Obesity Medicine Review and Updates

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Objectives

Prevent

Address the issue

Counsel

Treat

Lifestyle

AOM, Potential drugs

Bariatric surgery

Obesity

Defined by the World Health Organization as an abnormal or excessive fat accumulation that presents a risk to health

Obesity Medicine Association as a chronic condition

Major cause of morbidity and mortality

BMI and Waist Circumference

Categories	Most	Asian
BMI Kg/m2		
Overweight	25	23
Obesity	30	27.5
Class 1	30	
Class 2	35	
Class 3	40	
Waist Circumference cm		
Men	>94	>85
Women	>80	>74 to 80

Prevalence

16% of adults aged 18 years and older worldwide were obese in 2022 per WHO

Worldwide prevalence of obesity more than doubled between 1990 and 2022

Age-adjusted percentage of US adults with overweight, obesity, and severe obesity by sex, 2017–2018 NHANES Data[2]

	All (Men and Women)	Men	Women
Overweight	30.7	34.1	27.5
Obesity (including severe obesity)	42.4	43.0	41.9
Severe obesity	9.2	6.9	11.5

Obesity: A Multi-factorial Disorder

Genetic : account for 40% to 70% , Polygeneic

Environmental: neighborhood, psycholocial stress

Metabolic: Imbalance in Energy expenditure and energy intake . Energy expenditure decline with weight loss , physiologic drive: increase in hunger hormones, hedonic response

Behavioral: diet, physical activity,sleep

Initial Steps to Assess AHA/ACC/TOS Guideline

- Measure Height, Weight, and Calculate BMI
- Assess CVD risk factors and obesity related co-morbidities
- Assess Lifestyle History

Ask permission

- What could you say to **ask** permission to talk about weight?

- It looks like your blood pressure is under control, but we need to continue the lisinopril. Would you like to discuss your weight today, and consider how we could work together on weight loss to lower your blood pressure?

What could you say to advise weight loss?

Losing 5%–10% of your body weight will improve your health, help control your blood pressure, and may decrease number of medications needed to control your blood pressure. Losing more weight would be even better.

AHA/ACC/TOS guidelines for management of overweight and obesity

Recommendation 1 grade A (strong)
BMI as a first screening, waist circumference as an indicator of risk for CVD, type 2 DM, and all-cause mortality.
Recommendation 2 grade A
Counseling about benefits of weight loss (3%–5%) that leads to improvement in TG, blood glucose, hemoglobin A1c, and DM risk. Greater amounts will improve BP, LDL, and HDL-C.
Recommendation 3 grade A
Reduced caloric diet
Recommendation 4 grade A
Comprehensive program, 6 mo or longer, includes diet, physical activity, behavior modification and medications for BMI >30 or >27 with a comorbidity (expert opinion).
Recommendation 5 grade A
BMI >35 with a comorbidity or >40 bariatric surgery

Evaluation checklist

- History of weight-loss attempts What worked well, and what were barriers?
- Motivation and expectations. What most concerns the patient about their weight?
- Emotional eating and eating disorders.
- Weight trajectory
- Diet exercise and sleep habits
- Weight-related medical conditions
- Medication list- National Health and Nutrition Examination Survey (2017–2018) 20% of US adults on weight inducing medications
- Psychosocial factors. Identify factors relating to food behaviors, including stress and mood

