



MEDICATIONS THAT AFFECT WEIGHT STATUS

(and body composition)

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Disclosures

- *Advisor/consultant:* Altimune, Amgen, Astra Zeneca, Biohaven, Calibrate, Carmot/Roche, CINRx, Epitomee, Fractyl, Gila, Lilly, Nestle, Novo Nordisk, Scientific Intake, Structure Therapeutics, Wondr Health, Zealand
- *Speaker's Bureau:* Novo Nordisk, Lilly
- *Stock Options:* Epitomee, Calibrate, Roman, Scientific Intake
- *DSMB:* IQVIA setmelanotide (2); Lilly(1)

Objectives

At the conclusion of the presentation, learners will be more able to

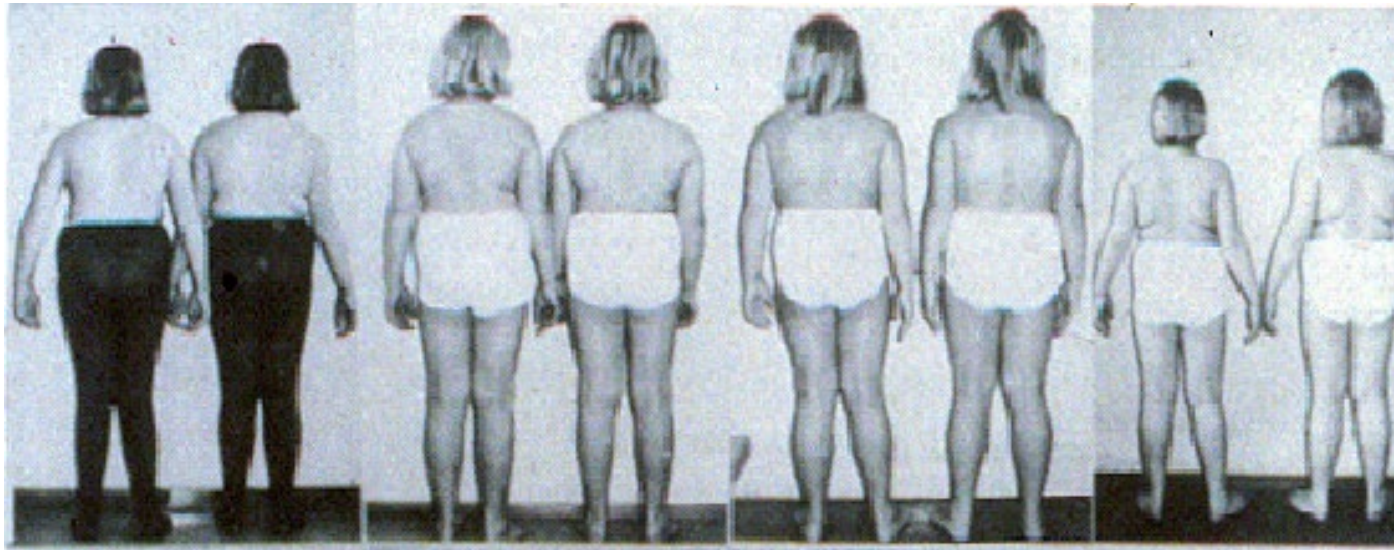
1. describe what is known about the biology of regulation of body weight and body composition;
2. describe the medications currently approved for chronic weight management within the context of drug development attempts over the last 100 years;
3. relate how medications approved for various indications can influence weight and body composition; and
4. discuss future approaches to obesity treatment with medications with the goal of optimizing body composition and function.

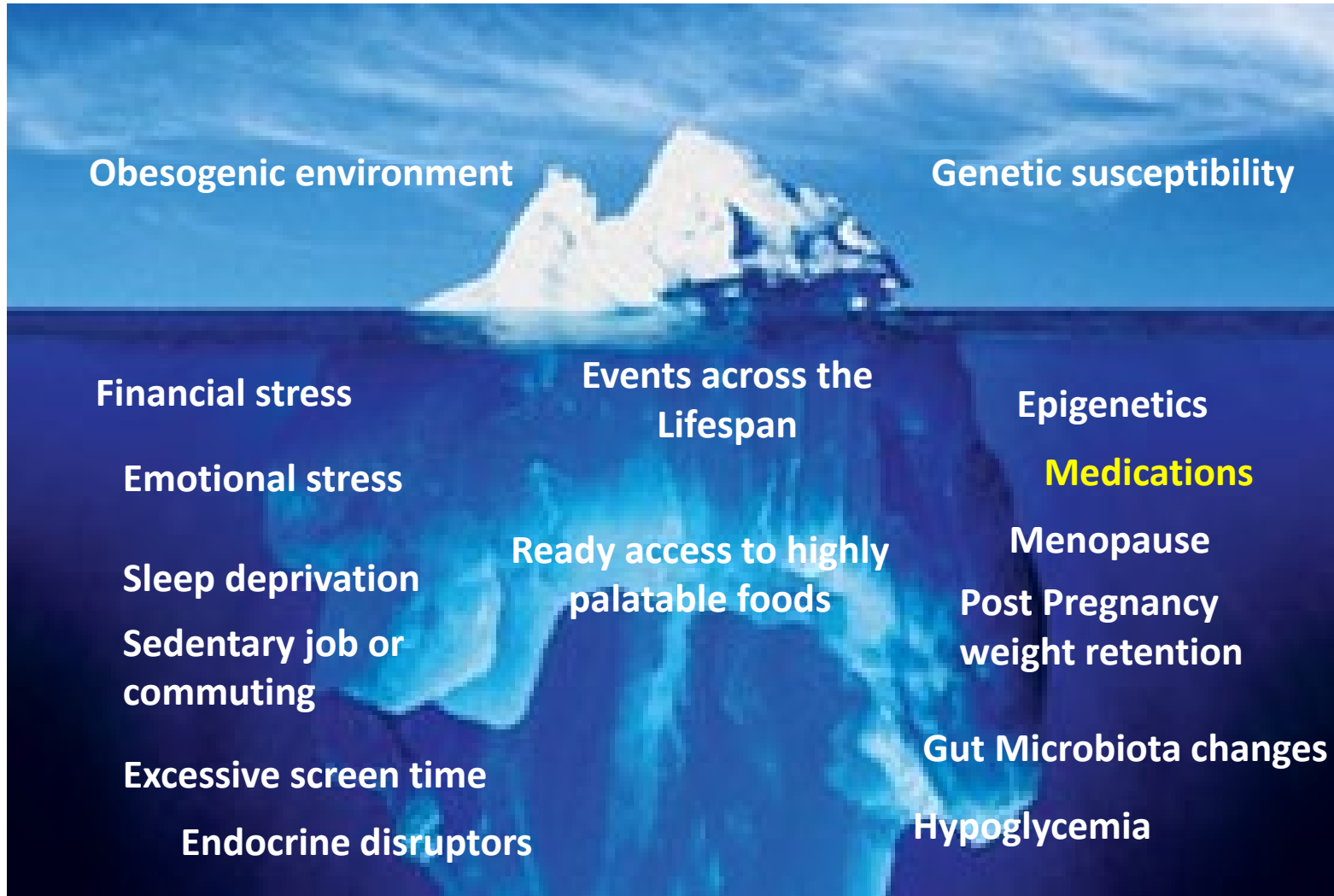
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Genetic Contribution to Body Habitus





