Obesity: A review of medications, devices, and surgeries for weight loss

UCLA FAMILY MEDICINE GRAND ROUNDS
NELSON BOLAND, MD PGY3

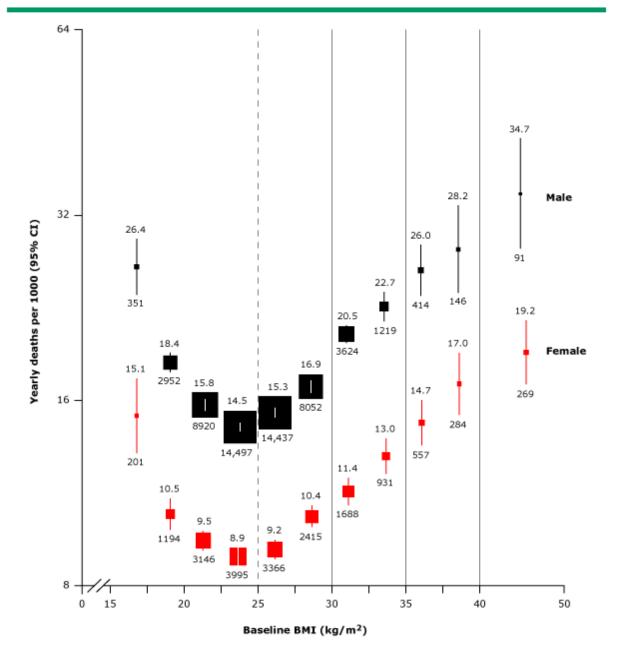
Financial Disclosures

- None
- ▶ I will be referencing many pharmaceutical companies in today's lecture, I have financial stakes in none of them

Obesity

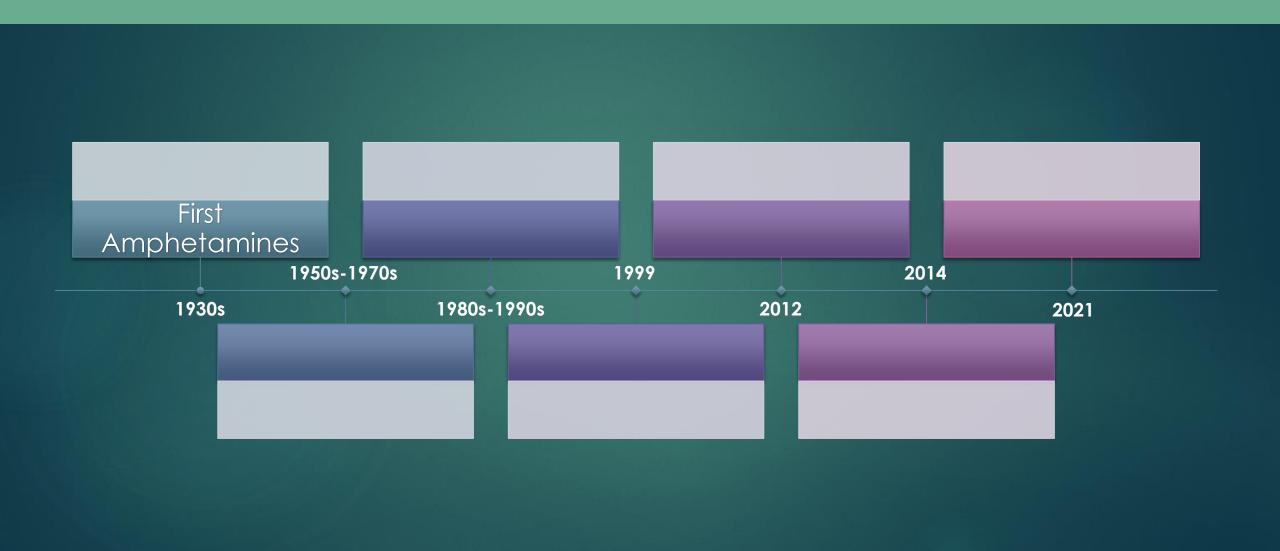
- Obesity is a disease associated with a significant increase in mortality
- Associated with multiple chronic medical conditions including, including type 2 diabetes mellitus, hypertension, dyslipidemia, and coronary heart disease.
- The relationship between BMI and mortality is likely to shared across gender, ethnicity, and races

All-cause mortality versus BMI for each sex in the range 15 to 50 kg/m² (excluding the first five years of follow-up)



Obesity: Weight Loss Goals

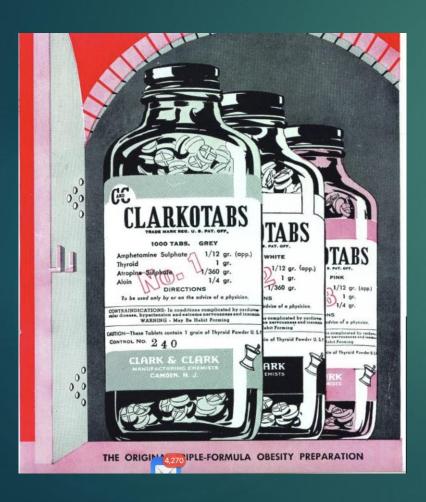
- Weight loss of 5% is where benefit is seen in patient's blood pressure, glycemic control, lipid profile, and risk factors for other cardiovascular disease
- Most RCTs studying patient directed "diet and exercise" show a 2-3% weight loss over 1 year
- Disconnect between main therapy options and treatment goals
 - ▶ Why don't we use more pharmacotherapy?



A History of Weight Loss Medications

- Benzedrine was the first amphetamine developed for narcolepsy¹
 - Developed in the 1930s
- Noticeable side-effect of decreased hunger and appetite
- ▶ By 1941, first diet pill was introduced to market Clarkotabs

Combination Diet Pills



CLARKOTABS

(T.M. REG. U.S. PAT. OFF.)

For Obesity

CLARKOTABS are a non-secret, proven formulae for pleasingly uniform reduction in weight and are being dispensed by thousands of physicians the country over. Many other physicians are prescribing CLARKOTABS which are not available for self-medication or over-the-counter sale.

CLARKOTABS FORMULAE (Active Ingredients)

FORMULA No. 1	FORMULA No. 2	FORMULA No. 3
Amphetamine Sulf.	Amphetamine Sulf.	Amphetamine Sulf.
Thyroid1 gr.	5 mgm.	5 mgm.
Atropine Sulf. 1/260 gr.	Thyroid1 gr.	Thyroid1 gr.
Aloin 1/4 gr.	Atropine Sulf. 1/360 gr.	Phenobarbital 1/4 gr.
In units of 3000 table	ts (1000 in each of 3	colors): No. 1, Grey or
Green; No. 2, White or	Blue; No. 3, Pink or \	fellow. \$20.00 a Unit.
	Potency tablets with 9	
Sulphate instead of	5 mgm. Price \$25.00 a	set of 3000 tablets.