Obesogenic medications

Medication Class	Obesogenic Medications	Mechanism of Weight Gain
Anticonvulsants	Carbamazepine Gabapentin Pregabalin	Hypothalamic mediated increase in appetite and decrease in energy expenditure
Antidepressants/Antianxiety	Amitriptyline Fluoxetine Mirtazapine Paroxetine	Appetite increase stimulated via serotonergic pathways
Antihistamines	Diphenhydramine Fexofenadine Hydroxyzine	Increase appetite. Alters body weight regulation
Antipsychotics	Olanzapine Quetiapine Risperidone	Increased orexigenic and decreased anorexigenic neuropeptide expression in the hypothalamus
Beta Blockers	Atenolol Carvedilol Metoprolol Propanolol	Inhibit sympathetic tone, decrease lipolysis, reduce exercise tolerance, increase fatigue, and reduce the resting energy expenditure
Corticosteroids and Hormones	Medroxyprogesterone Oral contraceptives Prednisone	Alters the energy intake and expenditure of the human body
Diabetes medications	Insulin	Anabolic and adipogenic hormone, decreases daily energy expenditure
	Sulfonylureas	Increase the secretion of insulin and cause water retention
	Thiazolidinediones	Act as insulin sensitizers, cause water retention

How Much Weight Loss Is Enough?

Look Ahead trial of adults with **type 2 diabetes** lifestyle who lost 5% to 10% body weight intervention

- improvements in SBP and DBP
- HbA_{1C}
- LDL, HDL, TG

- 2% to 5% body weight improved SBP, HbA_{1C} and TG
- Additional health benefits included improvements in obstructive sleep apnea, knee osteoarthritis, MASLD, quality of life, and depression.

Lifestyle

Diabetes Prevention Program after 3 years in lifestyle Change Program was associated with 58% reduction in diabetes

- At the 10-year follow-up Lifestyle Change Program continued to have a delay in the development of diabetes by 34 percent—and developed diabetes about 4 years later—compared with participants who took a placebo
- At the 15-year follow-up delay in the development of diabetes by 27 percent

Lifestyle

- Vegetables (≥3 servings per day)
- Fruits (2 to 3 servings per day)
- Legumes
- Grains (e.g., barley, freekeh, quinoa)
- Heart-healthy fats (e.g., olive oil, nuts, seeds, and avocados)
- Cold-water fatty fish (omega-3) at least twice per week
- Mindfulness may help differentiate emotional and physical cues, and make more conscious food choices.

Caloric Intake for Weight Loss

Females or weight <250 lb: 1200 to 1500 kcal/d

Males or weight >250 lb: 1500 to 1800 kcal/d

However, a more specific target is likely to be both more tolerable and more effective. For an individualized calorie goal, use the Mifflin-St Jeor Equation to determine daily caloric needs, then reduce by 500 to 1000 kcal/d to establish weight loss. Clinical benefits typically begin upon achieving 3–5% weight loss in patients with DM type2

AHA Evidence-Based Guidance on Dietary Patterns to Promote Cardiometabolic Health

1. Adjust energy intake and expenditure to achieve and maintain a healthy body weight
2. Eat plenty of fruits and vegetables, choose a wide variety
3. Choose foods made mostly with whole grains rather than refined grains
4. Choose healthy sources of protein
a. mostly protein from plants (legumes and nuts)
b. fish and seafood
c. low-fat or fat-free dairy products instead of full-fat dairy products
d. if meat or poultry are desired, choose lean cuts and avoid processed forms
5. Use liquid plant oils rather than tropical oils (coconut, palm, and palm kernel), animal fats (eg, butter and lard), and partially hydrogenated fats
6. Choose minimally processed foods instead of ultra-processed foods
7. Minimize intake of beverages and foods with added sugars
8. Choose and prepare foods with little or no salt
9. If you do not drink alcohol, do not start; if you choose to drink alcohol, limit intake
10. Adhere to this guidance regardless of where food is prepared or consumed

EMPHASIZE

- Fruits and vegetables
- Whole grain foods
- Healthy sources of proteins; fish and seafood, legumes and nuts, low-fat/fat-free dairy, poultry and if desired lean meat
- Liquid plant oils (eg, soybean oil and canola oil)

MINIMIZE

- Beverages and foods with added sugars
- Ultra-processed foods
- Processed meats
- Food high in salt
- Alcoholic beverages
- Tropic oils

- Adjust energy intake to achieve and maintain a healthy body weight
- Follow this guidance regardless of where food is prepared or consumed