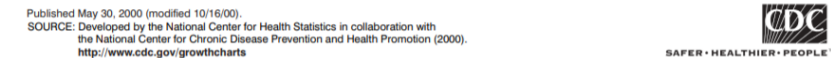
**What
influences
body weight
and body
composition
?**

NAME _____

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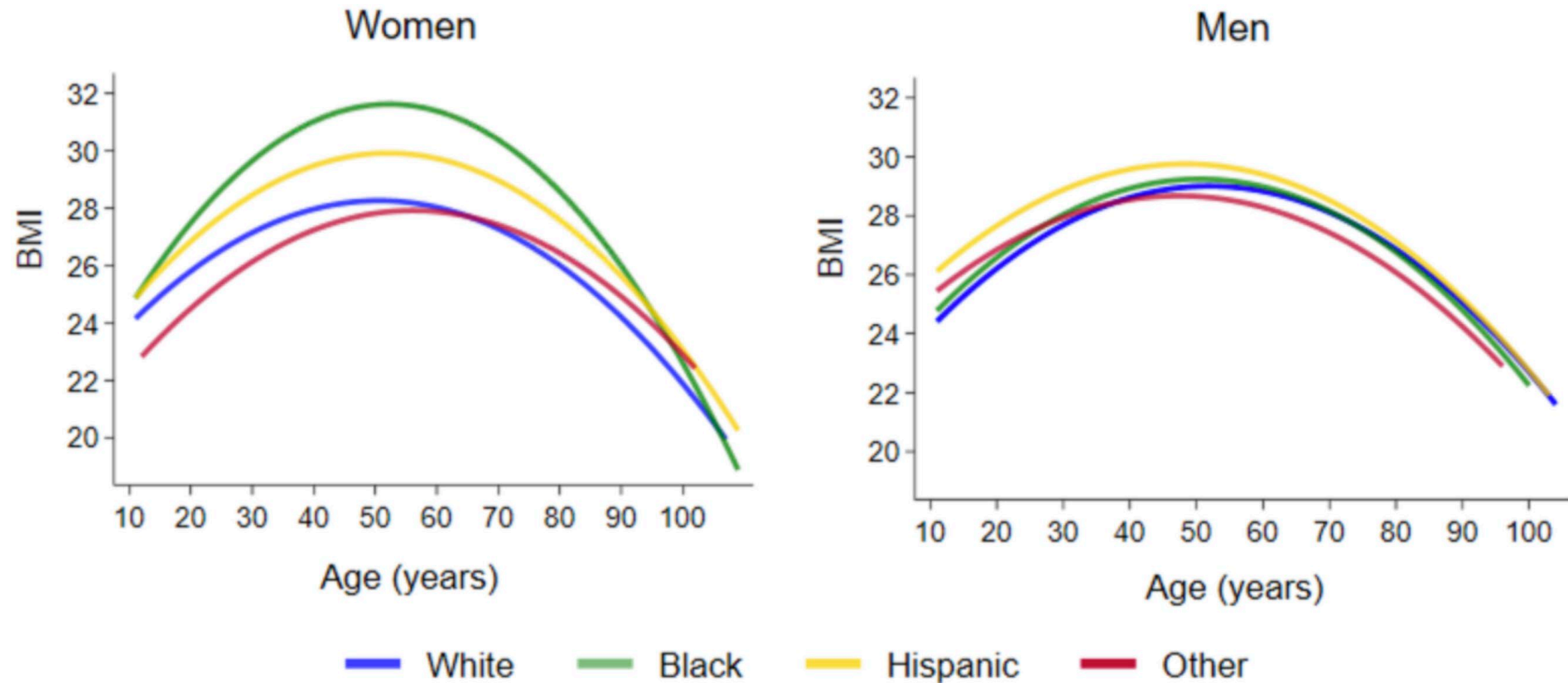
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Somatic Changes During Puberty

- Lean mass increases steadily from onset to completion of puberty but is greater in males.
- At the onset of puberty there is an increase in fat accumulation in females and a decrease in males.
- At time of somatic maturation, females have twice the body fat of males.
- 17% body fat required for onset of menses and 22% body fat required for maintenance of menses.

