



EMERGING CHALLENGES AND CLINICAL UPDATES IN PRIMARY CARE

Live Virtual Conference



Obesity Management in Primary Care

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This activity is part of the ***Obesity Management in Primary Care Training and Certificate Program*** provided by the National Association for Continuing Education (NACE) and the American Academy of Physician Associates (AAPA) in collaboration with The Obesity Society (TOS).

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OBESITY MANAGEMENT IN PRIMARY CARE TRAINING AND CERTIFICATE PROGRAM



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“Name not disclosed”

Disclosures

- **Angie Golden** has disclosed the following financial relationships*:
 - Advisory Boards and Consultant: Novo Nordisk, Gelesis, Currax
 - Speaker: Novo Nordisk
 - Royalties: Springer Nature

- **Robert Kushner** has disclosed the following financial relationships:
 - Advisory Boards and Consultant: Novo Nordisk, WW, Pfizer, Lilly
 - Speaker: none
 - Research Support: none

- **Karli Burridge** has disclosed the following financial relationships:
 - Consultant: Novo Nordisk
 - Advisor: Gelesis Biotechnology, Currax Pharmaceuticals, Vivus
 - Speaker's Bureau: Currax Pharmaceuticals, Vivus

Faculty for this educational activity not listed above have no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

*these are the disclosure relevant to this presentation.

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All relevant financial relationships and potential conflicts of interest have been mitigated.

Learning Objectives

Recognize

Recognize obesity as a chronic, relapsing disease with unique, distinct pathophysiology that contributes to adiposity, comorbidities, and complications

Summarize

Summarize long-term pharmacotherapy to manage obesity, including new and emerging pharmacologic agents, based on efficacy and safety data

Develop

Develop individualized treatment plans for patients with obesity that incorporate evidence-based and clinical practice guidelines

Pre-test Questions

Pre-test Question 1

Pre-T1: Which of the following factors mediate the link between obesity and comorbidities such as dyslipidemia and insulin resistance?

1. Secreted adipocyte factors
2. Increased anorexigenic signaling
3. Reduced ghrelin production in gut
4. Reduced circulating levels of estrogen

Pre-test Question 2

Pre-T2: Which of the following medications have demonstrated an average of \geq 15% weight loss in clinical trials?

1. Liraglutide
2. Naltrexone/bupropion
3. Phentermine/topiramate
4. Semaglutide

Pre-test Question 3

Pre-T3: 52 y/o man with obesity, T2D, hypertension, dyslipidemia.

Says he is concerned about weight gain over last 10 years (~25 lbs).

Workup: BMI 32.7 kg/m², BP 128/82 mmHg, A1C 6.9%, eGFR 52 mL/min/1.73m².

Meds: Metformin 1000 mg bid, canagliflozin 100 mg qd, lisinopril/hydrochlorothiazide 20 mg/25 mg qd, atorvastatin 80 mg qd.

Lifestyle: Walks briskly for 1 hour 6 days per week; follows a low-calorie, low-fat diet.

Notes that he hates needles and does not want injectable medications.

What would you do next for this patient?

1. Recommend bariatric surgery
2. Down-titrate obesogenic medications
3. Prescribe exenatide, lixisenatide, or dulaglutide
- 9 4. Discuss benefits of phentermine/topiramate or naltrexone/bupropion

Pre-test Question 4

Pre-T4: 38 y/o woman with history of T2D, hypertension, obesity.

Has gained 45 lbs in last 5 years.

Workup: BMI 34 kg/m², BP 142/86 mmHg, A1C 6.7%.

Meds: Lisinopril 20 mg qd, metformin 1000 mg bid, naltrexone/bupropion 2 tablets bid.

Lifestyle: Swims 45 min 5x week, lifts weights 2x week; goes to commercial weight-loss program. Started naltrexone/bupropion 3 months ago; has lost 5 lbs (2.4% baseline weight) in that time.

What might be appropriate at this time?

1. Maintain naltrexone/bupropion for at least 6 months
2. Stop naltrexone/bupropion and refer for bariatric surgery
3. Continue naltrexone/bupropion and prescribe phentermine
4. Discontinue naltrexone/bupropion and prescribe liraglutide or semaglutide

Pre-test Question 5

Pre-T5: How confident are you in your ability to select long-term pharmacotherapy to manage patients with obesity?

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident

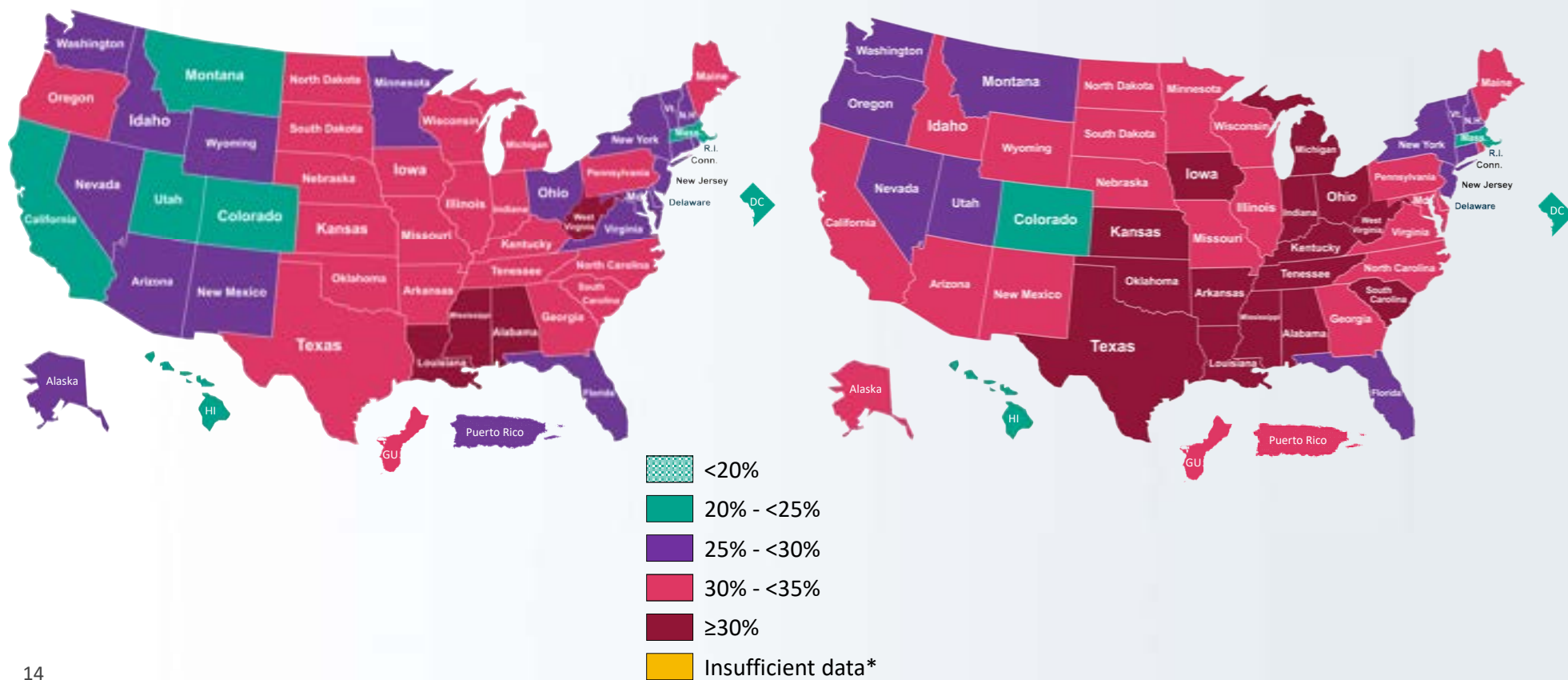
Pre-test Question 6

Pre-T6: How often do you assess comorbidities when considering anti-obesity therapies for patients with overweight/obesity?

1. Never
2. Rarely
3. Sometimes
4. Often
5. Always

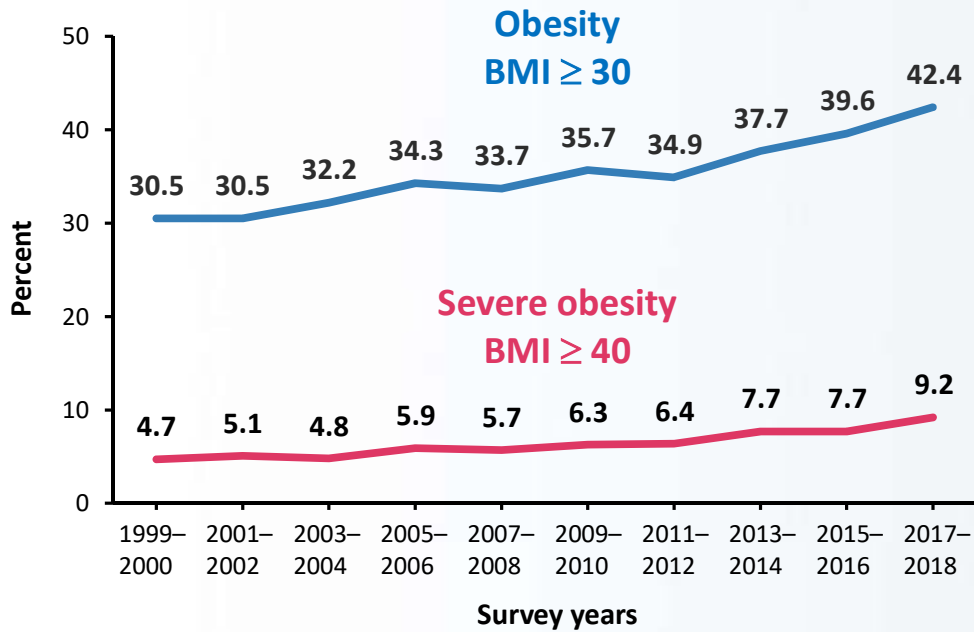
Understanding Obesity

Prevalence of Self-reported Obesity: U.S. Adults by State and Territory, BRFSS 2015—2020

