Pharmacologic Management of Obesity

Presented By:
Kevin Patellos, PharmD, MBA, BCPS
Assistant Director of Pharmacy
Licking Memorial Hospital

Obesity

- Obesity is defined as a BMI $\geq$ 30 kg/m^2
- Between 1999 and 2020 the prevalence of obesity in America increased from 30.5% to 41.9%.
- Obesity now accounts for more than $173 billion in annual medical expenditures.

BMI categories for adults

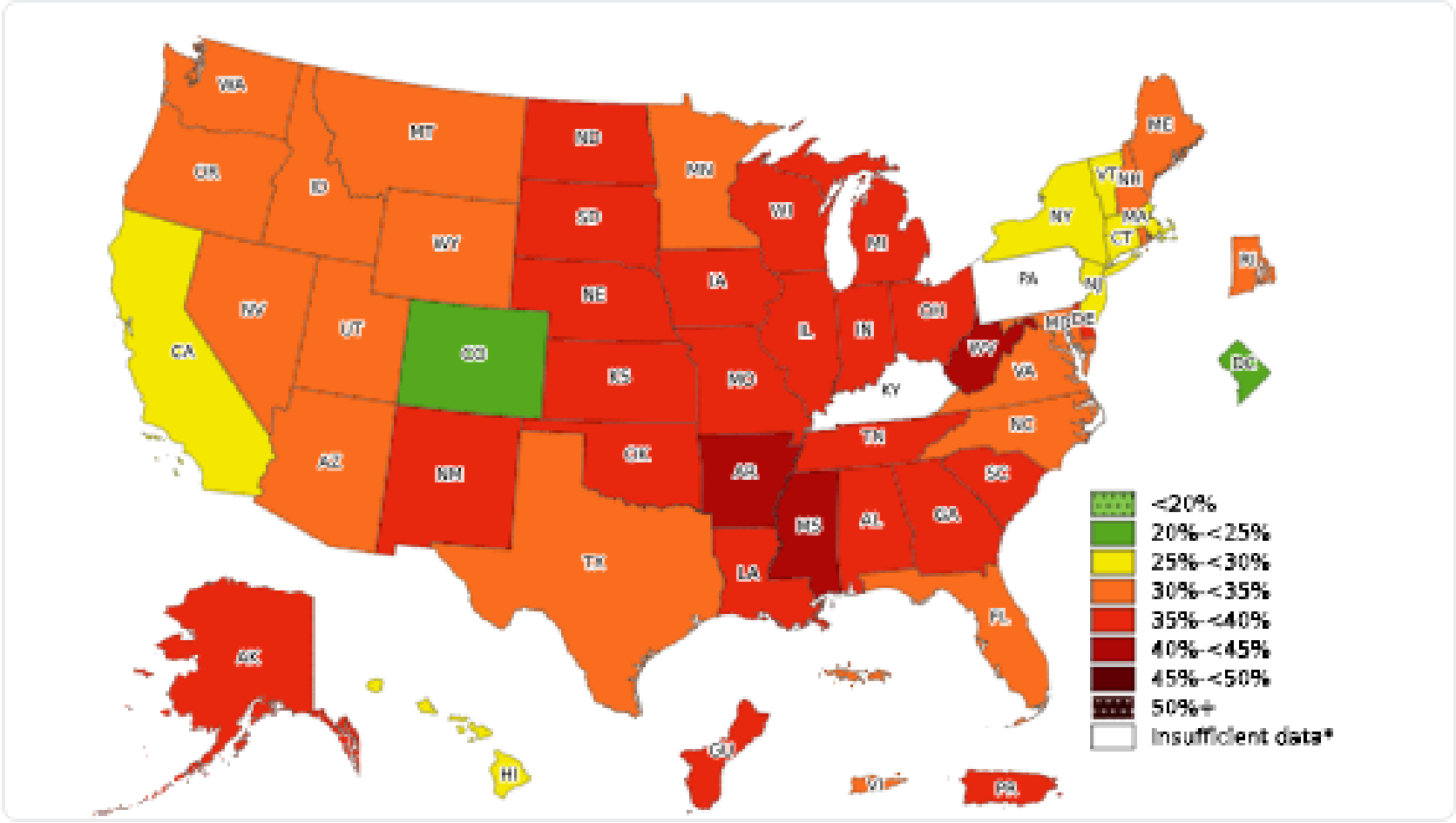
BMI is a calculation of a body person's weight (in kilograms) divided by the square of their height (in meters). For adults 20 and older, BMI categories are based on a person's BMI regardless of age, sex, or race.

BMI categories for adults 20 and older:

BMI Category	BMI Range (kg/m^2)
Underweight	Less than 18.5
Healthy Weight	18.5 to less than 25
Overweight	25 to less than 30
Obesity	30 or greater
Class 1 Obesity	30 to less than 35
Class 2 Obesity	35 to less than 40
Class 3 Obesity (Severe Obesity)	40 or greater

References: 1, 2

Prevalence of Obesity



References: 3

Obesity

- Multifactorial disease state.
  - Causes include lifestyle, metabolic disorders, hormones, medications, etc.
- Multiple treatment modalities.
  - Diet, exercise, behavioral modification, pharmacologic agents, surgical intervention.
- Up To Date lists 50+ links to different Society guidelines and treatment recommendations.
  - 2022 American Gastroenterological Association Clinical Practice Guideline on Pharmacological Interventions for Adults with Obesity

Management of Obesity

Nonpharmacological Interventions

- Diet modifications, exercise, and behavioral changes
- Difficult to maintain weight-loss through lifestyle interventions alone

Pharmacotherapy

- BMI $\geq$30 kg/m^2 OR $\geq$27 kg/m^2 with weight-related comorbidity.

Surgical Intervention

- BMI $\geq$ 35 kg/m^2 regardless of comorbidities
- BMI $\geq$ 27.5 kg/m^2 in Asian patient populations
- BMI $\geq$ 30 kg/m^2 without substantial weight loss through non-surgical interventions

References: 4,5,6,7,8

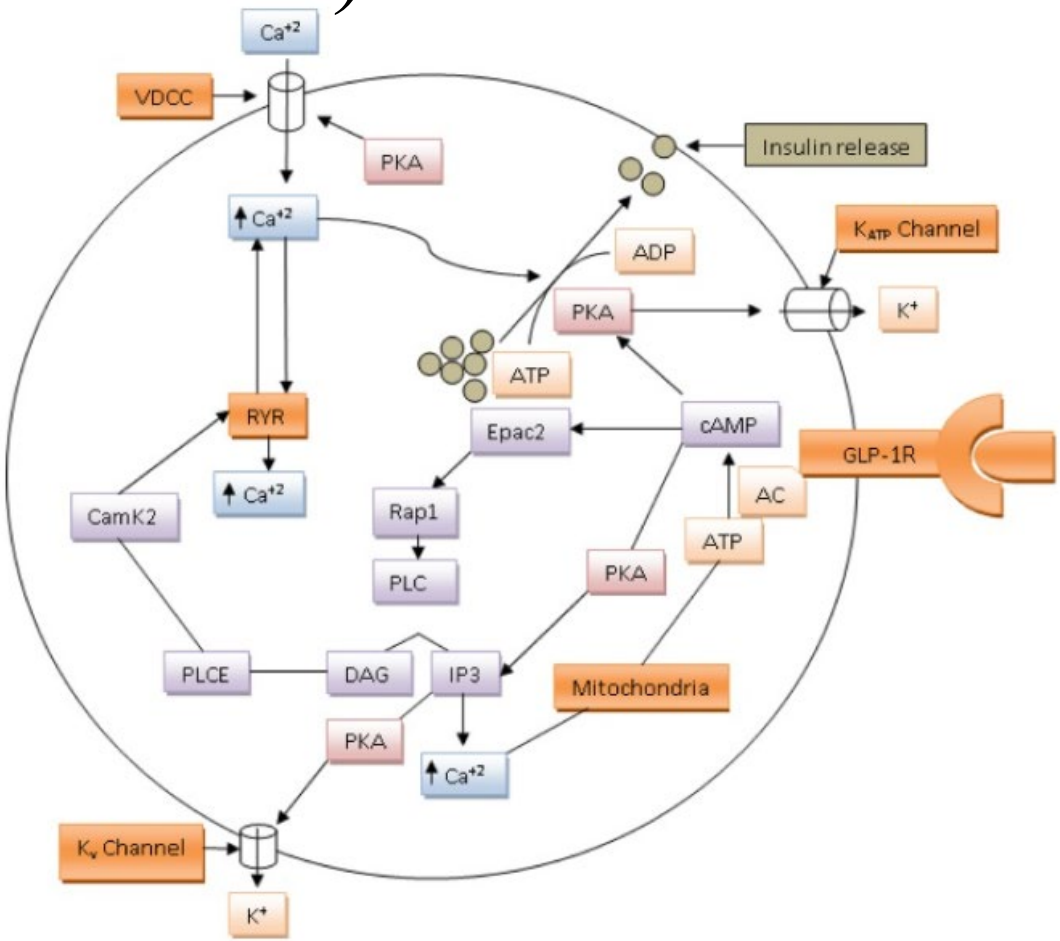
Obesity Pharmacotherapy

Pharmacologic options include:

- GLP-1 Receptor Agonists
- Phentermine
- Orlistat
- Phentermine/Topiramate ER
- Naltrexone/Bupropion ER

GLP-1 Receptor Agonists (GLP-1 RA)

- Primary Diabetes Mechanism
  - Mimic endogenous GLP-1
  - Bind to and activate GLP-1 receptors in the pancreas.
    - Promotes glucose-dependent insulin release and suppresses glucagon secretion.



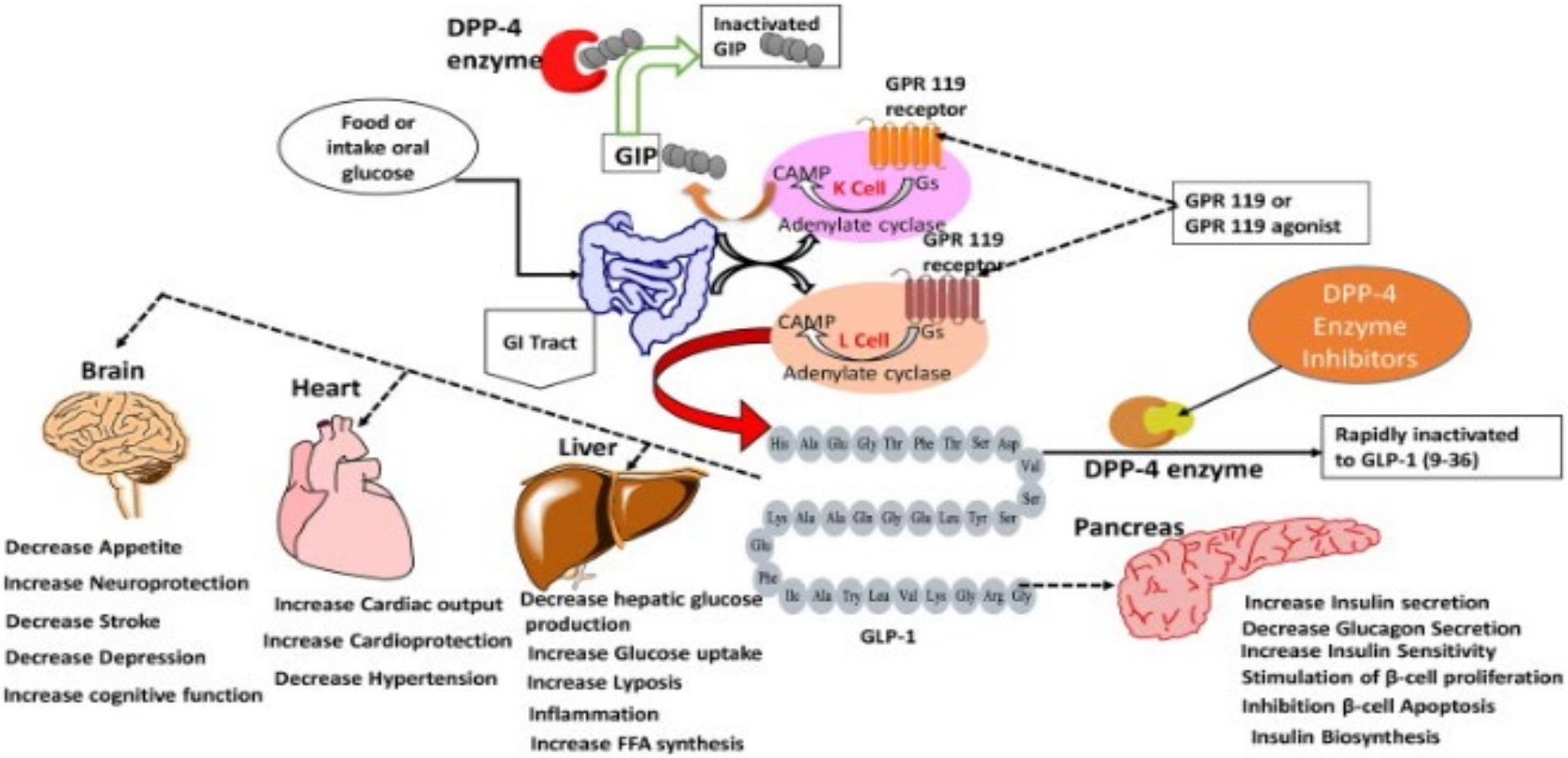
References: 9, 10, 11

GLP-1 Receptor Agonists

Weight Loss Mechanisms:

- Appetite Suppression
  - Delayed gastric emptying and reduced gut motility increases satiety.
  - GLP-1 receptors on orexigenic and anorexigenic neurons modulates central nervous system pathways involved in reward processing and motivated behaviors.
    - Leads to reduced food intake.
- Increased Insulin Secretion
  - Enhanced glucose-dependent insulin release promotes glucose homeostasis and indirectly reduces body weight.
    - Loss of lean mass and fat mass.
- Reduced Glucagon Secretion
  - Inhibit glucagon release leading to lower blood glucose levels.
    - Contributes to loss of lean mass.
- Energy Expenditure
  - Increase thermogenesis and improve mitochondrial function in adipose tissue.
    - Long-term negative energy balance.