Ref: https://www.ahajournals.org/doi/10.1161/CIR.0000000000001031#T1

AMDR Acceptable Macronutrient Distribution Range

Carbohydrate is 45–65% of energy

Fat is 20–35% of energy (heart healthy fat)

Protein 10–35% of energy

Consult dietician for indivisualized recommendations

Time-Restricted Eating in Adults With Metabolic Syndrome: A Randomized Controlled Trial

- 108 participants at USCD
- BMI; ≥25 kg/m^2 and ≤41 kg/m^2), fasting glucose 100 and 125 mg/dL or HbA_{1c} (between 5.7% and 7.0%)
- Standard-of-care (SOC) nutritional counseling VS SOC combined with a 8- to 10-hour TRE for 3 months
- **Results:**
- Compared with SOC, TRE improved HbA_{1c} by −0.10% (95% CI)

Ref: 1 October 2024 **Publication**: Annals of Internal Medicine https://doi.org/10.7326/M24-0859

Physical exercise recommendations for adult

AT LEAST 150 MINUTES TO 300 MINUTES A WEEK OF MODERATE-INTENSITY, OR 75 MINUTES TO 150 MINUTES A WEEK OF VIGOROUS-INTENSITY AEROBIC PHYSICAL ACTIVITY

PREFERABLY, AEROBIC ACTIVITY SHOULD BE SPREAD THROUGHOUT THE WEEK.

ADDITIONAL HEALTH BENEFITS ARE GAINED BY PHYSICAL ACTIVITY OVER 300 MINUTES OF MODERATE-INTENSITY PHYSICAL ACTIVITY A WEEK.

MUSCLE-STRENGTHENING 2 OR MORE DAYS A WEEK

Indications for pharmacotherapy

- BMI greater than or equal to 30Kg/m2
- BMI greater than or equal to 27Kg/m2 with weight related medical condition (diabetes, hypertnsion, OSA)
- Also can be used as adjunct to bariatric surgey

FDA Approved Anti Obesity Medications

CNS Stimulants/ Anorexiants: Phentermine
Phentermine/topiramate
Diethylpropion
Phendimetrazine
Benzphetamine

Anti-Depressants/ Dopamine Reuptake Inhibitors Opioid Antagaonists: Bupropion/ Naltrexone

Gastrointestinal Agents/Other: Orlistat

GLP-1 agonists

Orlistat

- FDA 1999
- Gastric and pancreatic lipase inhibitor
- Rectal leakage, abdominal distress, abdominal pain, flatulence with discharge, fecal urgency, steatorrhea, fecal incontinence, increased defecation
- Contraindications: Patients with chronic malabsorption (may prescribe with MVI) syndrome or cholestasis, pregnancy
- Caution with L-thyroxine and Warfarin due to absorption issue

Phentermine/Topiramate ER

- FDA 2012
- NE agonist/GABA agonist, glutamate antagonist
- Adverse effect: Elevation in heart rate, mood and sleep disorders, cognitive impairment, metabolic acidosis, paresthesia, dry mouth
- Contraindications: Glaucoma, uncontrolled hypertension, hyperthyroidism, during or within 14 days following the administration of monoamine oxidase inhibitors, hypersensitivity to sympathomimetic amines, pregnancy- teratogenic

Naltrexone/Bupropion

- FDA 2014
- Opioid receptor antagonist/DA and NE reuptake inhibitor
- Adverse effect: Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea, sleep disorder
- Contraindication: Chronic opioid use, acute opioid withdrawal, uncontrolled hypertension, seizure, high risk alcohol use, bulimia or anorexia nervosa, pregnancy

Liraglutide

- FDA 2014 EMA 2015
- GLP-1 agonist
- Adverse effects: Increased heart rate, hypoglycemia, constipation, diarrhea, nausea, vomiting, headache
- Contraindications: Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, pregnancy

Semaglutide

- FDA 2021 EMA 2021
- GLP-1 agonist
- Improved glycemia independent of weight loss
- Improved outcomes in HFpEF
- Adverse effects: Nausea, vomiting, diarrhea, abdominal pain, constipation, headache
- Contraindications: Personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2, pregnancy