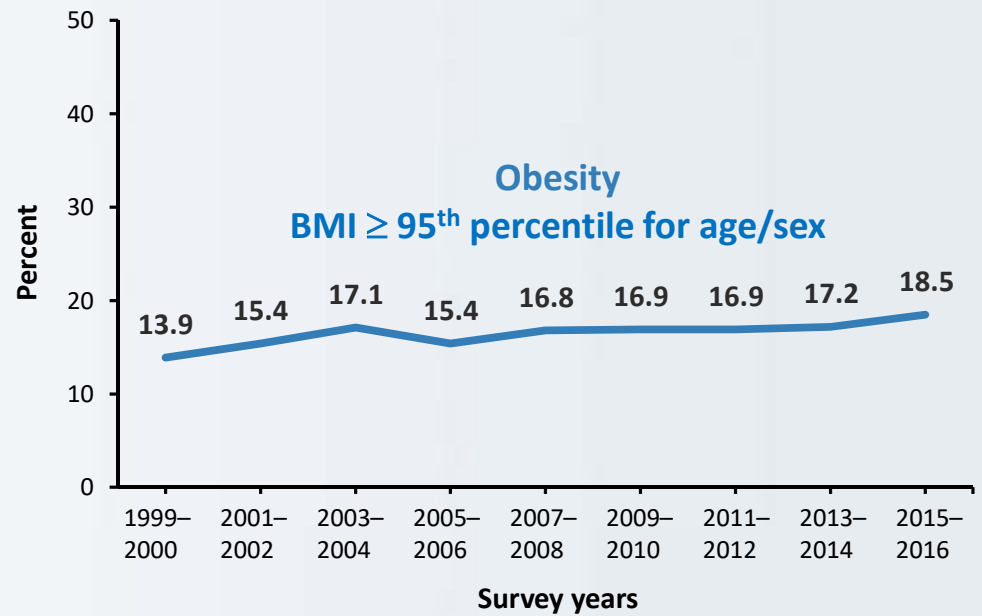


Trends in Obesity Prevalence, United States

Adults aged ≥20 years (age adjusted)¹

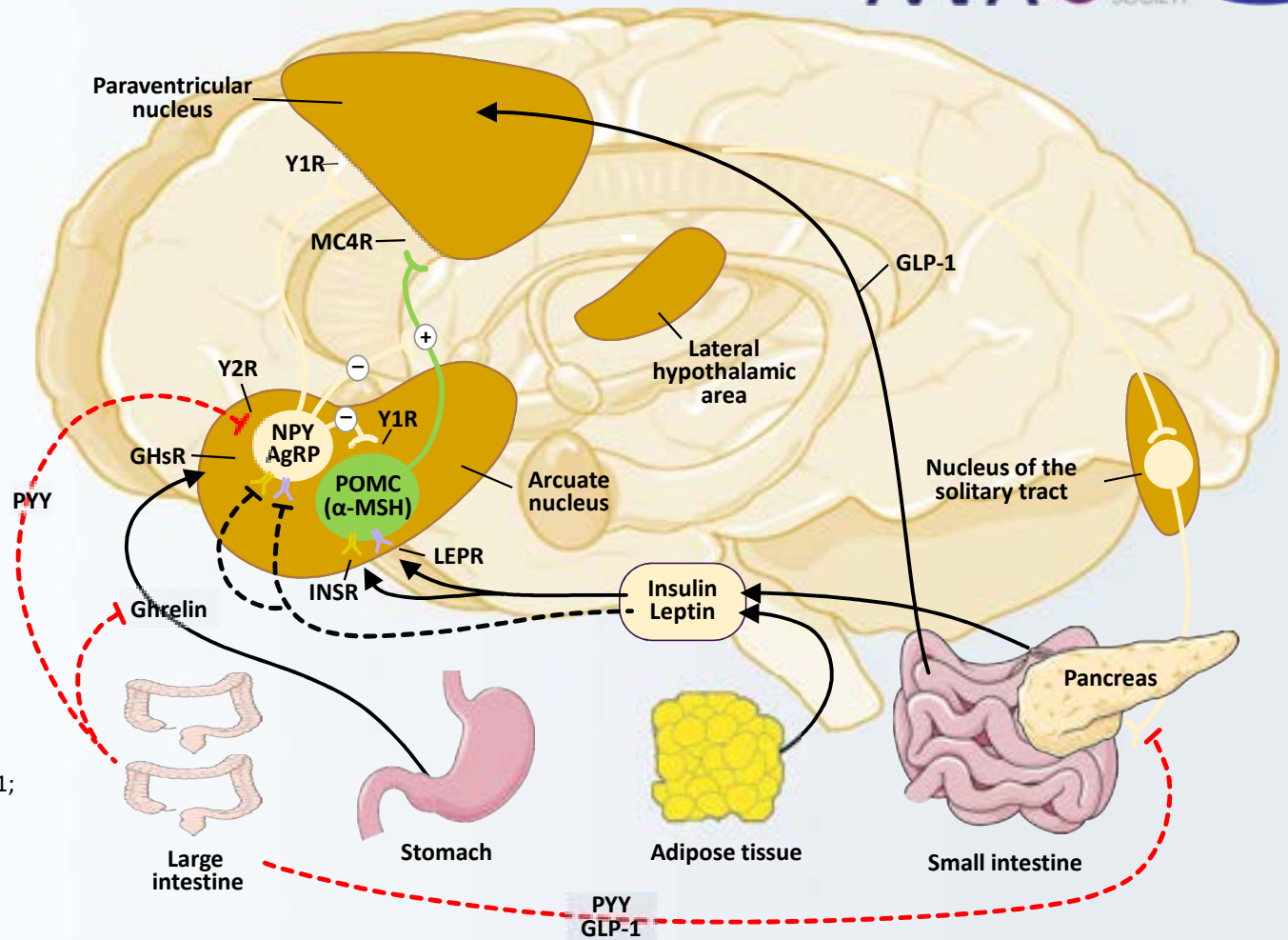


Youth aged 2–19 years²



Components of Appetite Regulation/ Dysregulation

Dysregulation of Biosignaling = Obesity



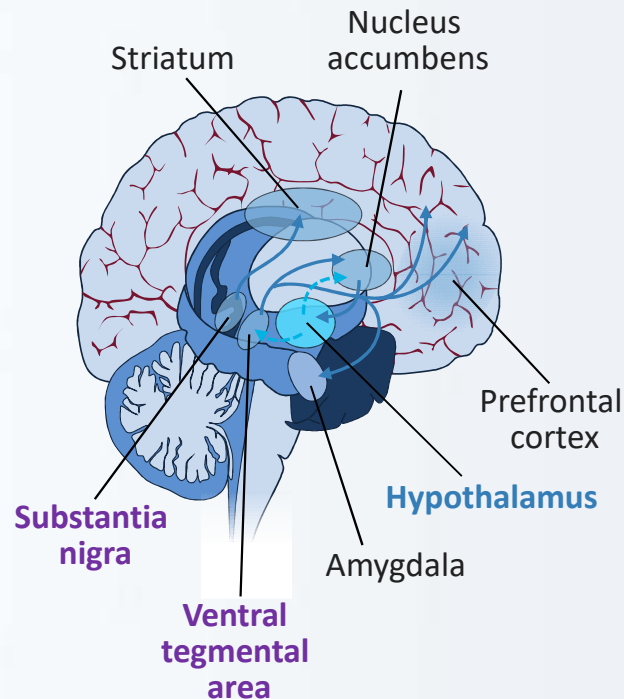
α-MSH, α-melanocyte-stimulating hormone; GHsR, growth hormone secretagogue receptor; INSR, insulin receptor; LEPR, leptin receptor; MC4, melanocortin-4 receptor; POMC, pro-opiomelanocortin; Y1R, neuropeptide Y receptor 1; Y2R, neuropeptide Y receptor 2.

Apovian CM, et al. J Clin Endocrinol Metab. 2015;100(2):342-362.

Integrated CNS Pathways Play a Key Role in Regulating Eating Behavior, Appetite, Cravings, and Weight

Homeostatic System Hunger / Satiety

- Primarily driven by the arcuate nucleus of the **hypothalamus**
- Detection and integration of energy state information
 - Leptin, insulin
- Lateral hypothalamus projects to the VTA and receives input from the nucleus accumbens



Hedonic or Reward System

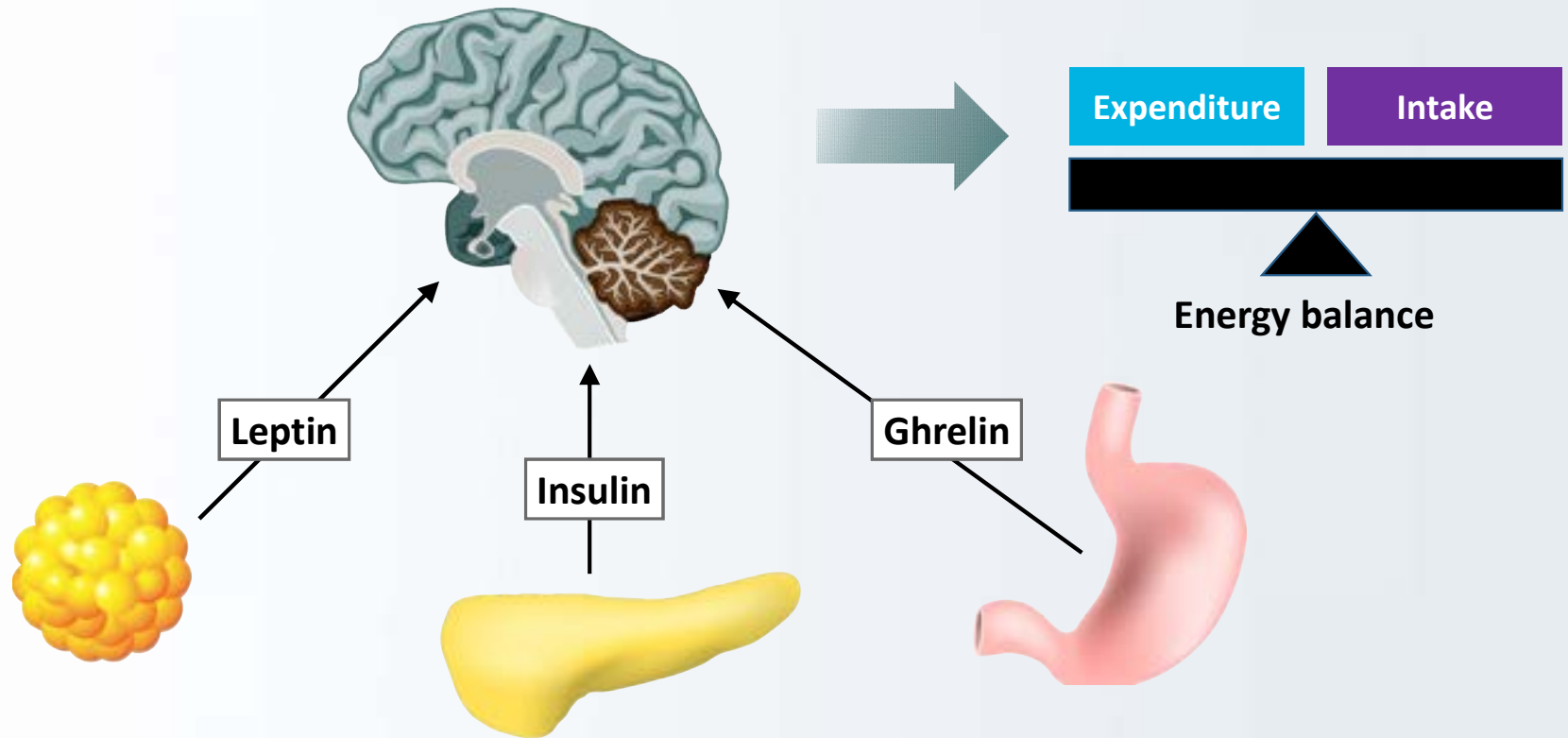
- Dopaminergic pathways from the **VTA or substantia nigra** to regions such as:
 - Striatum (movement, reward salience)
 - Nucleus accumbens (reward, addiction)
 - Prefrontal cortex (decision making, executive function)
 - Amygdala (memory, emotion)

CNS, central nervous system; VTA, ventral tegmental area.