References: 12

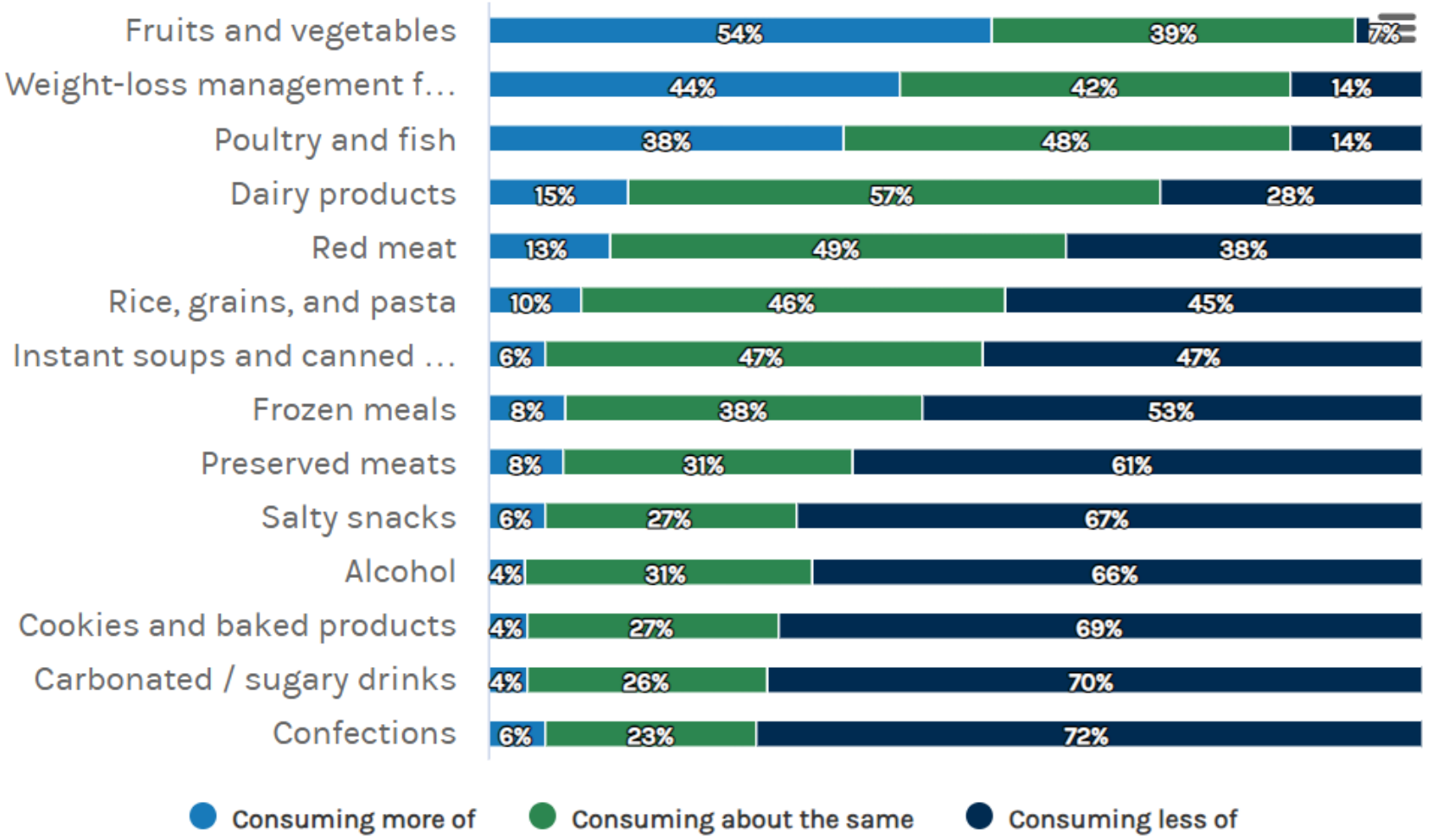


GLP-1 synthesis, release, metabolism and effects of GLP-1 on body organs: Stimulate secretion of GLP-1 after meal ingestion. GLP-1 and GIP rapidly converts inactive metabolites by DPP-4 enzyme. Inhibition of DPP-4 enzyme activity by specific DPP-4 enzyme inhibitors and prevents GLP-1 and GIP degradation.

GLP-1 actions in peripheral body tissue: Mostly GLP-1 action by specific GLP-1 receptors present on specific body tissues such as pancreas, GLP-1 increase insulin biosynthesis, secretion from beta cells and inhibits glucagon secretion from alpha cells in pancreas. However, the indirect action of GLP-1 in another body tissue liver (reduces hepatic gluconeogenesis), brain (Increase Neuroprotection), etc. provides benefits.

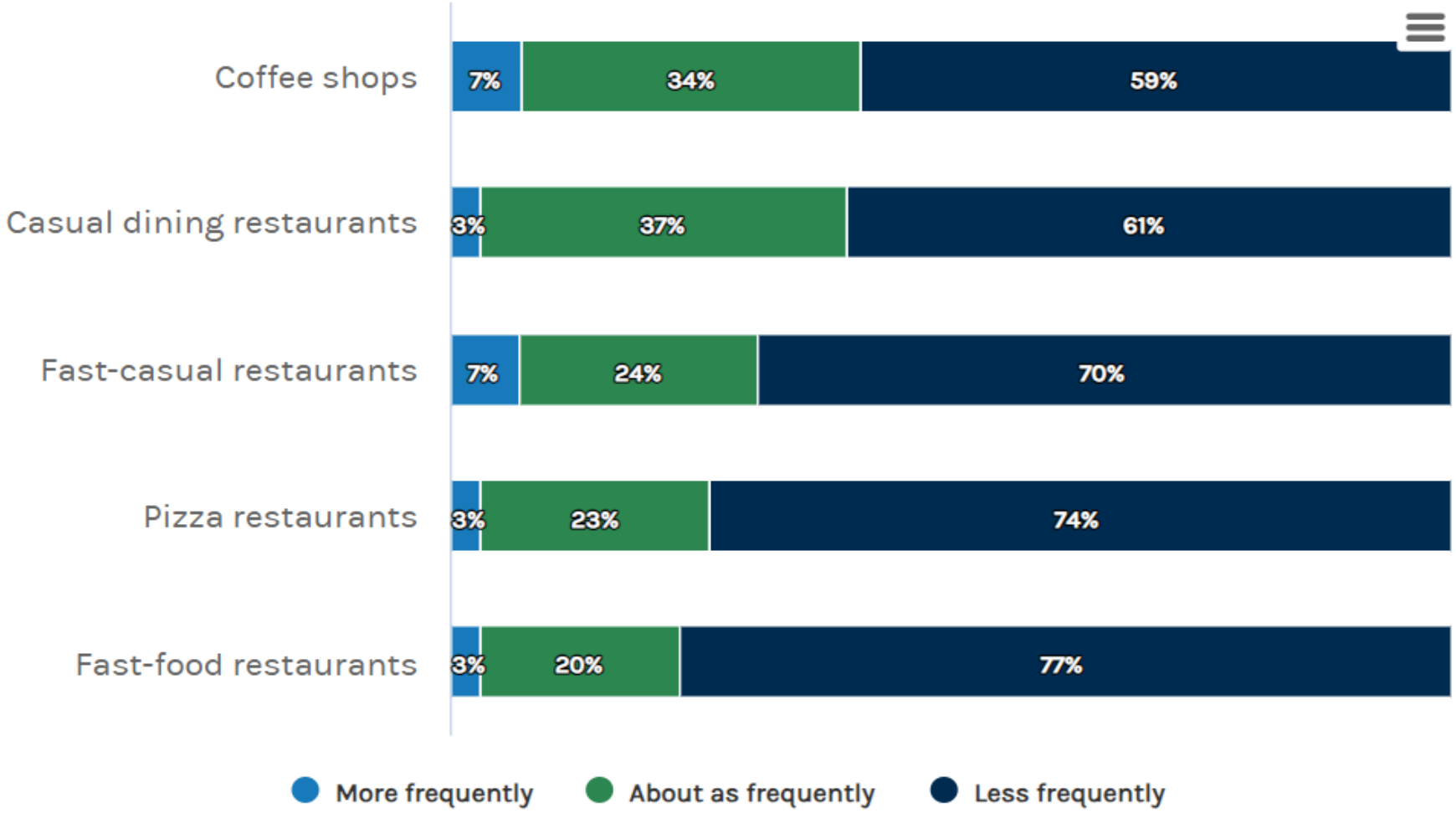
References: 11

Exhibit 10: Healthier categories see a boost in consumption by patients after starting on AOM



Source: Morgan Stanley Research (including estimates)

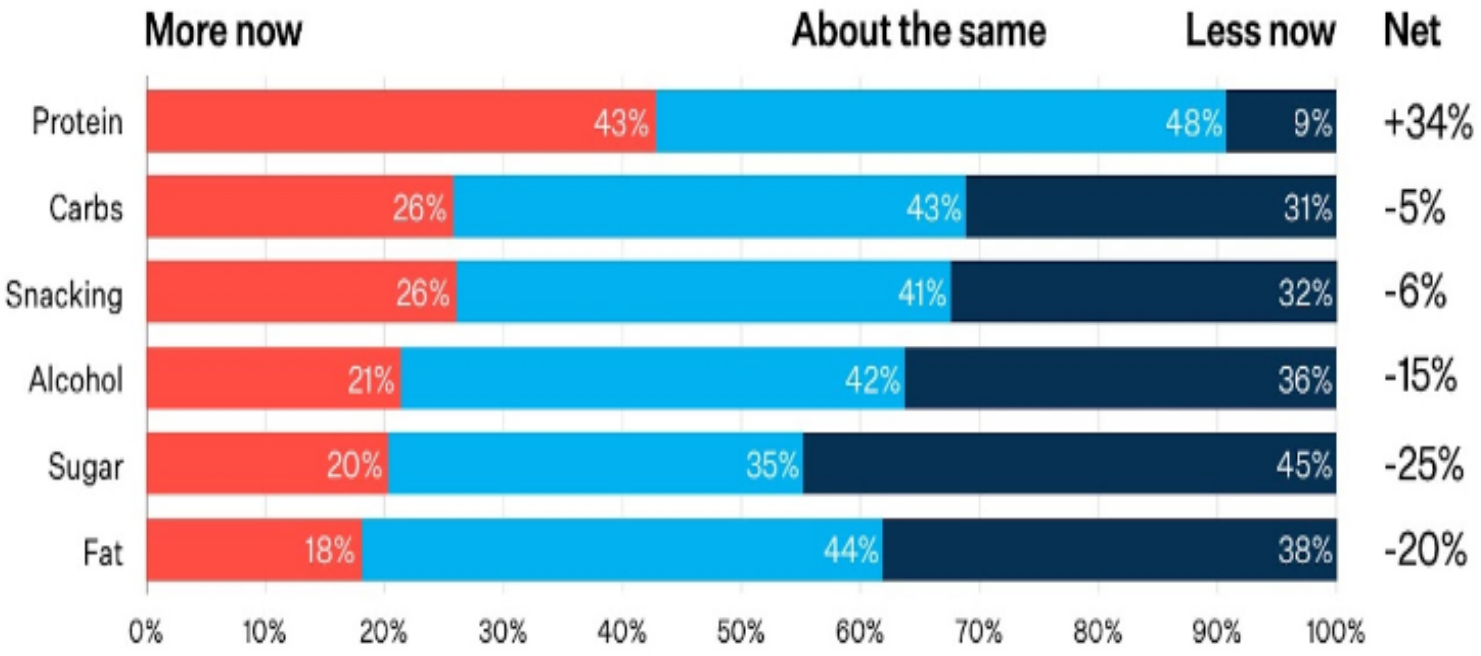
Exhibit 11: Patients report the most significant changes to fast food and pizza restaurant trips



Source: Morgan Stanley Research (including estimates)

GLP-1 users say they're eating more protein, less sugar, and drinking less

Percentage of responses: How has your *x* consumption changed since starting GLP-1 drugs?