Setmelanotide

- FDA 2020
- MC4R agonist
- proopiomelanocortin (POMC), PCSK1 or leptin receptor (LEPR) deficiency, confirmed by genetic testing
- Adverse effects: Injection site reactions, hyperpigmentation, nausea, headache, diarrhea, vomiting, abdominal pain
- Contraindication: None

Semaglutide on CV outcomes

STEP-HFpEF trial

- Dose 2.4mg week, Weight loss (13.3%)
- Improved composite heart failure score
- Improvement in 6minute walk time
- Lower hospitalization

SELECT trial

- Established CVD
- Dose 2.4mg week, Weight loss 9.4%
- lower combined CV end point (death, non fatale MI, non fatal strokes) 6.5% vs 8% in placebo

Effects on comorbid conditions

- Weight- weekly semaglutide (2.4 mg) to placebo showed a mean difference in total body weight loss 12.6% (95% CI 10.3–14.8) at 68 weeks
- Waist circumference In STEP 4- Maintenance trial, and after the run-in period, a mean WC reduction of 6.4 (8.3) cm was achieved with semaglutide group and an increase of 3.3 (8.3) cm in the placebo after 68 weeks ($p < 0.001$
- Glycemia-STEP 4-Maintenance trial, from randomization after the run-in period at week 20 to week 68, there was a drop in HbA1c by 0.1 (0.7) % with semaglutide 2.4 mg
- Reduction of lipids-In the STEP 3 trial LDL-C level dropped with semaglutide by 4.7%, while it increased by 2.6% with placebo ($p < 0.001$). Triglyceride levels decreased in both arms but favored semaglutide
- BP-STEP 3-IBT trial resulted in reductions in SBP and DBP of 5.6 mmHg and 3.0 mmHg, respectively, for participants receiving semaglutide 2.4 mg, compared to 1.6 mmHg and 0.8 mmHg, respectively, for those receiving placebo at 68 weeks
- Hepatic steatosis-Histologic findings at 72 weeks showed that the proportion of NASH resolution was higher in semaglutide groups compared to placebo but no difference in fibrosis

Tirzepatide

- FDA approved Nov 2023
- GIP/GLP-1 dual agonist
- Improved glycemia independent of weight loss
- SURMOUNT-1 dose 10mg weight loss 19.5% to 20.9%
- Adverse effects: Nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain
- Contraindications: Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, known serious hypersensitivity to Tirzepatide

SURMOUNT-1 trial

- weight reduction with tirzepatide was accompanied by greater improvements with respect to all measured cardiovascular and metabolic risk factors, including waist circumference, SBP,DBP, lipids.
- Nearly all participants (>95%) treated with tirzepatide who had prediabetes at baseline had converted to normoglycemia by the end of the primary trial period, as compared with 62% of participants who received placebo.

Approved for short term use

- Phentermine FDA approved 1959, less than 6months. Off label long term use as long as maintaining weight loss on this drug
- *Diethylpropion*
- *Phendimetrazine*
- *Benzphetamine*