We Are Your Nearest Distributors

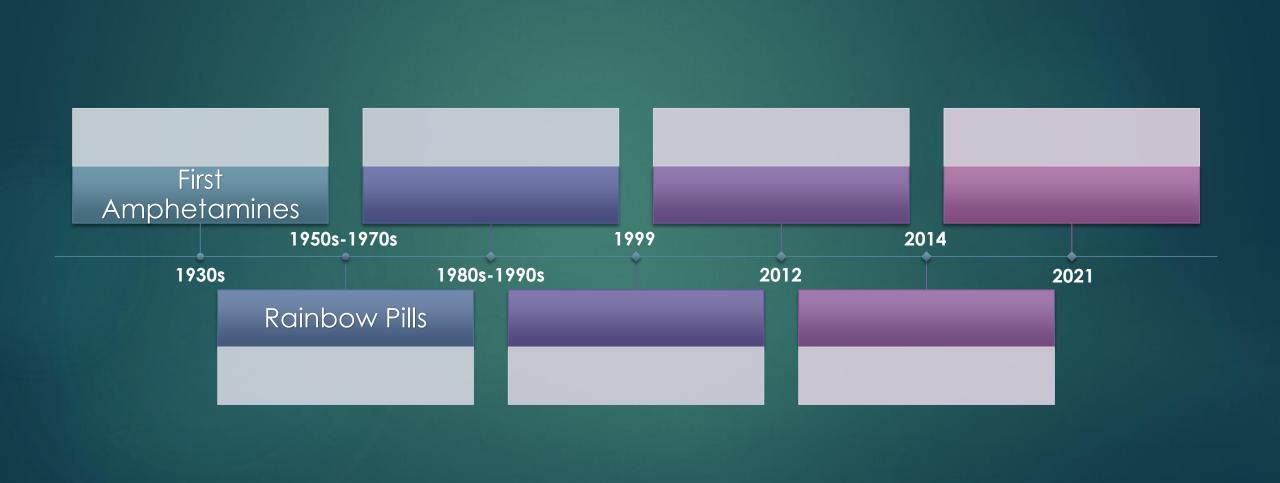
SAMUEL K. FAUCETT

5944 Germantown Ave. Philadelphia, Pa.



ALSO IN GREEN, BLUE, AND YELLOW

A History of Weight Loss Medications



Rainbow Pills

- New Amphetamines
 - 1959 Phentermine (amphetamine derivate)
 - ▶ 1960 Obetrol (methamphetamine, amphetamine, and dextroamphetamine combination)
 - ▶ 1994 methamphetamine was removed and medication was rebranded as Adderall

Typical Ingredients to Induce Weight Loss	Typical Ingredients to Mask Side Effects	
<i>d</i> -amphetamine	cardiac glycosides	
diuretics	barbiturates	
thyroid hormones	corticosteroids	
laxatives	potassium	
phenolphthalein	belladonna	
herbal ingredients	glandular extracts	

Requiem for a Dream



DEATHS OF 12 MD. WOMEN ATTRIBUTED TO DIET PILLS



U. S. Destroys 5 Red Ships

Broad Racial Reforms Put At \$25 Billion

WASHINGTON, March 1-(AP)-A presidential Attack Repelled commission demands compassionate, massive and sustained efforts-perhaps costing more money than the SAIGON, March 1-Victnam war-to end the destruction and bitterness U. S. forces destroyed five wrought by racial disorder in America's cities.

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Communists supply ships

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nan; Sen. Fred Harris (D. 4)-foot garrella suppers tried Ada.); Sen. Edward W. Brooks slipping into the Cas Viet River



SNOW PAINTS WINTER SCENE AT DRUID HILL PARK . . . but 2 to 4-inch fall causes trouble for Baltimore motorists.

Tissue Tests End Secrecy

By LEE BELSER

© 1968 by The News American

At least 12 Maryland women, perhaps more, have died as a result of "rainbow" diet pills dispensed by "fat doctors" specializing in obesity, an expert in texicology said here today.

All of the deaths, causes of which have been kept secret from the public, have occurred within the past

The spolesman, whose name is being withheld at his reneultarst in tests made

A Lion

Arrives

MORE DEATHS than we Rights Bill sow," he added, "result from issue of those pills. All drugs used in carting obesity). They Hit by Liberals

are dangerous, of course es-pecially the barbitarates (also

existe more suicide attempts WASHINGTON, March 1-The deaths of the Maryland (AP) Secure liberals have ac-The dentity at the attribute over a dense season have sparsed before ably cased Republican Leader Ever-sition and the season of the season of the season of the season of the siliners with the Food smilet Nr. Dirison of endangering siliners with the Food smilet Nr. Dirison of endangering Drug Adriabatisan to an all-the civil rists bill by prepa-our, war on the delt pill dis-list a modified open heating propers, but officials as if many justicies offer agreeing with them. he laset six months before the on broader legislation.

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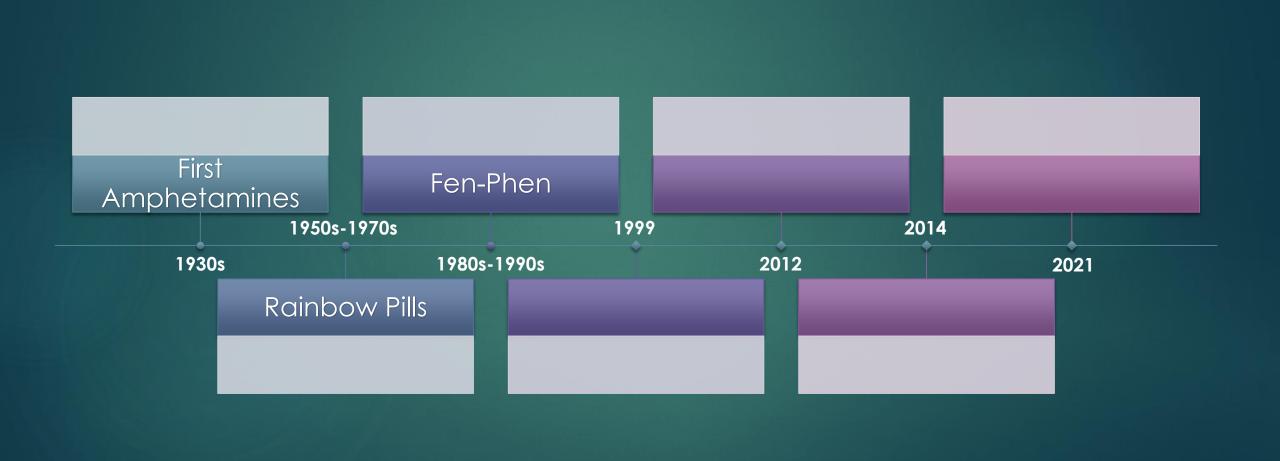
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End of Rainbow Pills (or so we think)