Data: Consumer Trends Survey, powered by toluna* (n=388)

The New Consumer | Coefficient

References: 15

GLP-1 Receptor Agonists

- Adverse Effects:
  - GI effects are most common.
    - Abdominal pain, cramping, constipation, decreased appetite, diarrhea, dysgeusia, dyspepsia, nausea, vomiting.
      - Associated with higher doses and rapid titration; may decrease over time.
  - Injection site reactions.
  - Rare, but serious side effects.
    - Pancreatitis, medullary thyroid carcinoma (BBW), gallbladder disease, diabetic retinopathy, and AKI (secondary to GI symptoms), suicidal ideations have been seen in case reports, animal studies, and early clinical trials.
      - Causality not established due to confoundment of risk associated with underlying disease state.
- Contraindications:
  - Patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2.
  - Avoid use during pregnancy.

References: 9, 13,16,17

GLP-1 Receptor Agonists

Available agents:

- FDA-approved for glycemic control
  - Dulaglutide subq (Trulicity)
  - Exenatide subq (Byetta)
  - Liraglutide subq (Victoza)
  - Liraglutide/insulin degludec (Xultophy)
  - Lixisenatide/insulin glargine (Soliqua)
  - Semaglutide oral & subq (Rybelsus; Ozempic)
  - Tirzepatide (dual GIP/GLP-1 receptor agonist) (Mounjaro)
- FDA-approved for weight loss:
  - Liraglutide subq (Saxenda)
  - Semaglutide subq (Wegovy)
  - Tirzepatide (Zepbound)

References: 13

GLP-1 Receptor Agonists

- Liraglutide:
  - First GLP-1 RA to be approved for chronic weight management.
  - Weight loss dosing is 3mg subq qday.
    - Start at 0.6mg subq qday and increase by 0.6mg weekly until 3mg dose is reached.
      - If dose escalation not tolerated, delay next up-titration by 1 week.
    - Discontinue if 3mg dose cannot be tolerated.

References: 9

GLP-1 Receptor Agonists

- Liraglutide Efficacy:
  - SCALE Program
    - 4 major RCTs investigating liraglutide 3mg subq qday vs placebo for 56-160 weeks.
    - SCALE Obesity and Prediabetes trial
      - N=3,371; t=56 weeks
      - Treatment group experienced significantly greater mean weight loss (-8.4kg vs -2.8kg)
      - 63.2% of treatment group vs 27.1% of placebo achieved ≥5% weight loss.
    - 3 year extension trial showed sustained benefit in treatment group at week 160. (-4.3% difference).
    - SCALE Maintenance Trial
      - Treatment group subjects that lost ≥5% BW during low calorie diet run-in achieved additional 6.2% weight loss vs 0.2% with placebo.
    - SCALE Intensive Behavioral Therapy Trial
      - Adding liraglutide to intensive lifestyle intervention added 7.5% weight loss vs 4% with placebo.

References: 9, 43, 44, 45, 46

GLP-1 Receptor Agonists

- Liraglutide Efficacy:
  - LEADER Trial
    - Double-blind RCT, liraglutide 1.8mg subq qday or placebo
    - N=9,340
    - T=3.8 years
    - Treatment group had significantly reduced major adverse cardiovascular events (MACE) vs placebo.
      - 13% vs 14.9% occurrence, respectively.
      - Has not specifically been established for liraglutide 3mg dose for chronic weight management in non-diabetic patients.

References: 9, 47

GLP-1 Receptor Agonists

- Semaglutide:
  - Weight loss dosing starts at 0.25mg subq q week.
    - Up-titrate q 4 weeks until goal dose of 2.4mg subq qweek is achieved.
      - May reduce dosing to 1.7mg subq q week if 2.4mg dose is not tolerated.
      - May delay up-titration by 4 weeks if adverse effects occur.
      - Discontinue if 1.7mg subq q week dose cannot be tolerated.

References: 9

GLP-1 Receptor Agonists

- Semaglutide Efficacy:
  - STEP Program
    - STEP 1
      - 68-week, double blind RCT
      - N=1,961 non-diabetics with obesity or overweight with ≥1 comorbidity.
      - Semaglutide 2.4mg q week or placebo, plus lifestyle interventions.
      - Treatment group had greater mean weight loss (-14.9% vs -2.4%).
      - 86.4% of treatment group achieved ≥5% weight loss vs 31.5% placebo group.
        - » 50.5% of treatment group achieved ≥15% weight loss vs 4.9% placebo.
    - STEP 4
      - 68-week RCT evaluating weight gain after 20-week semaglutide run-in.
      - Continued treatment achieved -7.9% additional weight loss vs 6.9% weight regain with placebo.
      - Treatment group maintained improved CV metrics (BP, cholesterol, etc.).

References: 9, 48, 49

GLP-1 Receptor Agonists

- Semaglutide Efficacy:
  - OASIS 1
    - Randomized, double-blind RCT.
    - Semaglutide 50mg po qday vs placebo in adult subjects obesity or overweight and weight-related non-diabetic complications.
    - T=68 weeks
    - Treatment group had significantly higher mean weight loss vs placebo (-15.1% vs -2.4%).
    - Cohort achieving specified % weight loss from baseline (treatment vs placebo):
      - 5%: 85% vs 26%
      - 10%: 69% vs 12%
      - 15%: 54% vs 6%
      - 20%: 34% vs 3%
  - Cardiovascular Effects
    - SUSTAIN-6 and SELECT showed cardiovascular benefits with injectable semaglutide; PIONEER 6 did not find cardiovascular benefits with PO semaglutide vs placebo; SOUL trial did find MACE decrease in T2DM with ASCVD or CKD.

References: 9, 50, 51, 52, 53, 58

GLP-1 Receptor Agonists

- Tirzepatide
  - Novel combination GIP & GLP-1 RA.
    - FDA approved for weight management in November, 2023.
  - Initiate therapy at 2.5mg subq q week x4 weeks; then increase to 5mg subq qweek.
    - May increase 2.5mg every 4 weeks up to a maximum dose of 15mg per week (if tolerated).
      - Initial 2.5mg dose minimizes GI adverse effects, but is sub-clinical.

References: 9

GLP-1 Receptor Agonists

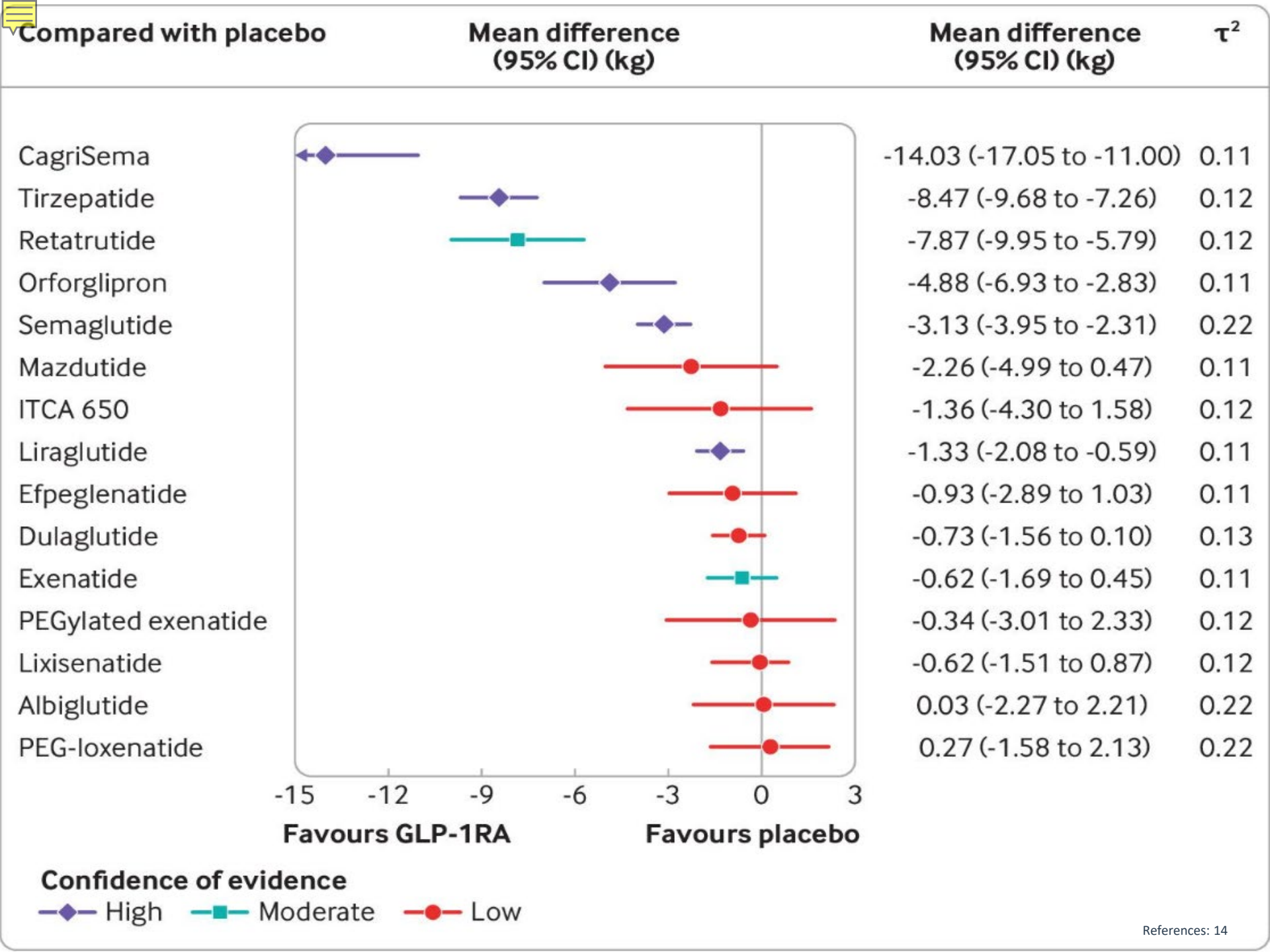
- Tirzepatide Efficacy:
  - SURMOUNT-1
    - Double-blind RCT
    - Tirzepatide 5mg, 10mg, or 15mg vs placebo.
    - N=2,539 adults with obesity or overweight and complications.
    - T=72 weeks.
    - Mean weight reductions significantly greater with tirzepatide use:
      - 5mg: -15%
      - 10mg: -19.5%
      - 15mg: -20.9%
      - Placebo: -3.1%
    - Proportion achieving ≥ 5% weight loss ranged from 85-91% in treatment groups vs 35% in placebo.
      - ~ half of 10mg and 15mg groups achieved ≥20% weight loss (3% placebo).
  - SURMOUNT-2
    - N=938 adults with T2DM
    - Mean weight change at 72 weeks:
      - 10mg: -12.8%
      - 15mg: -14.7%
      - Placebo: -3.2%

References: 9, 54, 55

GLP-1 Receptor Agonists

- Tirzepatide Efficacy:
  - SURMOUNT-3
    - Evaluated weight regain prevention after initial weight loss from a 12-week intensive lifestyle intervention.
      - Treatment group experienced continued mean weight reduction of -18.4% vs +2.5% weight gain with placebo at 72 weeks.
  - SURMOUNT-4
    - 36-week open-label lead-in phase of tirzepatide 10mg or 15mg subq q week.
    - Following lead-in, participants randomized to tirzepatide or placebo for 52 weeks.
      - Treatment group additional mean body weight loss of -5.5% vs +14% for placebo.
      - 89.5% of treatment group maintained $\geq$80% of initial weight loss vs 16.6% of placebo.
  - SURMOUNT-5
    - Recently published RCT comparing tirzepatide vs semaglutide for obesity (n=751; t=72 weeks) confirmed that tirzepatide lead to grater weight loss and grater decrease in waist circumference.
      - Mean % weight change -20.2% for tirzepatide vs. -13.7% with semaglutide.
      - Mean waist change -18.4 cm with tirzepatide and -13cm with semaglutide.