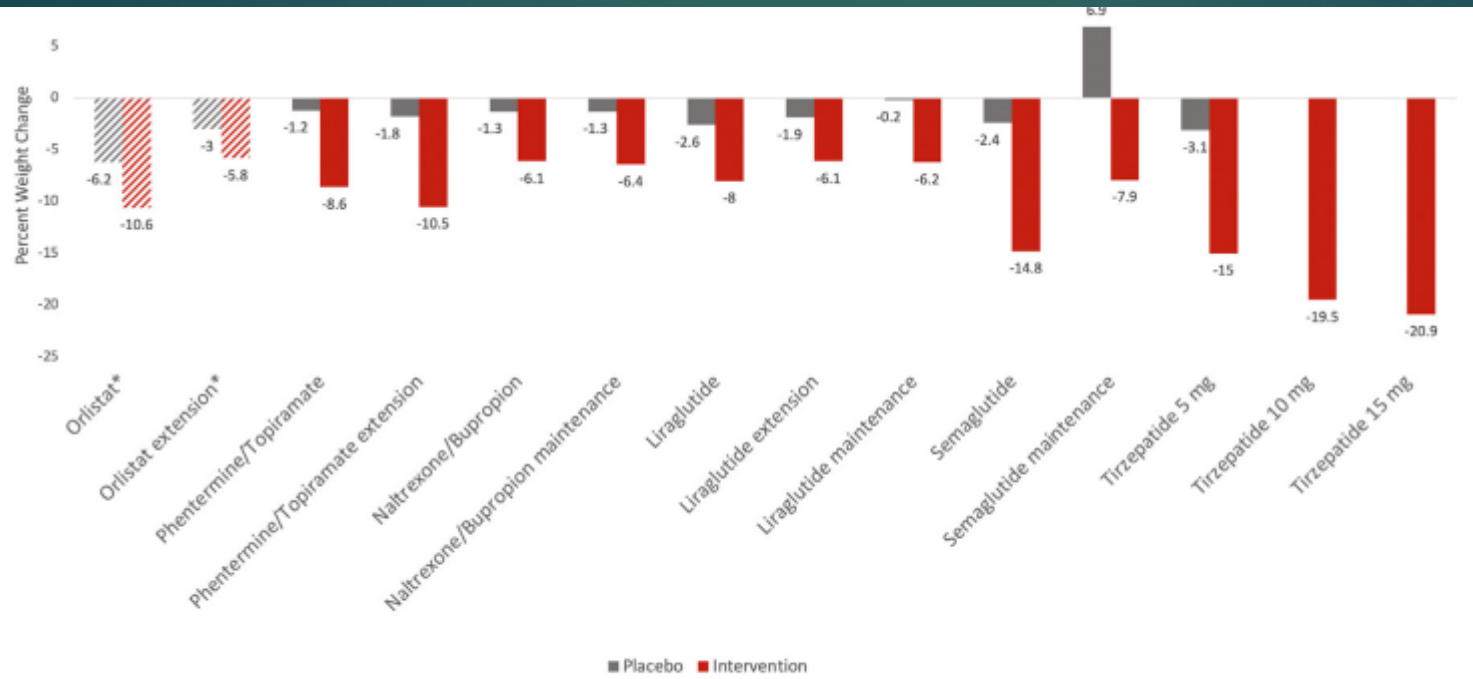


***Fig. 2:* Mean percent (%) weight change reported in the main phase 3 and extension trials of the FDA approved anti-obesity medications.** Orlistat: XENDOS trial (years 1 and 4). Phentermine/topiramate: CONQUER and SEQUEL trials. Naltrexone/bupropion: COR-I and COR-II trials. Liraglutide: SCALE Obesity, 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 (stripped bar charts). [b]Under expedited consideration for FDA approval.

Medications in the pipeline

- Medications in phase 3 trials-
  - **Methylphenidate** dopamine reuptake inhibitor reduce energy intake. The study completion date was December 2018, but no results are available online yet
  - **Tesofensine** is a noradrenaline, serotonin and dopamine reuptake inhibitor, appetite suppressant
  - **Dapagliflozin + Metformin**
- Medications in phase 2 trials-
  - **Tri-Agonist: GLP-1 RA, GIP and glucagon- LY3437943**. stimulates thermogenesis by acting on adipose tissue, in addition to its lipolytic effects in the liver
  - **Cagrilintide** is an amylin analogue that increases satiety signals, decreases gastric emptying peripherally; it is currently being investigated for total body weight loss in a phase 3 trial in combination with semaglutide

Case 1

- 54 year old woman comes in for discussion of weight gain concerns. She has long standing hypertension, atrial fibrillation on warfarin, history of kidney stones and seizure disorder. She is a non smoker, denies alcohol or drug use. She takes Losartan and Atorvastatin. BMI is 34Kg/m2 and BP is 134/88. HR is 98. She has irregular heart rate with no edema. Labs show fasting blood sugar 98, creatinine 1.1, sodium 139, LDL 89.

