Anti-Obesity Medications: Inside and Outside the Label

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Disclosures

Company	Disease State/Topic	Role
Novo Nordisk	Obesity	Promotional speaker Advisory board
Acella	Thyroid	Advisory board Promotional speaker
Currax	Obesity	Advisory board Promotional speaker
Lilly	Obesity and Sleep apnea	Advisory Board Promotional speaker
BI	Obesity	Advisory Board
WW	Obesity	Advisory board

- All relevant financial relationships have been mitigated.

Objectives

Recognize	Recognize the role of pharmacotherapy in obesity treatment.
Evaluate	Evaluate FDA approved medications for the pharmacologic management of chronic disease of obesity.
Identify	Identify available pharmacotherapeutics that can be utilized to support treatment of chronic disease of obesity that are not labeled for obesity by the FDA 20 minutes

Recognize

Recognize the Role of Pharmacotherapy in Obesity Treatment

Eating plans

Activity

Behavioral Intervention

Medication

Surgery

Case Study

Meet Ellen

Image: © Obesity Action Coalition

44-year-old woman presents today to discuss possible assistance with her increasing weight.

Ellen's Medical History

PMH:
Obstructive sleep apnea (OSA) – on BiPAP
Gastroesophageal reflux disease (GERD)
Hypertension
Depression
Stage 2 obesity

Medications:
Metoprolol 20 mg/day
Omeprazole OTC once daily
Vortioxetine 20 mg/day
Multivitamin once daily
Pregnancy prevention: IUD
NKDA

Ellen's Medical History

Image: © Obesity Action Coalition

Preventative screening:

- Mammogram – 3 months ago

Surgical History: None

Family History:

- HTN, DM (father, mother, sister) and all are "heavy"; no history of thyroid cancer

Social History:

- Married with two teenagers at home
- Works outside the house as a nurse
- ETOH 1x/week
- No history of tobacco use or drug abuse

Ellen's First Visit for Obesity

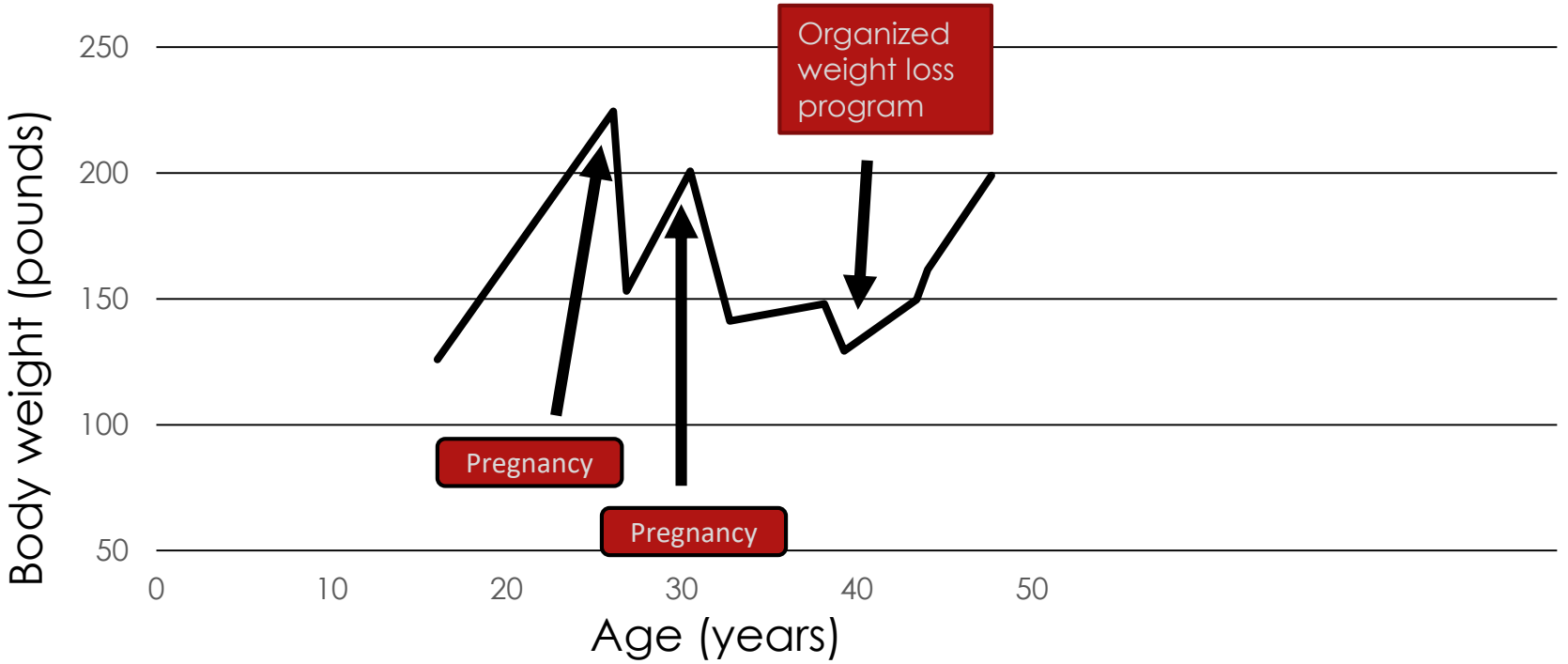
- Vital Signs:
  - 5'4"; 212 Lbs; BP 142/88 mmHg; HR 78 Bpm; RR 16; pOx 98%
- BMI: 36.30 Kg/M^2
- Waist Circumference: 42"
- Neck Circumference: 15"
- Screening Tools: PHQ-9 (4), BED7 (Neg), PAR-7, STOP-BANG Negative

	Yes	No
Has your NP or healthcare provider said you have a heart condition or high blood pressure?	x	
Do you feel pain in your chest at rest, during your daily activities of living or when you do physical activity?		x
Do you lose balance because of dizziness, or have you lost consciousness in the last 12 months (answer no if your dizziness was associated with over-breathing, including during vigorous exercise)?		x
Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)? Please list conditions here: Depression, Sleep apnea	x	
Are you currently taking prescribed medications for a chronic medical condition? Please list conditions and medications here:_____		x
Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please answer no if you had a problem in the past, but it does not limit your current ability to be physically active. Please list conditions here: _____		x
Has your healthcare provider ever said that you should only do medically supervised physical activity?		x

Form adapted from PAR 7 by Angela Golden for use at NP Obesity Treatment Center.
BED7, Binge Eating Disorder; PAR-7, Physical Activity Readiness. PHQ, Patient Health Questionnaire; STOP-BANG, snoring, tiredness, observed apnea, pressure, BMI, age, neck circumference, and gender.

Body Weight Graph

Use this graph to chart live events, health conditions, times of stress, and other factors that have influenced your weight



Polling Question

Are any of Ellen's medications obesogenic?

a. Metoprolol 20 Mg/Day
b. Omeprazole OTC Once Daily
c. Vortioxetine 20 Mg/Day
d. Multivitamin Once Daily
e. None Of The Above

Obesogenic Medications and Alternatives

Stop Obesogenic Drugs or Change to Weight-Neutral Alternatives (if possible)

Medication type	Weight-promoting	Weight neutral/less weight gain	Mechanism of Weight Gain
Antihypertensives	β-adrenergic blockers (propranolol, atenolol, metoprolol, nadolol), α-adrenergic blockers	ACE inhibitors, ARBs, β-adrenergic blockers (carvedilol, nebivolol), calcium channel blockers, thiazides	Inhibit sympathetic tone, decrease lipolysis, reduce exercise tolerance, increase fatigue, and reduce the resting energy expenditure
Antidiabetics	Insulin, sulfonylureas, thiazolidinediones (pioglitazone), meglitinides (nateglinide, repaglinide)	DPP-4 inhibitors, α-glucosidase inhibitors, bromocriptine, colesevelam HCL	Insulin: Anabolic and adipogenic hormone, decreases daily energy expenditure Sulfonylurea: Increase the secretion of insulin and cause water retention. Thiazolidinediones: Act as insulin sensitizers, cause water retention

Desalermos, A. et al. (2019). Effect of Obesogenic Medications on Weight-Loss Outcomes in a Behavioral Weight-Management Program. *Obesity (Silver Spring, Md.)*, *27*(5), 716–723. https://doi.org/10.1002/oby.22444
Apovian, C. M., et al & Endocrine Society (2015). Pharmacological management of obesity: an endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*, *100*(2), 342–362. https://doi.org/10.1210/jc.2014-3415

Stop Obesogenic Drugs or Change to Weight-Neutral Alternatives (if possible)

Medication type	Weight-promoting	Weight neutral/less weight gain	Mechanism of Weight Gain
Antidepressants	SSRIs (paroxetine), SRNIs, tricyclic antidepressants (amitriptyline, doxepin, imipramine, nortriptyline), lithium, MAOIs, mirtazapine,	SSRIs (fluoxetine, sertraline)	Appetite increase stimulated via serotonergic pathways
Antipsychotics	Risperidone, clozapine, olanzapine, quetiapine,	Aripiprazole, lurasidone, ziprasidone	Increased orexigenic and decreased anorexigenic neuropeptide expression in the hypothalamus

Desalermos, A. et al. (2019). Effect of Obesogenic Medications on Weight-Loss Outcomes in a Behavioral Weight-Management Program. *Obesity (Silver Spring, Md.)*, *27*(5), 716–723. https://doi.org/10.1002/oby.22444
Apovian, C. M., et al & Endocrine Society (2015). Pharmacological management of obesity: an endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*, *100*(2), 342–362. https://doi.org/10.1210/jc.2014-3415

Stop Obesogenic Drugs or Change to Weight-Neutral Alternatives (if possible)

Medication type	Weight-promoting	Weight neutral/less weight gain	Mechanism of Weight Gain
Anti-epileptics	gabapentin, pregabalin, valproic acid, carbamazepine,	Lamotrigine, levetiracetam, phenytoin	Hypothalamic mediated increase in appetite and decrease in energy expenditure
Antihistamines	First-generation antihistamines (chlorphenamine, doxylamine)	Second- & third-generation antihistamines (diphenhydramine, cetirizine)	Increase appetite. Alters body weight regulation Cetirizine more likely to cause modest weight gain compared to loratadine

Desalermos, A. et al. (2019). Effect of Obesogenic Medications on Weight-Loss Outcomes in a Behavioral Weight-Management Program. *Obesity (Silver Spring, Md.)*, *27*(5), 716–723. https://doi.org/10.1002/oby.22444
Apovian, C. M., et al & Endocrine Society (2015). Pharmacological management of obesity: an endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*, *100*(2), 342–362. https://doi.org/10.1210/jc.2014-3415

Stop Obesogenic Drugs or Change to Weight-Neutral Alternatives (if possible)

Medication type	Weight-promoting	Weight neutral/less weight gain	Mechanism of Weight Gain
Anti-inflammatories	Glucocorticoids (prednisone, hydrocortisone, etc.)	Inhaled steroids, topical steroids, NSAIDs, DMARDs	Alters the energy intake and expenditure of the human body Glucocorticoids (at super-physiologic doses for extended periods) are a major cause for central adiposity--with *increased* risk to cardiometabolic & bone health

Desalermos, A. et al. (2019). Effect of Obesogenic Medications on Weight-Loss Outcomes in a Behavioral Weight-Management Program. *Obesity (Silver Spring, Md.)*, *27*(5), 716–723. https://doi.org/10.1002/oby.22444
Apovian, C. M., et al & Endocrine Society (2015). Pharmacological management of obesity: an endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*, *100*(2), 342–362. https://doi.org/10.1210/jc.2014-3415

Ellen's First Visit for Obesity

- Most recent labs: Triglycerides 174 mg/dl; TC 236 mg/dl; LDL 134 mg/dl; HDL 48 mg/dl; AST 67 u/L; ALT 102 u/L; Vitamin D 34 ng/ml
- Fasting insulin 18 mIu/L; glucose 94 mg/dl; HOMA IR 4.17; QUICKI 0.31
- Obesity-related complications: elevated liver enzymes, hyperlipidemia, HTN
- Obesity comorbidities: OSA; depression
- Obesogenic medication: β blocker
- Staging of obesity
  - WHO – obesity class II
  - EOSS – stage 2
  - AACE/ACE – stage 2

Image: © Obesity Action Coalition

AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOSS, Edmonton Obesity Staging System; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; QUICKI, quantitative insulin sensitivity check index; TC, total cholesterol; WHO, World Health Organization.