References: 9, 56, 57, 59

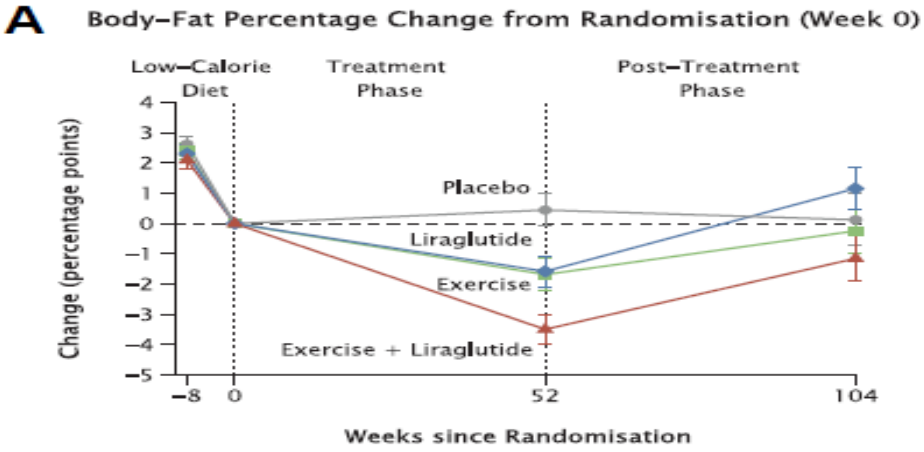


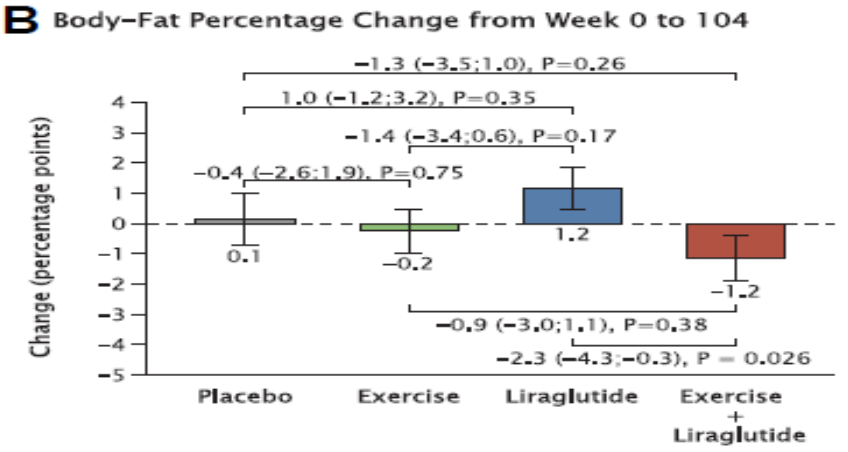
References: 14

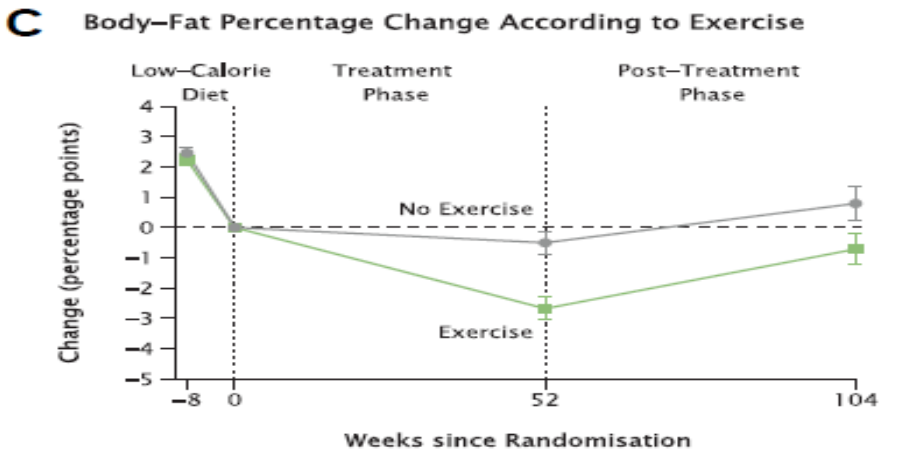
GLP-1 Receptor Agonists

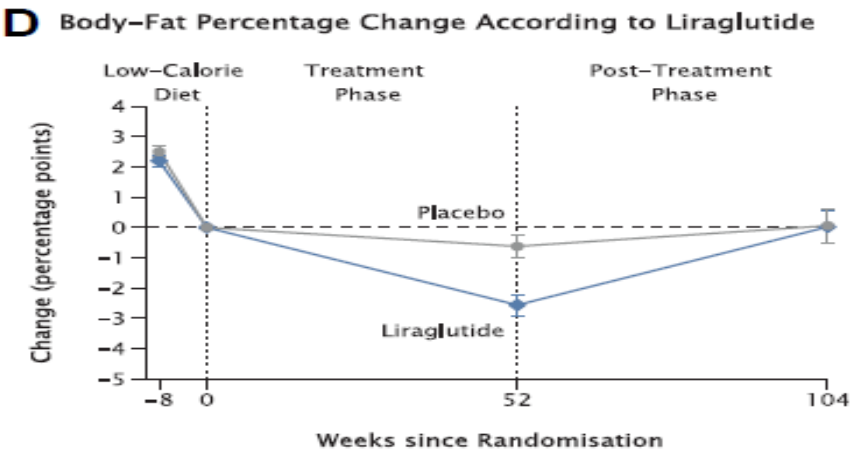
- Discontinuation
  - 30-75% of patients started on GLP-1 RAs discontinue use within the first year.
    - GI side effects and cost are primary reasons.
- Maintenance After Weight Loss & GLP-1 RA Discontinuation
  - Mixed results in the literature.
  - Studies with longer post-treatment periods find discontinuation is associated with rebound weight gain, fat gain.
    - Weight gained was proportionate to weight lost.

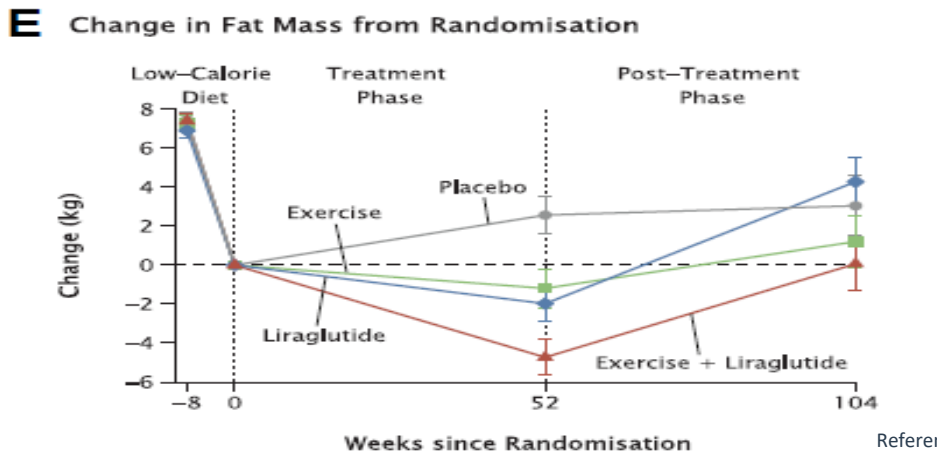
References: 22, 23, 24, 25, 26, 27, 28

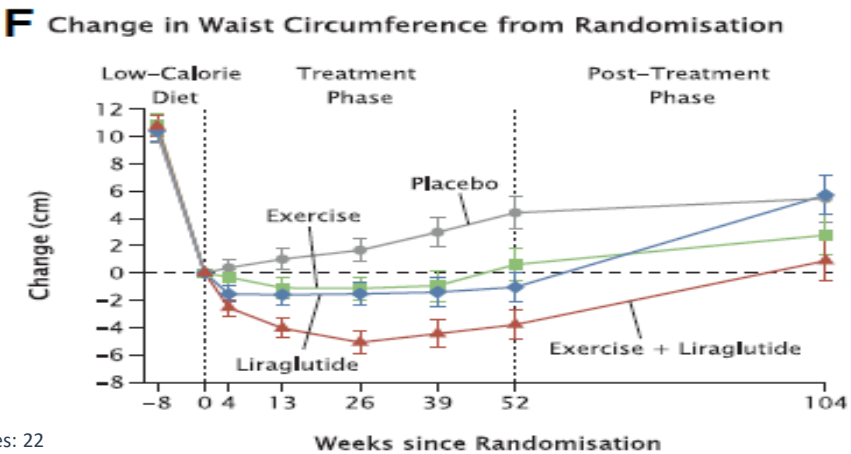










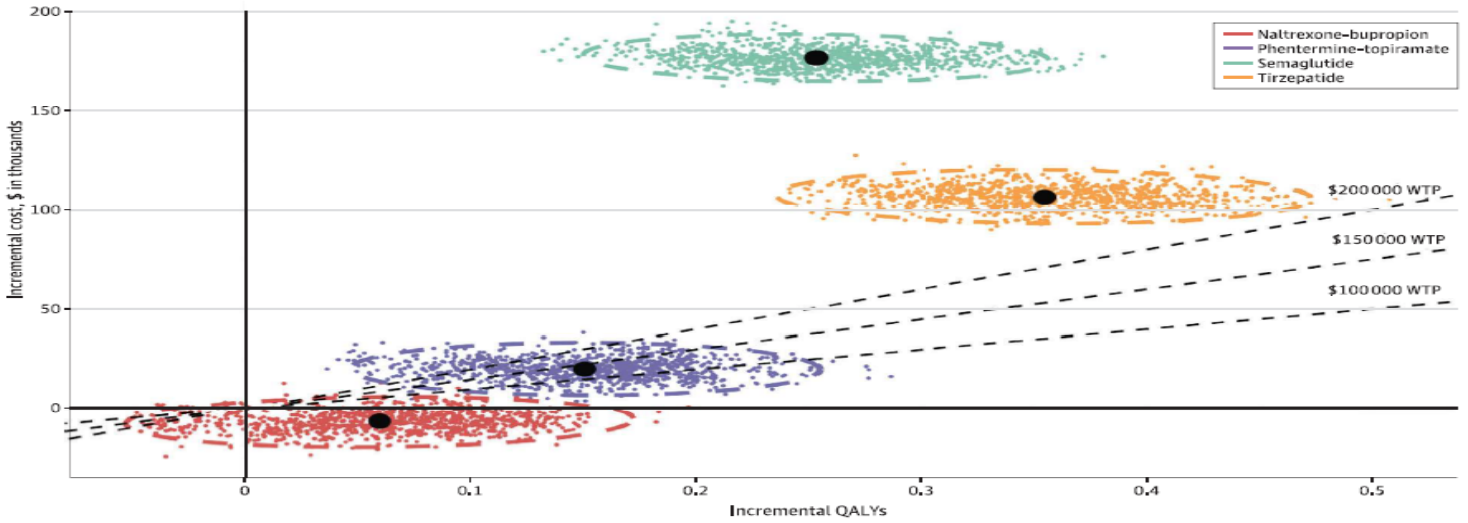


References: 22

GLP-1 Receptor Agonists

- Cost-Effectiveness
  - Recent large lifetime cost-effectiveness study in JAMA concluded that tirzepatide and semaglutide both offered substantial lifetime health benefits compared to non-GLP-1 RA AOMs, but were not cost-effective ($100,000/QALY) at current prices.
    - Tirzepatide would require 30.5% reduction from current price.
    - Semaglutide would require a 89.1% reduction from current price.