What is the best treatment for this patient?

- Bupropion-Naltrexone
- Phentermine-Topiramate
- Semaglutide
- Orlistat

Semaglutide

Case 2

- 58-year-old gentleman with hypertension, prediabetes, migraine, osteoarthritis. His blood pressure is 124/60 mm Hg. He takes Lisinopril and Hydrochlorothiazide. Height is 5 feet 2 inches, weight is 248 lb, and BMI is 45.4. He works as a parking lot attendant at the state university.
- He gained weight when he started working nights at age 30years it was 205 lb. Now he is working during the day, weight gradually increased over 20 years to 248lb.

Which medication(s) would you discuss with her?

GLP-1/GIP dual receptor agonist

Phentermine/topiramate

Bupropion/naltrexone

GLP1 Agonist

Phentermine/topiramate

Case 3:

- Lori a married 54-year-old, mom of 2 teenagers, works a per diem vet tech comes to discuss recent weight gain. She has hypertension, depression, anxiety, schizoaffective disorder. She takes lisinopril, sertraline and quetiapine. Her blood pressure is 134/72, weight is 186 lb, and her BMI is 32. She takes leftovers for lunch and eats dinner with family. She is very active while at work, involves lifting etc and walks with her husband 2 times per week.

Which medication(s) would you discuss with her?

- GLP-1/GIP dual receptor agonist
- Phentermine/topiramate
- Bupropion/naltrexone
- Metformin

Metformin

- Meta analysis of 12 published studies with a total of 743 patients
- Metformin compared to placebo : The mean change in weight was -3.27 kg (95 % CI -4.66 to -1.89) and reduced BMI -1.13 kg/m^2 (95 % CI -1.61 to -0.66
- **Conclusion:** This meta-analysis confirms that metformin is effective in treating antipsychotic induced weight gain in patients with schizophrenia or schizoaffective disorder.