Clinical Practice Guidelines and Algorithms

Current Guidelines/Algorithm Comparison

ES	AACE/ACE	OMA	OC
• Mention of nutrition, activity, behavioral intervention • Details on available pharmacology for anti-obesity medications • Obesogenic medications with options of other choices	• Complication-specific treatment guideline • Prevention reviewed • Staged recommendations for treatment • ORC-centric obesity treatment based on pharmacology	• Annually updated clinician tool • Review of bias and stigma implications • Podcast companions • Top 10 messages of each section • Obesity myths section	• Living document updated with emerging evidence • Created with sections for primary care professions, persons living with obesity, and policy holders • Prevention and treatment • Only 3 medications approved in Canada

ORC, obesity-related complications and comorbidities.

Apovian cm, et al. *J clin endocrinol metab*. 2015;100(2):342-362. Bays HE, et al. 2020. Https://obesitymedicine.Org/obesity-algorithm/ accessed february 12, 2020. Garvey WT, et al. *Endocr pract*. 2016;22(suppl 3):1-203. Wharton S, et al. *Cmaj*. 2020;192(31):e875-e891.

Evaluate

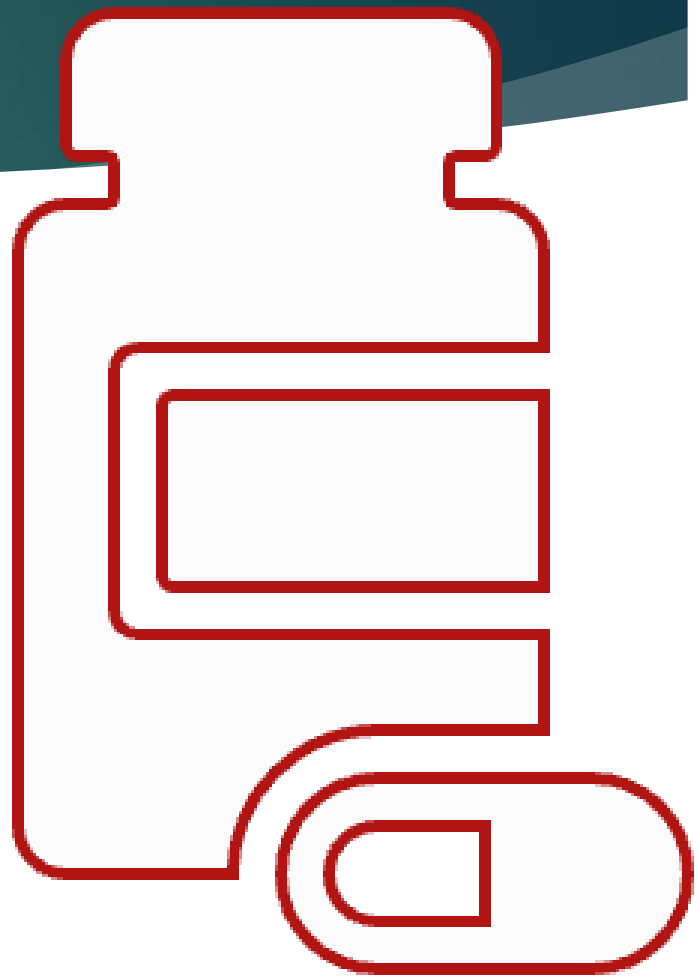
Evaluate FDA approved medications for the pharmacologic management of chronic disease of obesity.

Pharmacologic Therapy

Therapy Options, Factors to Consider When Selecting Therapy, and Efficacy/Safety Evidence

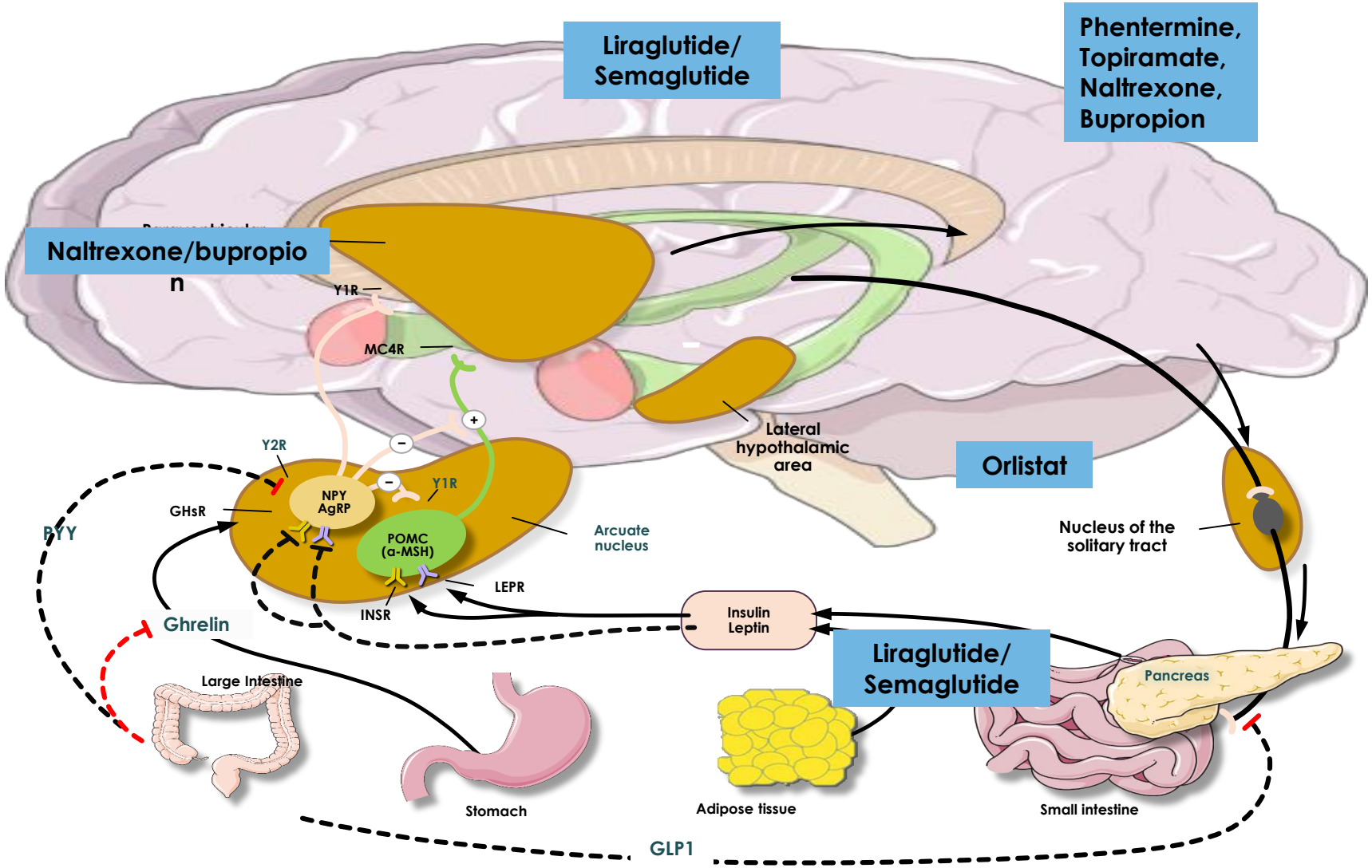
Why Use Medication With Obesity Treatment?

- Therapy aimed at the dysregulated weight regulated biology
- Metabolic adaptation difficult to treat with diet and behavior modification alone
- Anti-obesity medications can assist in managing the > 200 obesity induced complications/comorbidities



Greenway FL. *Int J Obes (Lond)*. 2015;39(8):1188–1196.

Medication Mechanisms



a-MSH, a-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.

Polling Question

What percentage of weight reduction should be the first therapeutic goal?