Figure 2. Probabilistic Sensitivity Analysis for the Cost-Effectiveness of the Antiobesity Medications vs Lifestyle Modification Over a Lifetime

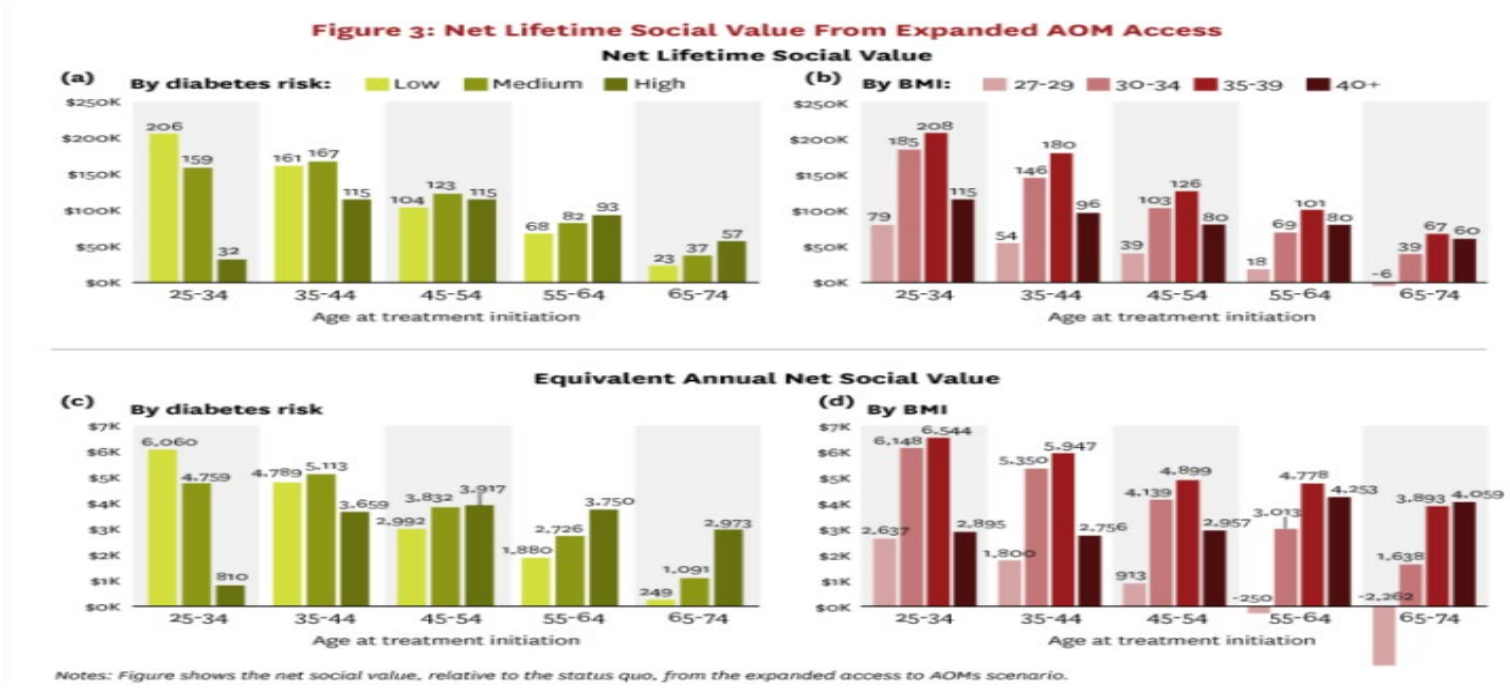


Each data point represents 1 of 1000 Monte Carlo simulations, and the encompassing ellipses illustrate the 95% uncertainty intervals for these results. The solid black circles indicate the mean values for the 1000 simulations. The willingness-to-pay (WTP) thresholds of $100 000, $150 000, and $200 000 per quality-adjusted life-year (QALY) are depicted by dashed lines.

References: 29

GLP-1 Receptor Agonists

- Cost-Effectiveness
  - Alternatively, a recent USC whitepaper found significant net lifetime cost-effectiveness from GLP-1 agents (more pronounced when started younger and in patients with lower DM risk factors) .
    - Non-clinical trial, these findings were heavily reliant on optimistic efficacy and price discounting assumptions.
      - EG Assumption of a 20% BMI reduction.
        - » Separate 47 RCT meta-analysis found GLP-1 RA BMI reduction benefit of -2.07 kg/m^2 .



References: 30, 31

GLP-1 Receptor Agonists

- 503A vs 503B Compounding
  - 503A
    - Compound on a patient specific, per prescription basis.
    - Regulated by state boards of pharmacy to comply with USP and other guidelines.
  - 503B
    - Outsourcing facility that compounds large, non-patient specific batches of drugs to be used by healthcare facilities and provider offices.
    - Must comply with Current Good Manufacturing Practices (CGMP).
      - Validation of all processes.
- Compounded Formulations
  - FDA allows compounding of drugs that are not commercially available.
    - Unique formulations, dosages, or commercial shortage.
  - GLP-1 RA compounding has proliferated over the last few years (up to 30% of all GLP-1 RAs used were compounded) due to high cost, high demand, and commercial shortage of GLP-1 RAs.
    - As of May 2025, the FDA has declared all GLP-1 RA shortages over.
      - Non-commercially available products (EG unique dosages, additives, etc.) will still be able to be compounded.

References: 18,19,20, 21

The following chart provides the status of GLP-1 drugs and the ability of Ohio pharmacies, prescribers, and outsourcing facilities to compound tirzepatide and semaglutide that are essentially copies of commercially available drug products:

Name of Drug	FDA Shortage?	Compounding Copies Permitted?
Tirzepatide (Mounjaro, Zepbound)	No	No Pharmacy or prescriber compounding: **Ended February 18, 2025** Outsourcing facility compounding: **Ended March 19, 2025**[i]

77 S. High Street, 17th Floor
Columbus, OH 43215 U.S.A.

Phone: 614 | 466 4143
Fax: 614 | 752 4836

Semaglutide (Ozempic, Rybelsus, Wegovy)	No	No Pharmacy or prescriber compounding: **Ended April 22, 2025** Outsourcing facility compounding: **Ended May 22, 2025**[ii]

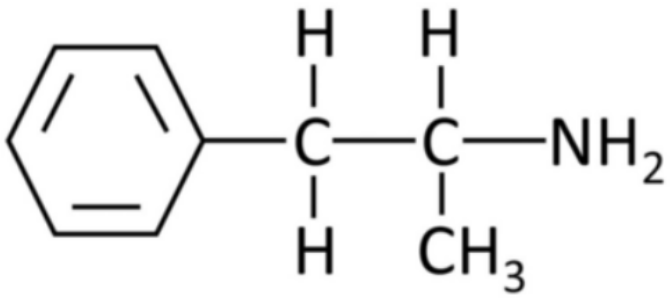
NOTE: This chart is not exhaustive. Please be advised that other GLP-1 products may be on the FDA drug shortage list.

Retatrutide & Cagrilintide Cannot Be Compounded

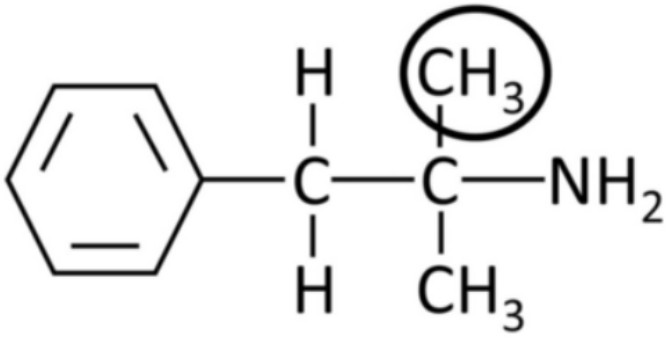
Retatrutide and/or Cagrilintide **cannot** be used in compounding under federal and state law. Additionally, they are not a component of an FDA-approved drug, are not listed on the FDA's "bulk drug list", do not have USP/NF monographs, and have not been found safe and effective for any condition.

Phentermine

Amphetamine



Phentermine



- One of the first FDA approved AOMs.
- Sympathomimetic that centrally stimulates hypothalamus to release norepinephrine, which leads to a reduction in appetite.

References: 9, 32

Phentermine

- Indicated for short-term use (max duration 12 weeks).
- Dosing:
  - 15-37.5mg po qday (prior to breakfast or 1-2 hours post-meal).
  - 9mg po tid prior to meals is also common.
- Adverse Effects:
  - Elevated blood pressure, palpitations, potential ischemia.
- Contraindications:
  - CVD, hyperthyroidism, glaucoma, substance abuse history, concurrent/recent MAOI usage, and pregnancy.
  - Caution in patients with structural heart disease, arrythmias, and uncontrolled hypertension.

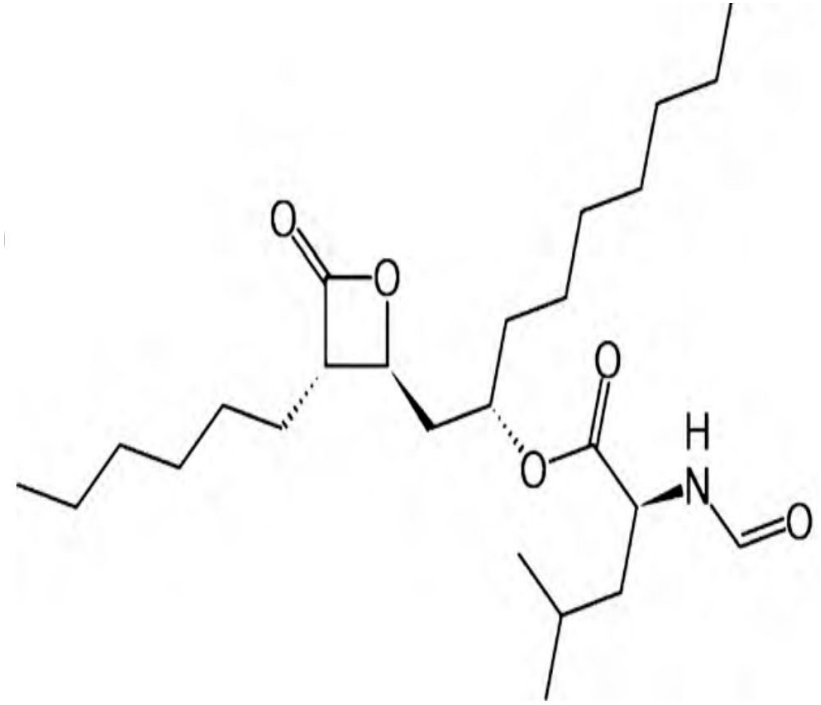
Phentermine

- Efficacy:
  - Observational study of short-term use (≤112 days) vs. long-term use (> 1 year)
    - n=13,972
    - Mean starting BMI 37.8 kg/m^2
    - Short-term arm
      - Initial weight loss followed by regain
        - » Weight reduction: -2.68% at 6 months, -1.38% at 12 months; -0.16% at 24 months.
    - Long-term arm
      - 7.4% greater weight loss than short-term arm at 24 months
    - 3-year follow-up CVD or death was rare (0.3%) and did not differ between treatment arms.

References: 9, 33

Orlistat

- FDA approved 1999
- Reversibly binds and inhibits pancreatic and gastric lipases.
  - Reduces dietary fat absorption by up to 30%.



Chemical structure of Orlistat.

References: 9, 13, 34

Orlistat

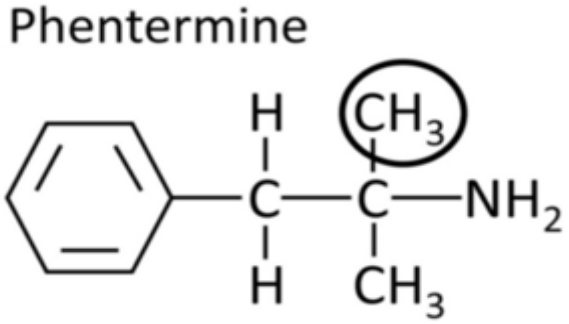
- Dosing:
  - RX
    - 120mg po tid concurrently or ≤ 1 hour post fatty meal
  - OTC
    - 60mg po tid concurrently or ≤ 1 hour post fatty meal
  - Low systemic absorption; no renal/hepatic adjustments.
- Adverse Effects:
  - GI intolerability (abdominal discomfort, flatulence, bowel urgency, oily spotting, steatorrhea).
    - Worse with higher fat content meals.
  - Reduced absorption of fat-soluble vitamins and β-carotene.
    - Supplement and separate dosing by at least 2 hours.
- Contraindications:
  - Chronic malabsorption syndromes, cholestasis, and pregnancy.