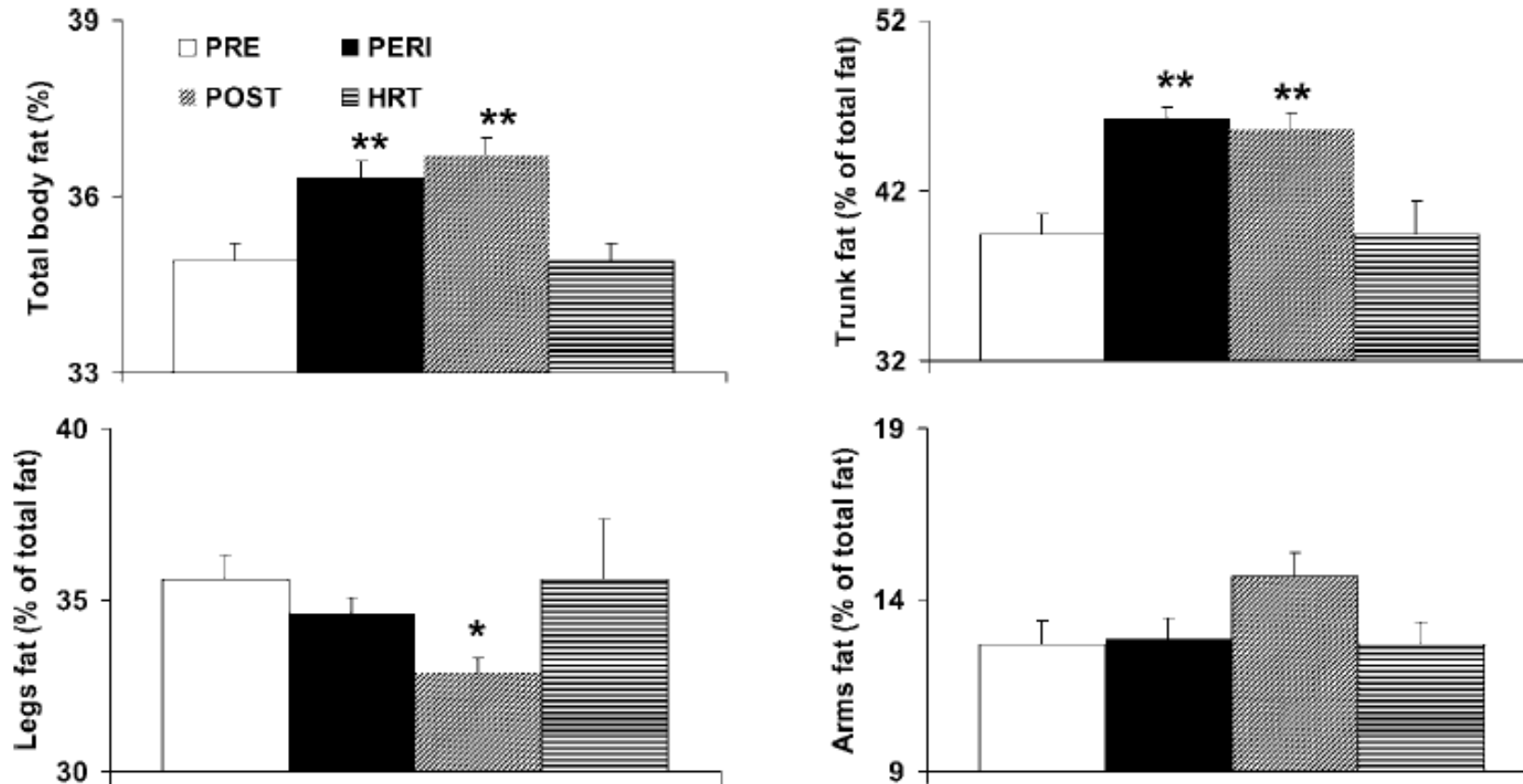
Most people gain weight over early and mid adulthood and lose weight (lean mass) beginning in mid-60's.



Somatic Changes During Menopause

- Weight gain is 0.5 kg/year during midlife
- Weight *per se* is not related to menopause
- Changes in body fat composition and distribution are related to ovarian hormones
- Matching for age, peri and post menopausal women have more fat mass and visceral fat than pre menopausal women

Body Fat Redistribution During Menopause (age-matched women)