In the 1970s, FDA also reconsidered obesity as a safe and effective use of amphetamine and its congeners, ruling that amphetamines were effective but only safe for short-term use, which essentially "marginalized the anorectics and contributed to the eventual decline in their use"²

A History of Weight Loss Medications



Fen-Phen

- ► Fenfluramine approved by FDA use in America in 1973
- Fenfluramine causes serotonin release and is used primarily as an appetite suppressant
- ▶ In 1984, American Home Products (re-branded as Wyeth in 2002, consolidated into Pfizer in 2009) combined fenfluramine with phentermine and marketed it as the ultimate weight loss drug
- Redux (Dexfenfluramine) and phentermine combination developed in 1992

The New England Journal of Medicine

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VALVULAR HEART DISEASE ASSOCIATED WITH FENFLURAMINE-PHENTERMINE

HEIDI M. CONNOLLY, M.D., JACK L. CRARY, M.D., MICHAEL D. McGOON, M.D., DONALD D. HENSRUD, M.D., M.P.H., BROOKS S. EDWARDS, M.D., WILLIAM D. EDWARDS, M.D., AND HARTZELL V. SCHAFF, M.D.

ORIGINAL ARTICLE

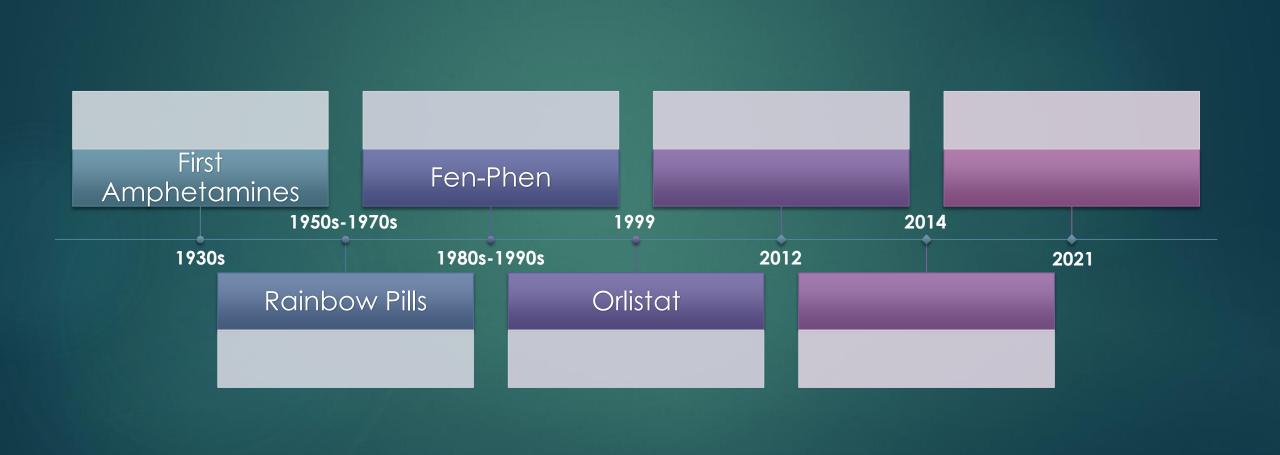
The Prevalence of Cardiac Valvular Insufficiency Assessed by Transthoracic Echocardiography in Obese Patients Treated with Appetite-Suppressant Drugs

Mehmood A. Khan, M.D., Charles A. Herzog, M.D., John V. St. Peter, Pharm.D., Guilford G. Hartley, M.D., Richard Madlon-Kay, M.D., Candace D. Dick, M.D., Richard W. Asinger, M.D., and John T. Vessey, Ph.D.

Fen-Phen

- Reported serious side effects included primary pulmonary hypertension, cardiac fibrosis, cardiac valvular disease
- Fenfluramine and Dexfenfluramine were removed from the market by manufacturers after pressure from FDA
 - Fenfluramine reintroduced to market in 2020 as an anti-epileptic drug
- Phentermine was not withdrawn from market but received a warning about risk of cardiac valvular disease

A History of Weight Loss Medications



Standardized Weight – Example Calculation

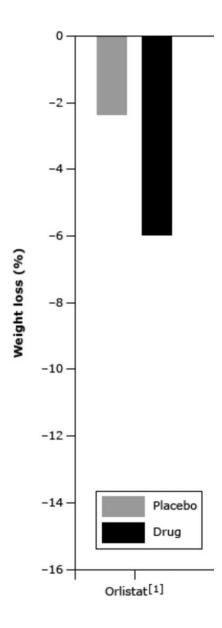
	Men	Woman
Height	5'9"	5'4"
Weight	200 lbs	171 lbs
BMI	30	30
IBW (Ideal body weight)	156 lbs	121
EBW (Excess body weight)	44 lbs	50lbs