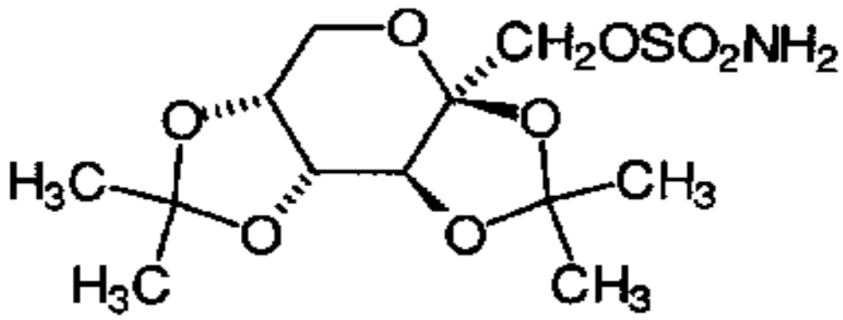
Orlistat

- Efficacy:
  - XENDOS trial
    - Design:
      - 4-year double-blind placebo-controlled trial.
      - n=3,305 with BMI $\geq$ 30 kg/m^2
    - Results:
      - Mean Weight Loss: -5.8 kg in orlistat arm vs -3.0 kg in placebo
        - » 72.8% of treatment arm achieved $\geq$5% reduction at year 1 vs 45.1% of placebo
      - Adverse Effects: GI events in 91% of treatment vs 65% placebo at year 1
        - » 36% vs 23%, respectively at year 4
        - » Discontinuation due to AEs was 8% vs 4%, respectively.
      - Additional benefits (treatment vs. placebo):
        - » SBP reduction (4.9 vs 3.4 mm Hg)
        - » DBP reduction (2.6 vs 1.9 mm Hg)
        - » LDL reduction (12.8% vs 5.1%)
        - » Total cholesterol reduction (7.9% vs 2.3%)

References: 9, 35

Phentermine/Topiramate ER





Chemical structure of topiramate

- Appetite suppression from phentermine mechanism with additive effect of topiramate's GABA mediated decreased appetite and increased satiety.
- Dosing:
  - Phentermine/topiramate ER 3.75mg/23mg po qday x2 weeks; then 7.5mg/46mg po qday x12 weeks
    - If weight loss <3% at may increase per tolerance to max of 15mg/92mg po qday.
  - Adjustment for moderate hepatic impairment or CrCl <50ml/min
    - 7.5mg/46mg po qday
    - Use not recommended in ESRD or severe hepatic impairment.

References: 9, 13, 32, 36

Phentermine/Topiramate ER

- Adverse Effects:
  - Increased heart rate, constipation, dry mouth, insomnia.
  - Increased risk of kidney stones.
- Contraindications:
  - Pregnancy (phenteramine risks; topiramate is teratogenic), CVD, hyperthyroidism, glaucoma, recent/concurrent MAOI usage.
- When stopping therapy, a gradual taper should be performed to avoid increased seizure risk.
- Caution with prolonged use.

References: 9, 13

Phentermine/Topiramate ER

- Efficacy:
  - CONQUER Trial
    - Placebo RCT
    - n=2,487; BMI 27-45 kg/m^2 and $\geq$ 2 weight related comorbidities
      - Placebo vs. phentermine/topiramate ER 7.5mg/46mg po qday vs. phentermine/topiramate ER 15mg/92mg po qday
    - Results at t=56 weeks (placebo/low-dose/high-dose):
      - Mean weight change: -1.4kg/-8.1kg/-10.2kg
      - % cohort with $\geq$5% weight loss: 21%/62%/70%
  - SEQUEL
    - Extension study of CONQUER
    - N=676
    - Results at t=108 weeks:
      - Mean weight change:-2.1kg/-9.6kg/-10.9kg
      - Mean % weight change: -1.8%/-9.3%/-10.5%

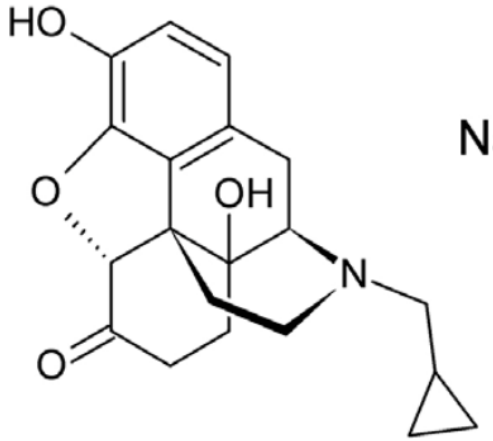
References: 9, 37, 38

Phentermine/Topiramate ER

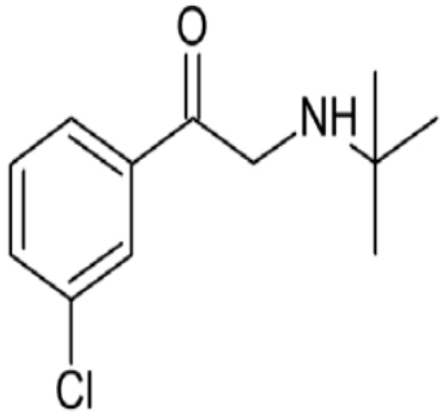
- Efficacy:
  - Lei, et al.
  - Meta-analysis of 6 RCTs
  - Comparison of various phentermine/topiramate ER doses
    - 3.75mg/23mg vs. 7.5mg/46mg vs. 15mg/92mg vs. placebo
  - Results:
    - All dose average increased weight loss of 7.73kg vs placebo.
      - 15mg/92mg dosing had greatest effect vs. placebo (8.25kg)
  - Adverse Effects:
    - Treatment group had increased dysgeusia, paresthesia, dry mouth, and constipation.
    - Treatment group had better CVD measures than placebo.
      - Average SBP reduction of 2.92mm Hg
      - Average DBP reduction of 0.96 mm Hg
      - Total cholesterol reduction 2.3%
      - Triglyceride reduction 13.38%

References: 9, 39

Naltrexone/Bupropion ER



Naltrexone



Bupropion

- Combination therapy opioid antagonist with norepinephrine and dopamine reuptake inhibitor.
- Exact mechanism for weight loss unknown.
  - Modulation of appetite and reward pathways?

References: 9, 40

Naltrexone/Bupropion ER

- Dosing:
  - Naltrexone/Bupropion ER 8mg/90mg po qday x7 days
    - Gradually increase as tolerated to max of two tablets bid
  - Max dose of one tablet po bid for patients with moderate/severe renal or hepatic impairment.
  - Not recommended in patients with ESRD or severe hepatic impairment.
  - Bupropion is a CYP450 substrate, dose adjustments may be required with CYP interacting medications.
- Adverse Effects:
  - GI & neuro disturbances (HA; sleep disturbances)
  - Minor increase in BP and HR have been noted.
- Contraindications:
  - Chronic opioid use, opioid withdrawal, uncontrolled HTN, seizure disorders, eating disorders, concurrent/recent MAOI usage, patients at risk for alcohol withdrawal, and pregnancy.
- Black Boxed Warning for increased suicidal ideations (especially in patients <24 yo)

Naltrexone/Bupropion ER

- Efficacy:
  - COR-I trial
    - Randomized, double-blind, placebo-controlled RCT
    - N=1,742 with BMI 30-45 kg/m^2 or 27-45 kg/m^2 with weight-related comorbidities
    - Lifestyle modifications plus naltrexone/bupropion ER 32mg/360mg OR naltrexone/bupropion ER 16mg/360mg OR placebo
    - T=52 weeks
    - Results (32mg/16mg/placebo):
      - % mean weight change: -6.1%/-5.0%/-1.3%
      - % cohort with $\geq$5% body weight lost: 48%/39%/23%
      - Treatment groups had an initial SBP increase of ~1.5 mm Hg; return to baseline by week 12; reduction of ~1mm Hg from baseline thereafter.
        - » Similar DBP trend.
      - Heart rate increased 1.5-2.5 BPM vs. placebo.
      - No increased suicidal ideation or depression was seen.

References: 9, 41

Naltrexone/Bupropion ER

- Efficacy:
  - Onakpoya, et al.
    - Systematic review and meta-analysis of 4 RCTs investigating benefits and harms of naltrexone-bupropion ER for weight loss.
    - Results:
      - Significantly larger portion of treatment groups achieved ≥5% reduction in body weight compared with placebo.
        - » Average 2.53kg greater weight loss from baseline.
      - Treatment groups also had more favorable changes in LDL reduction and BG.
      - Treatment groups experienced small, but significant changes in BP compared to placebo:
        - » SBP +1.47 mm Hg
        - » DBP +0.98 mm Hg

References: 9, 42

Table 2. Outcomes of Select Trials Evaluating Weight Loss in Adults after 1 to 2 Years with FDA-Approved Medications[a]

Drug	Study	Duration, weeks	Study arms (No. participants)	Baseline weight,[b] kg	Baseline BMI,[b] kg/m²	≥5% weight loss, %	≥10% weight loss, %	Difference from placebo in weight reduction
Orlistat	XENDOS[35]	52	Placebo (1,295) vs orlistat 120 mg 3 times daily (1,487)	110.6 (16.5) vs 110.4 (16.3)	37.4 (4.5) vs 37.3 (4.2)	45 vs 73	21 vs 41	−4.4 kg ($P < 0.001$)
Phentermine/topiramate ER	CONQUER[37]	56	Placebo (994) vs phentermine/topiramate7.5 mg/46 mg (498) vs phentermine/topiramate15 mg/92 mg (995)	103.3 (18.1) vs 102.6 (18.2) vs 103.0 (17.6)	36.7 (4.6) vs 36.2 (4.4) vs 36.6 (4.5)	21 vs 62 vs 70	7 vs 37 vs 48	−6.6% (95% CI, −7.4 to −5.8) vs −8.6% (95% CI, −9.3 to −8.0)
Naltrexone/bupropion ER	COR-I[41]	56	Placebo (581) vs 4 mg/90 mg, 2 tablets twice daily (578) vs 8 mg/90 mg, 2 tablets twice daily (583)	99.5 (14.3) vs 99.5 (14.8) vs 99.7 (15.9)	36.2 (4.0) vs 36.2 (4.3) vs 36.1 (4.4)	16 vs 39 vs 48	7 vs 20 vs 25	−3.7% ($P < 0.0001$) vs −4.8% ($P < 0.0001$)
Liraglutide	SCALE Obesity and Prediabetes[44]	56	Placebo (1,244) vs liraglutide 3.0 mg daily (2,487)	106.2 (21.7) vs 106.2 (21.2)	38.3 (6.3) vs 38.3 (6.4)	27 vs 63	11 vs 33	−5.4% (95% CI, −5.8 to −5.0)
Semaglutide	STEP 1[45]	68	Placebo (655) vs semaglutide 2.4 mg weekly (1,306)	105.2 (21.5) vs 105.4 (22.1)	38.0 (6.5) vs 37.8 (6.7)	32 vs 86	12 vs 69	−12.4% (95% CI, −13.4 to −11.5)
Tirzepatide	SURMOUNT-1[46]	72	Placebo (643) vs tirzepatide 5 mg weekly (630) vs tirzepatide 10 mg weekly (636) vs tirzepatide 15 mg weekly (630)	104.8 (21.4) vs 102.9 (20.7) vs 105.8 (23.3) vs 105.6 (22.9)	38.2 (6.9) vs 37.4 (6.6) vs 38.2 (7.0) vs 38.1 (6.7)	35 vs 85 vs 89 vs 91	19 vs 69 vs 78 vs 84	−11.9% (95% CI, −13.4 to −10.4) vs −16.4% (95% CI, −17.9 to −14.8) vs −17.8% (95% CI, −19.3 to −16.3)

Abbreviations: CI, confidence interval; ER, extended-release; FDA, Food and Drug Administration.
[a]In addition to lifestyle modification, which typically involved calorie-restricted diets (deficit of 500–600 calories/day) plus at least 150 minutes of physical exercise every week.
[b]Data shown as mean (SD).