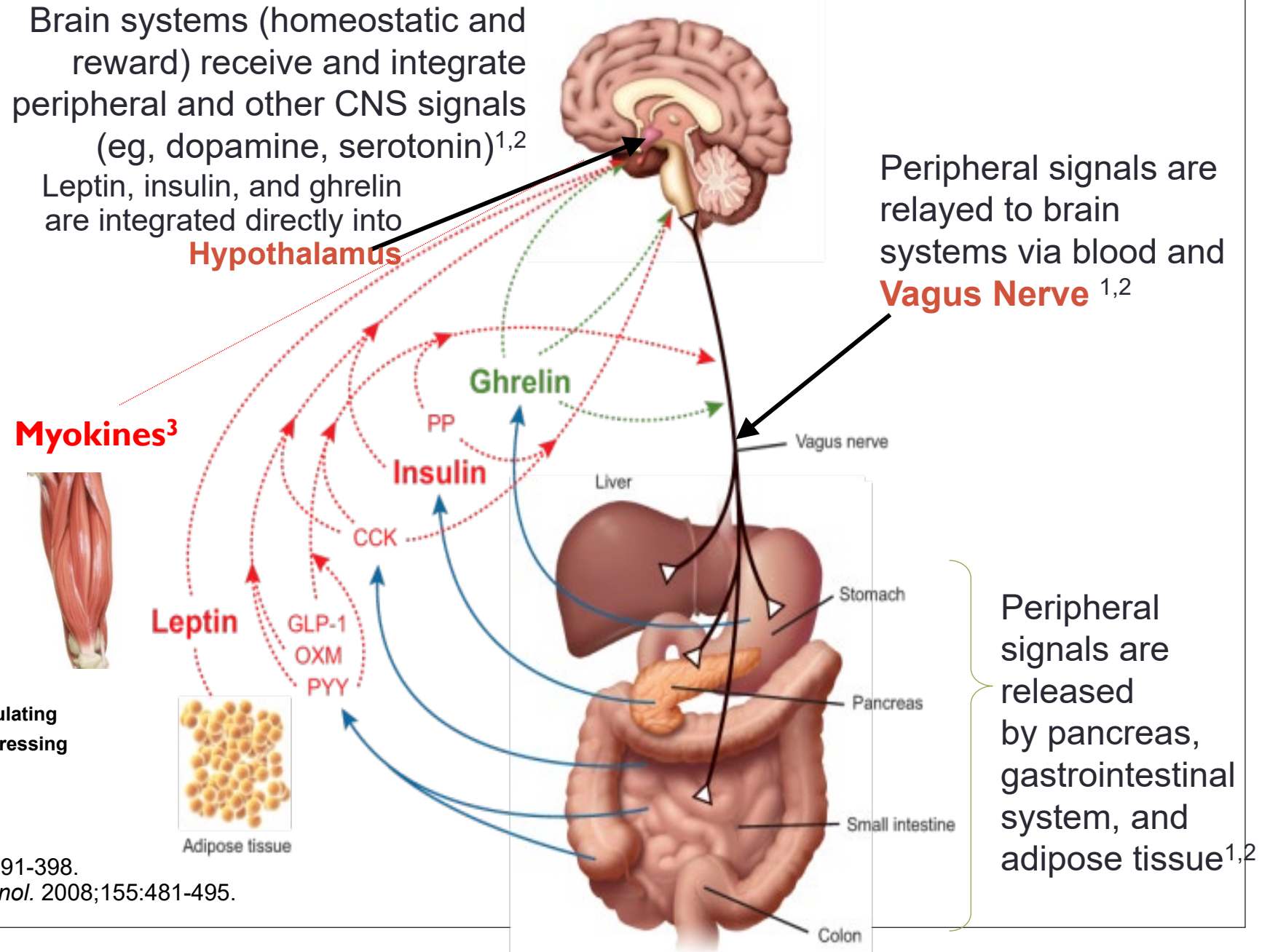


Genazzani AR, Gambacciani M. Gynecological Endocrinology. 2006; 22(3): 145–150

Complex Peripheral Signals are Integrated Into CNS Systems to Regulate Body Weight

CNS, central nervous system
 PFC, prefrontal cortex
 NAc, nucleus accumbens
 VTA, ventral tegmental area
 PP, pancreatic polypeptide
 CCK, cholecystokinin;
 GLP-1, glucagon-like peptide 1
 OXM, oxyntomodulin
 PYY, peptide YY.
 Primarily based on data from animal studies.

... Appetite Stimulating
 ... Appetite Suppressing



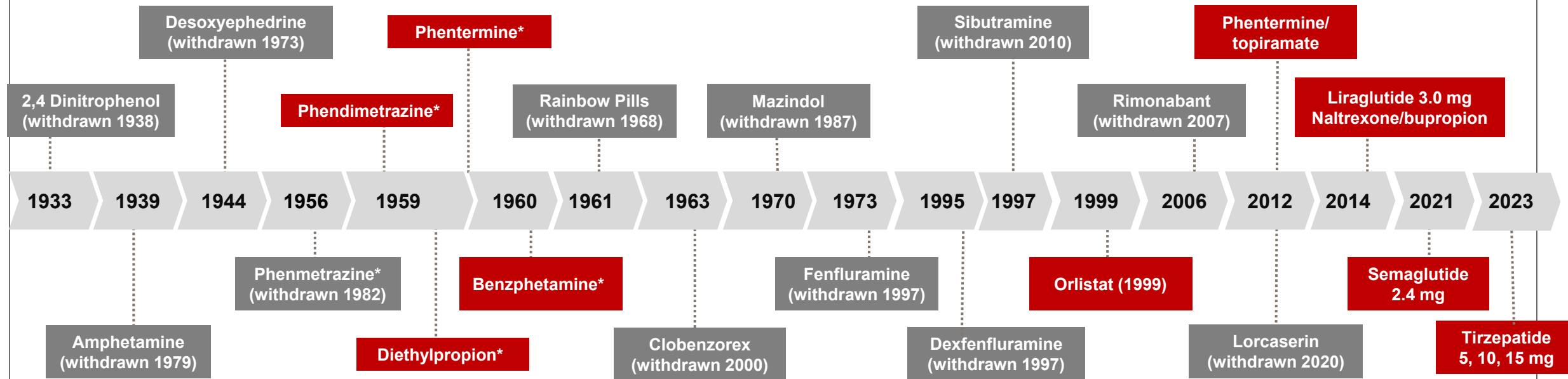
1. Yu JH et al. *Diabetes Metab J.* 2012;36(6):391-398.
2. Mendieta-Zerón H et al. *Gen Comp Endocrinol.* 2008;155:481-495.
3. Grannell A, et al. *Muscles* 2022, 1, 26–47.

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Progress in Anti-Obesity Pharmacotherapies¹⁻⁴