Orlistat

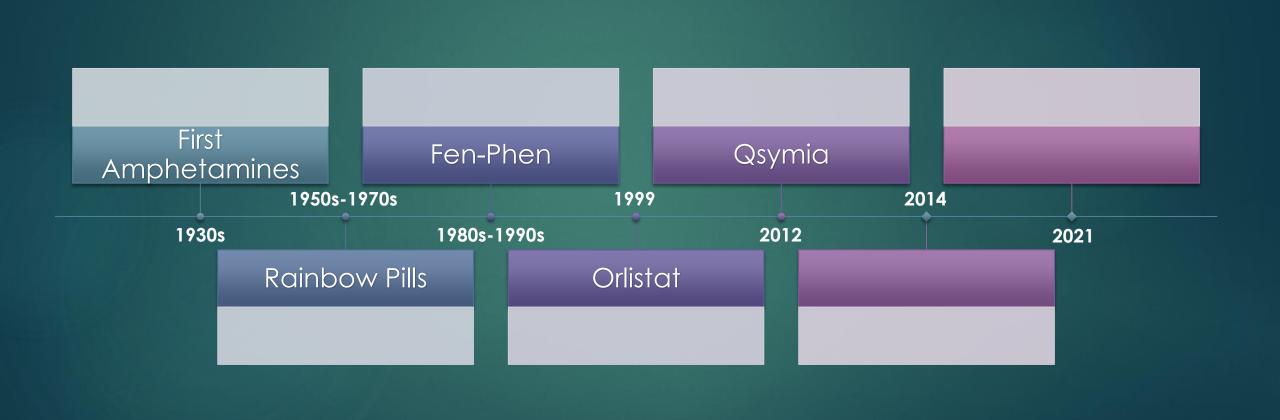
- Orlistat (Xenical Brand Name, Alli generic) was approved by the FDA in 1999 for obesity management
- Orlistat is a derivate of lipstatin, a lipase inhibitor
- Mechanism of action: Inhibit pancreatic lipase, thereby decreasing fat hydrolyzation in intestine and subsequent absorption
 - ▶ Estimated that ~25% fewer calories absorbed from fat
- Dosing/Route of Administration: 120mg PO TID
- Side effects: Cramps, flatulence, fecal incontinence, oily spotting, absorption of fat-soluble vitamins may be reduced. Rarely reported: severe liver injury, oxalate-kidney injury.

Orlistat (continued)

- ► How much weight loss?
 - ➤ ~6% weight loss at 1 year³



A History of Weight Loss Medications



Phentermine-Topiramate

- Phentermine-Topiramate was developed by a Harvard physician,
 Dr. Najarian, who helped developed Redux (Phentermine-dexfenfluramine)
- Known as Qnexa, it was rejected in 2010 and 2011 by the FDA due to safety concerns over cardiovascular complications
- In 2012, it was approved under the name Qsymia after additional safety data was submitted

Phentermine-Topiramate

Mechanism of action:

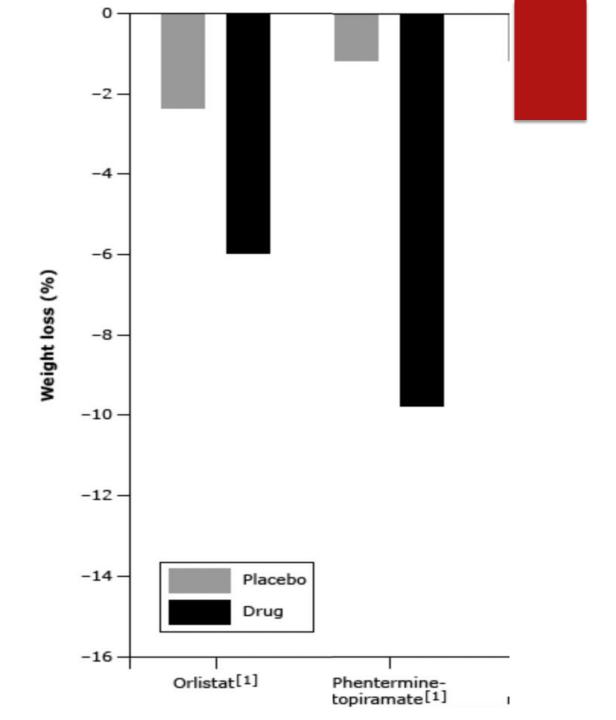
- Phentermine Sympathomimetic amine likely releases catecholamines in hypothalamus, decreasing appetite
- ➤ Topiramate Extended-release antiepileptic induces appetite suppression via augmentation of neurotransmitter GABA, modulation of voltage-gated ion channels and inhibition of AMPA/kainite excitatory glutamate receptors
- Dosing/Route of Administration:
 - 3.75 mg PO phentermine/23 mg topiramate once daily in the morning for 2 weeks
 - ▶ 7.5 mg PO phentermine/46 mg topiramate daily for 12 weeks
 - ▶ 11.25 mg PO phentermine/69 mg topiramate daily for 2 weeks
 - ▶ 15 mg PO phentermine/92 mg topiramate daily

Phentermine-Topiramate – Side effects and Cautions

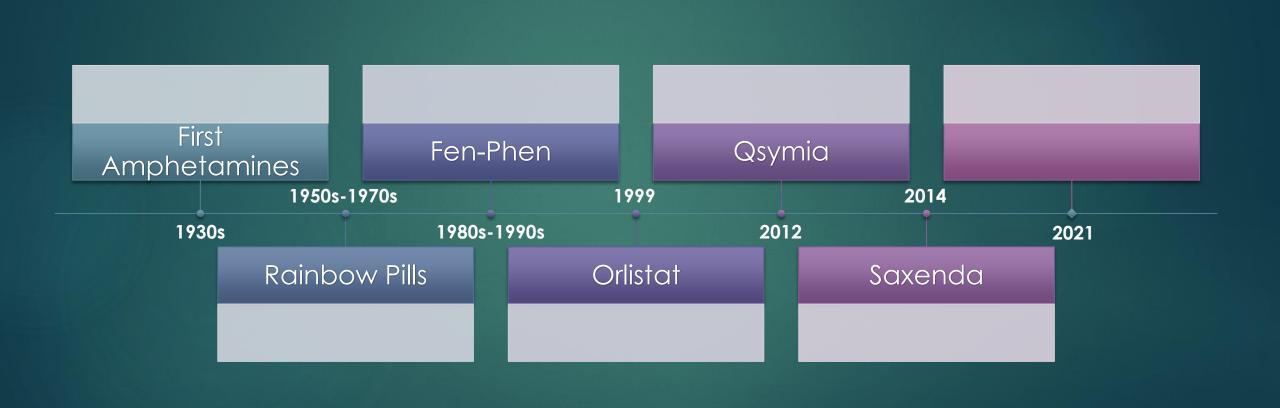
- SE Dry mouth, taste disturbance, constipation, depression, anxiety, elevated heart rate, parathesis cognitive disturbances, insomnia Abuse potential due to phentermine component.
- ► Topiramate is teratogenic (increased risk of oral cleft defects, T1); negative pregnancy test prior to and during treatment and 2 forms of contraception necessary for women of child-bearing potential.
- Abrupt withdrawal can cause seizures NEEDS to be tapered
- Not recommended in anyone with heart cardiovascular disease including hypertension
- Not recommended in anyone with a history of substance abuse, phentermine is addictive and has high abuse potential

Phentermine-Topiramate (Qsymia)