a. <5%
b. 5-10%
c. 11-15%
d. Depends on the individual's baseline BMI

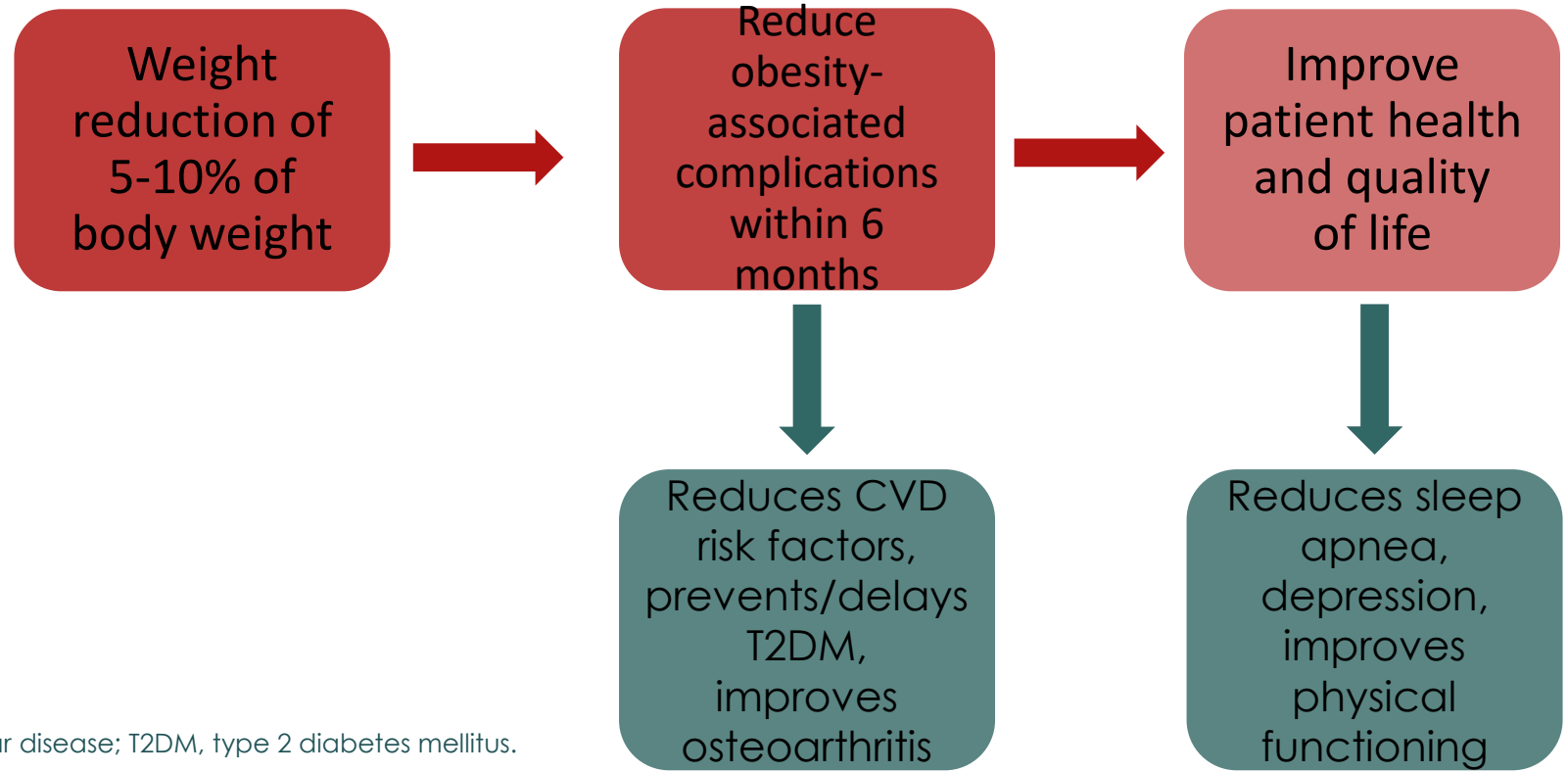
General Considerations in Pharmacologic Initiation

Pharmacologic interventions may be helpful as adjuvant therapy with lifestyle interventions for patients 18 years and older* with BMI ≥30 kg/m^2 or ≥27 kg/m^2 with comorbidities.

- Different patients respond to different medications
  - If one option does not work, consider others
- Discontinue medication in patients who do not respond with weight loss of at least 5% at 12 weeks after maximum dose†
- Avoid in pregnancy
  - Pregnancy tests at baseline
  - Consider a disclosure signature

*December 2020: liraglutide label change to include 12–17-year-olds with body weight of >60 kg and initial BMI corresponding to 30 kg/m^2 or greater for adults.
†Liraglutide label suggests only 4% weight loss at 12 weeks after maximum dose.
Apovian CM, et al. *J Clin Endocrinol Metab* 2015;100(2):342-362.

Therapeutic Goals

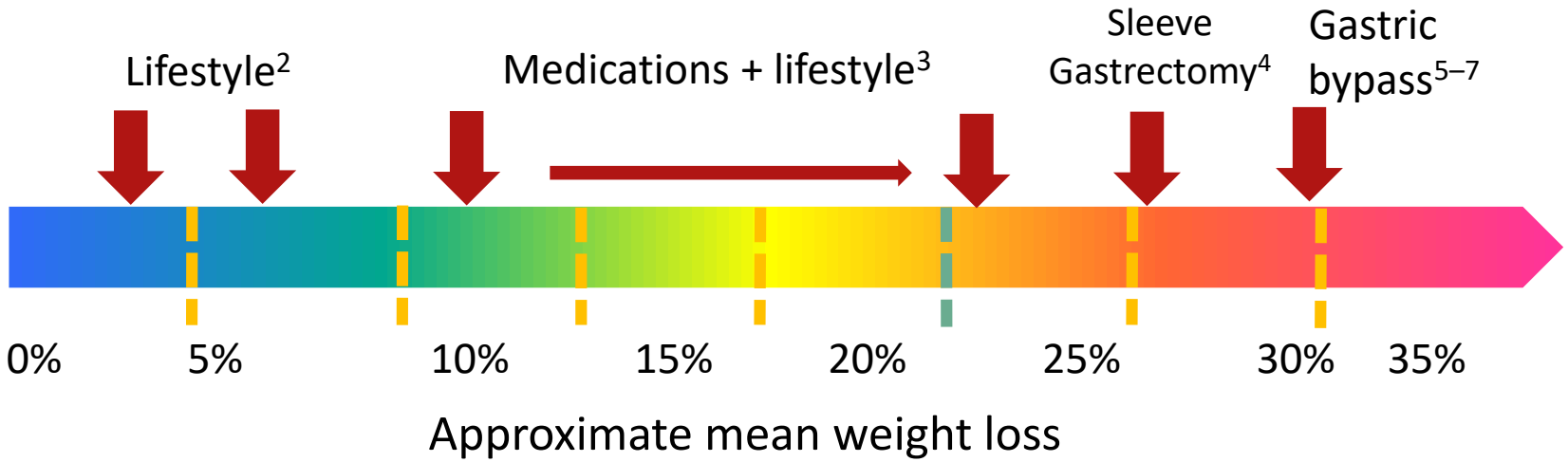


CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.

Jensen MD, et al. *Circulation*. 2014;129:S102-S138. Garvey WT, et al. *Endocr Pract*. 2016;22 Suppl 3:1-203. Yanovski SZ, et al. *JAMA*. 2014;311:74-86. Apovian CM, et al. *J Clin Endocrinol Metab*. 2015;100(2):342-362.

Comprehensive Lifestyle Management ± Pharmacotherapy and/or Surgery

Reduced caloric intake[1,2]	Increased activity[1,2]	Behavioral interventions[1,2]
• Set calorie limits **OR** cut calories **OR** restrict certain food types (eg, dietary fat) • Many dietary approaches work • Consider patient health status and preferences	• Moderate aerobic activity >150 minutes/week (min/wk) • Resistance training to preserve lean mass • 200–300 min/wk moderate aerobic activity for maintenance	<u>Weight reduction</u> • On-site, high-intensity intervention (eg, ≥14 sessions (group or individual) in 6 mo)*† • Provide strategies‡ <u>Weight maintenance</u> • Continued contact (≥1 per month) for ≥1 year*



*With trained interventionist; †face-to-face preferred; telephone or electronic counseling are options but may produce less weight loss; ‡includes goals, self-monitoring.

1. Obesity medical association. Obesity algorithm, 2023 (https:// https://obesitymedicine.Org/resources/obesity-algorithm). 2. Jensen MD, et al. *Obesity (silver spring)*. 2014;22(suppl 2):S5-S39. 3. Colman E, et al. *N engl J med*. 2012;367:1577-1579. 4. Ames, AE, et al. *Bariatric times*, 2016; 13(7):10-18. 5. Flum DR, et al; longitudinal assessment of bariatric surgery (LABS) consortium. *N engl J med*. 2009;361:445-454. 6. Courcoulas AP, et al. *Jama*. 2013;310:2416-2425. 7. Courcoulas AP, et al. *JAMA surg*. 2018;153:427-434.

Medications to Treat Obesity

FDA Approved

Orlistat
Phentermine
Phentermine/Topiramate ER #
Bupropion/Naltrexone XL
Liraglutide 3mg #
Semaglutide 2.4mg. #
Tirzepatide 15 mg
Setmelanotide *monogenic obesity**

approved for adults and adolescents

Additional Medications that May Cause Weight Loss and Used Off Label

	Topiramate
	Zonisamide
	Bupropion
	Naltrexone
	Metformin
GLP-1 RA	Dulaglutide
GLP-1 RA	Exenatide
GLP-1 RA	Liraglutide
GLP-1 RA	Lixisenatide
GLP-1 RA	Semaglutide
GIP/GLP-1 RA	Tirzepatide
Amylin analogue	Pramlintide
SGLT2I	Canagliflozin
SGLT2I	Dapagliflozin
SGLT2I	Empagliflozin

FDA-Approved Short-Term (Anti) Obesity Medications

Generic Drug*	Dose	Contraindications	Side Effects
Phentermine	8-37.5 mg	Anxiety disorder, CVD, hypertension, MAO inhibitors, glaucoma, hyperthyroidism, seizures, pregnancy/ breastfeeding, drug abuse history	Insomnia, palpitations, tachycardia, dry mouth, taste alterations, dizziness, tremors, headache, diarrhea, constipation, vomiting, gastrointestinal distress, anxiety, restlessness, increased blood pressure
Diethylpropion	25 mg or 75 mg, SR		
Phendimetrazine	17.5-70 mg or 105 mg, SR		
Benzphetamine	25-50 mg		

*Mechanism of action = sympathomimetic-noradrenergic causing appetite suppression.
MAO, monoamine oxidase; SR, sustained release.
DailyMed. https://dailymed.nlm.nih.gov/dailymed/index.cfm. Accessed February 23, 2021. Bray GA, et al. *Circulation*. 2012;125(13):1695-1703. Apovian CM, et al. *J Clin Endocrinol Metab*. 2015;100(2):342-362.

Phentermine

- US Drug Enforcement Agency scheduled IV drug
  - Risk for addiction
- Not indicated for long-term use
  - 13 weeks by label

Endocrine Society allows for possible long-term use:

- No CVD
- No psychiatric/substance abuse history
- Has been informed about therapies that are approved for long-term use
- Document off-label use in patient's medical record
- No clinically significant increase in pulse/BP when taking phentermine
- Demonstrates significant weight loss with phentermine
- Start at 7.5 or 15 mg/d—dose escalate if not achieving significant weight loss
- Monitor monthly during dose escalation

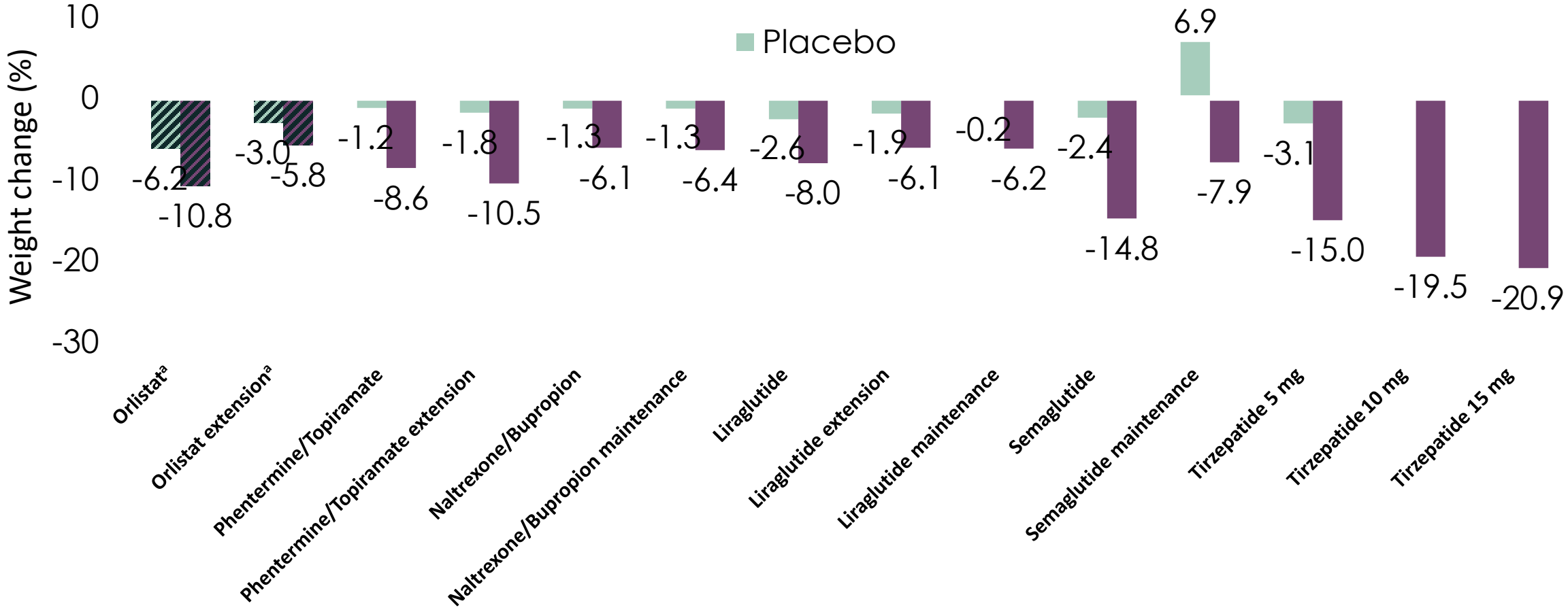
Apovian CM, et al. *J Clin Endocrinol Metab.* 2015;100(2):342-362.