References: 9

Table 1. Therapies for Adults with Obesity[a]

Medication (trade name)	Drug class	Dosing[b]	Adverse effects	Contraindications	Additional comments
Phentermine (Adipex-P, Lomaira)	Sympathomimetic	Orally: • Phentermine (excluding Lomaira): 15 to 37.5 mg daily in 1 or 2 divided doses • Lomaira: 8 mg 3 times daily	Increased HR/BP, insomnia, irritability, nervousness, dry mouth, taste disturbance, constipation	History of CVD, hyperthyroidism, glaucoma, history of drug abuse, use during or within 14 days following MAOI therapy, pregnancy	• Approved for short-term use (8–12 weeks) • Potential for abuse due to amphetamine-like effects; controlled substance (C-IV) • Dose adjustments recommended in patients with renal impairment
Orlistat (Alli [nonprescription], Xenical)	Lipase inhibitor	Orally: • Alli: 60 mg 3 times daily with each main meal containing fat • Xenical: 120 mg 3 times daily with each main meal containing fat	Intestinal cramps, flatulence, fecal incontinence, oily spotting/leakage	Chronic malabsorption syndrome (eg, chronic diarrhea, celiac disease, inflammatory bowel disease, bariatric surgery), cholestasis, pregnancy	• Administer during or up to 1 hour after each main meal containing fat; omit dose if a meal is missed or contains no fat • Patients should take a daily multivitamin containing fat-soluble vitamins; separate administration from orlistat by ≥2 hours
Phentermine/topiramate ER (Qsymia)	Sympathomimetic + GABA receptor modulator	Orally: • Initially phentermine 3.75 mg/topiramate 23 mg daily • Titrate gradually up to phentermine 15 mg/topiramate 92 mg daily if needed	Increased HR/BP, constipation, dry mouth, paresthesia, taste disturbance, depression, anxiety, cognitive impairment, insomnia; *rare*: metabolic acidosis, kidney stones	History of CVD, hyperthyroidism, glaucoma, history of drug abuse, use during or within 14 days following MAOI therapy, pregnancy	• Controlled substance (C-IV) • Teratogenic (topiramate): increased risk of oral cleft; negative pregnancy test recommended before initiation and monthly • Dose adjustments recommended in patients with hepatic or renal impairment

References: 9

References: 9

Naltrexone/ bupropion ER (Contrave)	Opioid antagonist + dopamine/ norepinephrine reuptake inhibitor	Orally (1 tablet = naltrexone 8 mg/bupropion 90 mg): • Week 1: 1 tablet every morning • Week 2: 1 tablet twice daily • Week 3: 2 tablets every morning and 1 tablet every evening • Week 4+: 2 tablets twice daily	Nausea, vomiting, constipation, headache, dizziness, insomnia, dry mouth, transient increase in BP (average of 1–2 mm Hg) and/ or HR	Uncontrolled HTN, seizure disorder, eating disorder, use of other bupropion-containing products, short- or long-term opioid therapy, use during or within 14 days following MAOI therapy, pregnancy	• Boxed warning: suicidal thinking • Potential neuropsychiatric effects • Take early in the day (potential for insomnia) • Dose adjustments recommended in patients with hepatic or renal impairment
Liraglutide (Saxenda)	GLP-1 receptor agonist	Subcutaneously: • Week 1: 0.6 mg daily • Week 2: 1.2 mg daily • Week 3: 1.8 mg daily • Week 4: 2.4 mg daily • Week 5+: 3 mg daily	Nausea, vomiting, diarrhea, constipation, hypoglycemia (if used in conjunction with diabetes medications known to cause hypoglycemia), injection site reactions; *rare*: pancreatitis, gallbladder disease	Personal or family history of medullary thyroid carcinoma, personal history of multiple endocrine neoplasia syndrome type 2, pregnancy	• Monitor glucose and adjust co-administered sulfonylureas and insulin as needed to prevent potentially severe hypoglycemia • Should not be used with other GLP-1 receptor agonists or DPP4 inhibitors
Semaglutide (Wegovy)	GLP-1 receptor agonist	Subcutaneously: • Weeks 1-4: 0.25 mg weekly • Weeks 5-8: 0.5 mg weekly • Weeks 9-12: 1 mg weekly • Weeks 13–16: 1.7 mg weekly • Week 17+: 2.4 mg weekly	Nausea, vomiting, diarrhea, constipation, hypoglycemia (if used in conjunction with diabetes medications known to cause hypoglycemia), injection site reactions; *rare*: pancreatitis, gallbladder disease	Personal or family history of medullary thyroid carcinoma, personal history of multiple endocrine neoplasia syndrome type 2, pregnancy	• Monitor glucose and adjust co-administered sulfonylureas and insulin as needed to prevent potentially severe hypoglycemia • Semaglutide: monitor patients with diabetic retinopathy for eye complications • Should not be used with other GLP-1 receptor agonists or DPP4 inhibitors
Tirzepatide (Zepbound)	GIP/GLP-1 receptor agonist	Subcutaneously: • Weeks 1-4: 2.5 mg weekly • Weeks 5-8: 5 mg weekly • Week 9+: may increase in 2.5-mg increments every 4 weeks if needed • Max dose of 15 mg/week	Nausea, vomiting, diarrhea, constipation, hypoglycemia (if used in conjunction with diabetes medications known to cause hypoglycemia), injection site reactions	Personal or family history of medullary thyroid carcinoma, personal history of multiple endocrine neoplasia syndrome type 2, pregnancy	• Monitor glucose and adjust co-administered sulfonylureas and insulin as needed to prevent potentially severe hypoglycemia • Should not be used with other GLP-1 receptors agonists or DPP4 inhibitors

Abbreviations: BP, blood pressure; CVD, cardiovascular disease; DPP4, dipeptidyl peptidase-4; ER, extended-release; GABA, γ-aminobutyric acid; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HR, heart rate; HTN, hypertension; MAOI, monoamine oxidase inhibitor.

[a]Information derived from package inserts.[25-33]

[b]Dosing is for adults with normal kidney and liver function unless otherwise noted in the comments.

References: 9

Guideline Recommendations

Table 1. American Gastroenterological Association Recommendations on Pharmacological Interventions for Management of Obesity

Recommendation	Strength of recommendation	Quality of evidence
1. In adults with obesity or overweight with weight-related complications, who have had an inadequate response to lifestyle interventions, the AGA recommends adding pharmacological agents to lifestyle interventions over continuing lifestyle interventions alone. Implementation considerations: • AOMs generally need to be used chronically, and the selection of the medication or intervention should be based on the clinical profile and needs of the patient, including, but not limited to, comorbidities, patients' preferences, costs, and access to the therapy.	Strong	Moderate
2. In adults with obesity or overweight with weight-related complications, the AGA suggests using semaglutide 2.4 mg with lifestyle modifications, compared with lifestyle modifications alone. Implementation considerations: • Given the magnitude of net benefit, semaglutide 2.4 mg may be prioritized over other approved AOMs for the long-term treatment of obesity for most patients. • Semaglutide has glucoregulatory benefits and is also approved for the treatment of T2DM • Semaglutide may delay gastric emptying with adverse effects of nausea and vomiting. Gradual dose titration may help mitigate these adverse effects. • GLP-1 RAs have been associated with increased risk of pancreatitis and gallbladder disease.	Conditional	Moderate
3. In adults with obesity or overweight with weight-related complications, the AGA suggests using liraglutide 3.0 mg with lifestyle modifications, compared with lifestyle modifications alone. Implementation considerations: • Liraglutide has glucoregulatory benefits and is also approved for the treatment of T2DM • Liraglutide may delay gastric emptying with adverse effects of nausea and vomiting. Gradual dose titration may help mitigate these adverse effects. • Liraglutide has been associated with an increased risk of pancreatitis and gallbladder disease	Conditional	Moderate

References: 7

Guideline Recommendations

4. In adults with obesity or overweight with weight-related complications, the AGA suggests using phentermine-topiramate ER with lifestyle modifications, compared with lifestyle modifications alone. Implementation considerations: • Because topiramate is effective for treating migraine headaches, phentermine-topiramate ER may be preferentially used in patients with comorbid migraines. • Phentermine-topiramate ER should be avoided in patients with a history of cardiovascular disease and uncontrolled hypertension. • Topiramate is teratogenic. Women of childbearing potential should be counseled to use effective contraception consistently. • Blood pressure and heart rate should be monitored periodically while taking medications with phentermine.	Conditional	Moderate
5. In adults with obesity or overweight with weight-related complications, the AGA suggests using naltrexone-bupropion ER with lifestyle modifications, compared with lifestyle modifications alone. Implementation Considerations: • Naltrexone-bupropion ER may be considered for the treatment of overweight or obesity in patients who are attempting smoking cessation, and in patients with depression. • Naltrexone-bupropion ER should be avoided in patients with seizure disorders and used with caution in patients at risk of seizures. • Naltrexone-bupropion ER should not be used concomitantly with opiate medications. • Blood pressure and heart rate should be monitored periodically while taking naltrexone-bupropion ER, especially in the first 12 weeks of treatment.	Conditional	Moderate

References: 7

Guideline Recommendations

Recommendation	Strength of recommendation	Quality of evidence
6. In adults with obesity or overweight with weight-related complications, AGA suggests against the use of orlistat. *Comment:* Patients who place a high value on the potential small weight loss benefit and low value on GI adverse effects may reasonably choose treatment with orlistat. Implementation Considerations: • Patients using orlistat should take a multivitamin daily. Vitamins should contain fat-soluble vitamins (A, D, E, K) and should be taken 2 hours apart from orlistat.	Conditional	Moderate
7. In adults with obesity or overweight with weight-related complications, the AGA suggests using phentermine with lifestyle modifications, compared with lifestyle modifications alone. Implementation Considerations: • Phentermine monotherapy is approved by the FDA for short-term use (12 weeks). However, given the chronic nature of weight management, many practitioners use phentermine longer than 12 weeks in an off-label fashion. • Phentermine should be avoided in patients with a history of cardiovascular disease. • Blood pressure and heart rate should be monitored periodically while taking phentermine.	Conditional	Low
8. In adults with obesity or overweight with weight-related complications, the AGA suggests using diethylpropion with lifestyle modifications, compared with lifestyle modifications alone. Implementation considerations: • Diethylpropion monotherapy is approved by the FDA for short-term use (12 weeks). However, given the chronic nature of weight management, many practitioners use diethylpropion longer than 12 weeks in an off-label fashion. • Diethylpropion should be avoided in patients with a history of cardiovascular disease. • Blood pressure and heart rate should be monitored periodically while taking diethylpropion.	Conditional	Low
9. In adults with BMI between 25 and 40 kg/m^2, the AGA recommends using Gelesis100 oral superabsorbent hydrogel only in the context of a clinical trial.	No recommendation	Knowledge gap

References: 7

Drug	Package Size	Price (30-day supply)
Liraglutide 3mg	5x3ml pens	$1,262.28 (Saxenda)
Semaglutide 2.4mg	4x0.75ml pens	$1,262.28 (Wegovy)
Tirzepatide 15mg	4x0.5ml pens	$1,010.34 (Mounjaro) $1,016.52 (Zepbound)
Naltrexone/Bupropion ER 8mg/90mg	120 tablets	$526.50 (Contrave)
Orlistat 120mg	90 capsules	$405.51(Xenical) $608.65 (generic)
Phentermine/topiramate ER 15mg/92mg	30 capsules	~$275 (Qsymia)
Phentermine 37.5mg	100 capsules	$26.22 (generic)

Case Questions

A 60 yof (height 66”, weight 175lbs) with a PMH of dyslipidemia, HTN, MI, obesity, and T2DM presents for evaluation. Home medications include amlodipine 10mg po qday, ASA 81mg po qday, atorvastatin 40mg po qday, lisinopril 20mg po qday, metformin 1000mg po bid, and metoprolol succinate 100mg po qday. Her home BP readings have been 138-155/85-95 mm Hg over the last two months. A1C is 8.2% today. Patient reports losing 4lbs over the last 6 months despite efforts to follow a healthy diet and exercise 150+ minutes per week.

Which of the following would be most appropriate for this patient?

A. Semaglutide
B. Continue lifestyle interventions alone
C. Phentermine
D. Extended-release phentermine/topiramate

Case Questions

A 36 yof is seen for weight management. She has a pmh of chronic back pain, CKD stage 3, HTN, hypothyroidism, and major depressive disorder. She is a 1 PPD smoker and expresses a desire to quit smoking. Current medications include chlorthalidone 25mg po qday, levothyroxine 125mcg po qday, lisinopril 40mg po qday, sertraline 100mg po qday, and tramadol 50mg po q6h prn (pt typically uses 1-2 tabs per day). Current BP is 126/76 mm/Hg and BMI is 34 kg/m^2. Pt's eGFR is 40 ml/min/1.73 m^2. All other labs are WNL.

Given the patient's desire to quite smoking, would extended-release naltrexone/bupropion be a good choice for this patient?

A. No, given the patient's hypertension.
B. No, given the patient's renal impairment.
C. No, given the patient's concurrent use of tramadol.
D. Yes, given the benefit of extended-release naltrexone/bupropion on both weight loss and smoking cessation.

Case Questions

A 62 yom with PMH of dyslipidemia, GERD, migraines, obesity, and T2DM presents for a routine visit. Current medications include atorvastatin 40mg po qday, metformin 1000mg po bid, naproxen 500mg po qday prn migraines (typical use 1-2x per month), omeprazole 20mg po qday, and sitagliptin 100mg po qday. A1C is 6.8%, BP 120/80mm Hg, BMI is 36 kg/m^2. Pt's renal and hepatic function are WNL. For the past 9 months the patient has been maintaining 40 minutes of exercise 4-5x per week, but states that he struggles with food (especially portion control with unhealthy snacks).

Which of the following AOMs would be most appropriate for this patient?

