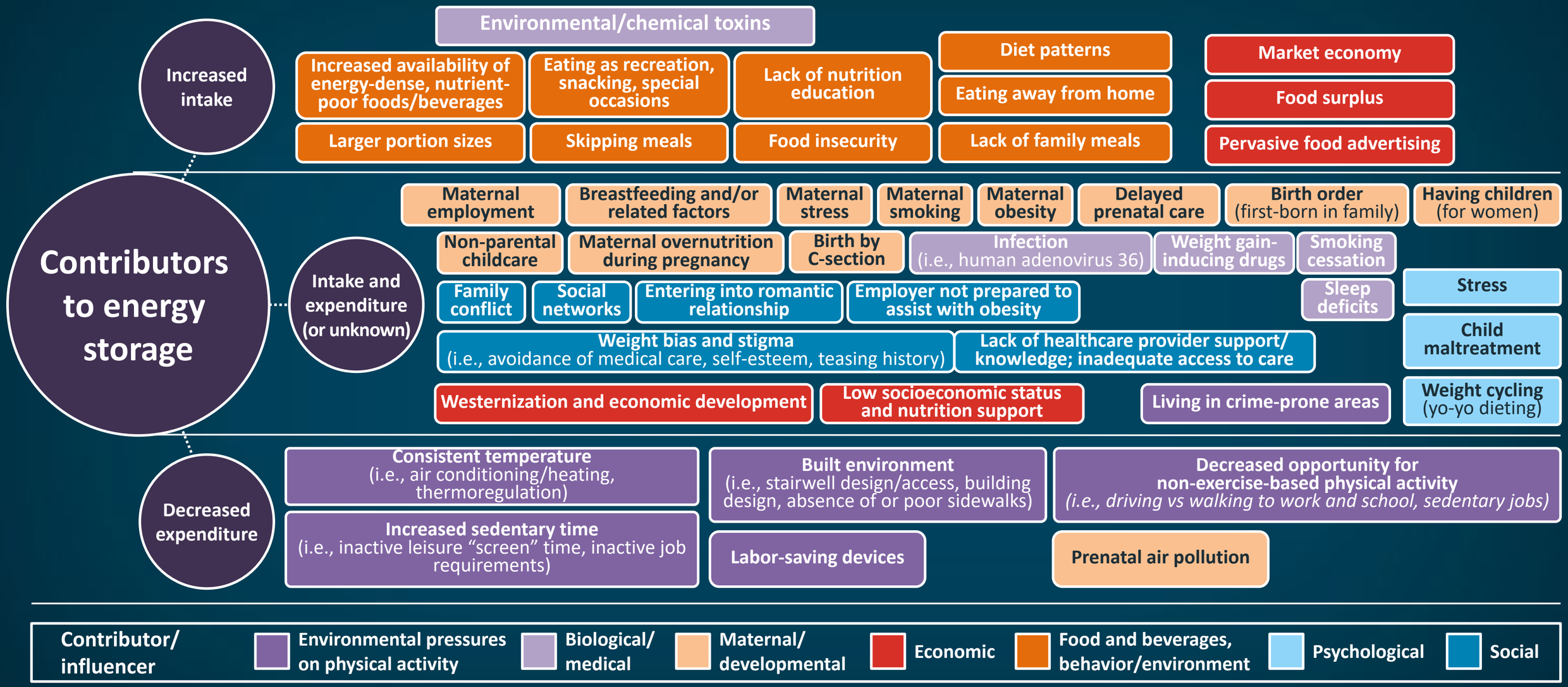


*Potential contributors = anything put forth in research literature as question of investigation and is not intended to be verification of whether or not, or extent to which, each may or may not contribute.

PCOS = polycystic ovary syndrome.

Obesity Society. Potential contributors to obesity, 2015 (www.obesity.org/wp-content/uploads/2020/05/TOS-Reasons-for-obesity-infographic-2015.pdf). Accessed 6/19/2023.

Potential* Contributors to Obesity: Outside the Person



*Potential contributors = anything put forth in research literature as question of investigation and is not intended to be verification of whether or not, or extent to which, each may or may not contribute.

Obesity Society. Potential contributors to obesity, 2015 (www.obesity.org/wp-content/uploads/2020/05/TOS-Reasons-for-obesity-infographic-2015.pdf). Accessed 6/19/2023.

Assess and Treat CV Risk Factors and Obesity-Related Comorbidities

- **History and physical examination**
- **Clinical and laboratory assessments**
  - Blood pressure
  - Fasting blood glucose
  - Fasting lipid panel (expert opinion)
  - Waist circumference measurements for people with BMI 25 to 34.9 kg/m^2 are
    - >88 cm (>35 in) for women
    - >102 cm (>40 in) for men
- **Intensive management of risk factors, including**
  - Cardiovascular
    - Hypertension
    - Dyslipidemia
    - Prediabetes/diabetes
  - Other obesity-related medical conditions
    - Obstructive sleep apnea
    - Other risk factors

Jensen MD, et al. *Circulation*. 2014;129(25 suppl 2):S102-S138.

Assess Weight and Lifestyle Histories

- Ask about weight gain and loss history
- Dietary habits
- Physical activity
- Family history of obesity
- Other medical conditions or medications that may affect weight

Jensen MD, et al. *Circulation*. 2014;129(25 suppl 2):S102-S138.

Common Weight-Promoting Medications

Antipsychotics

- Risperidone
- Lithium
- Quetiapine
- Aripiprazole
- Olanzapine
- Valproic acid

Antidepressants

- Citalopram
- Duloxetine
- Venlafaxine

Neuropathic agents

- Gabapentin
- Pregabalin

Sleep agents

- Zolpidem
- Eszopiclone
- Trazadone
- Zaleplon

β-blockers

Steroids

Insulin

Hypoglycemic agents

Obesity Action Coalition (OAC). Prescription medications & weight gain (www.obesityaction.org/wp-content/uploads/prescription_medications.pdf). Accessed 6/19/2023. Igel LI, et al. *Gastroenterology*. 2017;152:1765-1779.

Treatment Strategy for Weight-Promoting Medications

- Investigate whether medications are a likely source of weight gain in patients
- If weight-promoting drug may be discontinued, discontinue the agent
- If discontinuation of a weight-promoting medication is not feasible, consider using anti-obesity pharmacotherapy for weight loss in conjunction with appropriate lifestyle changes

Igel LI, et al. *Gastroenterology*. 2017;152:1765-1779.

Managing Obesity

FDA-Approved Anti-Obesity Pharmacotherapy Agents

Drug	Main mechanism of action
Phentermine	Noradrenalin releaser
Phentermine with topiramate	Noradrenalin releaser and anticonvulsant
Diethylpropion	Secondary to CNS effects, including stimulation of hypothalamus to release norepinephrine
Phendimetrazine	Stimulates release of norepinephrine
Benzphetamine	Stimulates release of norepinephrine
Bupropion with naltrexone	Noradrenaline/dopamine reuptake inhibitor and opioid receptor antagonist
Orlistat	Gastric and pancreatic lipase inhibitor
Liraglutide	GLP-1 receptor agonist
Semaglutide	GLP-1 receptor agonist
Tirzepatide	GLP-1/GIP receptor agonist

GLP-1 = glucagon-like peptide 1.

Adan RAH. *Trends Neurosci*. 2013;36:133-140. FDA. Semaglutide for obesity (www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014). Accessed 6/19/2023.

FDA-Approved Anti-Obesity Medications: Safety

Medication	Adverse effects	Contraindications
Orlistat	• Diarrhea, oily stools • Fecal incontinence • Fat soluble vitamin deficiency	• Pregnancy • Chronic malabsorption • Cholestasis
Phentermine/topiramate ER	• Headache, dizziness, fatigue • Nausea, dry mouth, constipation • Hypoglycemia, back pain, cough	• Pregnancy • Glaucoma, hyperthyroidism • Uncontrolled hypertension
Naltrexone/bupropion ER	• Headache, dizziness, insomnia • Nausea, dry mouth • Constipation, diarrhea	• Pregnancy • Uncontrolled hypertension, seizure disorder • Opioid use, eating disorder, monoamine oxidase inhibitors (MAOI) use

Patel DK, Stanford FC. *Postgrad Med*. 2018;130(2):173-182.