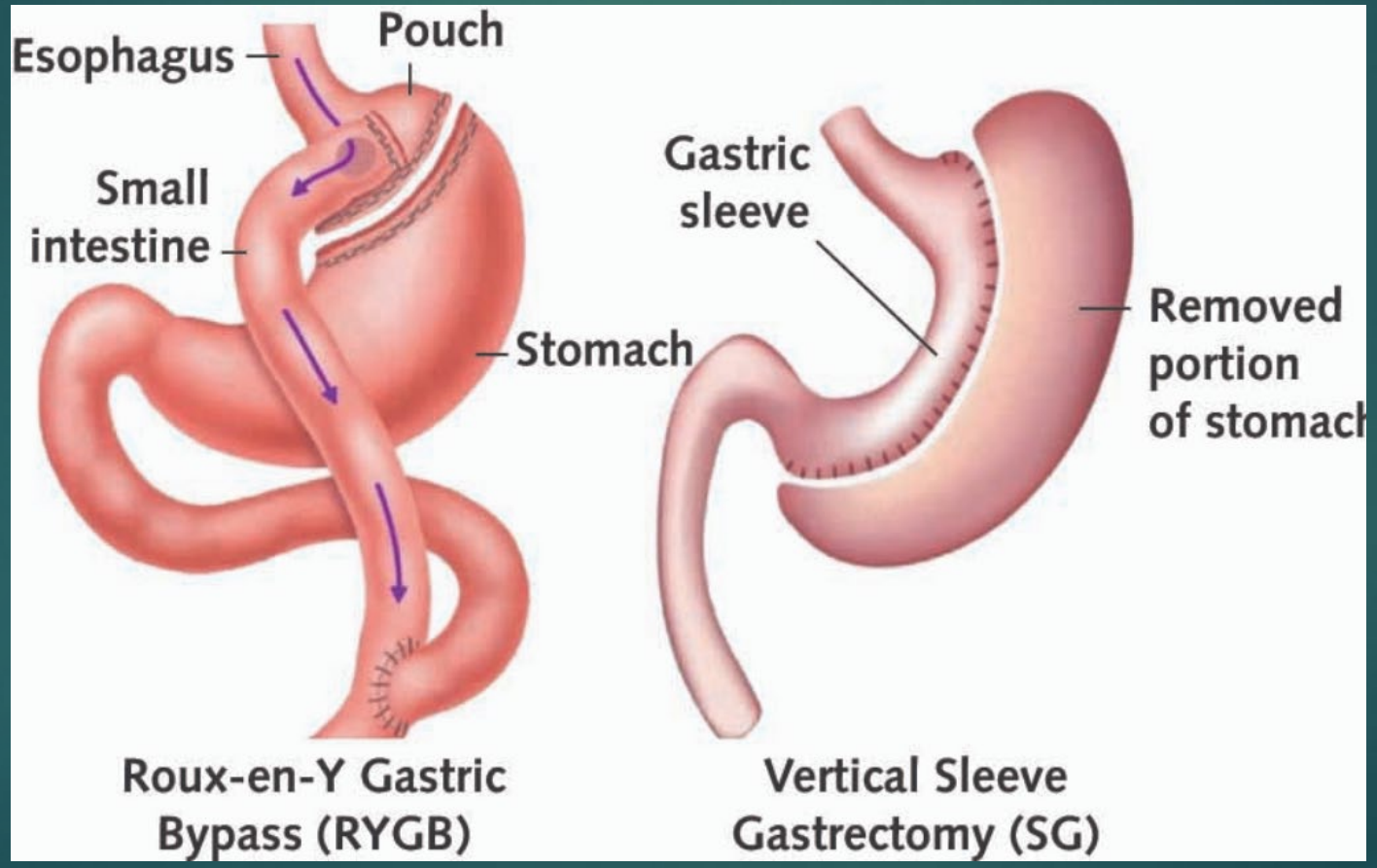
- de Silva VA, Suraweera C, Ratnatunga SS, Dayabandara M, Wanniarachchi N, Hanwella R. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. BMC Psychiatry. 2016 Oct 3;16(1):341. doi: 10.1186/s12888-016-1049-5. PMID: 27716110; PMCID: PMC5048618.

JAMA Research Letter

- October 25, 2024
- Metabolic Bariatric Surgery in the Era of GLP-1 Receptor Agonists for Obesity Management
- GLP-1 RAs and metabolic bariatric surgeries per 1000 unique patients without diabetes and with obesity using a generalized linear regression model.
- privately insured patients found a more than 2-fold increase in use of GLP-1 RAs as antiobesity medications from 2022 to 2023, with a 25.6% decrease in the rate of metabolic bariatric surgery.
- Limitations : Limitations of this study include its cross-sectional nature, insurance and potential confounding from variations in patient adherence to GLP-1 RAs.

Lin K, Mehrotra A, Tsai TC. Metabolic Bariatric Surgery in the Era of GLP-1 Receptor Agonists for Obesity Management. *JAMA Netw Open.* 2024;7(10):e2441380. doi:10.1001/jamanetworkopen.2024.41380

Bariatric Surgery



Bariatric surgery patients

- Can attain 25% to 30% weight loss at 12 months

Indications for surgery

- BMI ≥40 kg/m^2
- or BMI ≥35 kg/m^2 and at least 1 serious weight-related comorbid condition, such as T2D, OSA, or osteoarthritis of the hip or knee

In conclusion

- Evidence based obesity treatment combines behavioral interventions, nutrition, physical activity, pharmacotherapy, and metabolic/bariatric procedures

Patient resources

- https://www.nhlbi.nih.gov/resources/keep-beat-recipes-deliciously-healthy-dinners
- https://www.nhlbi.nih.gov/resources/heart-healthy-home-cooking-african-american-style
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THANK YOU!