*Approved for short term use in the US

■ Withdrawn AOMs

■ AOMs on market

AOMs = Antiobesity medications

1. Pilitsi E, et al. *Metabolism*. 2019;92:170-192.

2. Müller TD, et al. *Nat Rev Drug Discov*. 2021;1-23.

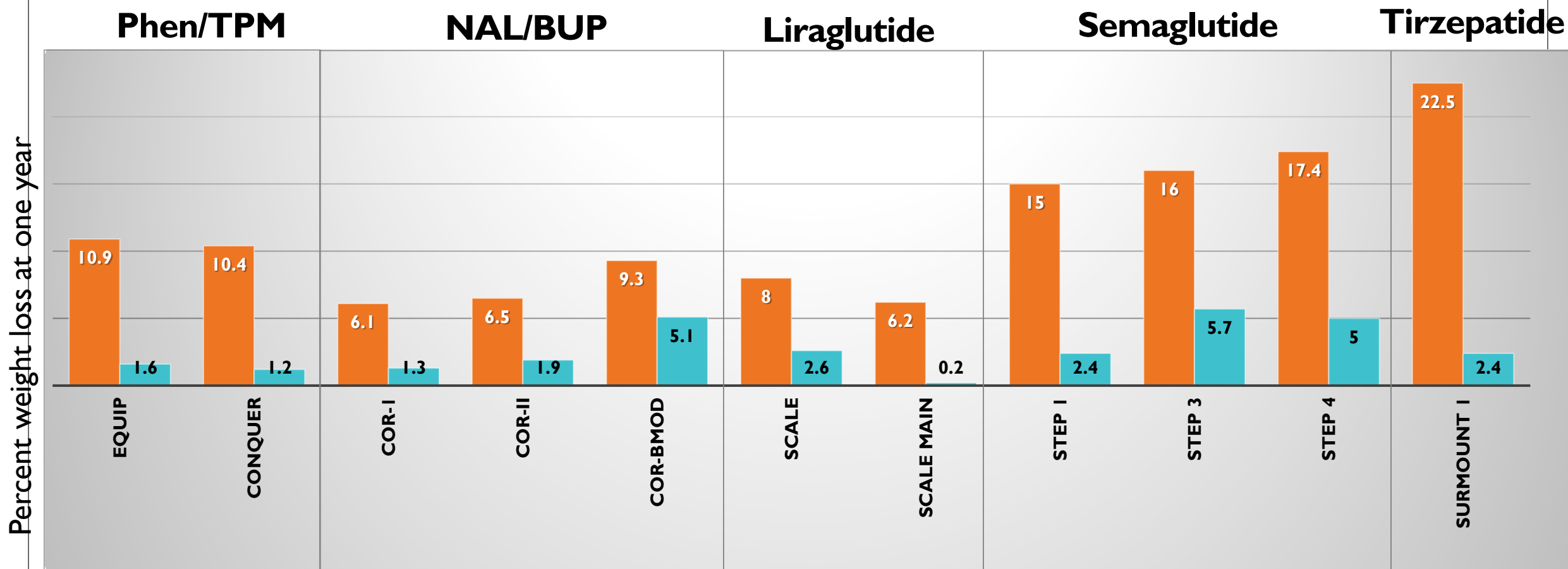
3. Onakpoya IJ, et al. *BMC Med*. 2016;14:191.

4. <https://www.ajmc.com/view/fda-approves-diabetes-drug-tirzepatide-for-chronic-weight-management>

Slide courtesy Louis J. Aronne, M.D.

A Decade of Obesity Drug Discovery

Percent weight loss (drug vs placebo) for anti-obesity medications



Allison DB, et al. *Obesity*. 2012;20(2):330-342. [EQUIP]; Gadde KM, et al. *Lancet*. 2011;37:1341-1352. [CONQUER]; Greenway FL, et al. *Lancet*. 2010;376:595-605. [COR I]; Apovian CM, et al. *Obesity*. 2013;21:935-943 [COR II]; Wadden TA, et al. *Obesity*. 2011;19(1):110-120. [COR-BMOD]; Pi-Sunyer X, et al. *N Engl J Med*. 2015;373(1):11-22. [SCALE]; Wadden TA, et al. *Int J Obes*. 2013;37:1443-1451. [SCALE MAIN]; Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989-1002 [STEP 1]; Wadden TA, et al. *JAMA*. 2021;325(14):1403-1413. [STEP 3]; Rubino E, et al. *JAMA* 2021;325(14):1414-1425 [STEP 4]; Jastreboff A, et al. *N Engl J Med* 2022 Jun 4, DOI: 10.1056/NEJMoa2206038.

Drug
Placebo

Objectives

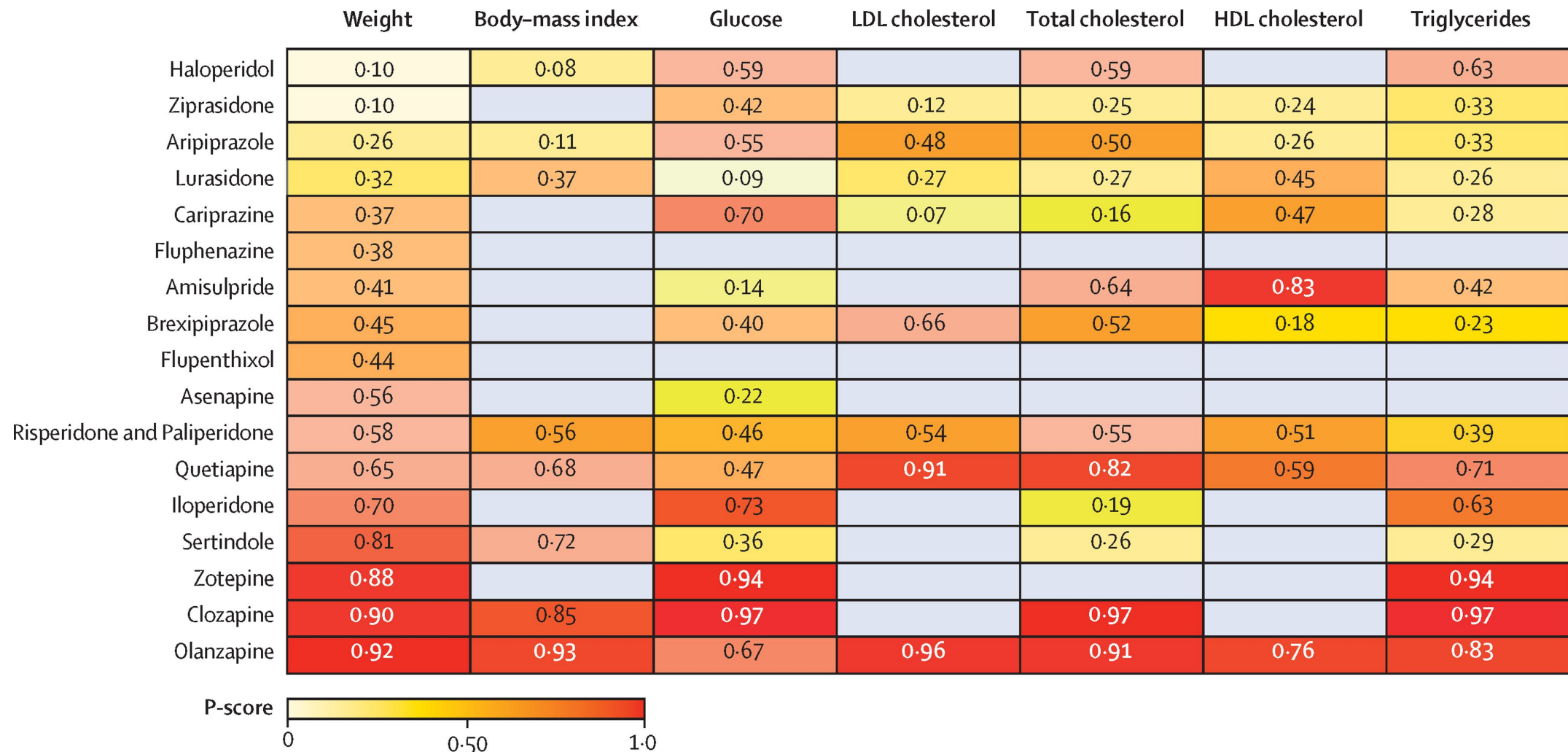
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Drugs That Cause Weight Gain