Billes SK, et al. *Pharmacol Res.* 2014;84:1-11.

The Pathology of Obesity

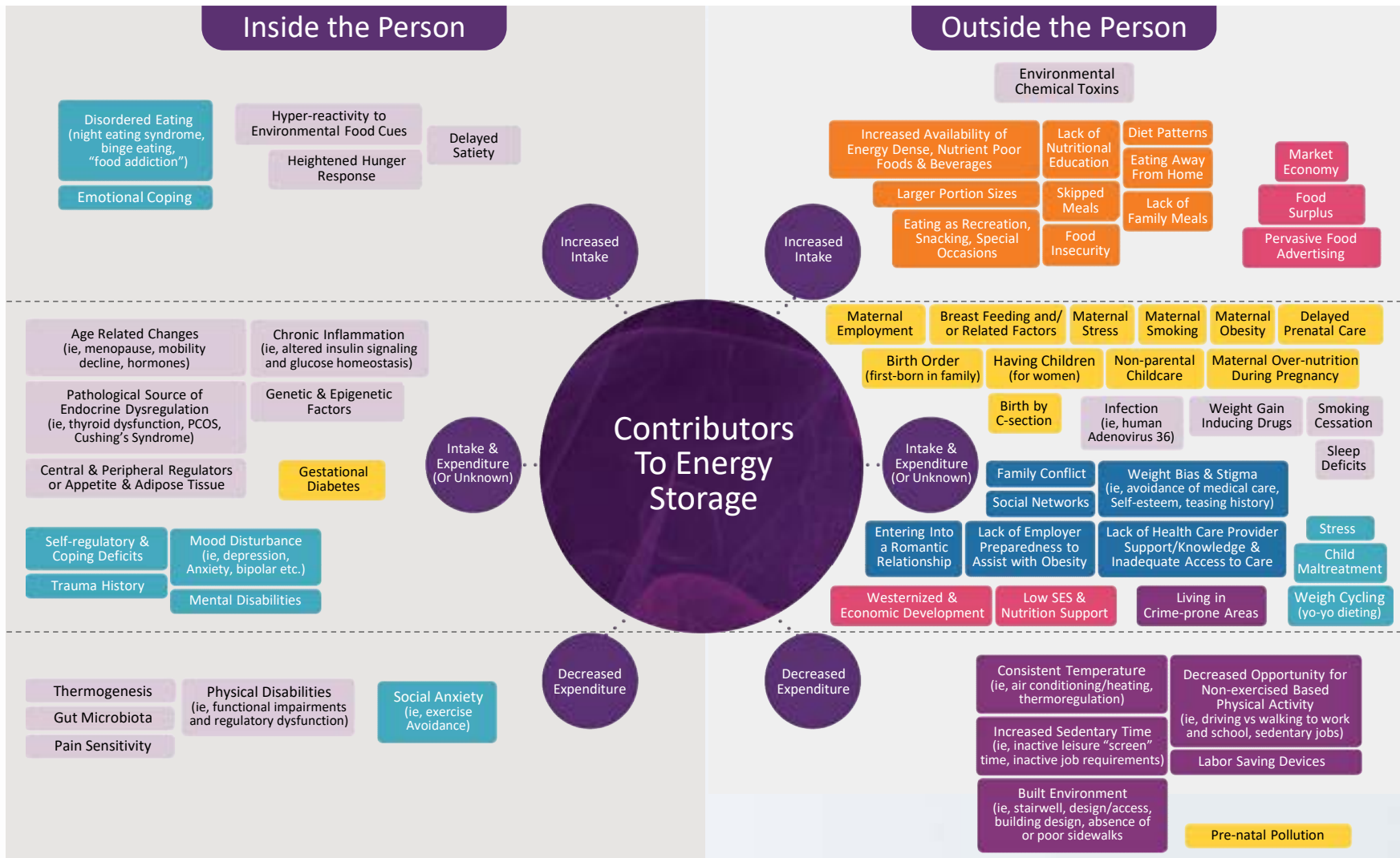
Energy Balance Dysregulation



Potential Contributors to Obesity 2015

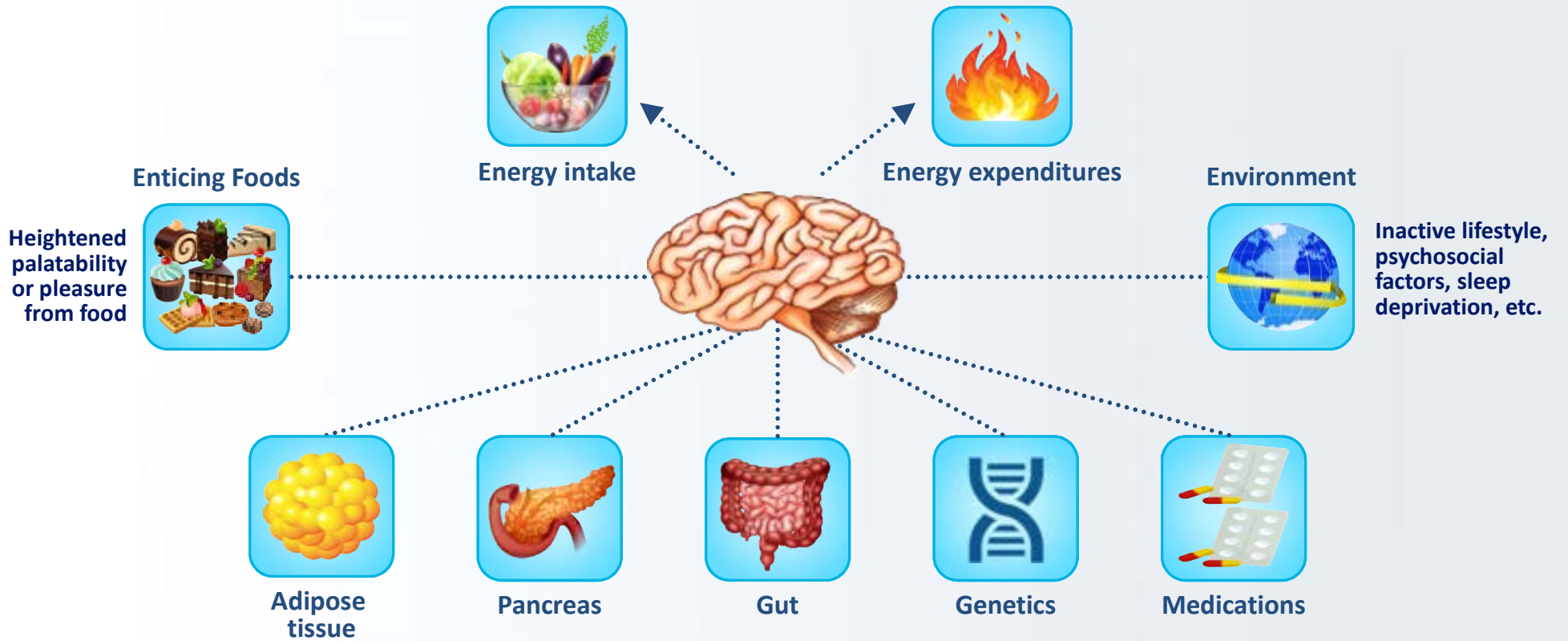
Contributor/Influencer

- Environmental Pressures on Physical Activity
- Biological/Medical
- Maternal/Developmental
- Economic
- Food and Beverage Behavior/Environment
- Psychological
- Social