FDA-Approved Anti-Obesity Medications: Safety

Medication	Adverse effects	Contraindications
Liraglutide	• Nausea/vomiting • Diarrhea, constipation • Headache, dizziness, fatigue • Hypoglycemia, abdominal pain	• Pregnancy • Personal/family history of medullary thyroid cancer • Multiple endocrine neoplasia type 2 (MEN2), caution in history of pancreatitis
Semaglutide		
Tirzepatide	• Nausea/ vomiting • Diarrhea, constipation • Decreased appetite • Abdominal pain	

Patel DK, Stanford FC. *Postgrad Med*. 2018;130(2):173-182; Zepbound [prescribing information]. Eli Lilly. 2023.

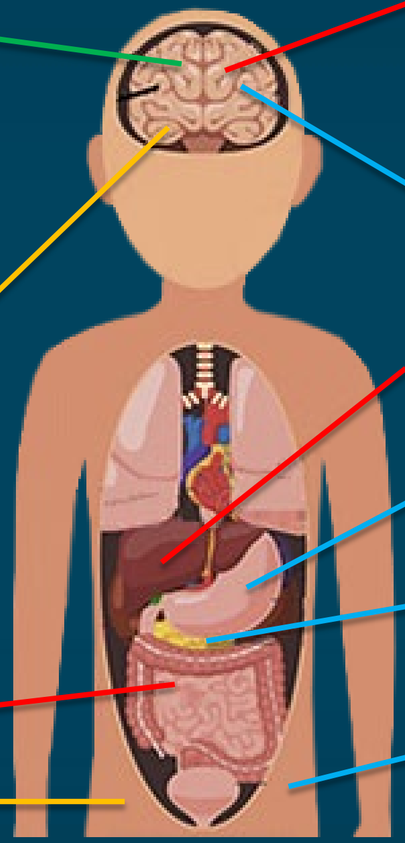
Other Anti-Obesity Pharmacotherapy Agents*

Drug class/name
Topiramate
Zonisamide
Bupropion
Metformin
Amylin agonist (pramlintide)
SGLT2 inhibitors (canagliflozin, dapagliflozin)

*Not FDA-approved for treating obesity.
SGLT2 = sodium-glucose cotransporter-2.

Stanford FC, et al. *Surg Obes Relat Dis*. 2017;13(3):491-500.

Drug-Induced Weight Loss Mechanism



↓ Food intake by inhibiting norepinephrine reuptake in hypothalamus

↓ Food intake by modulating on signaling pathway of NPY neurons, leptin, and GLP-1

↓ Food intake by inhibiting NPT/AgRP neurons and stimulating POMC/CART neurons

↓ Food intake by stimulating GABA secretion, thereby inhibiting AMPA/kainite excitatory glutamate receptors

↓ Hepatic gluconeogenesis

↓ Gastric emptying

↑ Insulin secretion
↓ Glucagon secretion

↓ Intestinal glucose uptake

↑ Resting energy expenditure

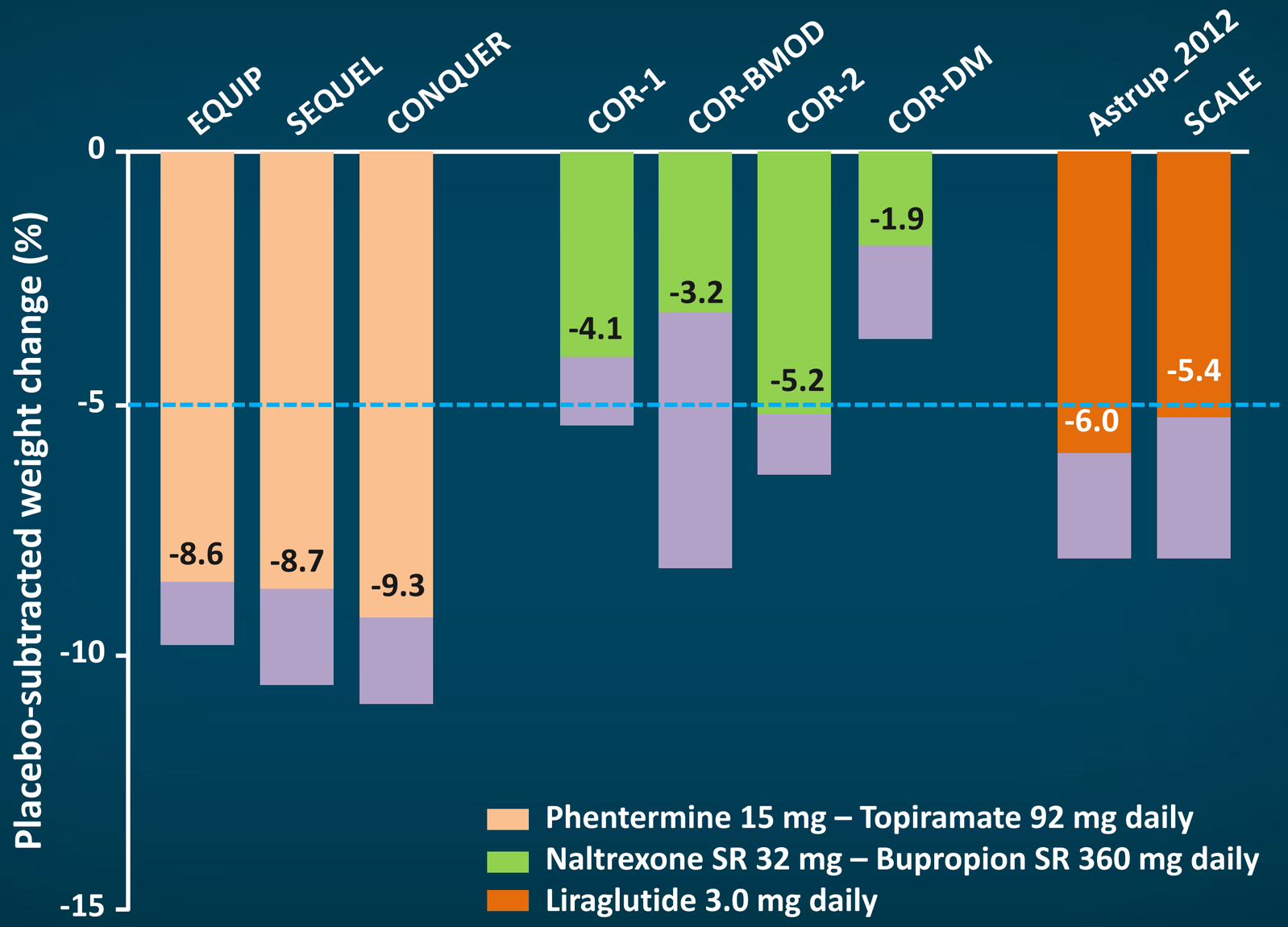
↑ Browning of white adipose tissue
↑ Thermogenesis of brown adipose tissue
↑ Resting energy expenditure

GLP-1 RA
Phentermine
Topiramate
Metformin

GLP-1RA = GLP-1 receptor agonist; NPT/AgRP = neuropeptide Y/agouti-related peptide; POMC/CART = proopiomelanocortin/cocaine- and amphetamine-regulated transcript; GABA = gamma-aminobutyric acid; AMPA = α-amino-3-hydroxy 5-methyl-4-isoxazolepropronic acid receptor.

Grandone A, et al. *Best Pract Res Clin Endocrinol Metab*. 2018;32:535-549.