FDA-Approved (Anti) Obesity Medication

Generic (listed alphabetically)	Mechanism of Action
Liraglutide (subcutaneous injection)	GLP-1 receptor agonist
Naltrexone/bupropion ER (oral)	Opioid receptor antagonist; dopamine and noradrenaline reuptake inhibitor
Orlistat (oral)	Pancreatic lipase inhibitor—impairs gastrointestinal energy absorption, causing excretion of approximately 30% of ingested triglycerides in stool
Phentermine/topiramate-ER (oral)	Noradrenergic + GABA-receptor activator, kainite/AMPA glutamate receptor inhibitor causing appetite suppression
Semaglutide (subcutaneous injection)	GLP-1 receptor agonist
Tirzepatide (subcutaneous injection)	GLP-1/GIP receptor agonist

Tchang BG, Aras M, Kumar RB, et al. Pharmacologic Treatment of Overweight and Obesity in Adults. [Updated 2024 Aug 20]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279038/

Mean Percent (%) Weight Change Reported in the Main Phase 3 and Extension Trials of Antiobesity Medications



Orlistat: XENDOS trial (years 1 and 4). Phentermine/topiramate: CONQUER and SEQUEL trials. Naltrexone/bupropion: COR-I and COR-II trials. Liraglutide: SCALE obesity, SCALE obesity and prediabetes extension, and SCALE maintenance trials. Semaglutide: STEP 1 and STEP 4 trial.
All trials are listed in order as seen in the figure from left to right. The grey color represents placebo arms; the red color represents intervention arms.
[A]the mean weight change in the orlistat group is in kg not in percent (striped bar charts).

Chakhtoura M, et al. *EClinicalMedicine*. 2023;58:101882.

Orlistat

Dose Frequency	Efficacy	Contraindications/ Precautions/Warnings	Side Effects
60 mg OTC 120 mg TID within 1 h of fat-containing meal	• Mean weight loss ranged from 3.9-10.2% at Year 1 in 17 RCTs (120 mg TID) • ↓ BP, TC, LDL-C, fasting glucose at 1 year • Slows risk of progression to T2DM	Chronic malabsorption syndrome, pregnancy, breastfeeding, cholestasis, some medications (eg, warfarin, antiepileptic agents, levothyroxine, cyclosporine)	Oily spotting, cramps, flatus with discharge, fecal urgency, fatty oily stool, increased defecation, fecal incontinence

Practical Considerations

- Consider fat-soluble multivitamin
- Limit fat intake to 30% of calories
- Counsel on risk of GI adverse events

Bragg R, et al. *J Am Assoc Nurse Pract* 2016;28(2):107-115. Kahan S. *Am J Manag Care*. 2016;22(7 Suppl):S186-S196.

Phentermine/Topiramate ER

Dose Frequency	Efficacy	Contraindications/ Precautions/Warnings	Side Effects
• Initiate treatment at 3.75 mg/23 mg for 2 weeks • Increase to 7.5 mg/ 46 mg • Escalate to 11.25 mg/ 69 mg for 2 weeks then to max 15 mg/92 mg	• 10% weight loss with treatment vs 2% with placebo • Improved cardiometabolic markers • Reduced progression to T2DM	Pregnancy and breastfeeding, hyperthyroidism, glaucoma, use of MAO inhibitors	Paresthesia, dizziness, taste alterations, insomnia, constipation, dry mouth, elevation in heart rate, memory or cognitive changes

Practical Considerations

- Titrate dose at initiation and discontinuation
- Drug Enforcement Agency Schedule IV drug
- Risk evaluation and mitigation strategy
- Counsel about risk for mood disorders, suicidal thoughts
- Taper highest dose every other day for 1 week if discontinuation is necessary
- Women of childbearing age: pregnancy prevention plan and monthly pregnancy testing
- 7/2022 approved for adolescents >12 years old with BMI of 95th percentile or greater

Tchang BG, Aras M, Kumar RB, et al. Pharmacologic Treatment of Overweight and Obesity in Adults. [Updated 2024 Aug 20]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279038/

Liraglutide

Dose Frequency	Efficacy	Contraindications/ Precautions/Warnings	Side Effects
Weekly titration by 0.6 mg over 5 weeks to target dose of 3.0 mg	• Mean weight loss 9% at 1 year • Reduced progression to T2DM in patients with prediabetes • Reduced risk of weight regain at 1 year	Medullary thyroid cancer history, multiple endocrine neoplasia type 2 history, history of pancreatitis, pregnancy, breastfeeding	Nausea, vomiting, diarrhea, constipation, hypoglycemia in patients with T2DM, increased lipase, increased heart rate, pancreatitis

Practical Considerations

- Injectable administration
- FDA approved for use in adults with BMI ≥30kg/m^2 or ≥27 kg/m^2 with at least one complication
- Generic summer 2024, price expected at $700
- Approved 12/2020 label change: treatment of obesity in adolescents aged 12 to 17 years with a body weight of at least 60 kg and an initial BMI corresponding to 30 kg/m² or greater for adults

Tchang BG, Aras M, Kumar RB, et al. Pharmacologic Treatment of Overweight and Obesity in Adults. [Updated 2024 Aug 20]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279038/

Naltrexone/Bupropion ER

Dose Frequency	Efficacy	Contraindications/ Precautions/Warnings	Side Effects
• Initiate 8 mg/90 mg x 1 week • Weekly escalation to target dose of 32 mg/360 mg (2 tablets BID)	• Weight loss of 8.2% vs 1.4% (placebo) • Improved cardiometabolic parameters • Fewer cravings • Lowered HbA1c in patients with T2DM	Uncontrolled hypertension, seizure disorder, anorexia or bulimia, drug or alcohol withdrawal, chronic opioid use, MAO inhibitors, caution with renal/ hepatic impairment	Nausea, constipation, headache, dizziness, vomiting, insomnia, dry mouth Transient increase in BP

Practical Considerations	Titrate dose on initiation Monitor BP Monitor closely for depression

Tchang BG, Aras M, Kumar RB, et al. Pharmacologic Treatment of Overweight and Obesity in Adults. [Updated 2024 Aug 20]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279038/

Semaglutide

Dose Frequency	Efficacy	Contraindications/ Precautions/Warnings	Side Effects
Weekly injections with titration every four weeks, 0.25 mg, 0.5 mg, 1 mg, 1.7 mg or 2.4 mg dose of 2.4 mg	• Mean weight loss 14.9% at 68 weeks	Medullary thyroid cancer history, multiple endocrine neoplasia type 2 history, suicidal behavior and ideation, pregnancy, breastfeeding, acute gallbladder disease, diabetic retinopathy, acute kidney injury	Nausea, vomiting, diarrhea, constipation, hypoglycemia in patients with T2DM, increased lipase, increased heart rate, pancreatitis

Practical Considerations

- Injectable administration
- FDA approved for use in adults with BMI ≥30kg/m^2 or ≥27 kg/m^2 with at least one obesity related comorbid condition
- 12/2022 approved for 12–17-year-old with obesity
- Nausea most common issue – slow titration
- 1.7mg and 2.4 mg as maintenance doses

2024 Label update: reduce the risk of MACE in adults with established CV disease and overweight or obesity

https://www.novo-pi.com/wegovy.pdf

MACE: Major Adverse Cardiovascular events (cardiovascular death, non-fatal MI, or non-fatal stroke

Tirzepatide

Dose Frequency	Efficacy	Contraindications/ Precautions/Warnings	Side Effects
Weekly injections with titration every four weeks, 2.5mg, 5mg, 7.5mg, 10mg, 12.5mg, 15mg	• Mean weight loss 20.9% at 72 weeks	Medullary thyroid cancer history, multiple endocrine neoplasia type 2 history, suicidal behavior and ideation, pregnancy, acute gallbladder disease, diabetic retinopathy, acute kidney injury	Nausea, vomiting, diarrhea, constipation, hypoglycemia in patients with T2DM

Practical Considerations

- Injectable administration
- FDA approved for use in adults with BMI ≥30kg/m^2 or ≥27 kg/m^2 with at least one obesity related comorbid condition
- Nausea most common issue – slow titration
- 5mg, 10mg, and 15mg as maintenance doses

Jasterboff AM, et al. N. Engl J Med 2022, 387(3) 205-216.

Rare Genetic Cause of Obesity Treatment

Uncommon Obesity

>20 rare genetic disorders

Common symptoms

- Early onset of severe obesity, often less than one year of age
- Insatiable hunger (hyperphagia)

Genetic testing is critical (free)

Patient eligibility criteria:

- ≤18 years of age, BMI ≥97th percentile or
- ≥19 years of age, BMI ≥40 kg/m^2, and a history of childhood obesity before age 10

Uncommon Obesity. https://www.uncommonobesity.com/. Accessed February 23, 2021. Rhythm Pharmaceuticals. https://www.rhythmtx.com/science-overview/. Accessed September 20, 2024.

Setmelanotide – Imcivree™

- Approved in November 2020 for patients with obesity due to POMC, PCSK1, or LEPR deficiency
  - Impaired MC4 receptor pathway
  - Adults and pediatric patients 6 years of age and older with deficiency confirmed by genetic testing
- Action: MC4 receptor agonist
  - Restore impaired MC4 receptor pathway activity arising due to genetic deficits upstream of the MC4 receptor
- Rare pediatric disease priority review voucher, breakthrough therapy designation, orphan drug designation

PCSK1, proprotein convertase subtilisin/kexin type 1.