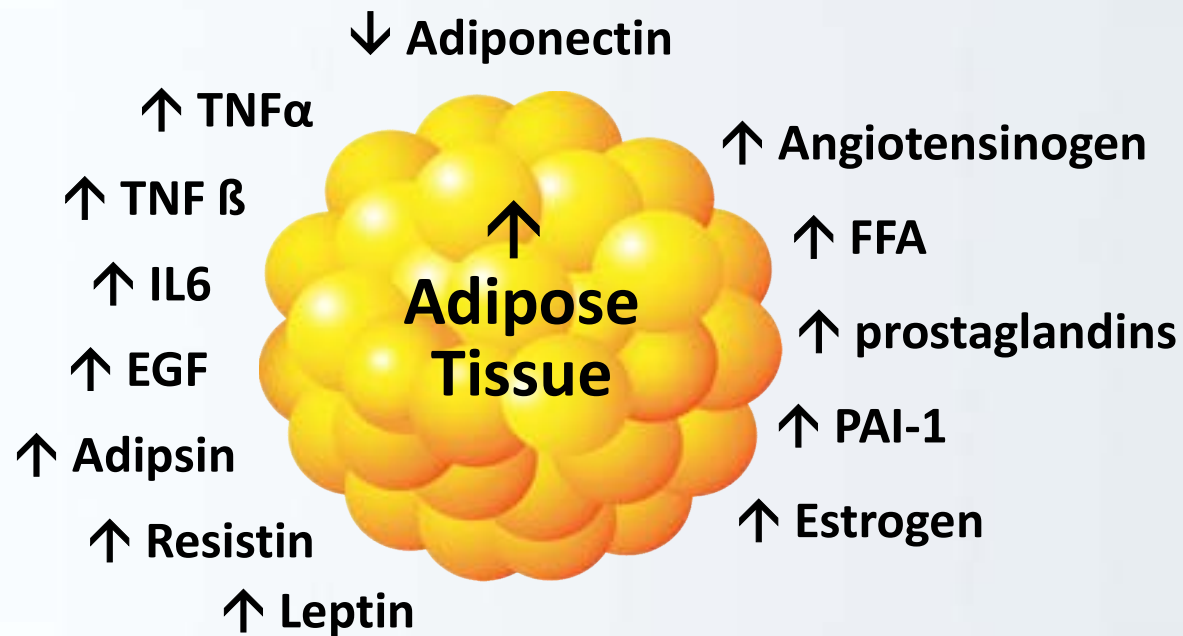
Adapted from The Obesity Society

Energy Balance Dysregulation



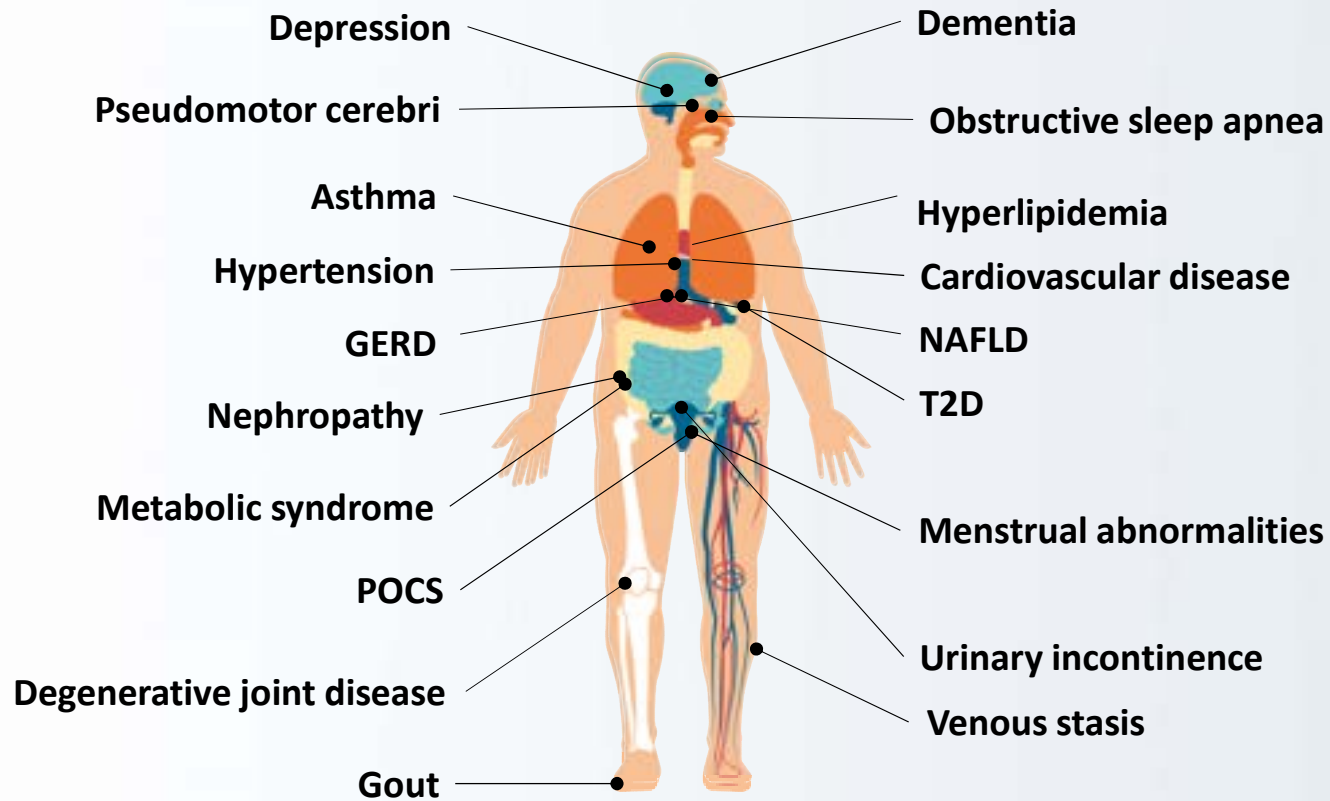
The Pathology of Obesity

Organ System Impairment

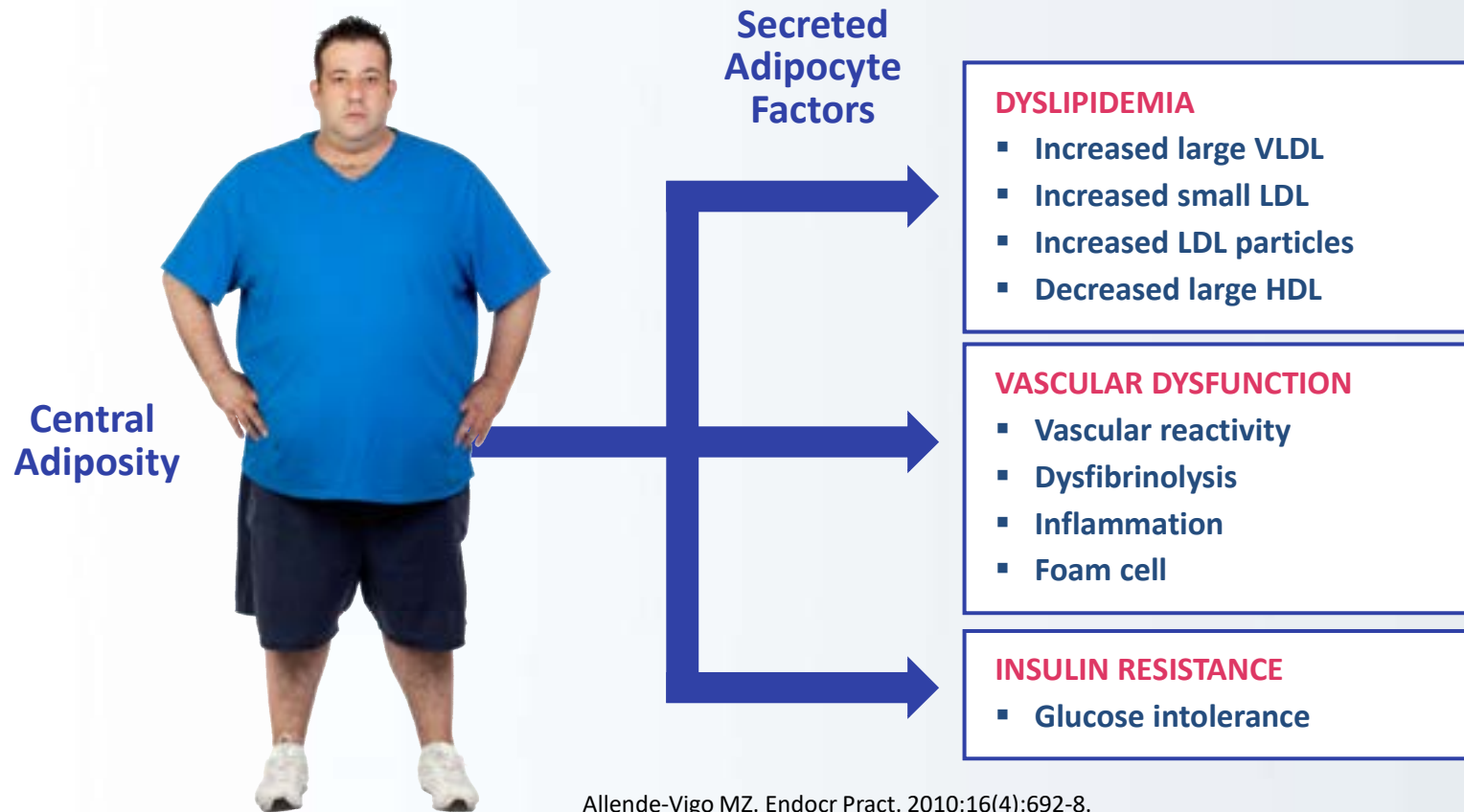


LIPOTOXICITY

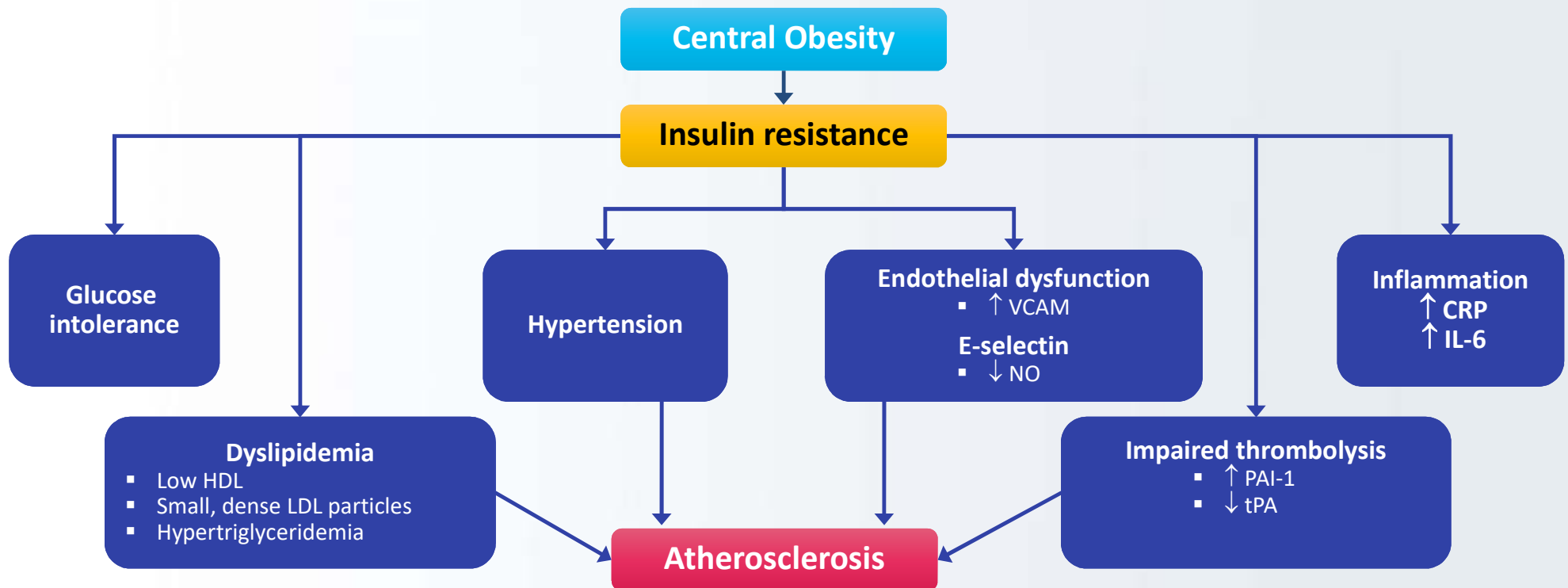
Obesity-Related Diseases



Link Between Pathophysiology of Obesity and Comorbid Conditions



Association of Insulin Resistance With Cardiovascular Risk Factors and Atherosclerosis



CRP, c-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NO, nitric oxide; PAI-1, plasminogen activator 1; tPA, tissue plasminogen activator; VCAM, vascular cell adhesion molecule

McFarlane SI, et al. J Clin Endocrinol Metab. 2001;86(2):713-718.

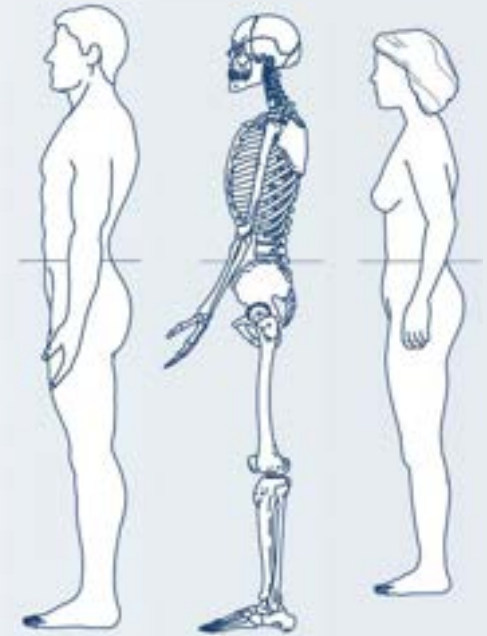
How Do We Define Obesity?