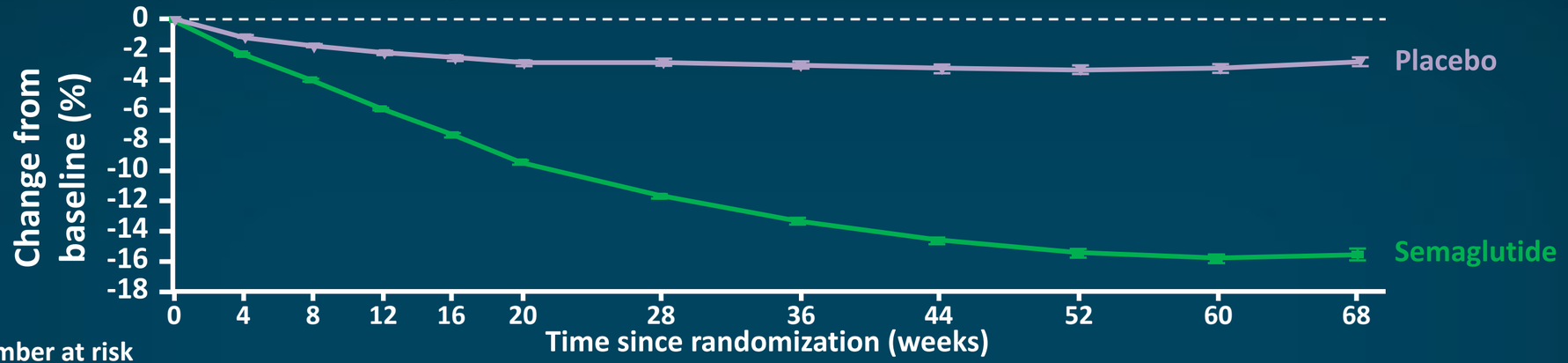
Modest Weight Loss With NEW Anti-Obesity Medications



Adapted from Rueda-Clausen CF, et al. *Nat Rev Endo.* 2013;9:467-478. Astrup A, et al. *Int J Obes.* 2012;36:843-854. Pi-Sunyer X, et al. *N Engl J Med.* 2015;373:11-22.

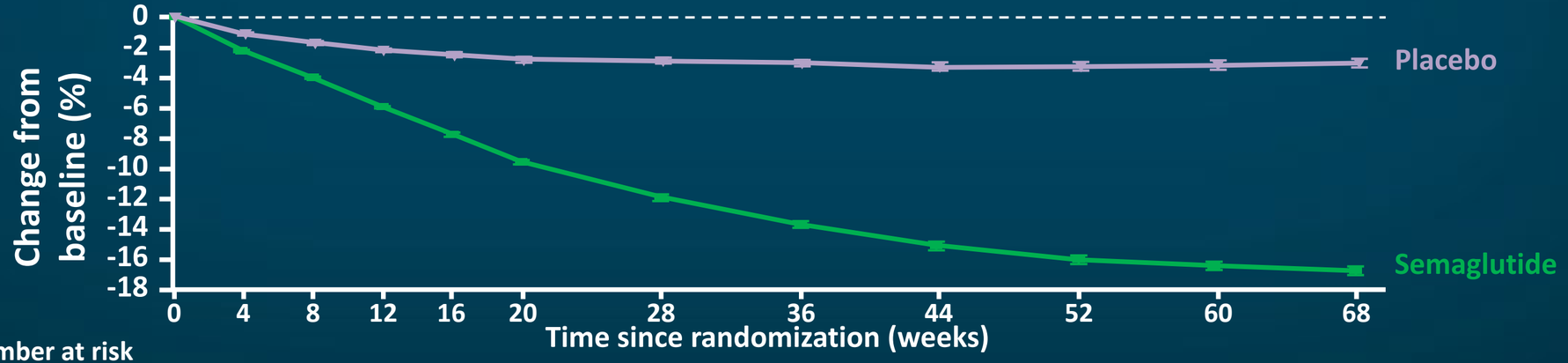
Effect of Once-Weekly Semaglutide vs Placebo

Body weight change from baseline by week, observed in-trial data



Number at risk												
Placebo	655	649	641	619	615	603	592	571	554	549	540	577
Semaglutide	1306	1290	1281	1262	1252	1248	1232	1228	1207	1203	1190	1212

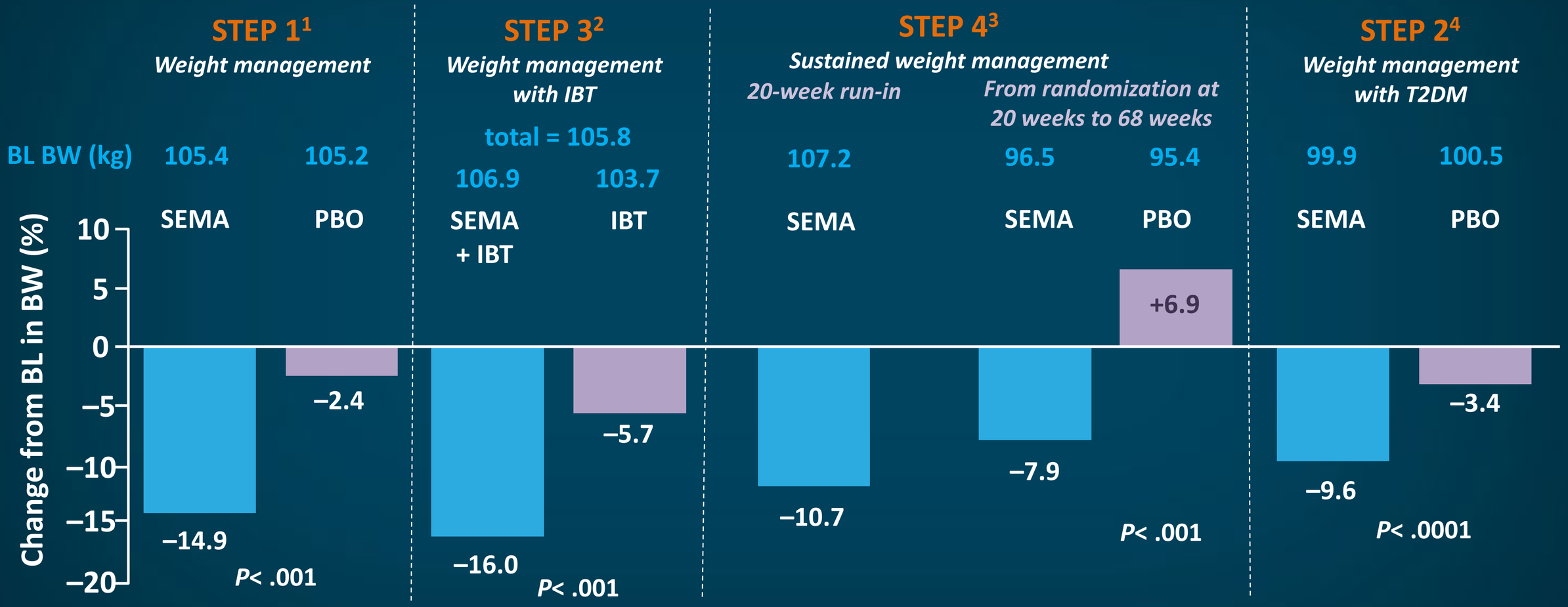
Body weight change from baseline by week, on-treatment data



Number at risk												
Placebo	655	647	637	613	607	593	576	444	629	520	514	499
Semaglutide	1306	1283	1259	1225	1206	1193	1176	1166	1135	1115	1100	1059