- ► How much weight loss?
 - ➤ ~10% weight loss at 1 year⁴



A History of Weight Loss Medications



Liraglutide

- ► Liraglutide is a GLP-1 agonist that was developed by Novo Nordisk and was FDA approved in 2010 (known as Victoza) for treatment of Type 2 Diabetes Mellitus
- During clinical trials, patients in the treatment group were losing weight
- New FDA approval in 2014 for liraglutide at a higher dose (Saxenda) treatment of obesity
 - Liraglutide 1.2mg or 1.8 mg subcutaneous injections daily (Victoza)
 - ► Liraglutide 2.4mg or 3mg subcutaneous injections daily (Saxenda)

Liraglutide

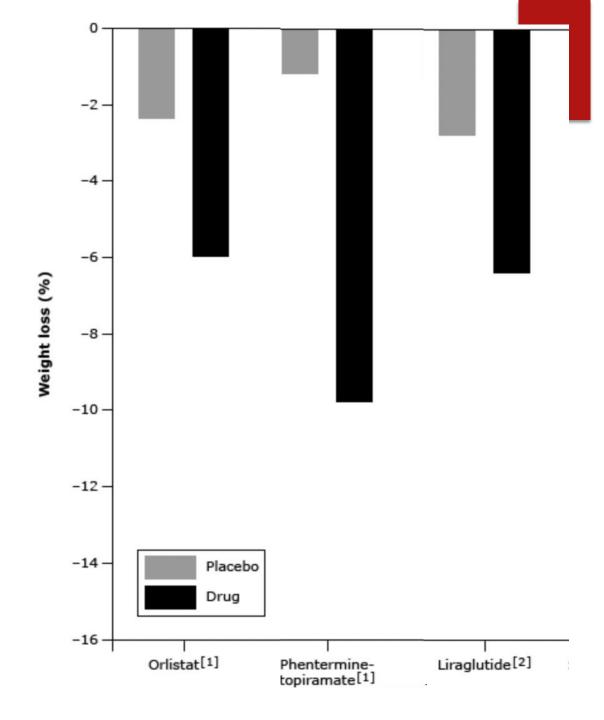
- Mechanism of action:
 - ► GLP-1 Agonist Glucagon-like peptide-1 is a gastrointestinal peptide that stimulates glucose-dependent insulin secretion. GLP-1 also inhibits glucagon release, gastric emptying, stimulate glucose-dependent insulin release from the pancreatic islets.
- Dosing/Route of Administration:
 - ▶ Initial: 0.6 mg subcutaneously daily.
 - Increase at weekly intervals (1.2, 1.8, 2.4, 3 mg) until recommended dose of 3 mg daily.

Liraglutide – Side Effects

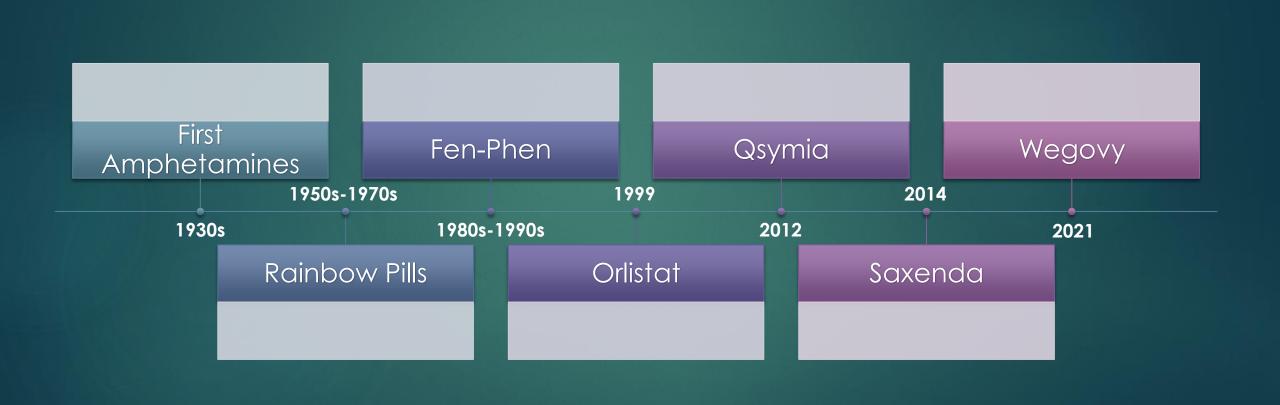
- Side effects Nausea, vomiting, diarrhea, constipation, hypoglycemia in patients with T2DM (especially if used in conjunction with diabetes medications known to cause hypoglycemia like sulfonylureas)
- Rare: pancreatitis, gallbladder disease, renal impairment
- Possible increase in thyroid cancer risk based on rat data, not show in humans.
- Contraindicated in pregnancy and in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B.
- Positive cardiovascular outcomes? only studied in lower doses (Victoza) for patients with T2DM so unknown

Liraglutide (Saxenda)

- ► How much weight loss?
 - ► ~6% weight loss at 68 weeks⁵



A History of Weight Loss Medications



Semaglutide

- Semaglutide was approved in 2017 (known as Ozempic) for treatment of Type 2 Diabetes Mellitus
- Similar to other GLP-1 agonists, semaglutide was seen to cause weight loss in clinical trials for diabetes
- New FDA approval in June 2021 for semaglutide at a higher dose (Wegovy) treatment of obesity
 - Semaglutide 0.25 mg, 0.5 mg, 1 mg sub-q injection weekly (Ozempic)
 - Semaglutide 1.7 mg or 2.4 mg sub-q injection weekly (Wegovy)
 - Semaglutide 3 mg, 7 mg, 14 mg PO daily (Rybelsus)

Semaglutide

- Mechanism of action:
 - ► GLP-1 Agonist Glucagon-like peptide-1 is a gastrointestinal peptide that stimulates glucose-dependent insulin secretion. GLP-1 also inhibits glucagon release, gastric emptying, stimulate glucose-dependent insulin release from the pancreatic islets.
- Dosing/Route of Administration:
 - ▶ Initial: 0.5 mg subcutaneously weekly.
 - ▶ Increase at 4-week intervals (1.0 mg, 1.7 mg, 2.4 mg) until recommended dose of 2.4 mg weekly.