- A condition characterized by excessive accumulation and storage of fat in the body
- Excess adiposity resulting in reduced health and longevity
- An abnormal or excessive fat accumulation that presents a risk to health.

Anthropometry = Science of measuring human body

- ✓ Skinfold thickness and circumferences
- ✓ Bioelectrical impedance analysis (BIA)
- ✓ Dual-energy x-ray absorptiometry (DXA)
- ✓ Air displacement plethysmography
- ✓ Computed Tomography (CT scan)

Measuring tape position for waist (abdominal) circumference



Plethysmography

NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults (US). Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. Bethesda (MD): National Heart, Lung, and Blood Institute; 1998 Sep. Chapter 4, Treatment Guidelines.

Patient Speaker – Perspectives on Bias

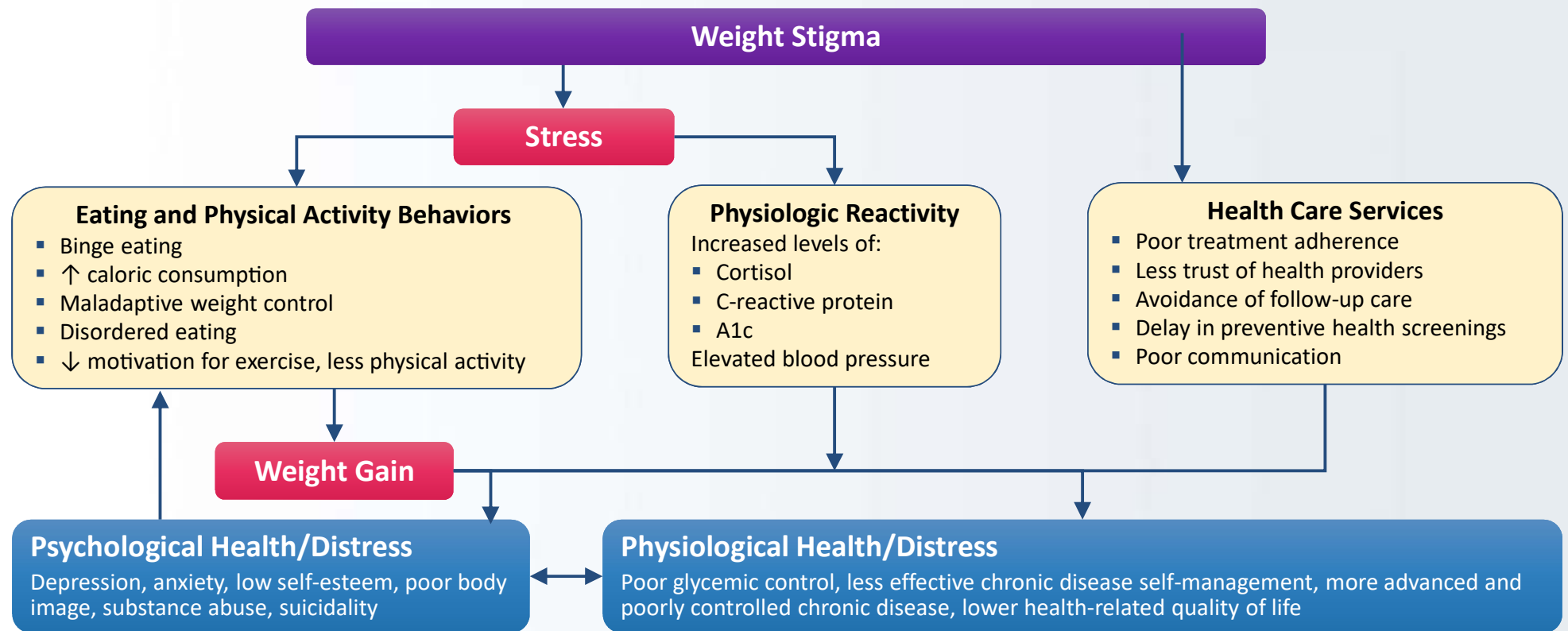


What Is Weight Bias?

- Negative attitudes toward individuals with obesity
- Stereotypes leading to:
 - Stigma
 - Rejection
 - Prejudice
 - Discrimination
- Verbal, physical, relational, cyber
- Subtle and overt



Weight Bias Internalization



The Approach to Obesity

Screening and Diagnosis

BMI

- Non-Asian
 - $\geq 25 \text{ kg/m}^2$ pre-obesity (overweight)
 - $\geq 30 \text{ kg/m}^2$ obesity
- Asian
 - $\geq 23 \text{ kg/m}^2$ pre-obesity (overweight)
 - $\geq 25 \text{ kg/m}^2$ obesity

Waist circumference

- Non-Asian
 - > 40 inches in men
 - > 35 inches in women
- Asian
 - > 35 inches in men
 - > 31.5 inches in women

Fat percentage

- Men > 30% obesity; 25%—29% pre-obesity
- Women > 35% obesity; 30%—34% pre-obesity

Category	BMI ranges (kg/m ²)	
	Non-Asian descent	Asian descent
Underweight	< 18.5	< 18.5
Normal	18.5—24.9	18.5—23.0
Pre-obesity/ overweight	25—29.9	23—27.5
Obesity	≥ 30	≥ 27.5

Staging: Identifying High-Risk Patients

AACE Staging System		
Stage	BMI (kg/m ²)	Complications
0	≥ 25-29.9 OR ≥ 30	No identified complications
1	≥ 25	≥ 1 mild-to-moderate complications that may be treated effectively by treating obesity
2	≥ 25	≥ 1 severe complication and may require more aggressive treatment

Edmonton Obesity Staging System				
Stage	Obesity-related risk factors	Physical symptoms	Psychological symptoms	Functional limitations
0	None	None	None	None
1	Subclinical	Mild – no medical treatment needed	Mild	QoL not impacted
2	Established ORC with medical intervention	Moderate	Moderate psychological sx (depression, anxiety, eating disorder)	Moderate – QoL is being impacted
3	Significant ORC with end organ damage (MI, heart failure, diabetes with complications)	Significant (incapacitating OA)	Significant (reduced mobility, unable to work or complete ADLs)	Significant – QoL is significantly impacted
4	Severe	Severe	Severe	Severe

ORC, obesity-related complication; MI, myocardial infarction; OA, osteoarthritis; ADLs, activities of daily living; QoL, quality of life ; AACE, American Association of Clinical Endocrinologists

APPROACH: The 5As

ASK

Ask the patient's permission

"Would you be willing to discuss your weight and the treatment options?"

ASSESS

Usual PMH/SH including weight history, family history of obesity, obesogenic medications; review food intake, current activity, sleep duration and stressors

ADVISE

Advise on treatment options

AGREE

Utilize motivational interviewing and shared decision making to develop a plan of treatment from the options discussed

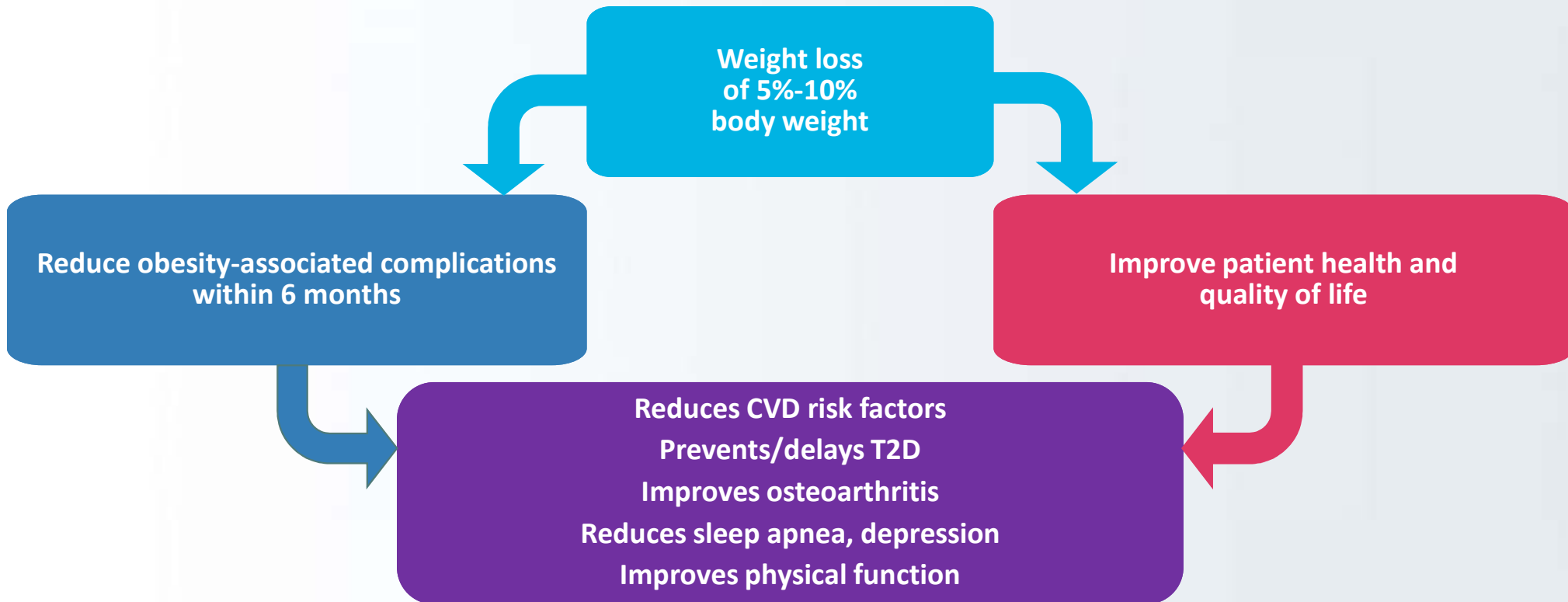
ASSIST

During follow-up visits assist the patient in staying on track, reassessing for needed changes in treatment; referrals and resources