Category	Drugs That May Cause Weight Gain	Possible Alternatives
Neuroleptics	Thioridazine, haloperidol, olanzapine, quetiapine, risperidone, clozapine	Ziprasidone, aripiprazole
Antidiabetic agents	Insulin, sulfonylureas, thiazolidinediones	AGIs, DPP-4is, SGLT2is, GLP-1 RAs, metformin
Steroid hormones	Glucocorticoids, progestational steroids and contraceptives	Barrier methods, NSAIDs
Tricyclic antidepressants	Amitriptyline, nortriptyline, imipramine, doxepin	Protriptyline, bupropion, nefazodone
MAOIs	Phenelzine	
SSRIs	Paroxetine	Fluoxetine, sertraline
Other antidepressants	Mirtazapine, duloxetine	Bupropion
Anticonvulsants	Valproate, carbamazepine, gabapentin, pregabalin, vigabatrin	Topiramate, lamotrigine, zonisamide, felbamate
Antihistamines	Cyproheptadine	Inhalers, decongestants
β- and α-blockers	Propranolol, doxazosin	ACEi, CCBs

Heat Map: Weight and Metabolic effects of Antipsychotics



Pillinger T, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. The Lancet Psychiatry, Volume 7, Issue 1, 64 - 77

Antipsychotic Associated Weight Gain Mechanism of Action (MOA)

MOA of antipsychotics – Central effects

- First generation antipsychotics are mostly **dopamine antagonists**, especially D2. Some are **norepinephrine blockers**, cholinergic blockers or **histaminergic blockers**.
- Second generation antipsychotics are serotonin 5-HT_{2A} and **5-HT_{2C} antagonists**, many also are **dopamine antagonists**

Antiobesity Medication MOA – Central effects

- Lorcaserin – **5 HT_{2C} agonist**
- Bupropion (Naltrexone/Bupropion) – **dopamine and norepinephrine re-uptake inhibitor**
- Phentermine – **norepinephrine release**
- Semaglutide, tirazepatide – GLP-I RA (multiple brain areas)

Antidepressants

May Decrease Body Weight:

- Bupropion
- Fluoxetine (variable)

Variable Effects on Body Weight:

- Some tricyclic antidepressants (secondary amines)
 - Desipramine
 - Nortriptyline
 - Protriptyline
- Some selective serotonin reuptake inhibitors
 - Escitalopram
 - Sertraline
- Some serotonin and norepinephrine re-uptake inhibitors
 - Desvenlafaxine
 - Duloxetine
- Some irreversible monoamine oxidase inhibitors (i.e., tranylcypromine)
- Some other serotonergic agents
 - Vortioxetine

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HIV medications

- May Increase Body Weight
 - Some highly active antiretroviral therapies (HAART) protease inhibitors without HIV-associated lipodystrophy
- May Alter Body Composition
 - HAART protease inhibitors may increase abdominal and visceral fat, and produce HIV-associated lipodystrophy

Weight Change with Hormones

- Glucocorticoids
 - Can increase weight and create truncal fat distribution
- Progestin contraceptives
 - Injectable or Implantable progestins have greatest risk for weight gain
- Testosterone
 - When used to replace testosterone in testosterone deficiency in men, reduces % body fat and increases lean mass