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

The STEP Trials: Higher-Dose Semaglutide in Obesity

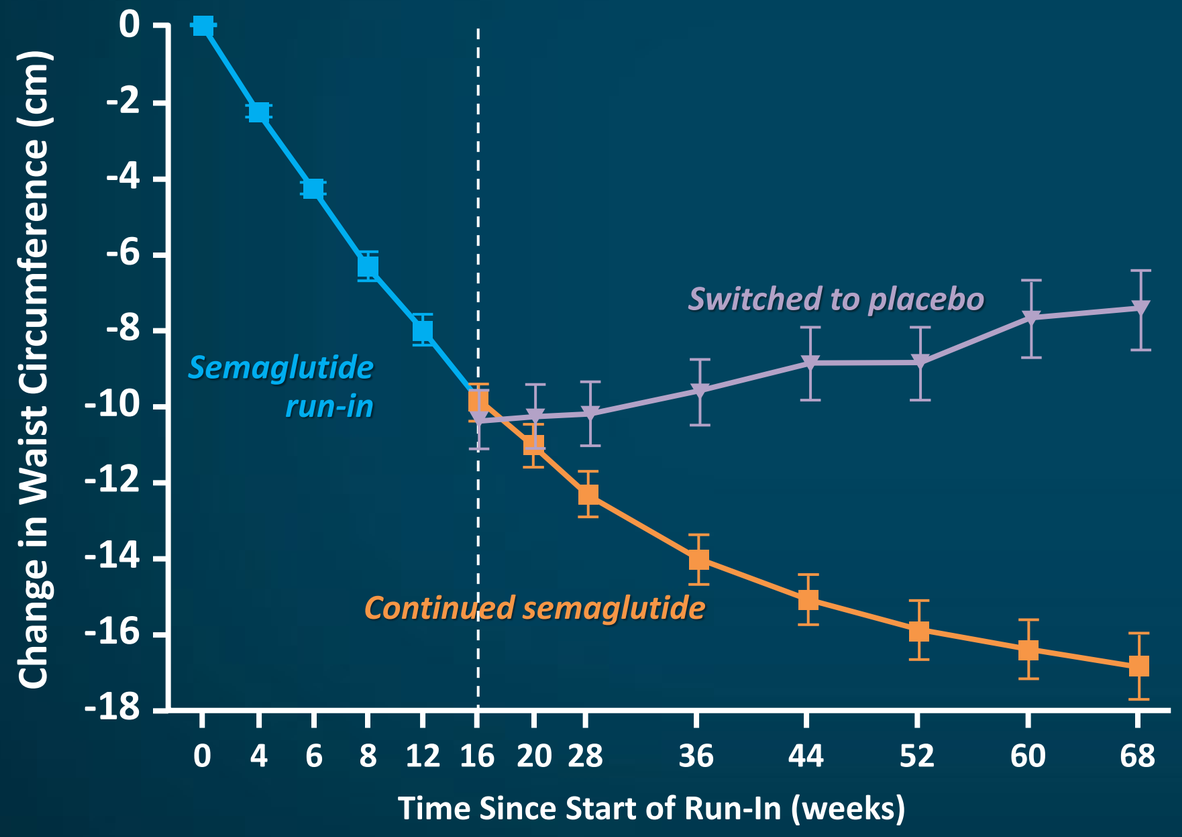


IBT = intensive behavioral therapy; BL = baseline; BW = body weight; SEMA = semaglutide; PBO = placebo.

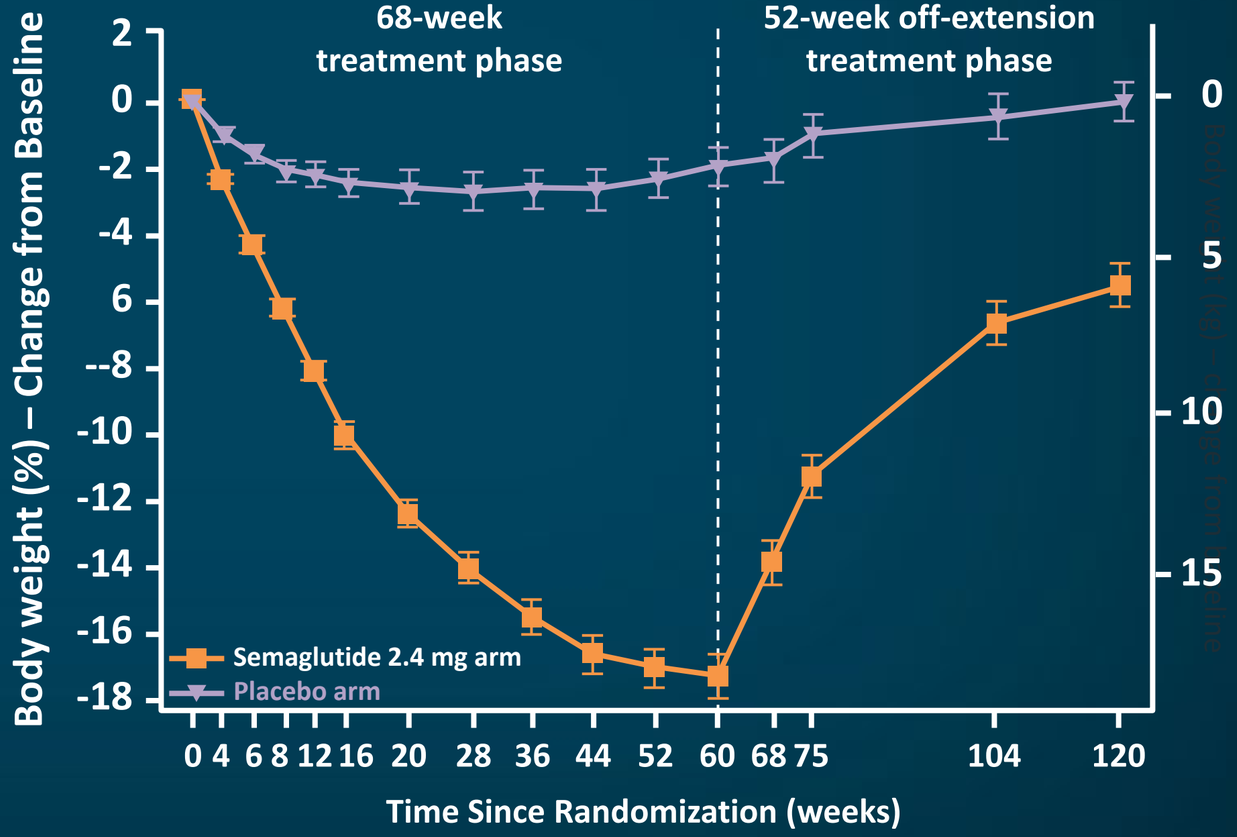
1. Wilding JPH, et al. *N Engl J Med.* 2021;384:989-1002. 2. Wadden TA, et al. *JAMA.* 2021;325:1403-1413. 3. Rubino D, et al. *JAMA.* 2021;325:1414-1425. 4. Davies M, et al. *Lancet.* 2021;397:971-984.

Semaglutide: Weight Regain After Drug Withdrawal

Mean change in waist circumference Weeks 0-68, observed in-trial data



Change from baseline in body weight for all participants in the extension analysis



Rubino D, et al. *JAMA*. 2021;325:1414-1425. Wilding JPH, et al. *Diabetes Obes Metab*. 2022;24(8):1553-1564.

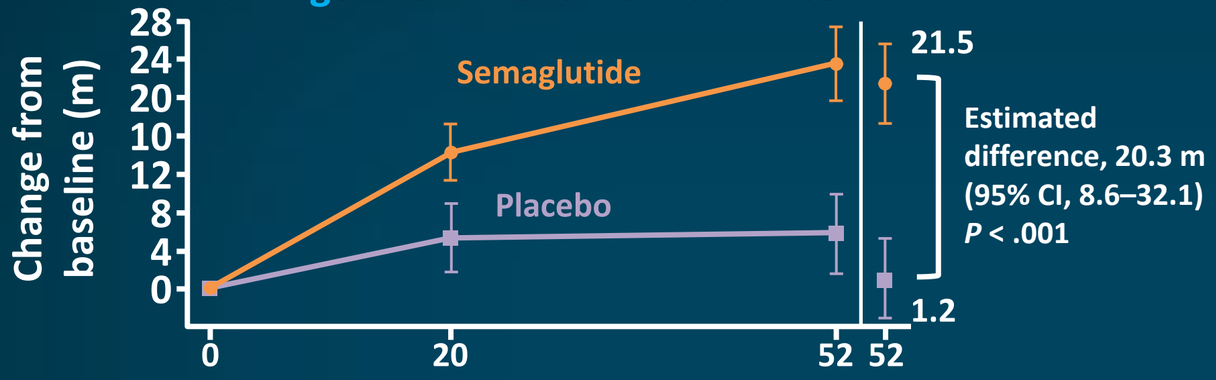
Semaglutide and Cardiovascular Outcomes: SELECT Trial

- International trial of 17,604 adults ≥45 years of age with body mass index (BMI) ≥27 kg/m^2 and established cardiovascular disease with no prior history of diabetes
- Compared subcutaneous once-weekly semaglutide 2.4 mg with placebo as an adjunct to standard of care for prevention of major adverse cardiovascular events (MACEs) over a period of up to 5 years
- Primary endpoint met with 20% (statistically significant) reduction in MACE for intervention group

Lincoff AM, et al. *N Engl J Med*. 2023 (https://doi.org/10.1056/NEJMoa2307563). Accessed 11/29/2023.