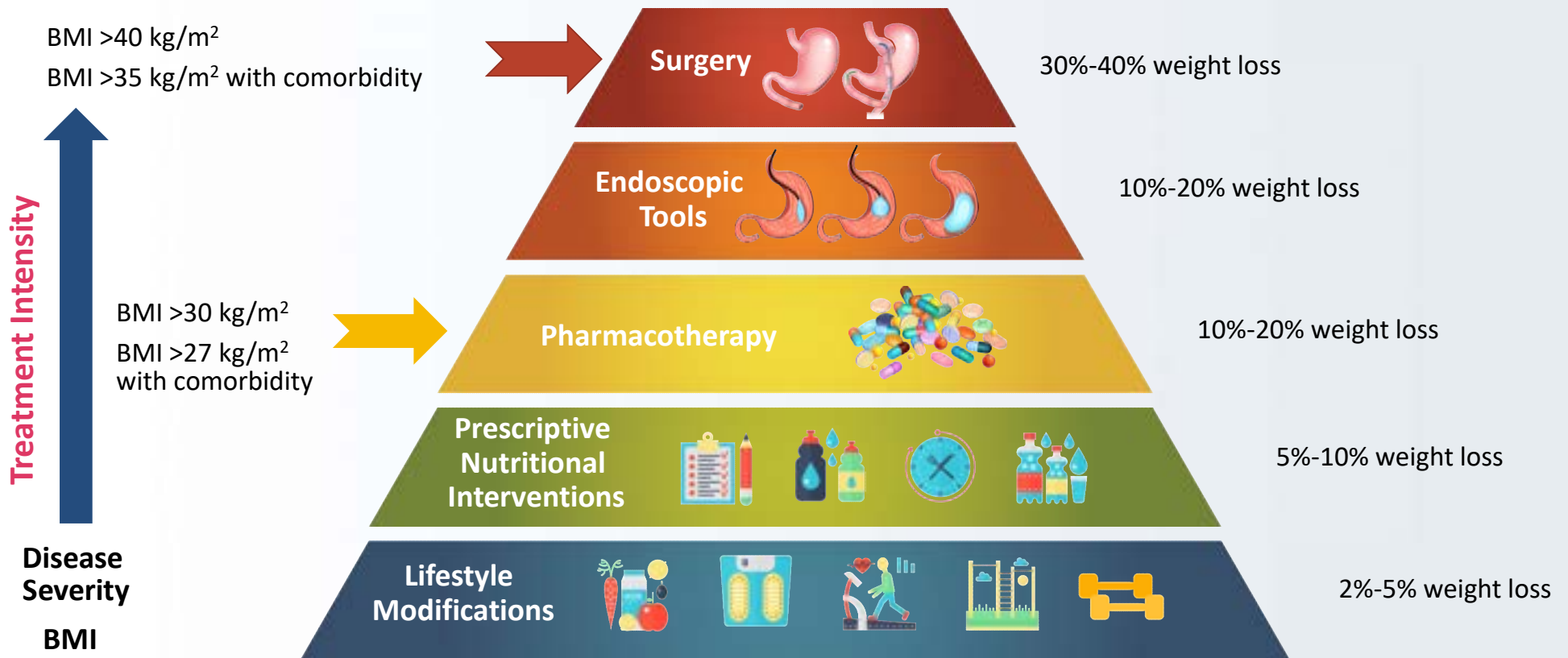
Patient Speaker – Perspectives on the Approach to Obesity Management



Obesity Management: Therapeutic Goals



Obesity Treatment Pyramid




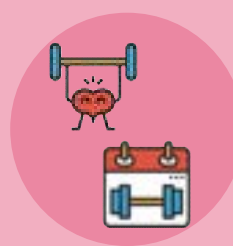
Lifestyle Interventions

EATING PLANS

-  Keto
-  Paleo
-  Vegetarian
-  Vegan
-  Mediterranean
-  Low Carb
-  DASH
-  No Sugar

ACTIVITY

- 



Aerobic exercise
During obesity treatment: 150 min per week
Maintain Weight Loss: 300-400 min per week
- 

Resistance Training
 Twice per week to maintain lean mass

BEHAVIORAL TECHNIQUES

- Motivational interviewing 
- Cognitive-behavioral therapy 

OTHER HEALTH FACTORS

- Sleep / Circadian enhancement 
- Stress reduction 

Obesity Pharmacotherapy

What Is the Primary Purpose of Adjunctive Medications Used in Obesity Treatment?

The primary purpose of anti-obesity medications is to

- Impact the pathophysiology of the disease,
- Facilitate weight loss and health improvements, and
- Support adherence to lifestyle interventions by helping patients change their relationship with food.

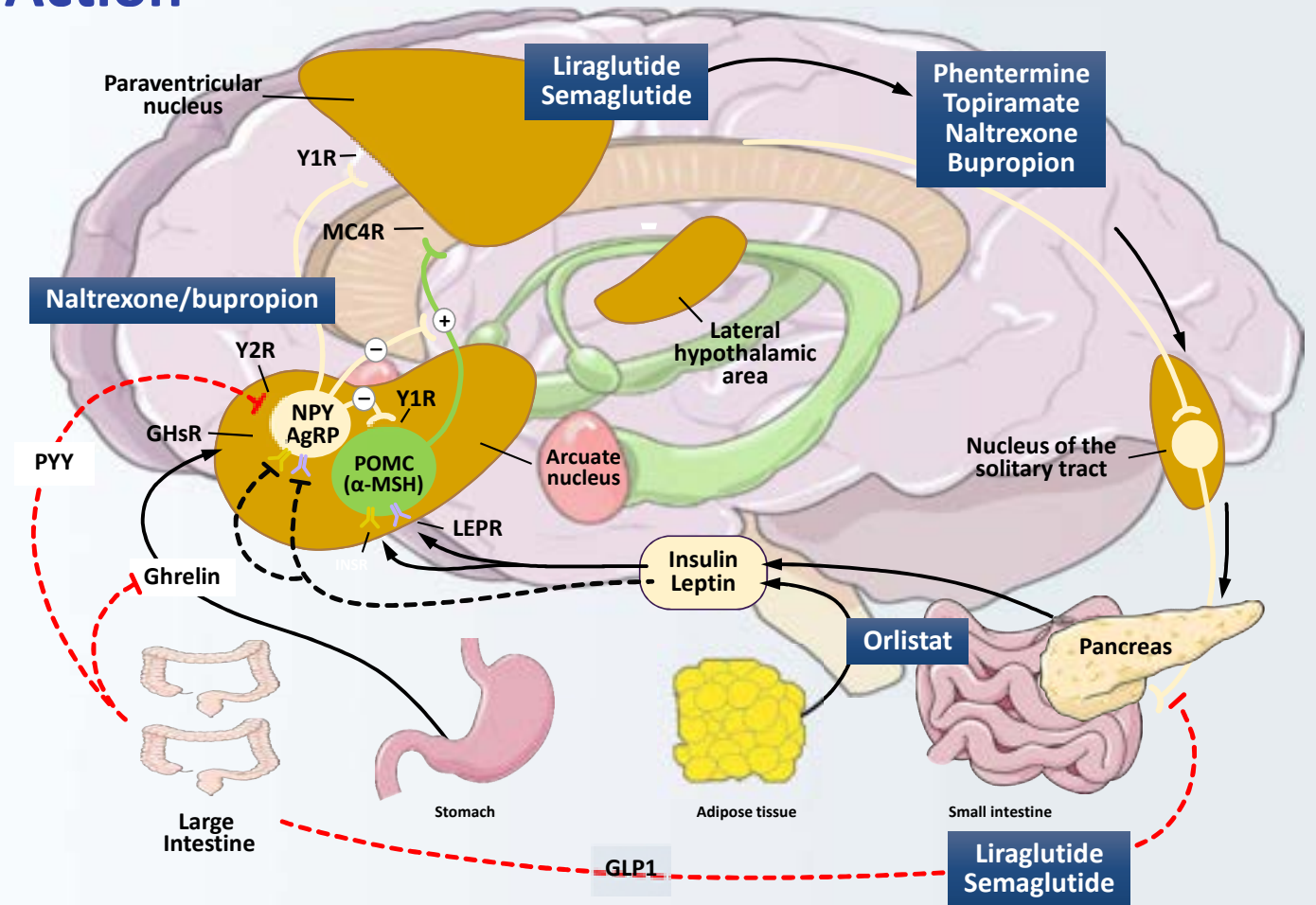
Indicated for patients with BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² with a comorbidity



FDA-Approved Medications for Obesity

Agent	Mechanism of Action	Effect	Approval Date
Phentermine (Lomaira/Adipex)	Sympathomimetic	Appetite regulation	1959
Orlistat (Xenical or Alli)	Pancreatic lipase inhibition	Reduces fat absorption	1999
Phentermine/topiramate ER (Qsymia)	Sympathomimetic, anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)	Appetite regulation	2012
Naltrexone/bupropion SR (Contrave)	Opioid receptor antagonist Dopamine/noradrenaline reuptake inhibitor	Appetite regulation	2014
Liraglutide (Saxenda)	GLP-1 receptor agonist	Appetite regulation	2014
Setmelanotide (IMCIVREE)	Melanocortin 4 (MC4) receptor agonist <i>[Indication: Obesity due to POMC, PCSK1, or LEPR deficiency]</i>	Appetite regulation	2020
Semaglutide (Wegovy)	GLP-1 receptor agonist	Appetite regulation	2021

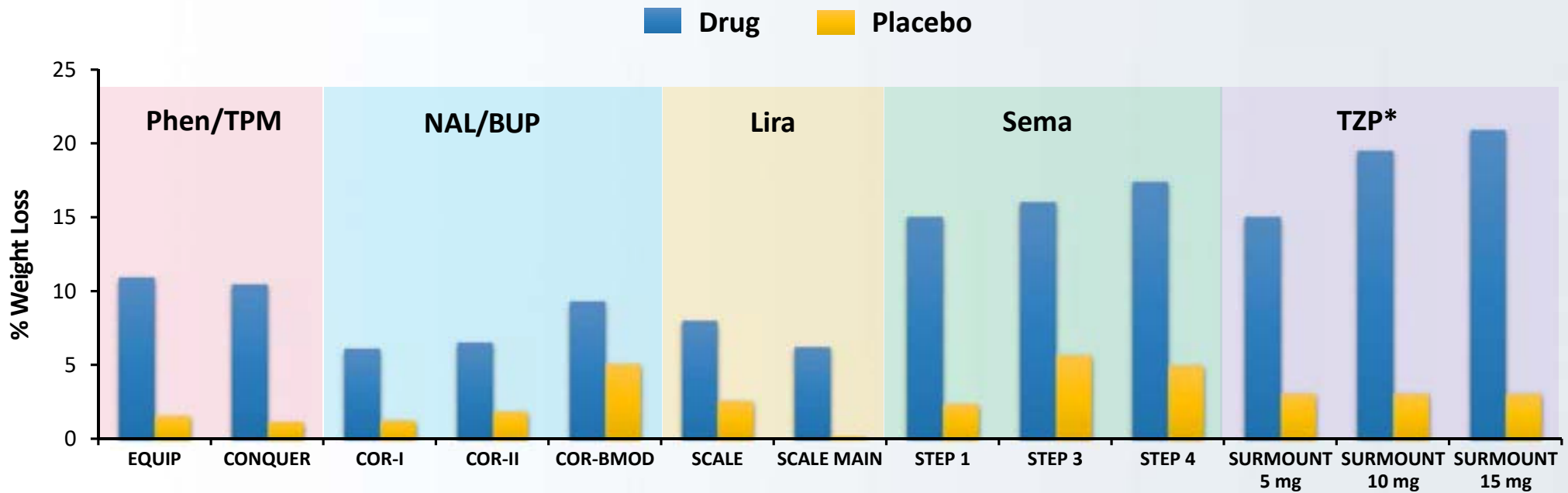
Medication Sites of Action



α-MSH, α-melanocyte-stimulating hormone; GHsR, growth hormone secretagogue receptor; INSR, insulin receptor; LEPR, leptin receptor; MC4, melanocortin-4 receptor; POMC, pro-opiomelanocortin; Y1R, NPY Y1 receptor; Y2R, NPY Y2 receptor.