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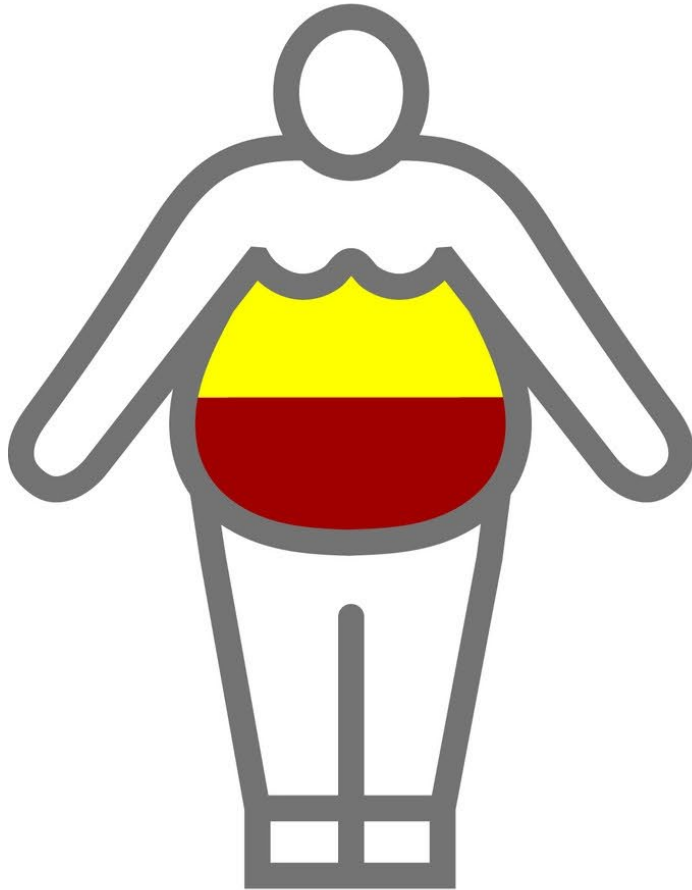
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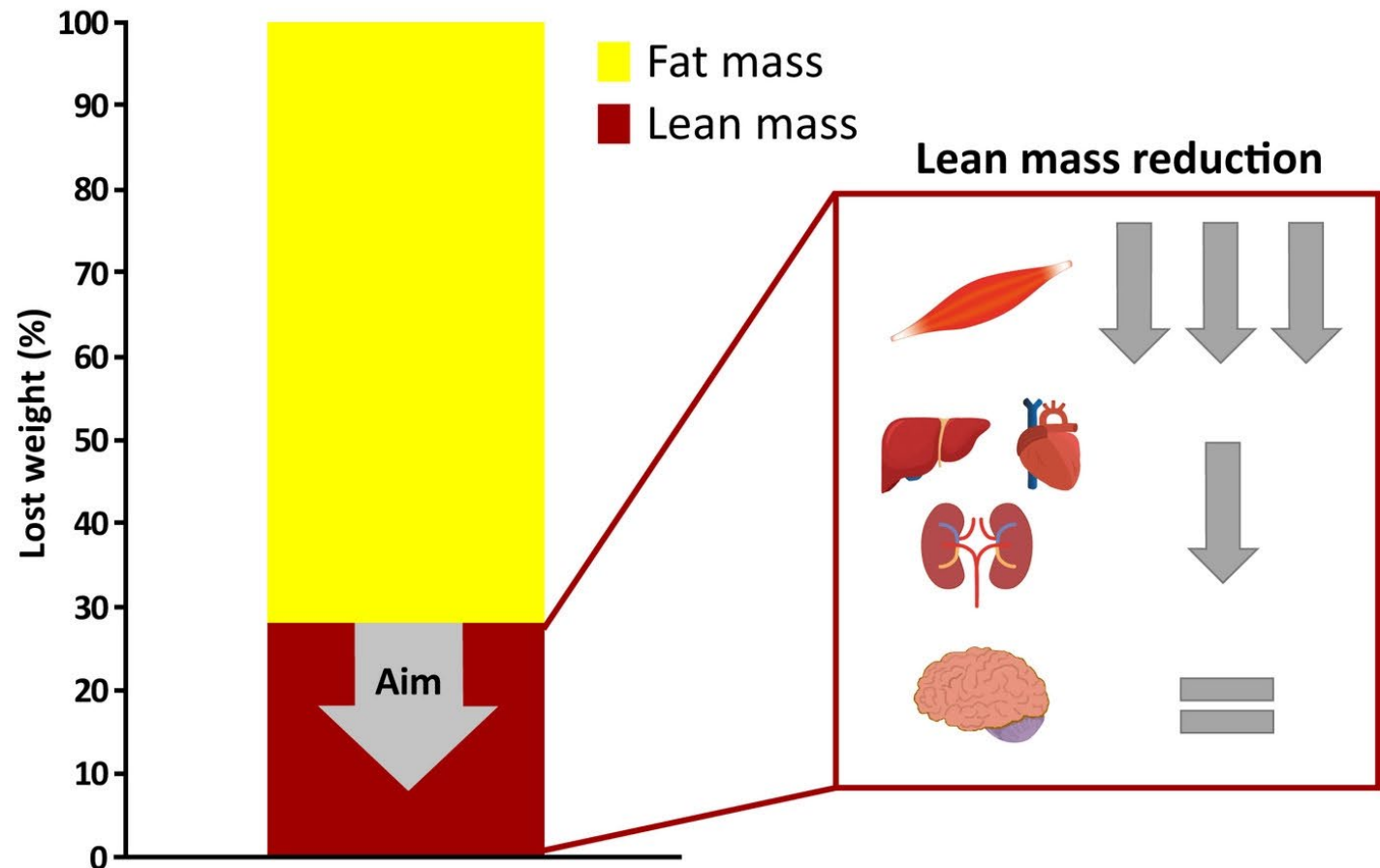
What is the goal of weight loss?

GOAL: Loss of excess abnormal fat mass, preservation of lean mass, optimizing organ function