A. Extended-release naltrexone/bupropion
B. Semaglutide
C. Extended-release phentermine/bupropion
D. orlistat

References

1. Centers for Disease Control and Prevention. Adult obesity facts. Accessed May 5, 2025. https://www.cdc.gov/obesity/adult-obesity-facts/index.html
2. Centers for Disease Control and Prevention. Adult BMI categories. Accessed May 5, 2025. https://www.cdc.gov/bmi/adult-calculator/bmi-categories.html#cdc_generic_section_1-bmi-categories-for-adults
3. Centers for Disease Control and Prevention. Adult obesity prevalence maps. Accessed May 5, 2025. https://www.cdc.gov/obesity/data-and-statistics/adult-obesity-prevalence-maps.html#cdc_data_surveillance_section_4-across-states-and-territories
4. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22(suppl 3):1-203. doi: https://doi.org/10.4158/EP161365.GL
5. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society. *Circulation*. 2014;129(25 suppl 2):S102-S138. doi: https://doi.org/10.1161/01.cir.0000437739.71477.ee
6. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342-362. doi: https://doi.org/10.1210/jc.2014-3415
7. Grunvald E, Shah R, Hernaez R, et al. AGA clinical practice guideline on pharmacological interventions for adults with obesity. *Gastroenterology*. 2022;163(5):1198-1225. doi:https://doi.org/10.1053/j.gastro.2022.08.045

References

8. Eisenberg D, Shikora SA, Aarts E, et al. 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): indications for metabolic and bariatric surgery. *Surg Obes Relat Dis*. 2022;18(12):1345-1356. doi: https://doi.org/10.1016/j.soard.2022.08.013
9. Lourdes Cross, Management of obesity, *American Journal of Health-System Pharmacy*, Volume 82, Issue 2, 15 January 2025, Pages 48–59, https://doi.org/10.1093/ajhp/zxae273
10. Pannacciulli N, Le DSNT, Salbe AD, et al. Postprandial glucagon-like peptide-1 (GLP-1) response is positively associated with changes in neuronal activity of brain areas implicated in satiety and food intake regulation in humans. *Neuroimage*. 2007;35(2):511-517. doi:https://doi.org/10.1016/j.neuroimage.2006.12.035
11. Sharma D, Verma S, Vaidya S, et al. Recent updates on GLP-1 agonists: Current advancements & challenges. *Biomedicine & Pharmacotherapy*, 2018; 108:952-962. doi:https://doi.org/10.1016/j.biopha.2018.08.088.
12. Olukorode JO, Orimoloye DA, Nwachukwu NO, Onwuzo CN, Oloyede PO, Fayemi T, Odunaike OS, Ayobami-Ojo PS, Divine N, Alo DJ, Alex CU. Recent Advances and Therapeutic Benefits of Glucagon-Like Peptide-1 (GLP-1) Agonists in the Management of Type 2 Diabetes and Associated Metabolic Disorders. Cureus. 2024 Oct 21;16(10):e72080. doi: 10.7759/cureus.72080.
13. *Lexi-Drugs*. UpToDate Lexidrug. UpToDate Inc. https://online.lexi.com. Accessed May 6, 2025.
14. Yao H, Zhang A, Li D, Wu Y, Wang C, Wan J et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis *BMJ* 2024; 384 :e076410 doi:10.1136/bmj-2023-076410
15. Watson E. From ‘GLP-1 companion foods’ to ‘Nature’s Ozempic…’ What the new breed of weight loss drugs means for the food industry. *AgFunderNews.* Accessed May 6, 2025. https://agfundernews.com/from-glp-1-companion-foods-to-natures-ozempic-what-the-new-breed-of-weight-loss-drugs-means-for-the-food-industry

References

16. Butler PC, Dry S, Elashoff R. GLP-1-based therapy for diabetes: what you do not know can hurt you. Diabetes Care. 2010 Feb;33(2):453-5. doi: 10.2337/dc09-1902. PMID: 20103562; PMCID: PMC2809301.
17. Huang CC, Wang CH, Su PH. Long-term safety and efficacy of glucagon-like peptide-1 receptor agonists in individuals with obesity and without type 2 diabetes: A global retrospective cohort study. Diabetes Obes Metab. 2024 Nov;26(11):5222-5232. doi: 10.1111/dom.15869. Epub 2024 Aug 22. Erratum in: Diabetes Obes Metab. 2025 Mar;27(3):1630. doi: 10.1111/dom.16204. PMID: 39171569.
18. The FDA Group LLC. 503A vs. 503B: A Quick-Guide to Compounding Pharmacy Designations & Regulations. Accessed May 6, 2025. https://www.thefdagroup.com/blog/503a-vs-503b-compounding-pharmacies
19. US Food & Drug Administration. FDA's Concerns with Unapproved GLP-1 Drugs Used for Weight Loss. Accessed May 6, 2025. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fdas-concerns-unapproved-glp-1-drugs-used-weight-loss
20. US Food & Drug Administration. FDA clarifies policies for compounders as national GLP-1 supply begins to stabilize. Accessed May 6, 2025. https://www.fda.gov/drugs/drug-safety-and-availability/fda-clarifies-policies-compounders-national-glp-1-supply-begins-stabilize
21. Hollowell A. 30% of GLP-1 medications acquired via compounding pharmacies. Becker's Hospital Review. Accessed May 6, 2025. https://www.beckershospitalreview.com/glp-1s/30-of-glp-1-medications-acquired-via-compounding-pharmacies/?oly_enc_id=5001J1452978F3Z

References

22. Jensen SBK, Blond MB, Sandsdal RM, et al. Healthy weight loss maintenance with exercise, GLP-1 receptor agonist, or both combined followed by one year without treatment: a post-treatment analysis of a randomized placebo-controlled trial. eClinical Medicine. 2024;69:102475 doi:https://doi.org/10.1016/j.eclinm.2024.102475.
23. Khan SS, Ndumele CE, Kazi DS. Discontinuation of Glucagon-Like Peptide-1 Receptor Agonists. *JAMA.* 2025;333(2):113–114. doi:10.1001/jama.2024.22284
24. Berg S, Stickle H, Rose SJ, Nemec EC. Discontinuing glucagon-like peptide-1 receptor agonists and body habitus: A systematic review and meta-analysis. Obes Rev. 2025 Apr 4:e13929. doi: 10.1111/obr.13929. Epub ahead of print. PMID: 40186344.
25. Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. *Diabetes Obes Metab*. 2022;24(8):1553-1564. doi:10.1111/dom.14725
26. Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA*. 2021;325(14):1414-1425. doi:10.1001/jama.2021.3224
27. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet*. 2017;389(10077):1399-1409. doi:10.1016/S0140-6736(17)30069-7
28. Aronne LJ, Sattar N, Horn DB, et al. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial. *JAMA.* 2024;331(1):38–48. doi:10.1001/jama.2023.24945
29. Hwang JH, Laiteerapong N, Huang ES, Kim DD. Lifetime Health Effects and Cost-Effectiveness of Tirzepatide and Semaglutide in US Adults. *JAMA Health Forum.* 2025;6(3):e245586. doi:10.1001/jamahealthforum.2024.5586
30. Rika Kanaoka. Lifetime Social Returns From Expanding Access to Anti-Obesity Medications. USC Schaeffer. Published March 27, 2025. https://schaeffer.usc.edu/research/lifetime-social-returns-from-expanding-access-to-anti-obesity-medications/
31. Wong HJ, Sim B, Teo YH, Teo YN, Chan MY, Yeo LLL, Eng PC, Tan BYQ, Sattar N, Dalakoti M, Sia CH. Efficacy of GLP-1 Receptor Agonists on Weight Loss, BMI, and Waist Circumference for Patients With Obesity or Overweight: A Systematic Review, Meta-analysis, and Meta-regression of 47 Randomized Controlled Trials. Diabetes Care. 2025 Feb 1;48(2):292-300. doi: 10.2337/dc24-1678. PMID: 39841962.

References

32. Lewis KH, Gudzune KA, Ard JD. (2024). Phentermine in the Modern Era of Obesity Pharmacotherapy: Does It Still Have a Role in Treatment?. Current Obesity Reports. 13. 1-9. 10.1007/s13679-023-00546-9.
33. Lewis KH, Fishcer H, Ard JD, et al. Safety and effictiveness of longer-term phenteramine use: clinical outcomes from an electronic health record cohort. *Obesity*. 2019;27(4):591-602. doi:10.1002?oby.22430
34. Novotna A, Vrzalova A, Vrzal R, et al. (2010). Investigation of Orlistat effects on PXR activation and CYP3A4 expression in primary human hepatocytes and human intestinal LS174T cells. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences. 41. 276-80. 10.1016/j.ejps.2010.06.019
35. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. Xenical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. 2004; 27(1):155-161. doi:10.2337/diacare.27.1.155
36. Mandil H, Sakur A, Alulu S. (2012). Polarographic Determination of Topiramate in Some Pharmaceuticals. Asian Journal of Chemistry. 22. 2129-2135.
37. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomized, placebo-controlled, phase 3 trial. *Lancet*. 2011;377(9774):1341-1352. doi:10.1016/S0140-6736(11)60205-5
38. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL):a randomized placebo-controlled, phase 3 extension study. *Am J Clin Nutr*. 2012;95(2):297-308. doi:10.3945/acjn.111.024927
39. Lei XG, Ruan JQ, LaiC, Sun Z, Yang X. Efficacy and safety of phentermine/topiramate in adults with overweight or obesity:a systematic review and meta-analysis. *Obesity*. 2021;29(6):985-994. doi:10.1002/oby.23152
40. Novack A, de Fátima A, Madeira C, et al. (2023). A Mid-Infrared Spectrophotometric Method for Simultaneous Quantification of Naltrexone and Bupropion with Multivariate Calibration. Journal of the Brazilian Chemical Society. 34. 10.21577/0103-5053.20220127.
41. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010;376(9741):595-605. doi:10.1016/S0140-6736(10)60888-4
42. Onakpoya IJ, Lee JJ, Mahtani KR, Aronson JK, Heneghan CJ. Naltrexone-bupropion (Mysimba) in management of obesity:a systematic review and meta-analysis of unpublished clinical study reports. *Br J Clin Pharmacol.* 2020;86(4):646-667. doi:10.1111/bcp.14210

References

43. Opi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015; 373(1):11-22. doi:10.1056/NEJMoa1411892
44. Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes.* 2013;37(11):1443-1451. doi:10.1038/ijo.2013.120
45. Wadden TA, Tronieri JS, Sugimoto D, et al. Liraglutide 3.0 mg and intensive behavioral therapy (IBT) for obesity in primary care: the SCALE IBT randomized controlled trial. *Obesity*. 2020;28(3):529-536. doi:10.1002/oby.22726
46. Le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes:a randomized, double-blind trial. *Lancet. 207;389(10077):1399-1409. doi:10.1016/S0140-6736(17)30069-7*
47. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2061;375(4):311-322. doi:10.1056/NEJMoa1603827
48. Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity:the STEP 4 randomized clinical trial. *JAMA.* 2021;325(14):1414-1425. doi:10.1001/jama.2021.3224
49. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med.* 2024;384(11):989-1002. doi:10.1056/NEJMoa2032183
50. Knopp FK, Aroda VR, do Vale RD, er al. Oral semaglutide 50mg taken once per day in adults with overweight or obesity (OASIS 1): a randomized, double-blind, plaebo-controlled, phase 3 trial. *Lancet*. 2023;402(10403):705-719. doi:10.1016/S0140-6736(23)01185-6
51. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Eng J Med.* 2016;375(19):1834-1844.
52. Hussain M, Birkenfield AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Eng J Med.* 2019;381(9):841-851. doi:10.1056/NEJMoa1901118
53. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Eng J Med.* 2023;389(24):2221-2232. doi:10.1056/NEJMoa2307563
54. Jasterboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatie once weekly for the treatment of obesity. *N Engl J Med.*2022;387(3):205-216. doi:10.1056/NEJMoa2206038
55. Garvey WT, Frias JP, Jasterboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2):a double-blind, randomized, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2023;402(10402):613-626. doi:10.1016/S0140-6736(23)01200-X
56. Wadden TA, Chao AM, Machineni S, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity:the SURMOUNT-3 phase 3 trial. *Nat Med.* 2023;29(11):2909-2918. doi:10.1038/s41591-023-02597-w
57. Aronne LJ, Sattar N, Horn DB, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity:the SURMOUNT-4 randomized clincal trial. *JAMA.* 2024;331(1):38-48. doi:10.1001/jama.2023.24945
58. McGuire DK, Marx N, Mulvagh SL, et al. Oral semaglutide and cardiovascular outcomes in high-risk type 2 diabetes. *N Engl J Med.* 2025;392(20):2001-20012. doi: 10.1056/NEJMoa2501006
59. Arrone LJ, Horn DB, le Roux CW, et al. Tirzepatide as compared with semaglutide for the treatment of obesity. *N Engl J Med.* 2025;393(1):26-36. doi:10.1056/NEJMoa2146394