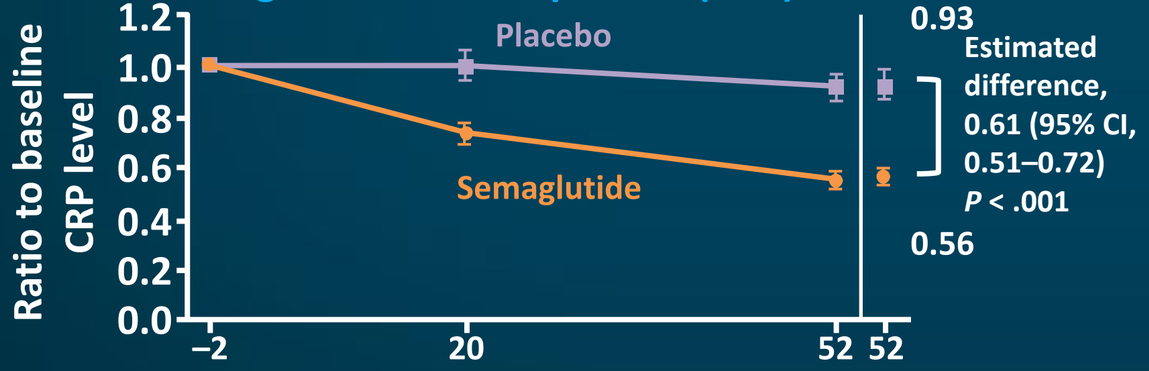
Semaglutide in Patients With Heart Failure With Preserved Ejection Fraction and Obesity: Changes in Baseline to Week 52 in Dual Primary Endpoints

Change in 6-minute walk distance



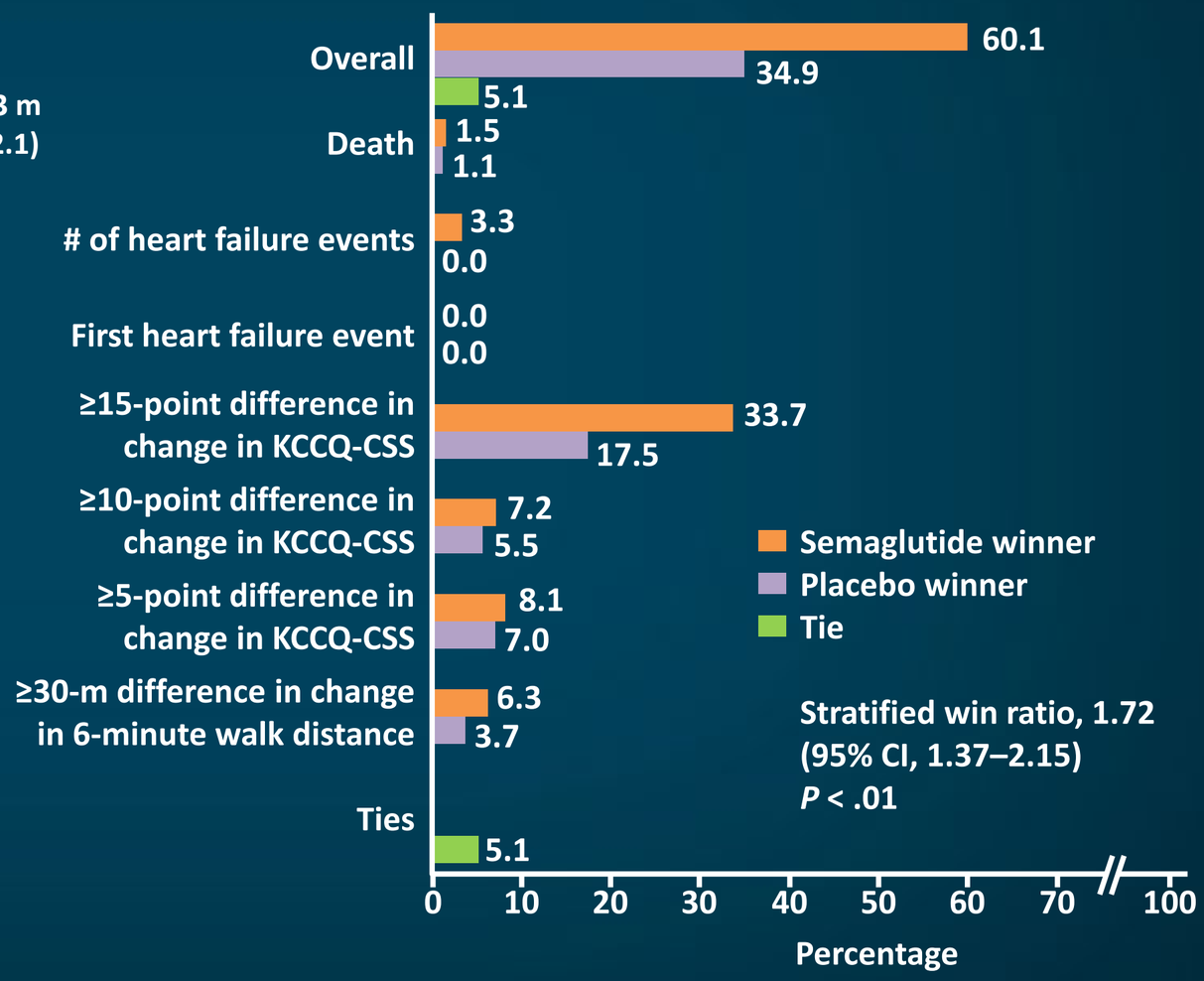
Number of participants				
Semaglutide	263	245	240	263
Placebo	266	232	225	266

Change in C-reactive protein (CRP) level



Number of participants				
Semaglutide	263	245	240	263
Placebo	266	232	225	266

Stratified win ratio for hierarchical composite endpoint



KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire clinical summary score. Kosiborod MN, et al. *N Engl J Med*. Published online 8/25/23 (doi:10.1056/NEJMoa2306963).

GLP-1 RA Meta-Analysis: Cardiovascular (CV) and Non-CV Outcomes

Parameter	Hazard ratio (95% CI)	NNT (95% CI)	*p* value
3-point MACE	0.86 (0.80–0.93)	65 (45–130)	< .0001
Cardiovascular death	0.87 (0.80–0.94)	163 (103–353)	.0010
Fatal or non-fatal myocardial infarction	0.90 (0.83–0.98)	175 (103–878)	.020
Fatal or non-fatal stroke	0.83 (0.76–0.92)	198 (140–421)	.0002
All-cause mortality	0.88 (0.82–0.94)	114 (76–228)	.0001
Hospital admission for heart failure	0.89 (0.82–0.98)	258 (158–1422)	.013
Composite kidney outcome including macroalbuminuria	0.79 (0.73–0.87)	47 (37–77)	< .0001
Worsening of kidney function	0.86 (0.72–1.02)	241 (120 to −1694)	.089

Trials

ELIXA
LEADER
SUSTAIN-6
EXSCEL
Harmony Outcomes
REWIND
PIONEER 6
AMPLITUDE-O

MACE = major adverse cardiovascular events; NNT = number needed to treat.

Sattar N, et al. *Lancet Diabetes Endocrinol*. 2021;9(10):653-662.

Metabolic Outcomes With Anti-Obesity Medications

Medication	LDL	TG	HDL	A1C	SBP
Phentermine/topiramate CR	↓	↓	↑	↓	↓
Naltrexone SR/bupropion SR	—	↓	↑	↓	↑
Liraglutide 3.0 mg	↓	↓	↑	↓	↓

A1C = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL =low-density lipoprotein; SBP = systolic blood pressure.

Vorsanger MH, et al. *J Am Coll Cardiol*. 2016;68(8):849-859.

Criteria for Metabolic and Bariatric Surgery (MBS)

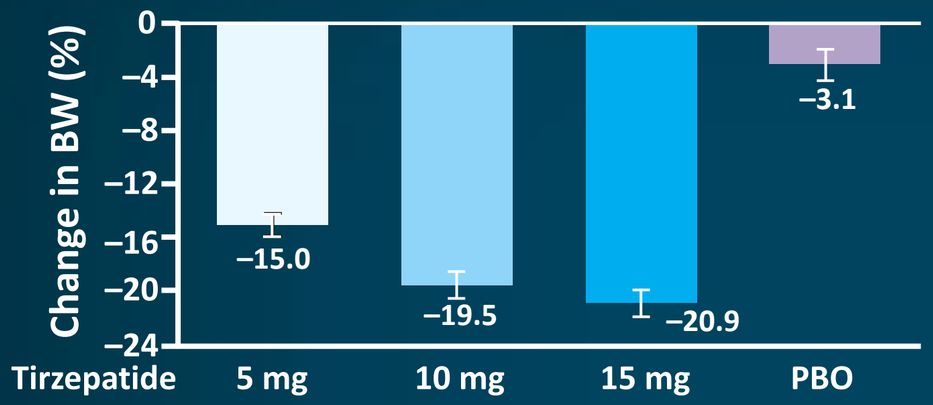
- MBS is recommended for individuals with BMI ≥35 kg/m^2, regardless of the presence, absence, or severity of comorbidities
- MBS is recommended for patients with T2DM and BMI ≥30 kg/m^2
- MBS should be considered for individuals with metabolic disease and BMI of 30 to 34.9 kg/m^2
- BMI thresholds should be adjusted in the Asian population; a BMI >25 kg/m^2 suggests clinical obesity, and individuals with a BMI >27.5 kg/m^2 should be offered MBS
- Children and adolescents with a BMI >120% of the 95th percentile and a major comorbidity, or a BMI >140% of the 95th percentile, should be considered for MBS after evaluation by a multidisciplinary team in a specialty center

Eisenberg D, et al. *Surg Obes Relat Dis*. 2022;18(12):1345-1356.