Uncommon Obesity. https://www.uncommonobesity.com/. Accessed February 23, 2021. Rhythm Pharmaceuticals. https://www.rhythmtx.com/science-overview/. Accessed September 20, 2024.

Identify

Identify Available Pharmacotherapeutics That Can Be Utilized to Support Treatment of Chronic Disease of Obesity That Are Not Labeled for Obesity by the FDA.

Off Label Options

Medication	Information	Weight loss	Cost
GLP1RA's		Semaglutide (lower doses with Ozempic or Rybelsus) weight reduction from baseline – Semaglutide 0.5mg 2.3 kg, Semaglutide 1.0 mg 6.5 kg Semaglutide 14mg orally 4.4kg Liraglutide (lower doses with Victoza) 1.0mg dose 3.1kg Dulaglutide 1.5mg 3.0kg Liraglutide 1.8mg generic launched June 2024	$500-1400 30 days for $334
Metformin	Go as high as patient can tolerate – 2500mg max	500 mg 120 tabs	Good RX ~ $12

Off Label Options

Medication	Information	Weight loss	Cost
Naltrexone	great for patients with cravings BUT it only comes as 50 mg so well beyond the 32 mg max. It is scored so you can get down to 25 mg pretty easily. BUT this is often too much for some patients with the headache, dizziness, fatigue, nausea, and anxiety showing up.	Range of weight loss is about 4-7# after 2 months	You can get it compounded to get the 8mg and 16 mg doses (then can increase to 25 mg from the cheaper version) ~ $25/month.
Bupropion XL		can expect about 5 pounds of weight loss with 150mg to 300mg	~$14

so you could do off label with naltrexone and bupropion together and likely have a lower cost BUT doses would be different so nothing in literature to support amount of weight loss

Off Label Options

Medication	Information	Weight loss	Cost
Phentermine	I suggest using low dose – 8mg tablets and start with one dose in am and ½ to 1 tablet about 3-4pm.	Approximately 5% weight loss	90 tablets ~ $35-50
Topiramate (not extended release)	Often works nicely for people with evening eating alone.	When used alone approximately 6% of patients at 50mg/day lose weight	25mg (using ½ to 1 tablet per day) ~ $12. NOTE Topiramate ER is capsule only and close to ~$75 so no savings.
so you could do off label with phentermine and topiramate together and likely have a lower cost BUT doses would be different so nothing in literature to support amount of weight loss			

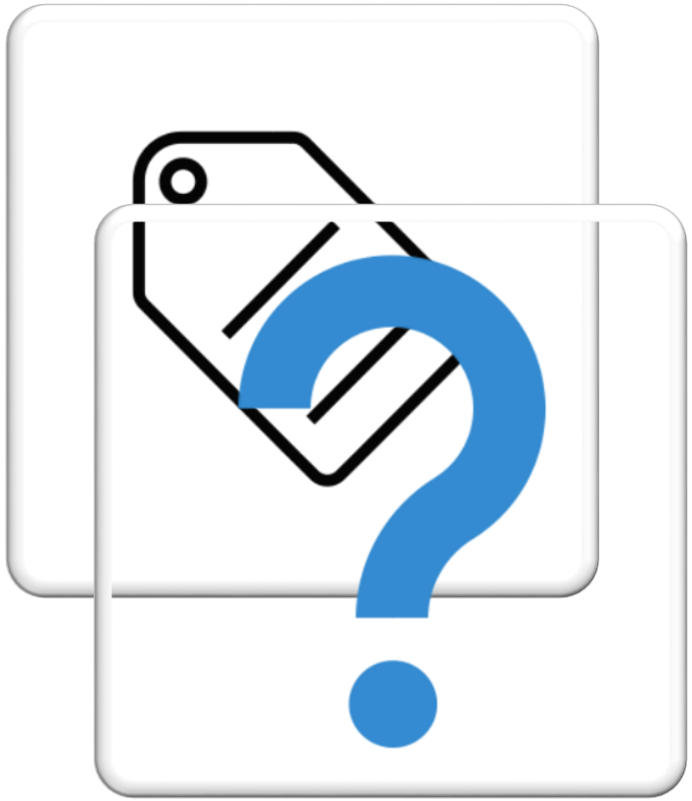
Off Label Options

Medication	Information	Weight loss	Cost
SGLT2Is – Canagliflozin (Invokana)	There is some literature to use phentermine with SGLT2I – 7.5% weight	Approximately 1.9% weight loss	~$550

Off Label Combinations (WHY)

- Central mechanisms of actions
  - GLP-1RA's and topiramate decrease signaling of AGRP and NPY (these stimulate food intake)
  - GLP1-RA's, phentermine, bupropion, and naltrexone increase signaling of POMC and CART (these decrease food intake)

Off Label Combinations (WHAT)



- GLP-1 plus any medication
  - Watch for nausea
- Orlistat plus any medication
  - Especially if constipation noted as side effect of GLP-1
- Phentermine plus GLP-1 or SGLT-2
- Metformin plus any medication

Shared Decision Making

Considerations for Selecting an Anti-Obesity Medication

Reimbursement/Cost

eXcluded for Contraindications or Side Effects

Additional benefit to use an AOM: Complications or patient history

Off label options

Medication selection with patient – shared decision making

How do I make a decision for an anti-obesity medication or prescribed device?
Options and choice for using medications to treat obesity

What are my options related to anti-obesity medications/prescribed device?

- You can choose to **do nothing and choose not to use an anti-obesity medication or the prescribed device**.
- Review this document with your prescriber to determine what on the list might be appropriate for you (any of the prescriptions that are contraindicated will be marked out).
- Decide which of the appropriate prescription you would prefer to start with.

This decision aid can help you and your healthcare professional decide together which is the best option for you.
The table gives some information about each prescription and the evidence for them for you to think about when choosing the best option for you.

Table: What are the options for prescriptions?

Decide to not use a prescription	
What does this involve?	• Carrying on as I am.
Pros	• No changes to make.
Cons	• Medications can support the treatment by impacting hunger and/or satiety or absorption of nutrients

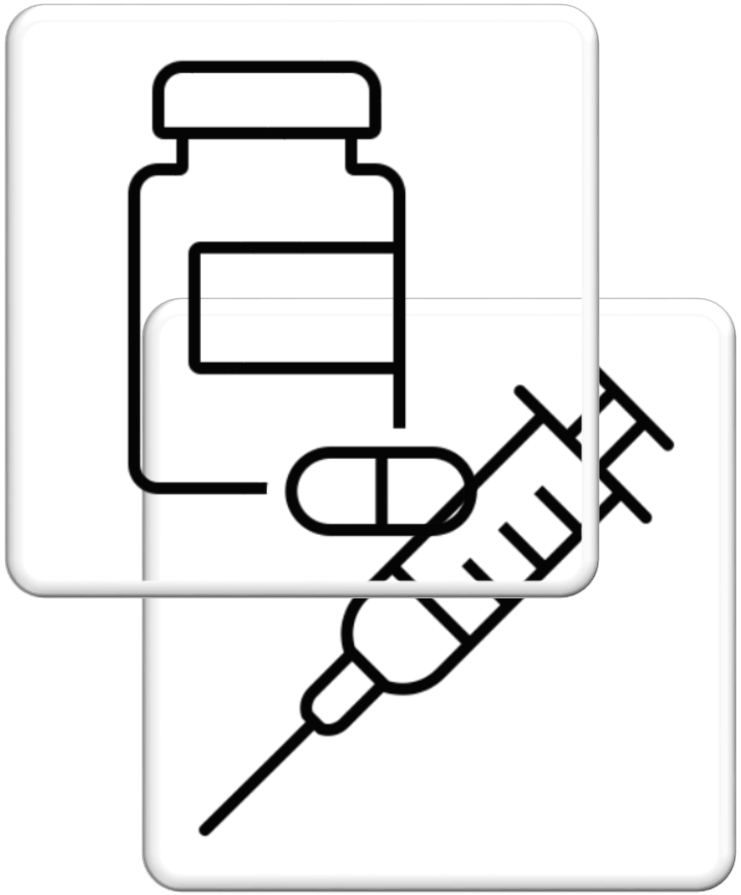
Select a prescription	
What does this involve?	• Reviewing the document with your prescriber
Pros	• Provides an intensification of treatment • Impact obesity related complications through increased weight loss beyond intensive lifestyle intervention
Cons	• Each prescription has the risk of side effects • Some prescriptions may not be covered by insurance or have co-pays

Shared Decision Making for Prescriptions (alphabetically)

Prescription	Dosing	Weight loss expectation	Contraindications	Common Side Effects	Further information
Liraglutide Saxenda	Starts at 0.6mg and escalates to 3.0mg	~ 8%	Medullary thyroid cancer history, MEN type 2 history, pregnancy and breastfeeding, history of pancreatitis (CAUTION only, not contraindication)	Nausea, vomiting, diarrhea, constipation, hypoglycemia in patients with T2DM, increased lipase, increased heart rate, pancreatitis	Injectable, GLP1 receptor agonist which helps with feeling full and may impact food cravings. Beneficial for diabetes, prediabetes, or insulin resistance. Approximately $1400 cash. https://www.saxenda.com/
Naltrexone-bupropion ER Contrave	Each tablet has 8mg naltrexone and 90 mg bupropion that escalates over time to two tablets twice a day	~ 6%	Uncontrolled HTN, seizure disorder, anorexia or bulimia, drug or alcohol withdrawal, chronic opioid use, MAO inhibitors use, pregnancy and breastfeeding,	Nausea, constipation, HA, dizziness	Opioid receptor antagonist combine with an antidepressant. Decreases hunger and helps with Food cravings. May benefit with treatment of depression. $98/month cash. https://contrave.com/
Orlistat	60 mg over the counter 120 mg 3 times a day within 1 hour of fat-containing meal	~ 6%	Chronic malabsorption syndrome, pregnancy and breastfeeding, cholestasis, some medications (ex. warfarin, antiepileptic, levothyroxine)	Decreased absorption of fat-soluble vitamins, steatorrhea, flatulence, fecal incontinence	Pancreatic lipase inhibitor, decreases the amount of fat absorbed from food https://reference.medscape.com/drug/alli-xenical-orlistat-342068
Phentermine	8 mg tablets that can be used two or three times a day	~ 5%	Anxiety disorder, CV disease, MAO inhibitors, pregnancy and breastfeeding, hyperthyroidism, hx of drug abuse, glaucoma	HA, increased BP and HR, insomnia, constipation, anxiety, palpitations, changes in libido	Sympathomimetic, decreases hunger https://lomaira.com/

Phentermine-topiramate ER Qsymia	Initiate treatment at 3.75 mg/23 mg table that can escalate up to 15 mg/92 mg	~ 10 %	hyperthyroidism, glaucoma, some medications (ex MAOI, sympathomimetic), pregnancy and breastfeeding,	Insomnia, constipation, dizziness, paresthesia, dysgeusia, dry mouth	Sympathomimetic combined with an antiseizure medication, decreases hunger. May benefit migraine headache prophylaxis. https://qsymia.com/
Semaglutide Wegovy	Starts at 0.25 mg and escalates to 2.4 mg	~ 15%	Medullary thyroid cancer history, multiple endocrine neoplasia type 2 history, suicidal behavior and ideation, pregnancy, breastfeeding, acute gallbladder disease, diabetic retinopathy, acute kidney injury	Nausea, vomiting, diarrhea, constipation, hypoglycemia in patients with T2DM, increased lipase, increased heart rate, pancreatitis	Injectable, GLP1 receptor agonist which helps with feeling full and may impact food cravings. Beneficial for diabetes, prediabetes, or insulin resistance. Approximately $1400 cash https://www.wegovy.com/
Tirzepatide Zepbound	Starts at 2.5mg and escalates to 15 mg	20%	Medullary thyroid cancer history, multiple endocrine neoplasia type 2 history, has not been studied in patients with a history of pancreatitis, pregnancy, breastfeeding. Precautions: Severe GI disease, Acute Kidney disease, acute gallbladder disease, acute pancreatitis, Suicidal behavior or ideation, and diabetic retinopathy	Nausea, diarrhea, vomiting, constipation, abdominal pain, hypoglycemia in patients with T2DM	Injectable, GLP1/GIP receptor agonist which helps with feeling full and may impact food cravings. Beneficial for diabetes, prediabetes, or insulin resistance. Approximately $1077 cash https://www.zepbound.lilly.com/

Medication Selection - Shared



- Complete RXAO
- List medications still appropriate
- Present to the patient
- Make the selection

Polling Question

Which medication would you recommend for Ellen?