Apovian CM, et al. *J Clin Endocrinol Metab.* 2015;100(2):342-362.

Average Percent Weight Loss (Drug vs. Placebo) from Randomized, Controlled Trials



*Not FDA approved for obesity

Phen/TPM, phentermine + topiramate; NAL/BUP, naltrexone + bupropion; Lira, liraglutide; Sema, semaglutide; TZP, tirzepatide

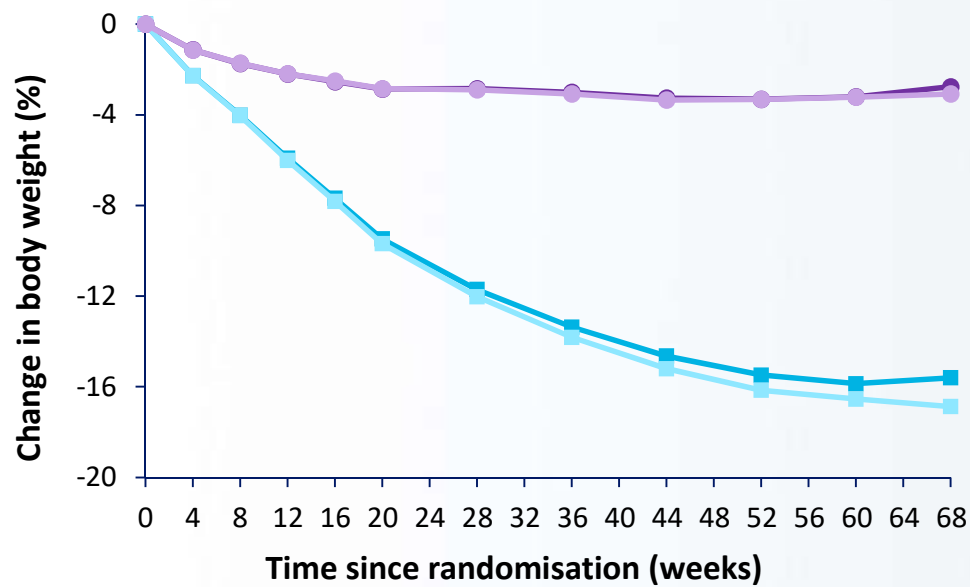
Allison DB et al. *Obesity* (Silver Spring). 2012;20(2):330-42; Gadde KM et al. *Lancet*. 2011;377:1341-52; Greenway FL et al. *Lancet*. 2010;376:595-605; Apovian CM et al. *Obesity* (Silver Spring). 2013;21(5):935-43; Wadden TA et al. *Obesity* (Silver Spring). 2011;19(1):110-20; Davies MJ et al. *JAMA*. 2015;314(7):687-99; Wilding JPH et al. *N Eng J Med*. 2021;384(11):989-1002; Wadden TA et al. *JAMA*. 2021;325(14):1403-13; Rubino D et al. *JAMA*. 2021;325(14):1414-25; Jastreboff AM et al. *N Eng J Med*. 2022 Jun 4. doi: 10.1056/NEJMoa2206038.

Emerging Anti-obesity Pharmacological Therapies

Category	Mechanism	Drug	Stage of Development
Hormonal	GLP-1 RA	Semaglutide	Approved 2021
	GLP-1/GIP RA	Tirzepatide	Approved for T2D 2022
	GLP-1/glucagon RA		Phase 2
	GLP-1/GIP/glucagon		Phase 2
	Amylin analogue	Cagrilintide	Phase 2
	GLP-1/amylin analogue		Phase 1
	Ghrelin antagonist		Phase 1
	PYY analogue		Phase 1
	GLP-1 small molecule RA	Danuglipron	Phase 1
Neuropeptide	Melanocortin-4 RA	Setmelanotide	Approved 2020 for rare genetic conditions
Enzyme inhibition	Sodium-glucose transporter-1 and 2 (SGLT1, SGLT2 inhibitor)	Licoglifloxin	Phase 2
Monoamine receptor uptake inhibition	Noradrenaline, dopamine, serotonin uptake inhibitor	Tesofensine	Phase 3
Monoclonal antibody	Activin type II RA	Bimagrumab	Phase 2

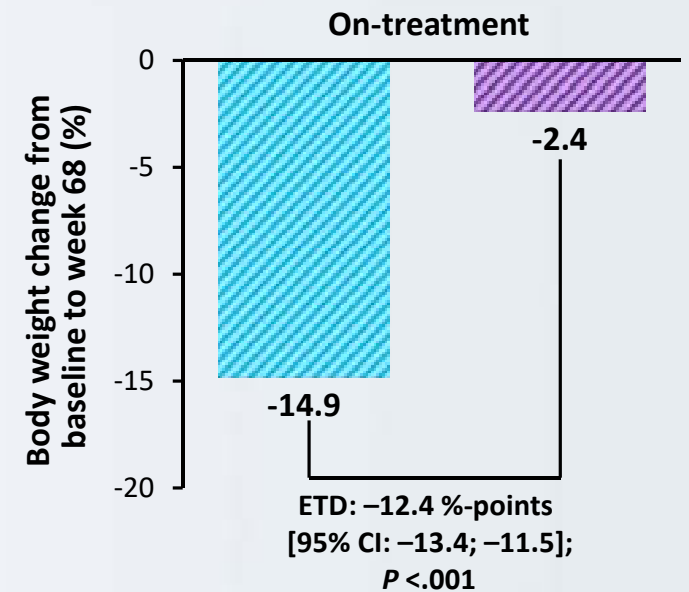
Semaglutide: STEP 1 Trial

Observed body weight change over time



Semaglutide 2.4 mg **Placebo**
In-trial:
On-treatment:

Estimated change from baseline to week 68



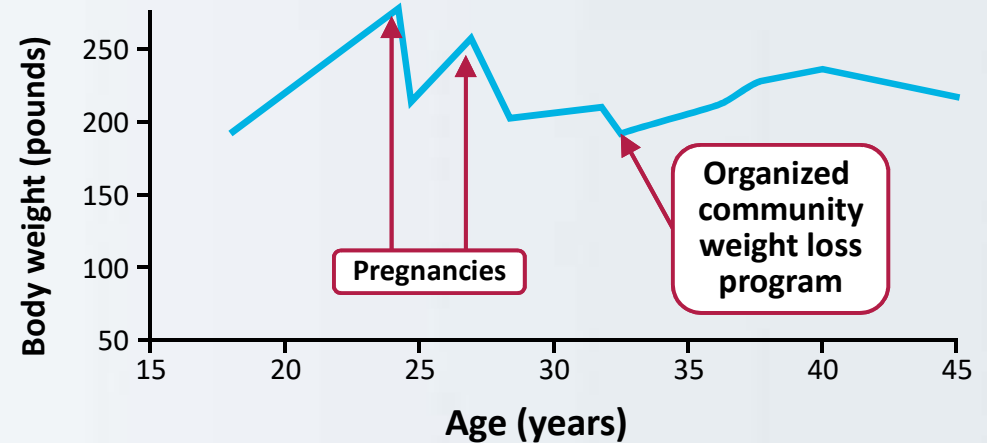
Semaglutide 2.4 mg (N=1306)
 Placebo (N=655)

Individualizing Obesity Management

ARS Question 1

Case 1: Ms. York

- 44 y/o female presents for well-woman visit.
- **PMH:** GERD, hypertension, depression, NAFLD, insulin resistance.
- **Meds:** Metoprolol 20 mg qd, omeprazole 20 mg qd, vortioxetine 20 mg qd, metformin 1000 mg bid.
- **Ask:** Patient gives permission to discuss her weight.
 - Reports 30-lbs weight gain in past 3 years.
- **Assess:**
 - Body-weight graph (above right)
 - Walks 20 min/day, 6 days/week
 - Tries to eat carefully everyday
 - Sleeps 7 hours most nights
 - Two teenage children at home



ARS QUESTION:

ARS-T1: What obesogenic medication is this patient taking?

1. Metformin
2. Metoprolol
3. Omeprazole
4. Vortioxetine

ARS Question 2

Case 1: Ms. York, Cont'd



- **Vitals:** BP 126/72 mmHg, HR 82 bpm, RR 16 bpm.
- **Biometrics:** Height 5'6", weight 216 lbs, BMI 34.86 kg/m², waist circumference 42".
- **Screening tools:** PHQ9 (score 4), BED7 (negative), STOP-BANG (score 2).
- **Shared decision making:**
 - Eating plan: Discuss very low calorie diet (VLCD) with meal replacement plan.
 - Activity: Increase steps to 7500 per day, add resistance training 2x per week.
- **Replaced metoprolol with ACE inhibitor.**
- Follow-up visit in 2 weeks.

ARS QUESTION:

ARS-T2: You are considering whether to start anti-obesity medication (AOM). What are the criteria for starting pharmacotherapy?

1. Initiate AOM only for adults with BMI ≥ 30 kg/m²
2. Initiate AOM for adults with BMI ≥ 30 kg/m² or ≥ 27 kg/m² with comorbidities
3. Initiate AOM for adults with BMI ≥ 35 kg/m² or ≥ 30 kg/m² with comorbidities
4. Initiate AOM for adults with BMI ≥ 25 kg/m² who are unable to lose weight with lifestyle changes

Case 2: Mr. Alves

- 52 y/o male presents for diabetes and hypertension follow-up and medication refill.
- **PMH:** T2D, hypertension, dyslipidemia, osteoarthritis in both knees, NAFLD, OSA.
- **Family Hx:** Obesity, CVD, T2D.
- **Social Hx:** No tobacco or alcohol use, no drug abuse.
- **Meds:** Canagliflozin/metformin 50 mg IR/1000 mg ER qd, lisinopril 40 mg qd, lovastatin 80 mg qd, ibuprofen 400 mg prn (up to tid).
- **Ask:** Patient gives permission to discuss his weight.
 - Responds: “Will it get me off any of my meds?”