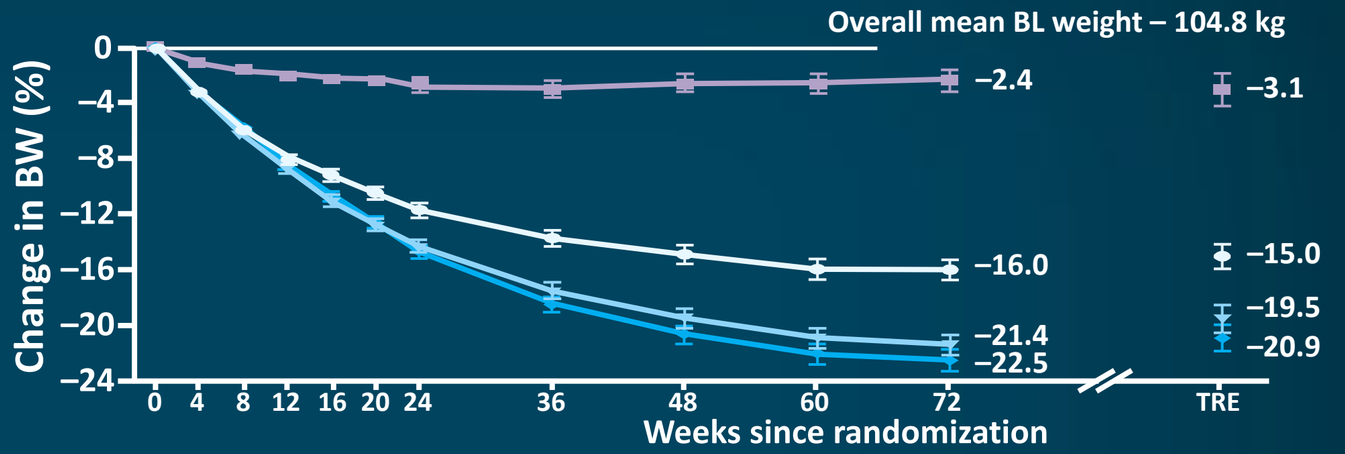
Effect of Once-Weekly Tirzepatide vs Placebo on Body Weight

Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg PBO

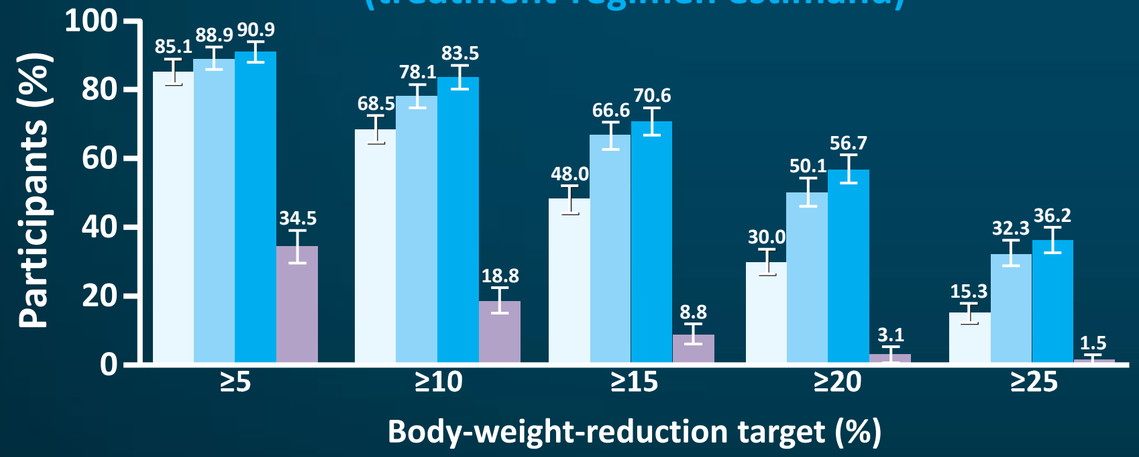
Change in BW from BL (treatment-regimen estimand)



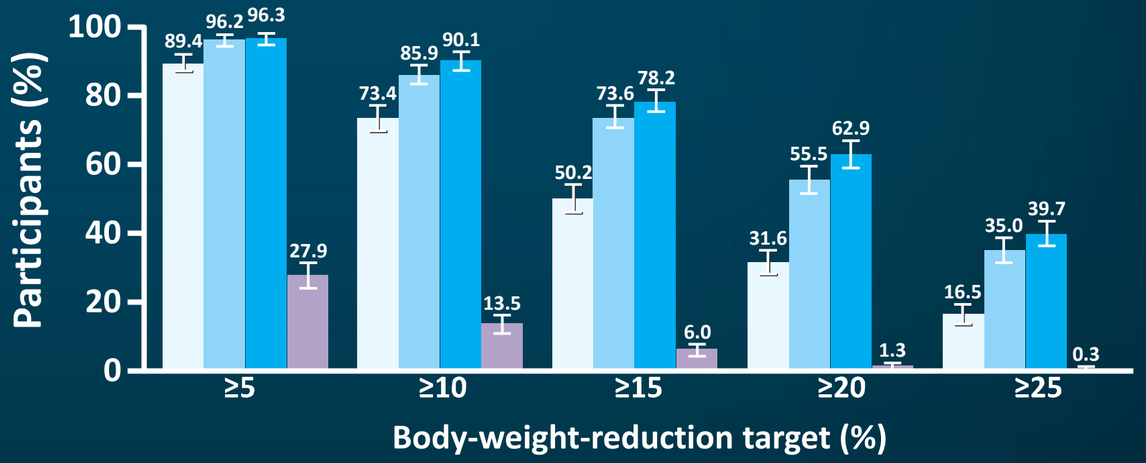
Change in BW by week (efficacy estimand)



Participants meeting weight-reduction targets (treatment-regimen estimand)



Participants meeting weight-reduction targets (efficacy estimand)



I bars indicate 95% confidence intervals.

Jastreboff AM, et al. *N Engl J Med.* 2022;387:205-216.

Tirzepatide (Dual Agonist) Safety

	5 mg, N = 630, (%)	10 mg, N = 636, (%)	15 mg, N = 630, (%)	Placebo, N = 643, (%)
Serious adverse events	40 (6.3)	44 (6.9)	32 (5.1)	44 (6.8)
Death	4 (0.6)	2 (0.3)	1 (0.2)	4 (0.6)
Most common AEs ≥5% in any treatment group)*				
Nausea	155 (24.6)	212 (33.3)	195 (31.0)	61 (9.5)
Diarrhea	118 (18.7)	135 (21.2)	145 (23.0)	47 (7.3)
Constipation	106 (16.8)	109 (17.1)	74 (11.7)	37 (5.8)
Dyspepsia	56 (8.9)	62 (9.7)	71 (11.3)	27 (4.2)
AEs leading to discontinuation of trial drug or placebo (nausea, diarrhea, abdominal pain, vomiting)	27 (4.3)	45 (7.1)	39 (6.2)	17 (2.6)

*Does not include COVID-19 infections.

AEs = adverse events.