A. Liraglutide
B. Naltrexone/bupropion ER
C. Orlistat
D. Phentermine
E. Phentermine/topiramate ER
F. Semaglutide
G. tirzepatide
H. None at this point

Ellen: Shared Decision-Making

AOM	Additional Benefit	eXcluded
Liraglutide (subcutaneous injection)	Insulin Resistance	None
Naltrexone/bupropion ER (oral)	+craving of sweets in the evening	None
Orlistat (oral)	None	GI side effects with OTC in past
Phentermine (oral)	Cost	None
Phentermine/topiramate-ER (oral)	Efficacy	None
Semaglutide (subcutaneous injection)	Insulin Resistance	None
Tirzepatide (subcutaneous injection)	Insulin Resistance	None

Ellen: Measuring Efficacy

Begin therapy with naltrexone/bupropion	Initiate 8 mg-90 mg tablet once/day, moving up weekly until 4 tablets/day
Effective response to therapy	>5% weight loss from baseline 12 weeks after maximum dose
Improvement in CV risk markers	Improvement in BP and insulin resistance

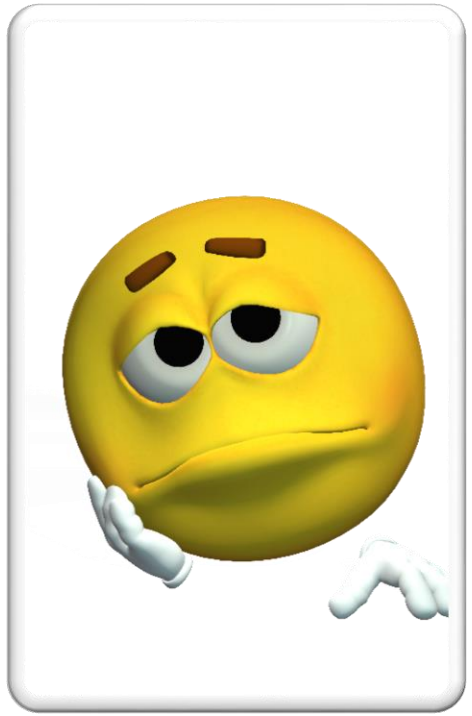
Continue to See the Patient Every 2-4 Weeks

Intensive Lifestyle Intervention

Can be done by other providers as well, e.g., dietitians, physical therapy/exercise physiologist, health coaches

Monitoring: BP, weight

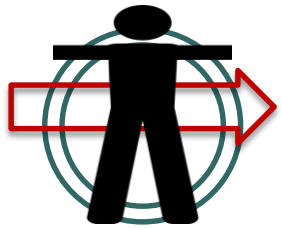
Ellen's Visit at 16 Weeks



- BP 124/66 mmHg; HR 82 bpm; RR 16 breaths/min; pOx 97%; weight 194 lbs
- Since being at maximum dosing of medication (12 weeks), has lost only 3% of total body weight
- Continues to eat plant-based, whole food
  - Has been able to stop BP medication (has lost 8% of body weight since beginning of treatment, only 3% with medication)
- Continues activity with jujitsu and walking
- Education at this meeting will be related to next medication

Ineffective Response to Therapy

- <4-5% weight loss at 12 weeks of maximum dose
  - Medications with escalating doses could be 16 weeks or longer
  - Unable to tolerate maximum doses
- < ? 3% weight loss but with improvement in ORCs



1. Decrease dose of existing AOM as appropriate
2. Switch to a different AOM

AOM, anti-obesity medication.

Bray GA, et al. *Lancet*. 2016;387(10031):1947-1956. Apovian CM, et al. *J Clin Endocrinol Metab*. 2015;100(2):342-362.

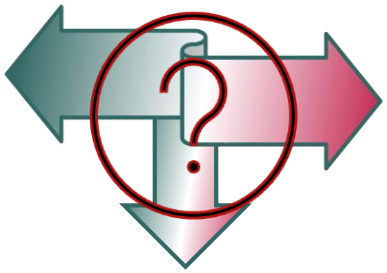
Ellen: Shared Decision-making

AOM	Additional Benefit	eXcluded
Liraglutide (subcutaneous injection)	Insulin Resistance	None
Naltrexone/bupropion ER (oral)	+craving of sweets in the evening	Ineffective
0rlistat (oral)	None	GI side effects with OTC in past
Phentermine (oral)	Cost	None
Phentermine/topiramate-ER (oral)	Efficacy	None
Semaglutide (subcutaneous injection)	Insulin Resistance	None
Tirzepatide (subcutaneous injection)	Insulin Resistance	None

Considerations for Switching Ellen's Therapy

Liraglutide?

- Insulin resistance
- No family history of thyroid cancer or pancreatitis



Semaglutide?

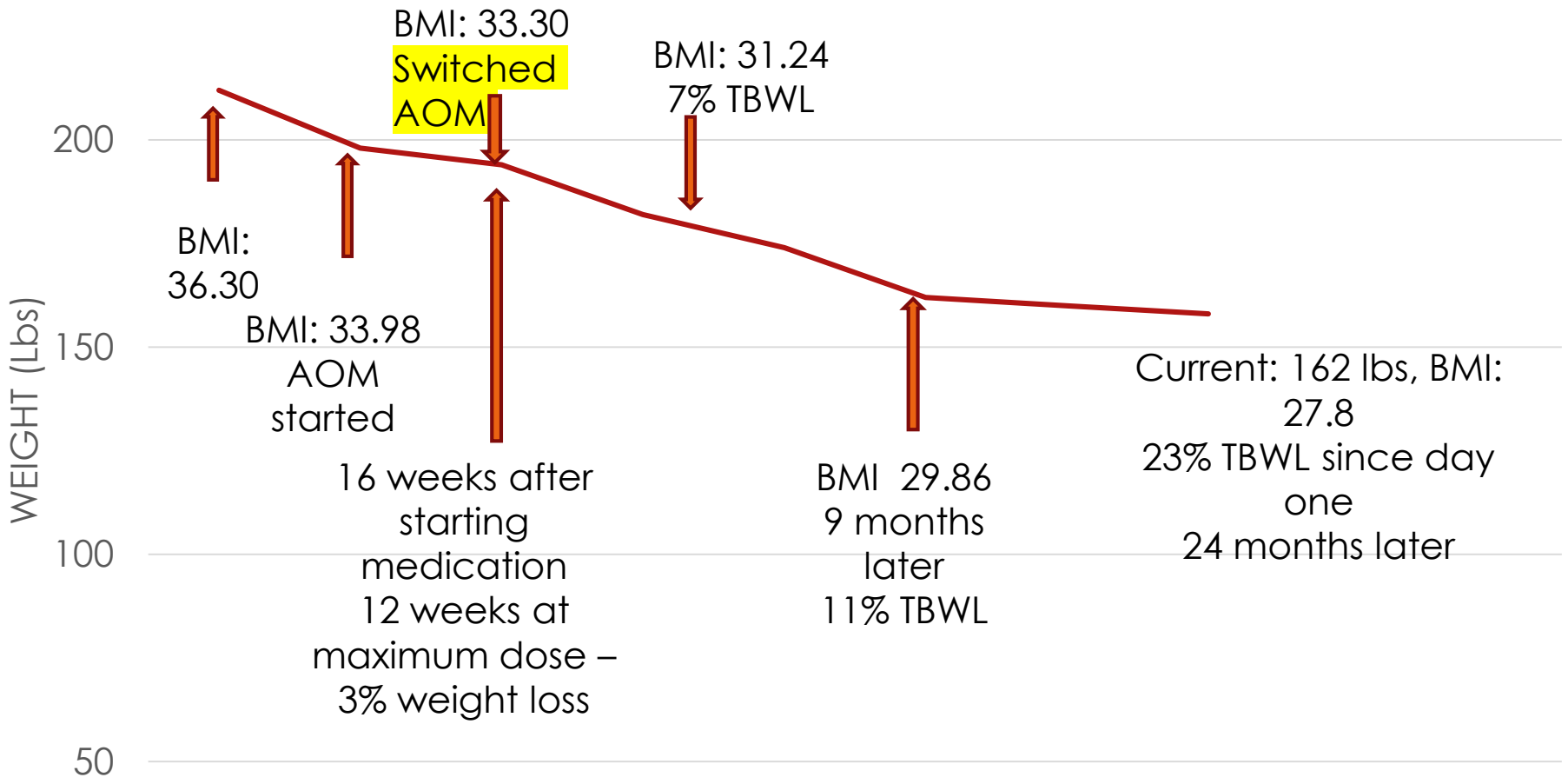
Tirzepatide?

- Insulin resistance
- No family history of thyroid cancer or pancreatitis
- Largest TBW - Tirzepatide

Phentermine/ topiramate ER?