ARS Question 3

Case 2: Mr. Alves, Cont'd



- **Vitals:** BP 138/78 mmHg, HR 82 bpm, RR 16 bpm.
- **Biometrics:** Height 6'1", weight 248 lbs, BMI 32.72 kg/m², waist circumference 43".
- **Screening tools:** PHQ9 (score 0), BED7 (negative), using CPAP every night.
- **Shared decision making:**
 - Eating plan: Rejoined community program
 - Activity: Joined a gym, swims 3 days/week
 - Patient reluctant to injectable medications
- No obesogenic medications noted.
- Follow-up in 2 weeks.

ARS QUESTION:

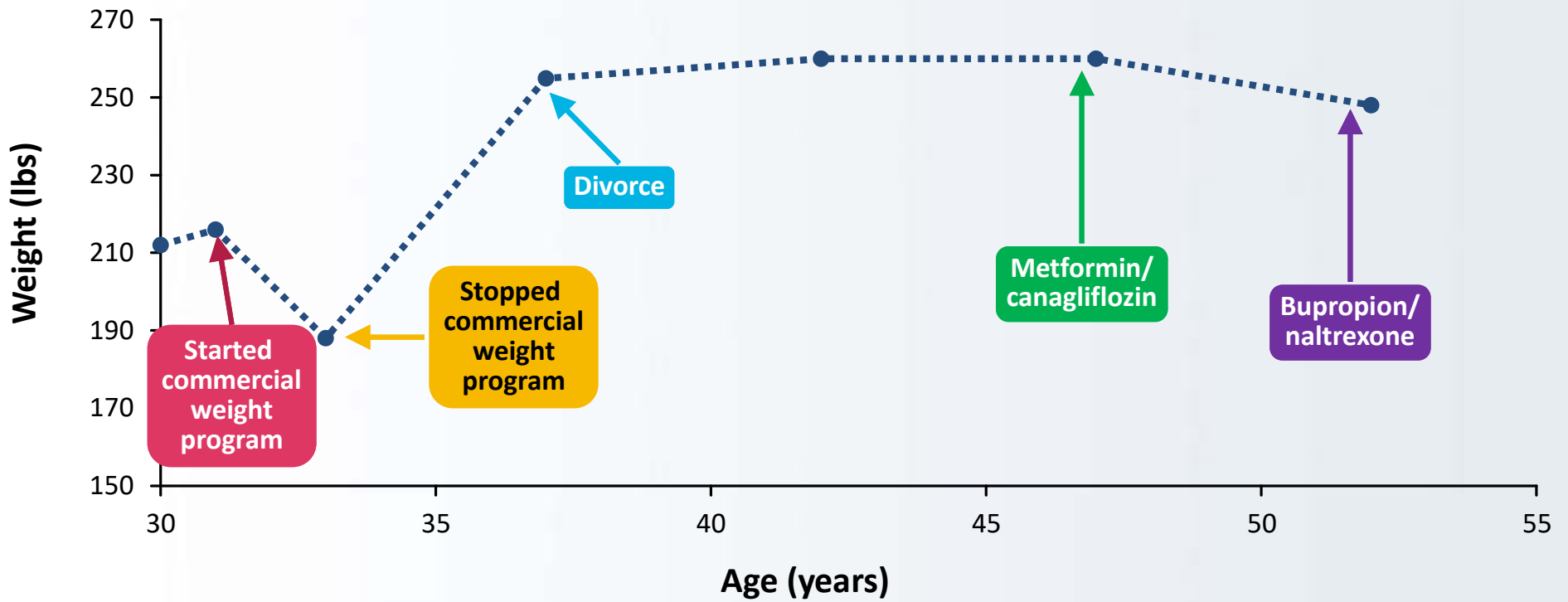
ARS-T3: Which anti-obesity medication would be appropriate for this patient?

1. GLP1-RA
2. Lipase inhibitor
3. Sympathomimetic with GABA receptor modulator
4. Opioid antagonist combined with norepinephrine dopamine reuptake inhibitor

Case 2: Mr. Alves, Cont'd

- **Eating plan:** Showed record of attending community commercial weight program.
- **Activity:** Over past 3 weeks has attended gym for weight lifting 2x week and swimming 3x week.
- **Behavior:** Completed education on obesity as a disease.
- **Medication:** During shared decision making, patient declines an injectable agent and decides to start bupropion/naltrexone.

Mr. Alves: Body-Weight Graph



ARS Question 4

Case 2: Mr. Alves, Cont'd



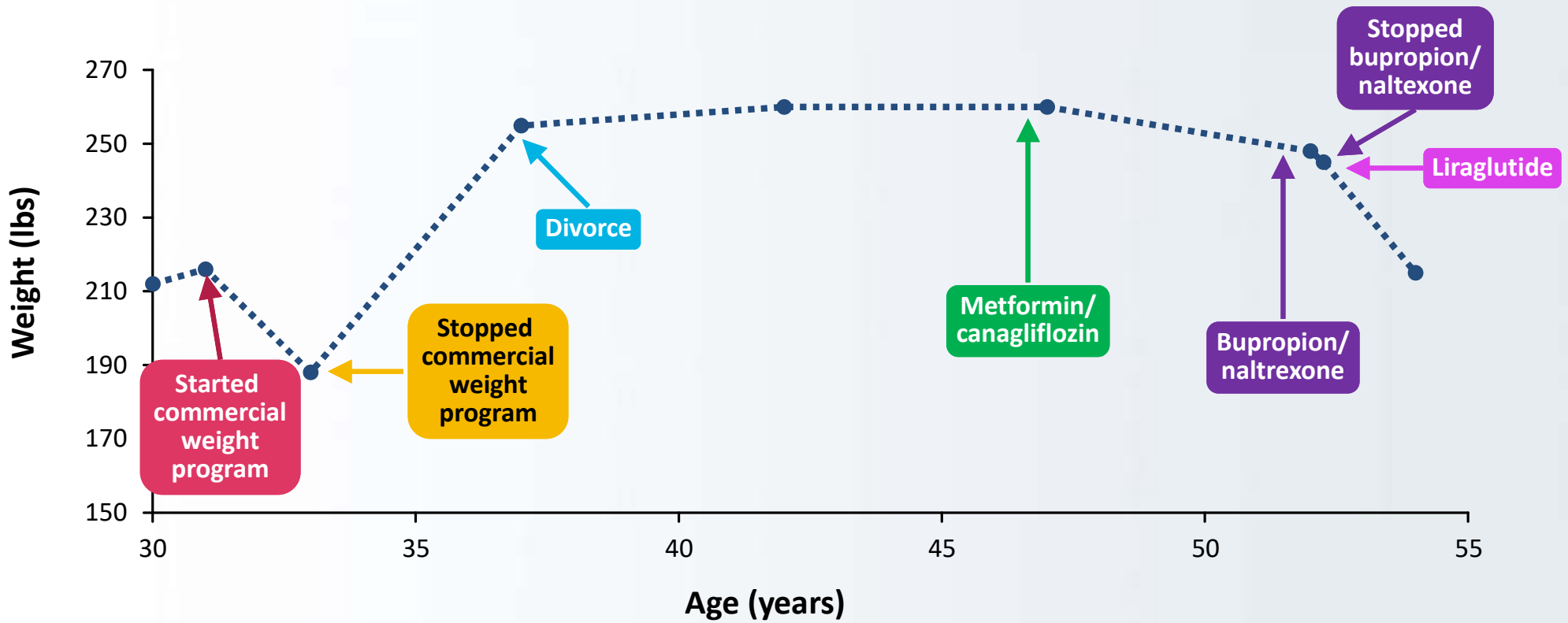
- 3 months later.
- Patient has lost 5 lbs (2% baseline weight).
 - Weight now 243 lbs.
 - BMI 32.3 kg/m².
- Reports consistent exercise and participation in commercial weight program.
- Reports adherence to bupropion/naltrexone.

ARS QUESTION:

ARS-T4: What would you recommend now for this patient?

1. Add lipase inhibitor
2. Maintain current therapy for 1 year
3. Switch from bupropion/naltrexone to GLP-1 RA
4. Switch from bupropion/naltrexone to sympathomimetic with GABA receptor modulator

Mr. Alves: Body-Weight Graph



Post-test Questions

Post-test Question 1

Post-T1: Which of the following factors mediate the link between obesity and comorbidities such as dyslipidemia and insulin resistance?

1. Secreted adipocyte factors
2. Increased anorexigenic signaling
3. Reduced ghrelin production in gut
4. Reduced circulating levels of estrogen

Post-test Question 2

Post-T2: Which of the following medications have demonstrated an average of $\geq 15\%$ weight loss in clinical trials?

1. Liraglutide
2. Naltrexone/bupropion
3. Phentermine/topiramate
4. Semaglutide

Post-test Question 3

Post-T3: 52 y/o man with obesity, T2D, hypertension, dyslipidemia.

Says he is concerned about weight gain over last 10 years (~25 lbs).

Workup: BMI 32.7 kg/m², BP 128/82 mmHg, A1C 6.9%, eGFR 52 mL/min/1.73m².

Meds: Metformin 1000 mg bid, canagliflozin 100 mg qd, lisinopril/hydrochlorothiazide 20 mg/25 mg qd, atorvastatin 80 mg qd.

Lifestyle: Walks briskly for 1 hour 6 days per week; follows a low-calorie, low-fat diet.

Notes that he hates needles and does not want injectable medications.

What would you do next for this patient?

1. Recommend bariatric surgery
2. Down-titrate obesogenic medications
3. Prescribe exenatide, lixisenatide, or dulaglutide
4. Discuss benefits of phentermine/topiramate or naltrexone/bupropion

Post-test Question 4

Post-T4: 38 y/o woman with history of T2D, hypertension, obesity.

Has gained 45 lbs in last 5 years.

Workup: BMI 34 kg/m², BP 142/86 mmHg, A1C 6.7%.

Meds: Lisinopril 20 mg qd, metformin 1000 mg bid, naltrexone/bupropion 2 tablets bid.

Lifestyle: Swims 45 min 5x week, lifts weights 2x week; goes to commercial weight-loss program. Started naltrexone/bupropion 3 months ago; has lost 5 lbs (2.4% baseline weight) in that time.

What might be appropriate at this time?

1. Maintain naltrexone/bupropion for at least 6 months
2. Stop naltrexone/bupropion and refer for bariatric surgery
3. Continue naltrexone/bupropion and prescribe phentermine
4. Discontinue naltrexone/bupropion and prescribe liraglutide or semaglutide

Post-test Question 5

Post-T5: After completing this activity, how confident are you in your ability to select long-term pharmacotherapy to manage patients with obesity?

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident

Post-test Question 6

Post-T6: After completing this activity, how often do you intend to assess comorbidities when considering anti-obesity therapies for patients with overweight/obesity?

1. Never
2. Rarely
3. Sometimes
4. Often
5. Always

Post-test Question 7

Post-T7: Approximately how many patients with obesity do you see on a weekly basis, in any clinical setting?

1. None
2. 1-5
3. 6-10
4. 11-15
5. 16-20
6. 21-25
7. >25

Q&A