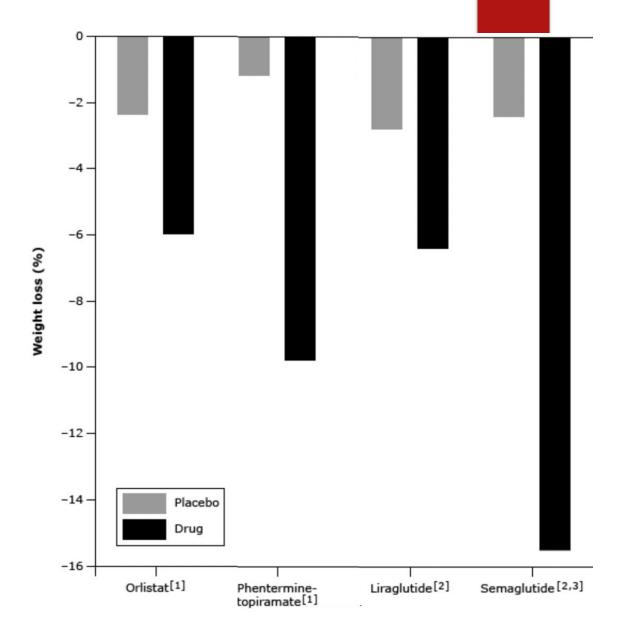
Semaglutide – Side Effects

- Side effects Nausea, vomiting, diarrhea, constipation, hypoglycemia in patients with T2DM (especially if used in conjunction with diabetes medications known to cause hypoglycemia like sulfonylureas)
- Rare: pancreatitis, gallbladder disease, renal impairment
- Possible increase in thyroid cancer risk based on rat data, not show in humans.
- Contraindicated in pregnancy and in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B, prior hx of pancreatitis.
- Patient's with known diabetic retinopathy need to be monitored
- Positive cardiovascular outcomes? only studied in lower doses (Victoza) for patients with T2DM but actively being studied in obese patients without DM

Semaglutide (Wegovy)

- ► How much weight loss?
 - ► ~15% weight loss at 68 weeks⁶

6. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med 2021; 384:989



The NEW ENGLAND JOURNAL of MEDICINE

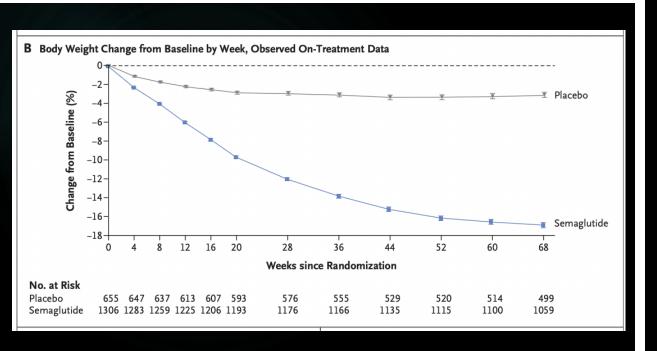
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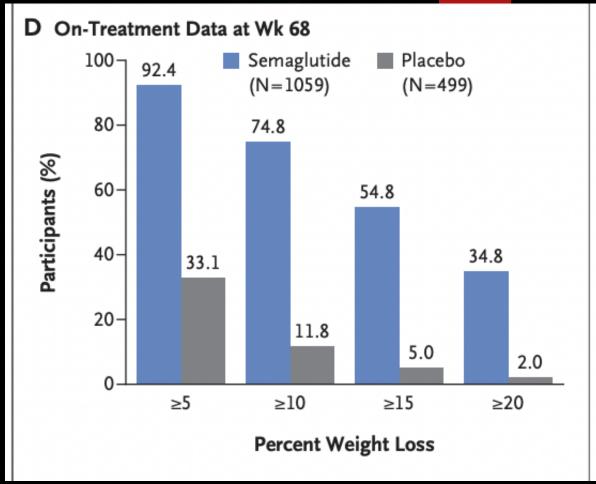
MARCH 18, 2021

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Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D.,





January 11, 2022

Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes The STEP 8 Randomized Clinical Trial

Domenica M. Rubino, MD¹; Frank L. Greenway, MD²; Usman Khalid, MD, PhD³; et al

Author Affiliations

JAMA. 2022;327(2):138-150. doi:10.1001/jama.2021.23619

Results Of 338 randomized participants (mean [SD] age, 49 [13] years; 265 women [78.4%]; mean [SD] body weight, 104.5 [23.8] kg; mean [SD] body mass index, 37.5 [6.8]), 319 (94.4%) completed the trial, and 271 (80.2%) completed treatment. The mean weight change from baseline was -15.8% with semaglutide vs -6.4% with liraglutide (difference, -9.4 percentage points [95% CI, -12.0 to -6.8]; *P*<.001); weight change with pooled placebo was -1.9%. Participants had significantly greater odds of achieving 10% or more, 15% or more, and 20% or more weight loss with semaglutide vs liraglutide (70.9% of participants vs 25.6% [odds ratio, 6.3 {95% CI, 3.5 to 11.2}], 55.6% vs 12.0% [odds ratio, 7.9 {95% CI, 4.1 to 15.4}], and 38.5% vs 6.0% [odds ratio, 8.2 {95% CI, 3.5 to 19.1}], respectively; all *P*<.001). Proportions of participants discontinuing treatment for any reason were 13.5% with semaglutide and 27.6% with liraglutide. Gastrointestinal adverse events were reported by 84.1% with semaglutide and 82.7% with liraglutide.

Indications for GLP-1 Agonists

- ▶ Obesity defined as BMI >30
- ▶ BMI > 27 with weight related co-morbidities (HTN, HLD, DM, OSA)

Costs of medications without insurance

Drug	Average cash price (2021)	Supply
Bupropion-naltrexone (<u>Contrave</u>)	\$369	30-day supply (4 pills per day)
Orlistat (<u>Xenical</u>)	\$873	30-day supply (120-mg capsules 3 times per day)
Phentermine-topiramate (<u>Qsymia</u>)	\$236	30-day supply (1 capsule per day)
Liraglutide (<u>Saxenda</u>)	\$1,626	28-day supply (3-mg injection once per day)

Insurance coverage of Wegovy

Type of insurance	Expected coverage for weight loss medications
Employer-provided insurance	It varies. If no coverage is available, you may be able to work with your healthcare provider to write a letter requesting coverage.
Medicare	No coverage
VA health benefits	Those participating in the MOVE! program may qualify for coverage.
Tricare (military) insurance	Maybe. Tricare Prime and Tricare Select plans <u>can</u> <u>offer coverage</u> if it's determined to be a medically necessary treatment of obesity.
Individual/family coverage via Healthcare.gov (the Affordable Care Act)	It varies. ACA marketplace plans aren't required to have obesity medication coverage, but some plans may offer it.

Pharmacotherapy for Obesity

- Why don't we prescribe it more
 - Historically has been a "poison" pill, physicians have been burned many times in past
 - ► Hippocratic Oath: Do No Harm
 - Previously had not been very effective or side effects weren't tolerable
- ▶ Should we re-evaluate this?