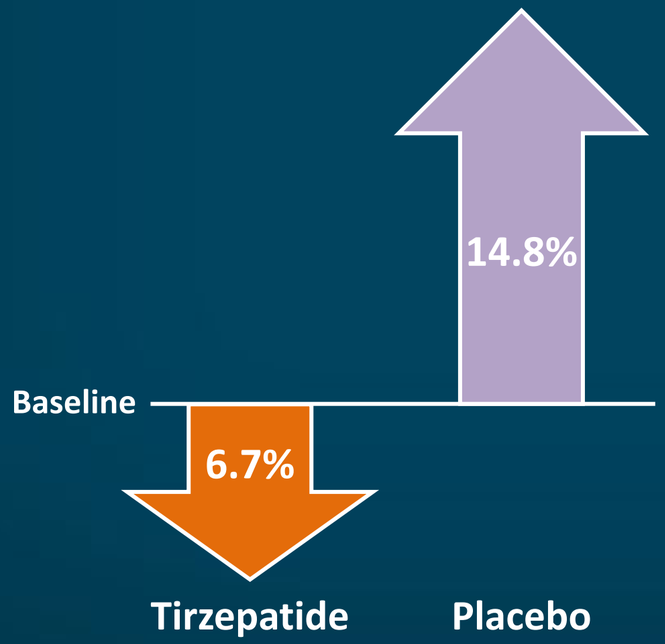
Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216.

SURMOUNT-4

36-week open-label tirzepatide lead-in period; then randomization to 52 weeks of tirzepatide or placebo

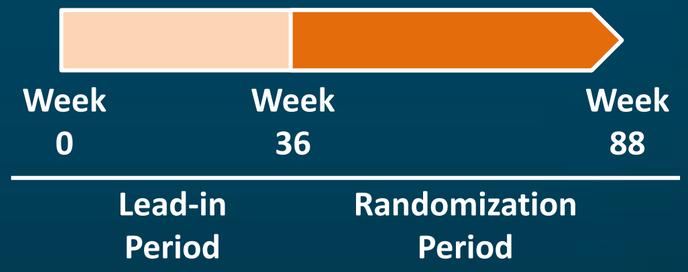
236.6 lbs
Baseline mean body weight

Additional Body Weight Change from Randomization at 88 Weeks



Primary endpoint met:

- Superior mean percent change in body weight compared to placebo from 36 weeks to 88 weeks, indicating sustained weight loss



26.0%
Total mean body weight reduction

from study entry over the 88-week period

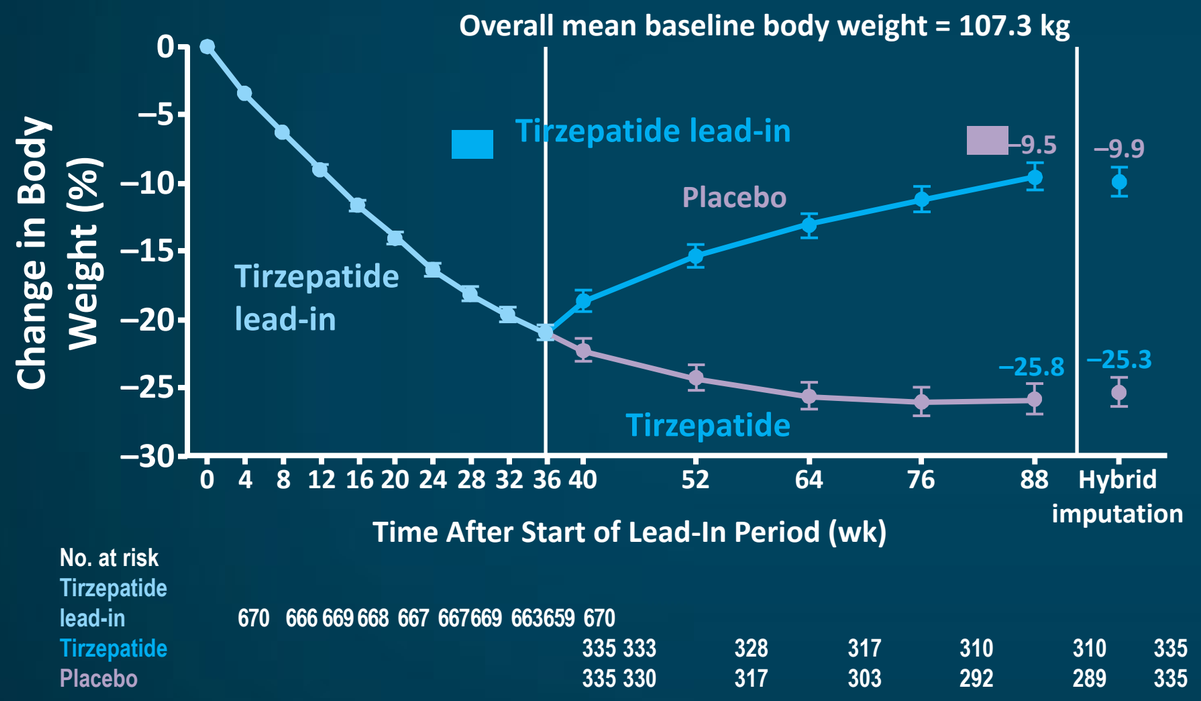
Most commonly reported adverse events were mild-to-moderate gastrointestinal related

Aronne LJ, et al. SURMOUNT-4 Trial results: the impact of tirzepatide on maintenance of weight reduction and benefits of continued therapy. Presented at the European Association for the Study of Diabetes. October 2023.

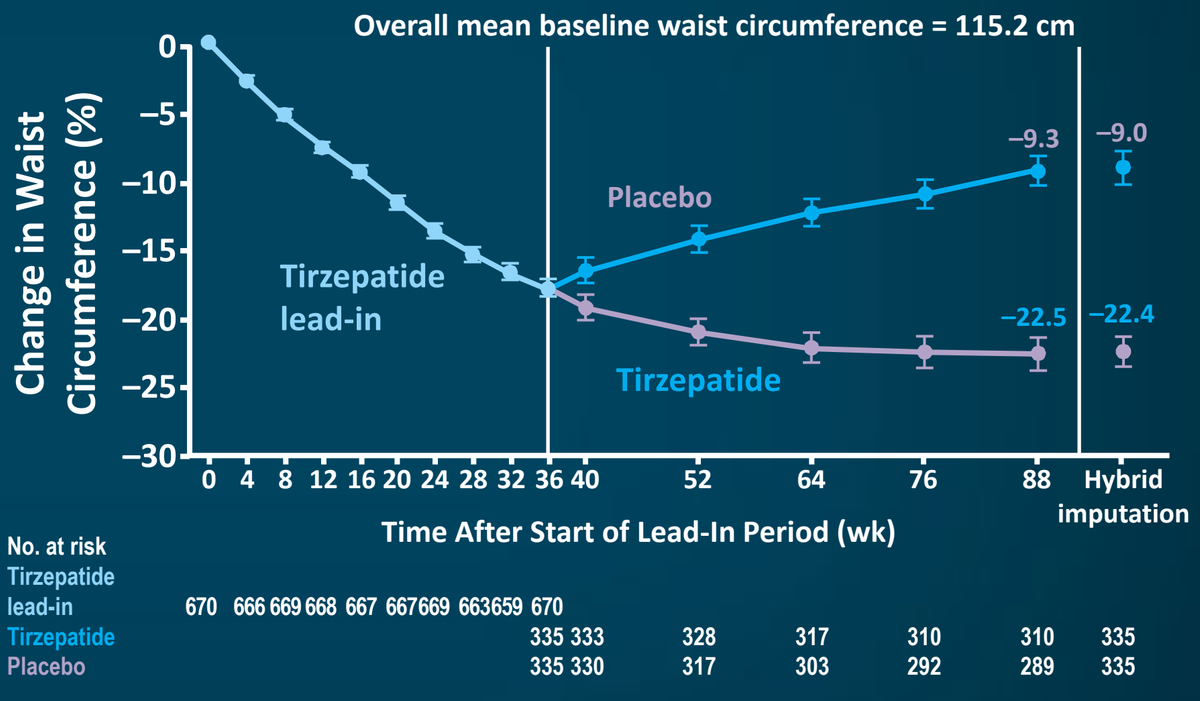
SURMOUNT-4

From: Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial

Percent Change in Body Weight (week 0-88)



Percent Change in Waist Circumference (week 0-88)