- More weight loss on average
- No history of seizures

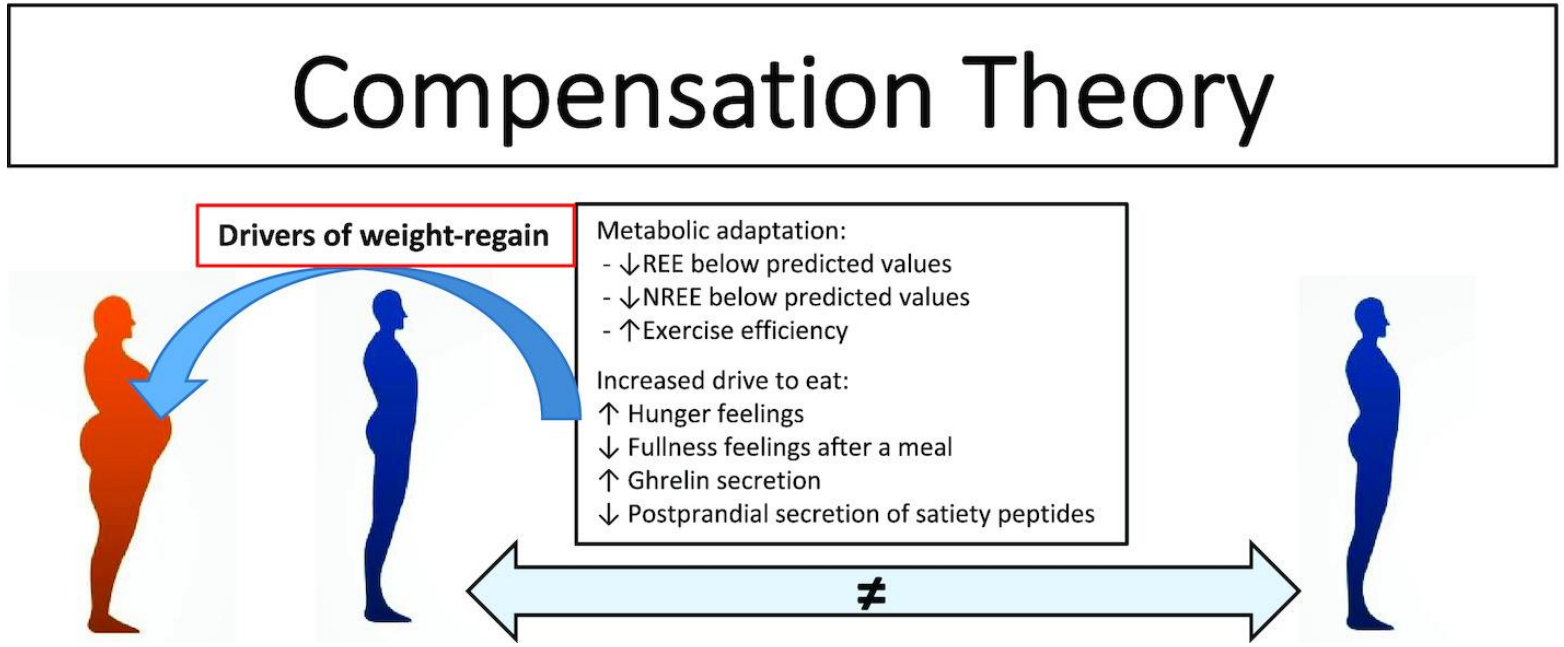
Ellen's Weight History - Medical Management



Pathology Of Weight Regain – Metabolic Adaptation

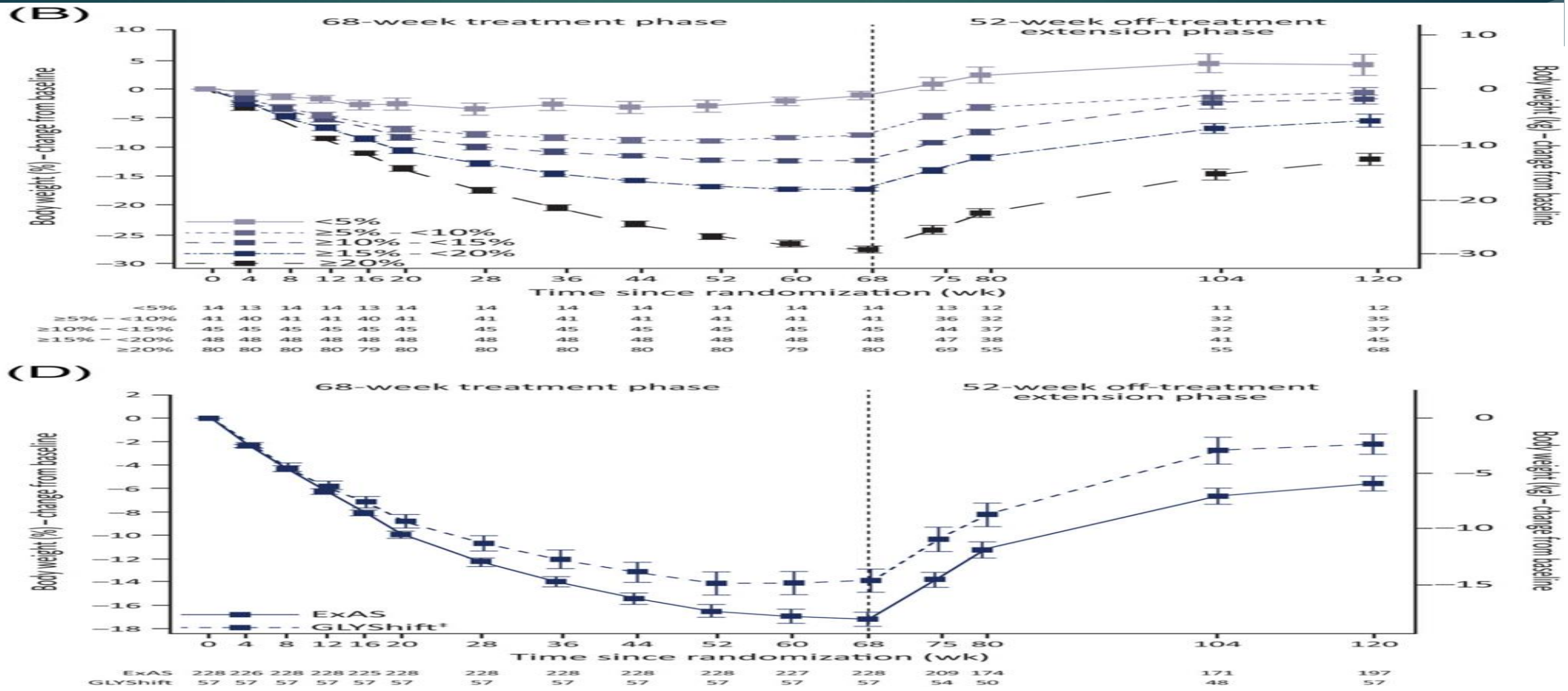
Adaptive responses to weigh loss promotes weight regain

- Fall in energy expenditure
- Increase in appetite
- Dysfunctional hormonal system



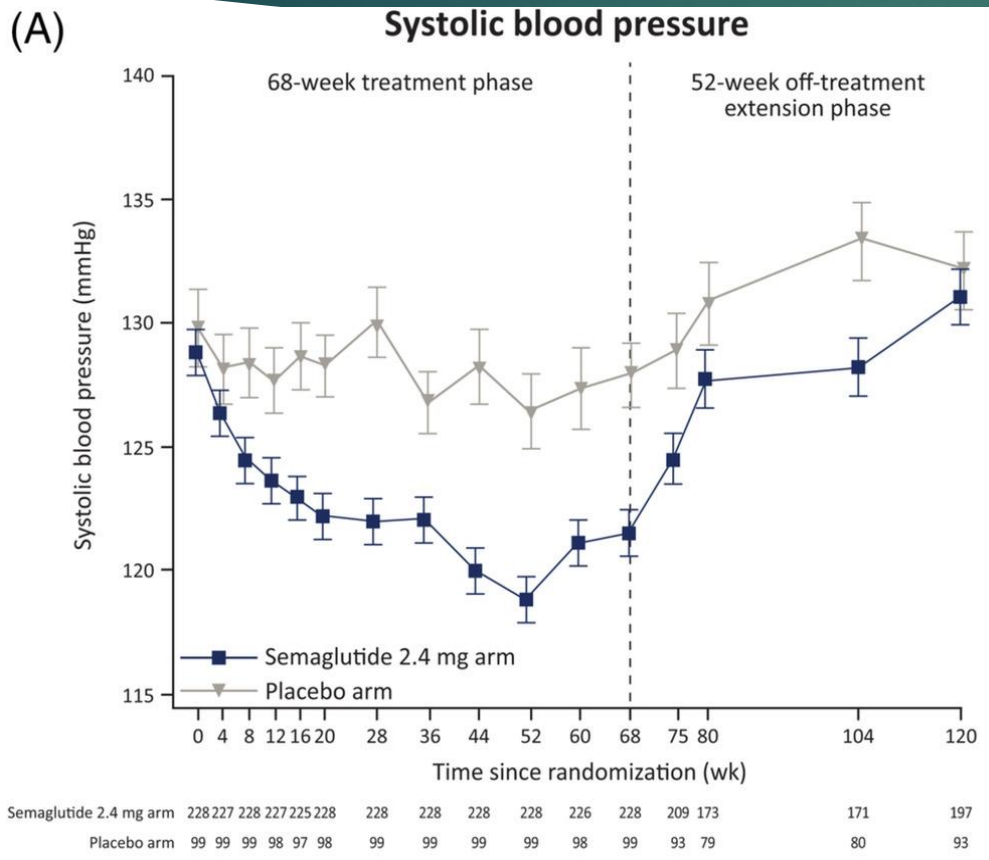
Martins, C., Dutton, G. R., Hunter, G. R., & Gower, B. A. (2020). Revisiting the Compensatory Theory as an explanatory model for relapse in obesity management. *The American journal of clinical nutrition*, *112*(5), 1170–1179. https://doi.org/10.1093/ajcn/nqaa243 Figure 1. open access CC 4.0

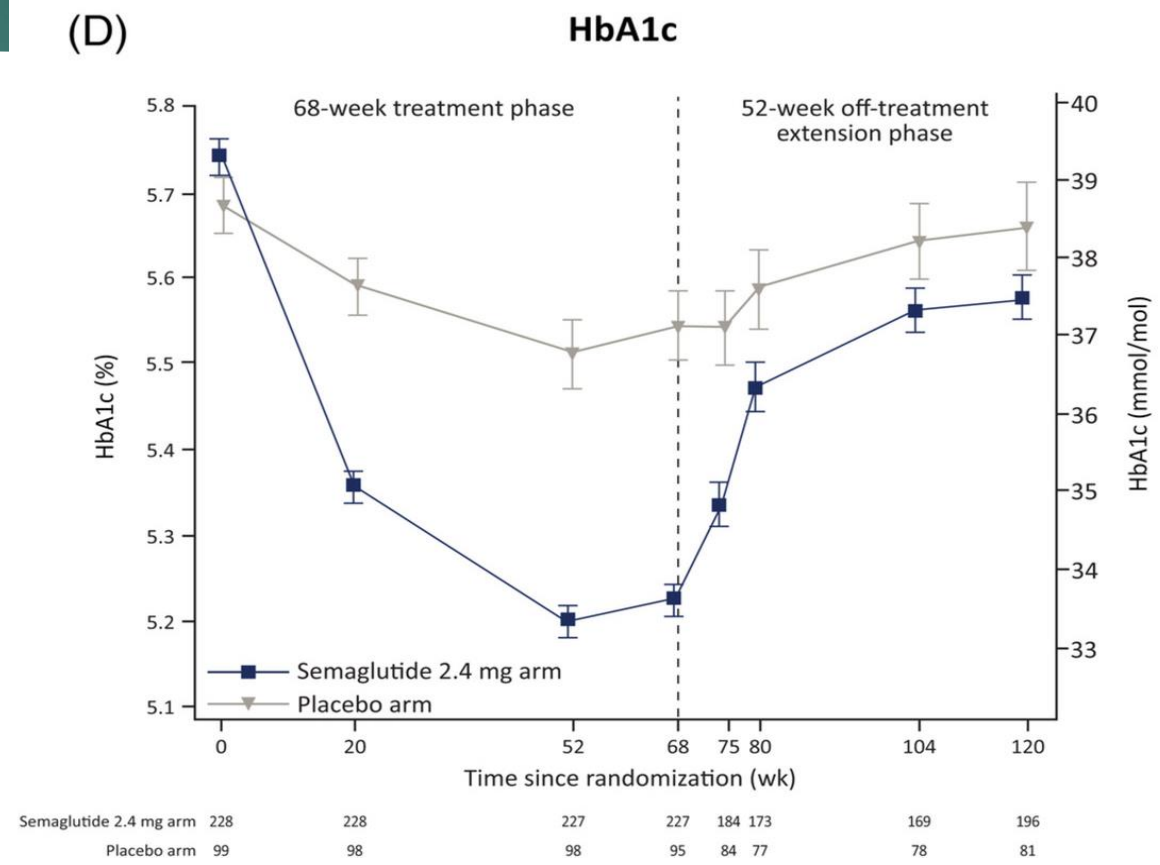
Metabolic Adaptation – STEP 1 Extended



Wilding, J., et al., & STEP 1 Study Group (2022). Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. *Diabetes, obesity & metabolism*, 10.1111/dom.14725. Advance online publication. https://doi.org/10.1111/dom.14725 open access Figure 1