Dietary Supplements – A word of caution

- Over the counter supplements have been marketed towards consumers
- No FDA regulation of these supplements
- Independent testing has shown various stimulant-like compounds, diuretics, thyroid hormone, and anti-cholinergics in these supplements – a modern day rainbow pill
- Sibutramine, fenproporex, fluoxetine, bumetanide, furosemide, phenytoin, cetilistat, and phenolphthalein have been found in OTC weight loss supplements⁸

Indications for Bariatric Surgery

- ▶ BMI > 40
- BMI 35-39.9 with an obesity related co-morbidity (diabetes, hypertension, HLD, gastroesophageal reflux disease, osteoarthritis)
- ▶ BMI 30-34.9 with difficult to control T2DM

Bariatric Surgery

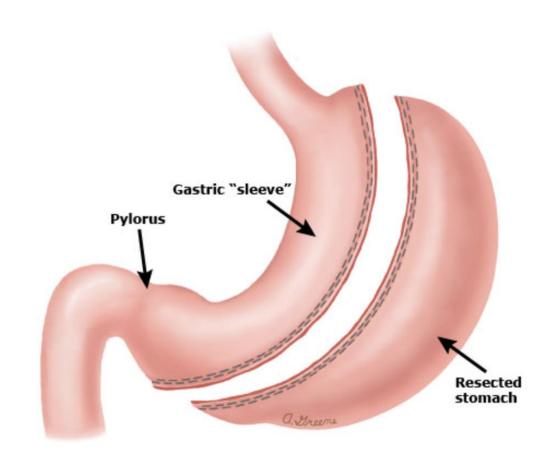
- Only 0.5 percent of eligible patients underwent bariatric surgery in 2016
- Why the low percentage of utilization?
 - Some patients are not suitable surgical candidates because of behavioral or psychosocial issues.
 - Referral bias from clinicians who still believe either that obesity is a behavior problem rather than a disease for which surgery can be therapeutic?
 - Physicians or patients feel bariatric surgery is too risky?
 - Payer resistance to covering bariatric surgery despite its welldocumented cost effectiveness

Bariatric Surgery

- Mechanism of Action
- Restriction Restrictive procedures limit caloric intake by reducing the stomach's reservoir capacity via resection, bypass, or creation of a proximal gastric outlet.
- ▶ Malabsorption Malabsorptive procedures decrease the effectiveness of nutrient absorption by shortening the absorption length of the functional small intestine, either through bypass of the small bowel absorptive surface area or diversion of the biliopancreatic secretions that facilitate absorption.

Sleeve Gastrectomy

- Most common gastric surgery in US and world performed today
- Nowadays a laparoscopic procedure
- At two years, the expected excess weight loss is approximately 60 percent⁹



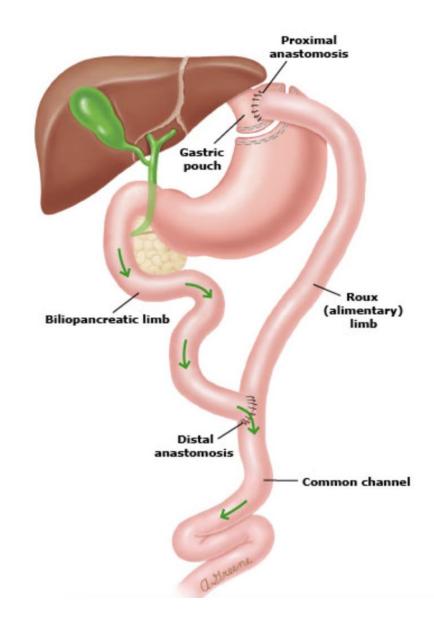
Standardized Weight – Example Calculation

	Men	Woman
Height	5'9"	5'4"
Weight	270 lbs	230 lbs
BMI	40	40
IBW (Ideal body weight)	156 lbs	121 lbs
EBW (Excess body weight)	114 lbs	109 lbs

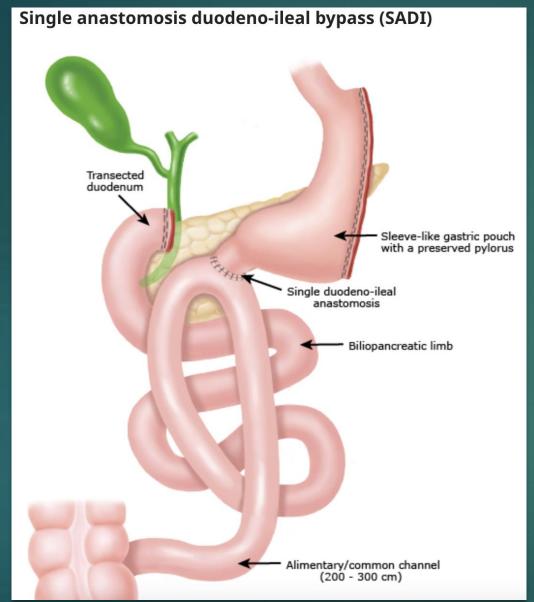
Roux-en-Y Gastric Bypass Surgery

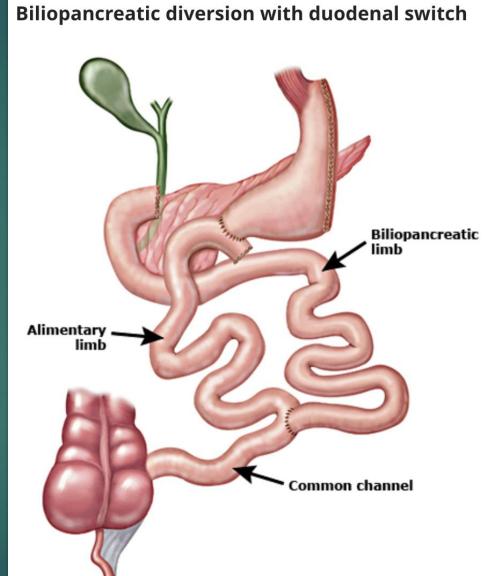
- 2nd most common bariatric surgery in US
- Also laparoscopic surgery
- At two years, the expected excess weight loss is approximately 70 percent¹⁰

Components of Roux-en-Y gastric bypass procedure



Many more variations!





What about liposuction?