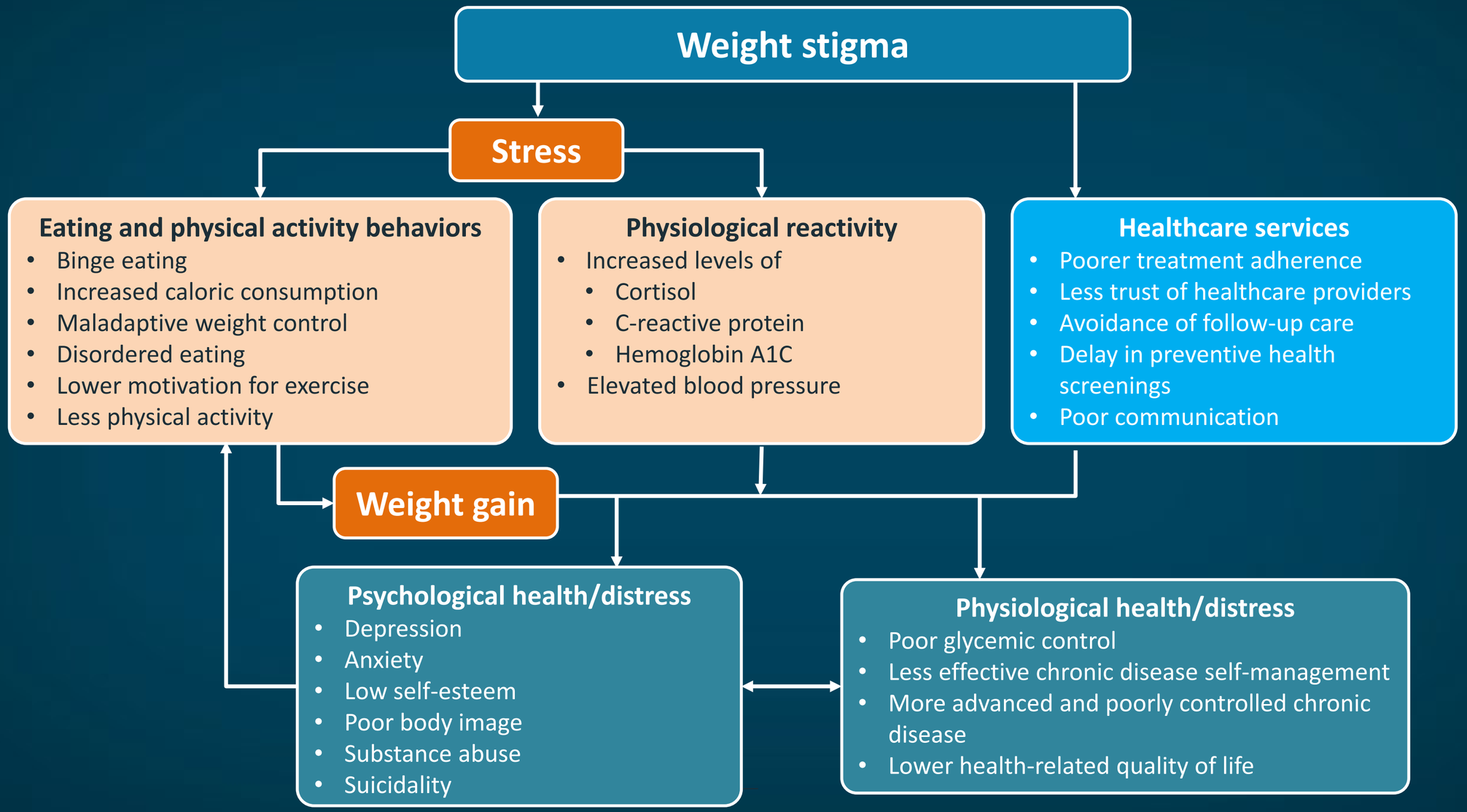
Effect of Tirzepatide vs Placebo on Body Weight and Waist Circumference Observed mean values from the full analysis set are shown. Error bars represent 95% CI for the mean. The dashed vertical line at week 36 represents the randomization point. Analysis of covariance using the full analysis set with hybrid imputation least-square mean values at week 88 is also shown on the right.

JAMA. 2024;331(1):38-48. doi:10.1001/jama.2023.24945

Shared Decision-Making

Overcoming the Stigma

Overcoming Weight Stigma in the Treatment of Obesity

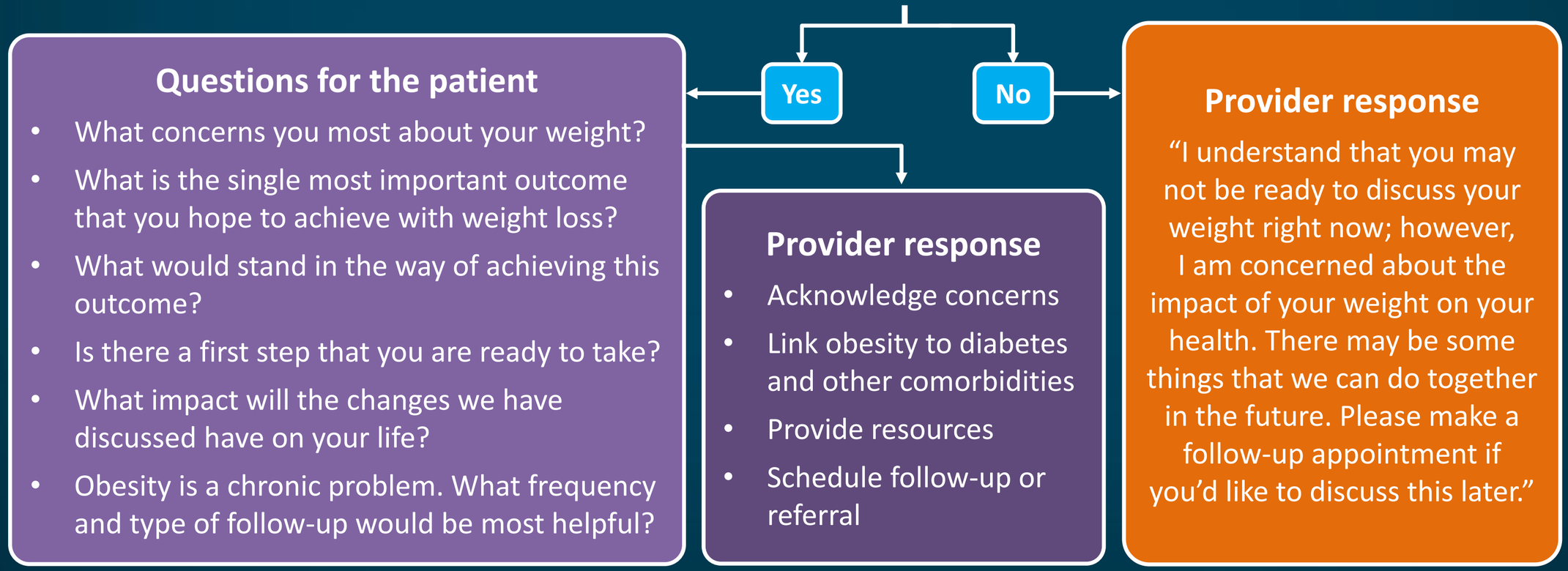


Puhl RM, et al. *Clin Diabetes*. 2016;34:44-50.

Suggested Script for Initiating Discussion of Obesity

Pre-screen: BMI and weight trajectory; 24-hour dietary recall; personal weight history; medications; physical activity; existing comorbidities or risk factors (eg, stress, sleep, quality of life, depression)

"Is now a good time for us to discuss how your weight and health may be affecting each other and how we can work together on it?"



Modified from Gallagher C, et al. *Obesity (Silver Spring)*. 2021;29:821-824.

Take-Home Points

- Track weight loss progress in terms of excess body weight and total body weight at each visit.
- Listen to patient cues about hunger, satiety, and side effects to drive weight management.
- Continue to encourage healthy lifestyle behaviors with weight loss medications as an adjunct.
- If a patient has a superior response to medication (5%-10% of total body weight loss), continue medications indefinitely.
- Advise women of reproductive potential about discontinuing medication prior to conception.

Program Resources

https://linktr.ee/STRIVEobesity

- **CREATE** a free personalized office poster
- **REGISTER** for a variety of CME activities
- **VISIT** the STRIVE website - https://strive-obesity.com/
- **VIEW** supplemental resources and animations

Whiteboard animation: Pathophysiology of Obesity

https://youtu.be/uZIiy_0_JMg