Metabolic Adaptation – Step 1 Extended





Wilding, J., et al , & STEP 1 Study Group (2022). Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. *Diabetes, obesity & metabolism*, 10.1111/dom.14725. Advance online publication. https://doi.org/10.1111/dom.14725 open access Figure 2

Obesity Treatment to Impact ORCs Long Term = Maintaining Weight Loss

Self-monitoring

Frequent/regular attendance at obesity treatment program

Self-belief that weight can be controlled

Continue the medical treatment program

Maintaining weight loss is made difficult by the reduction in energy expenditure that weight loss induces

Weight regain typically occurs when medication is stopped

Apovian CM, et al. *J Clin Endocrinol Metab* 2015;100(2):342-62. Thomas JG, et al. *Am J Prev Med*. 2014;46(1):17-23

Post Bariatric Surgery

- Optimal time for pharmacotherapy
  - At weight plateau
  - Maximize weight loss outcomes
- In the literature
  - Topiramate 7.7% weight loss post surgery (Stanford)
  - Non-GLP1RA's at 9 months 5.6% weight loss, GLP1RA's at 9 months 6.9% (Gazda)

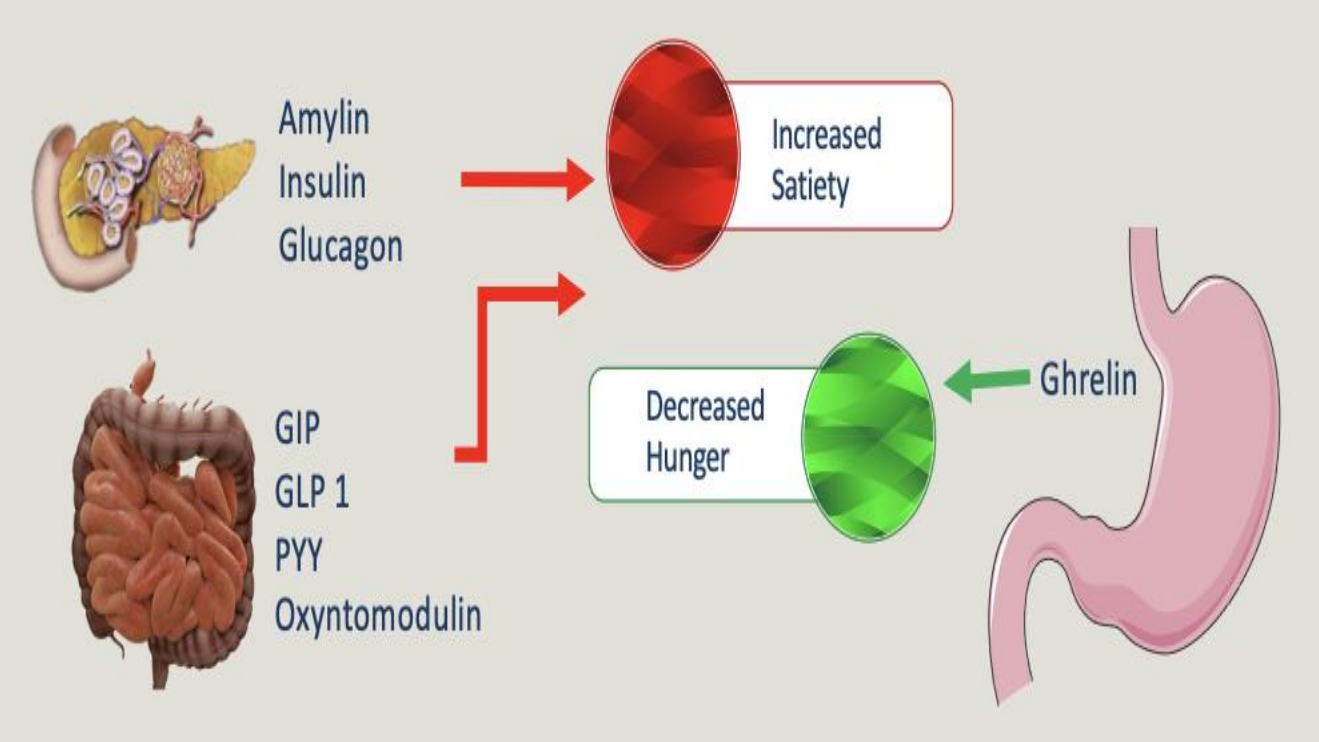
Stanford F. C. (2019). Controversial issues: A practical guide to the use of weight loss medications after bariatric surgery for weight regain or inadequate weight loss. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery*, *15*(1), 128–132. https://doi.org/10.1016/j.soard.2018.10.020
Gazda, C. L., Clark, J. D., Lingvay, I., & Almandoz, J. P. (2021). Pharmacotherapies for Post-Bariatric Weight Regain: Real-World Comparative Outcomes. *Obesity (Silver Spring, Md.)*, *29*(5), 829–836. https://doi.org/10.1002/oby.23146

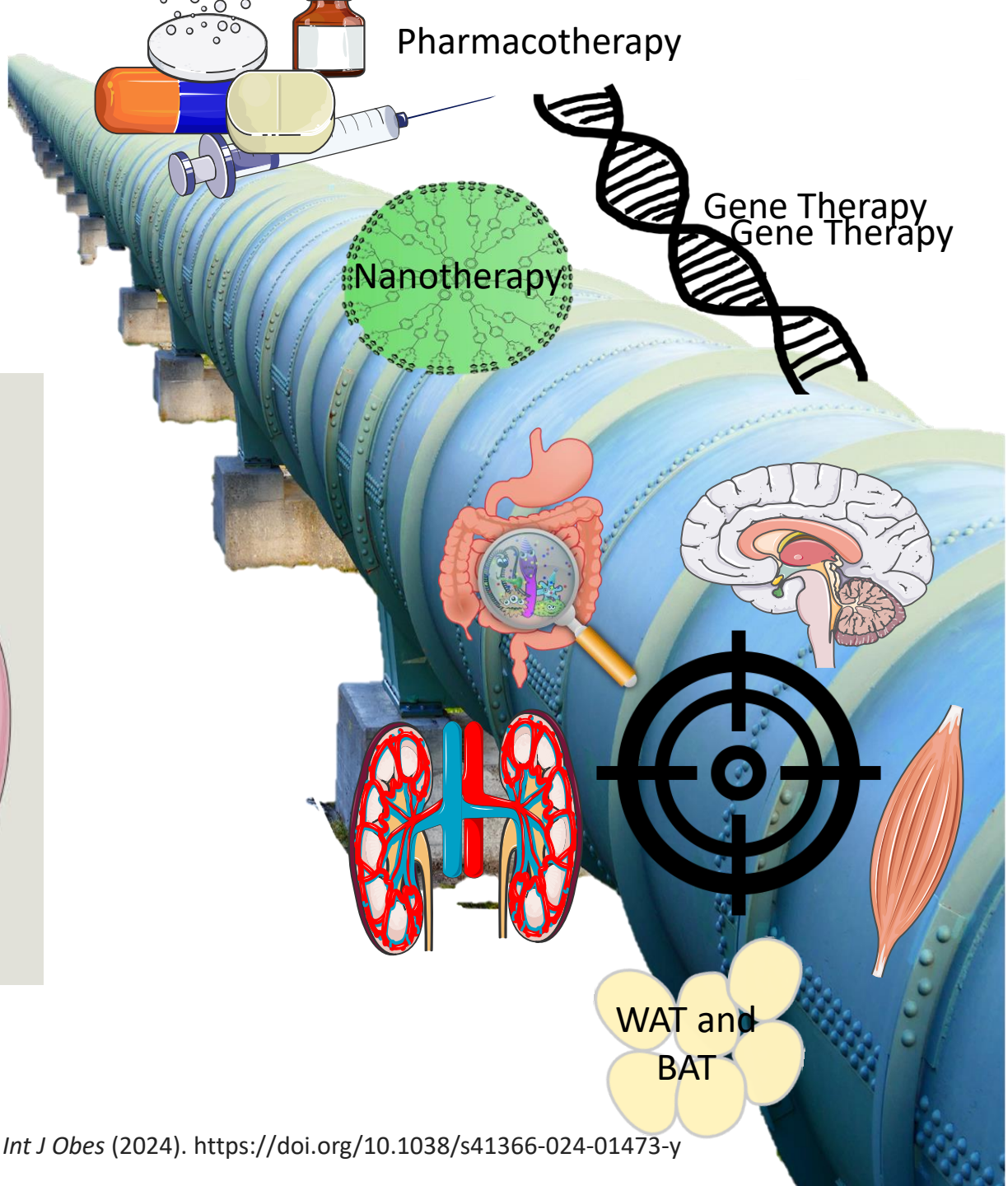
Recognize

Recognize Medications That Are In The Pipeline For Treating Obesity

In The Pipeline

- 50 + companies are developing obesity therapies
- 80 + therapies in trials





Melson, E., Ashraf, U., Papamargaritis, D. *et al.* What is the pipeline for future medications for obesity?. *Int J Obes* (2024). https://doi.org/10.1038/s41366-024-01473-y

Practice Pearls

- Obesity is a chronic and often progressive condition
- Obesity management is not about simply reducing numbers on the scale
- Intensify treatment with pharmacology
- Evaluate medication success at “12 weeks”
- If one medication doesn’t work, try another
- **With success, continue medical management**

Thank you!

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Resources

Image resources

- https://www.worldobesity.org/resources/image-bank
- https://www.obesityaction.org/get-educated/public-resources/oac-image-gallery/
- Canadian Obesity Network Image Bank: https://www.flickr.com/photos/144769815@N06/