- Liposuction The removal of fat by aspiration and injection of physiologic saline in its place
- Can have significant result on fat mass reduction and waist circumference
 - Liposuction did not alter plasma concentrations of C-reactive protein, interleukin-6, tumor necrosis factor-alpha, or adiponectin, and there were no significant improvements in other risk factors for coronary heart disease, including blood pressure, plasma glucose, lipid, or insulin concentrations
- In order to achieve the metabolic benefits of weight loss, there needs to be a negative energy balance from decreased caloric intake or increased expenditure

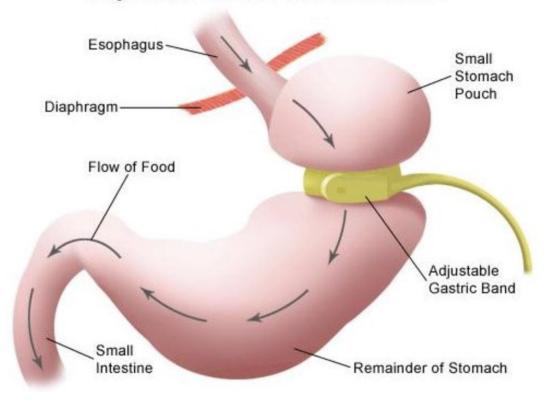
Medical Devices approved for weight loss

- Usually used as a bridging gap to surgery which is a more definitive management
- Many are experimental
- Almost none are covered by insurance

Laparoscopic Adjustable Gastric Banding

- Fallen out of favor due to high rates of need for revision and weight recidivism
- ▶ Went from 24% of bariatric procedures in 2003 to <1% in 2019.
- At two years, the expected excess weight loss is approximately 50 percent

Adjustable Gastric Band Procedure



Intragastric Balloon Therapy

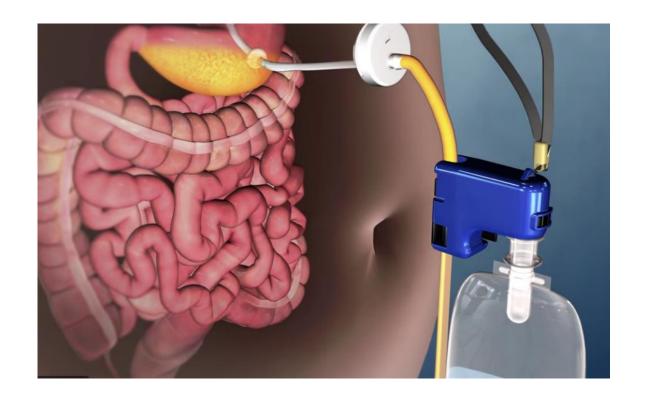
- ► A silicone balloon is placed in the stomach endoscopically and filled with 400 to 700 mL of <u>saline</u>. After residing in the stomach for six months, it is also removed endoscopically.
- 6 to 15 percent total body weight loss expected at 6 months
- Weight gain is expected after removal

Intragastric balloon



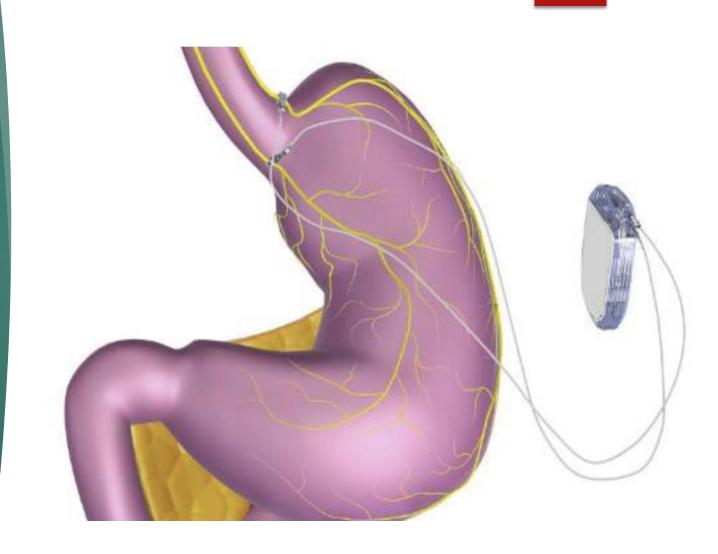
AspireAssist Aspiration Therapy

- G-tube is placed endoscopically in stomach
- At approximately 20 to 30 minutes after each meal, the patient opens a port valve to allow the device to drain stomach contents into the toilet



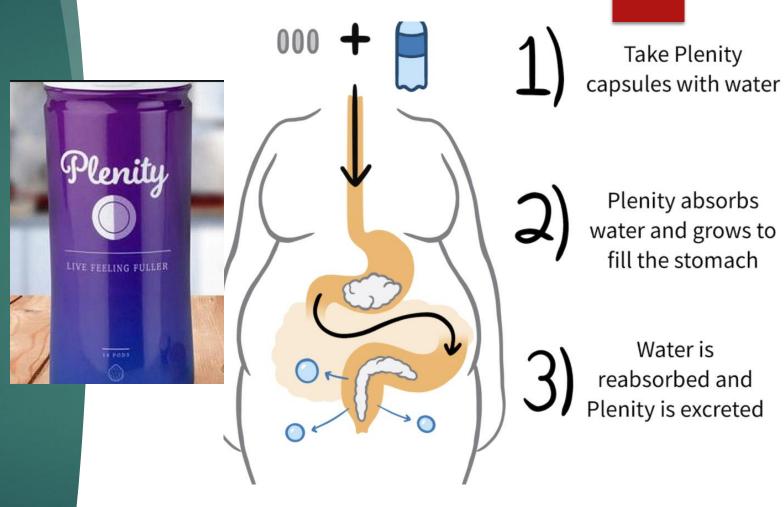
Vagal Blockade System

- These systems deliver small electrical pulses to block transmission of nerve signals in the vagus nerve.
- Promotes weight loss by suppressing neural communication between the brain and the stomach.
- ► These systems include a rechargeable pulse generator implanted in the abdomen which delivers electrical signals to electrodes placed on the trunks of the vagus nerve.



Plenity: Cellulose Hydrogel

- Orally administered hydrogels (pills) taken BID before meals
- ► They are not systemically absorbed, and are eliminated through the feces
- ▶ 1 study showed 6.4% weight loss compared to 4.4% with placebo



Conclusions

- ▶ BMI >35, strongly consider referral to bariatric surgeon
 - Bariatric team has a nutritionist, psychologist, and surgeon who work together to ensure patient has best possible outcomes
- ▶ BMI 27-35, consider pharmacotherapy, especially GLP-1 agonists if covered by insurance
 - ▶ If not covered for obesity, see if covered for T2DM while weight loss isn't as robust, still >5% which has cardiovascular and other benefits
- Encourage patients to avoid OTC supplements for weight loss as many may have dangerous and unregulated substances

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Questions?