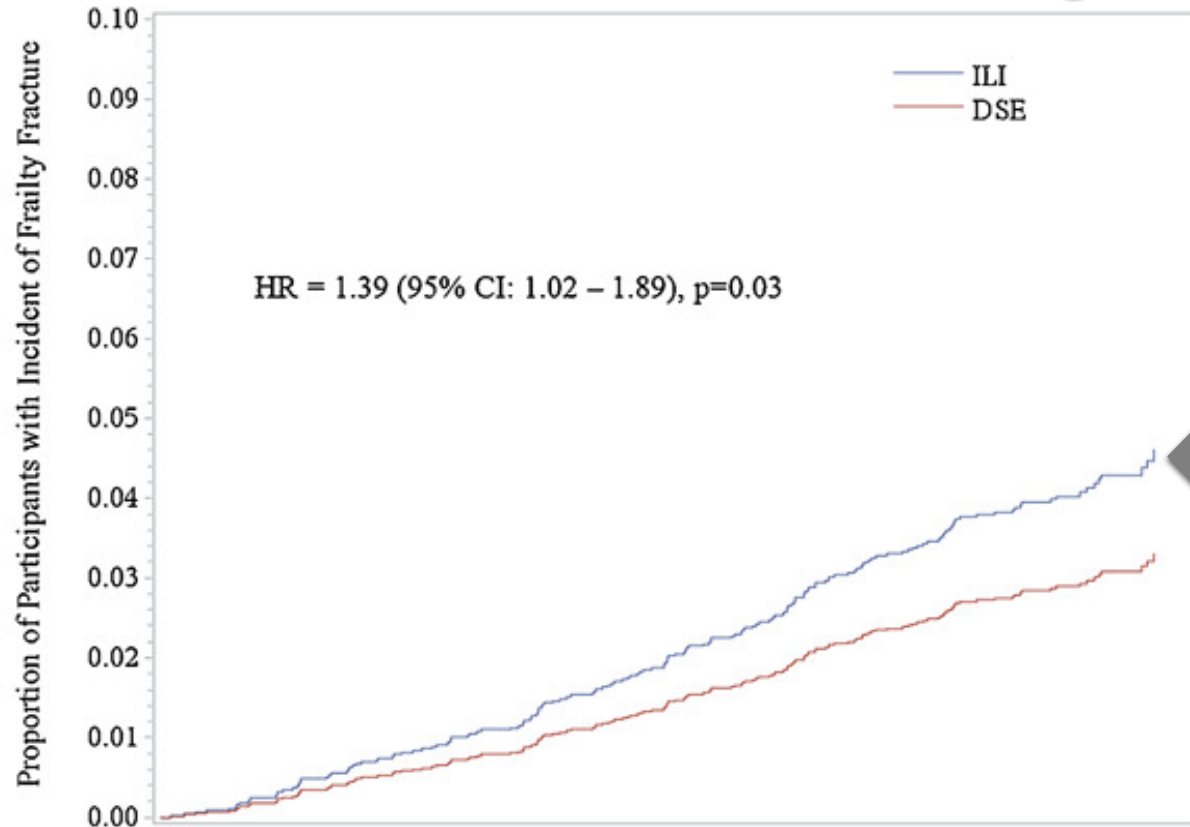
Before Weight Loss



Composition of Weight Loss



Look AHEAD Trial – Modest Weight Loss and Frailty Fractures



Increased risk of frailty fractures in Look AHEAD intensive lifestyle intervention.

Time (Years)	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Number at Risk														
DSE	2575	2526	2515	2477	2442	2407	2372	2336	2296	2228	2113	1810	1111	0
ILI	2570	2545	2499	2474	2452	2427	2391	2339	2299	2235	2184	1871	1173	0

Johnson KC, Bray GA, Cheskin LJ, et al. Look AHEAD Study Group. J Bone Miner Res. 2017 Nov;32(11):2278-2287.

Emerging Approaches to Improving Body Composition with Weight Loss

- Activin and Myostatin as targets
 - Bimagrumab - Monoclonal Ab blocks ActRIIB signaling
 - Taldefgrobep alfa – an adnectin that blocks active myostatin and inhibits ActRIIB signaling
 - Apitegromab – Monoclonal Ab targets pro- and latent Myostatin
- Selective Androgen Receptor Modulators
 - Enobosarm

The Last Word

- Medications can promote weight loss or weight gain, body composition improvement or body composition deterioration, and metabolic improvement or metabolic deterioration.
- We need to improve our understanding of these processes, bearing in mind that the goal of obesity management is not reducing body size, but improving body function and body health.



THANK YOU!

Questions?

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Antipsychotic Drugs and Effects on Weight

Most consistently increase weight (kg)

- Olanzapine 9.06
- Haloperidol 7.97
- Risperidone 7.81
- Clozapine 6.21
- Quetiapine 6.14

Neutral/variable effects on weight (kg)

- Aripiprazole 3.31
- Ziprasidone 2.18
- Paliperidone 1.24

Medicating for Antipsychotic Weight Gain

Metformin in antipsychotic weight gain

- Meta analysis 12 studies, 743 patients, metformin produced -3.24% weight loss and metabolic improvement.

de Silva et al. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. BMC Psychiatry (2016) 16:341

Liraglutide for antipsychotic weight gain

- Randomized trial of 103 patients on olanzapine or clozapine. Liraglutide 3 mg produced -5.3 kg and metabolic improvement.

Larsen JR, et al. Effect of Liraglutide Treatment on Prediabetes and Overweight or Obesity in Clozapine- or Olanzapine-Treated Patients With Schizophrenia Spectrum Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2017 Jul 1;74(7):719-728.

Topiramate for antipsychotic weight gain

- Review of meta-analysis and randomized trials. Modest loss 1.27 to 3.95 kg at 12 weeks

Generali JA, Cada DJ. Topiramate: antipsychotic-induced weight gain. Hosp Pharm. 2014;49(4):345-347.

- **Semaglutide** (awaiting studies)

Sass et al. BMJ Open 2023;13:e068652;

Hypnotics and Mood Stabilizers and Body Weight effects

Hypnotics

May Increase Body Weight:

- Diphenhydramine
- Zolpidem (may increase risk of sleep-related eating disorder)

May Have Limited Effects on Body Weight:

- Benzodiazepines
- Melatonergic hypnotics
- Trazodone

Mood Stabilizers

May Increase Body Weight:

- Gabapentin
- Divalproex
- Lithium
- Valproate
- Vigabatrin
- Cariprazine
- Carbamazepine

Variable/Neutral Effects on Body Weight:

- Lamotrigine (sometimes reported to decrease body weight)
- Oxcarbazepine

Cardiovascular Medications May Increase Weight

Beta blockers

- Propanolol
- Atenolol
- Metoprolol
- ? Carvedilol

Calcium channel blockers

- Older and less lipophilic dihydropyridine ca channel blockers
- Nifedipine
- Amlodipine

Weight Change with Diabetes Medications

Weight Gain	Weight Neutral	Weight Loss
Insulin	Alpha-glucosidase inhibitors	GLP-1 Receptor Agonists
Meglitinides	Bromocriptine	Metformin
Sulfonylureas	Colesevelam	Pramlintide
Thiazolidinediones	DPP-4 inhibitors	SGLT2 inhibitors

Chemotherapies and Anti-Inflammatory Agents

- May Increase Body Weight
 - Tamoxifen
 - Cyclophosphamide
 - Methotrexate
 - 5-fluorouracil
 - Aromatase inhibitors
 - TNF- α inhibitors
- May Decrease Body Weight
 - Apremilast

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