Rethinking and Reframing Obesity as a Chronic Disease

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SPEAKER DISCLOSURE

I do not have (nor does any immediate family member have):

- a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity
- any affiliation with an organization whose philosophy could potentially bias my presentation

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CPE INFORMATION

iCARE Pharmacy Services, Inc. is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider for continuing pharmacy education.

This activity offers 1.5 contact hours (0.15 CEU).

- Target Audience: Pharmacists and Technicians
- ACPE #: 0675-0000-24-022-L01-P/T
- Activity Type:
  Knowledge based

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Learning Objectives

1) Discuss the definition and epidemiology of Obesity.

2) Identify Obesity as a chronic relapsing chronic disease.

3) Discuss the challenges and development of Anti-Obesity Medications.

4) Discuss ACC/AHA/TOS and AACE/ACE Overweight and Obesity Guideline.

5) Provide overweight and obesity treatment recommendations giving patient cases.

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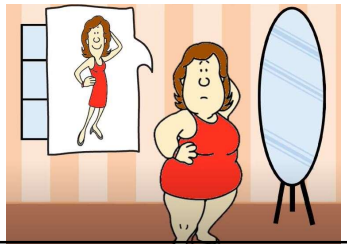
Definition of Obesity

- "Obesity is a chronic, relapsing, multi-factorial, neurobehavioral disease, where an increase in body fat promotes adipose tissue dysfunction, resulting in adverse metabolic, biomechanical and psychosocial health consequences" - Obesity Medicine Association
- In 2013 the American Medical Association designated OBESITY as a chronic disease
- Obesity is NOT A result of lack of moral fiber or lack of willpower
- Obesity causes metabolic dysregulation making it a "chronic relapsing disease"
- Meta-analysis of 29 long-term weight loss studies, > 50% of the weight loss was regained within 2 years and by 5 years > 80% of the loss weight was regained



Hall et al. Maintenance of loss weight and long-term management of obesity Med Clin North Am 2018;102(1):183-197

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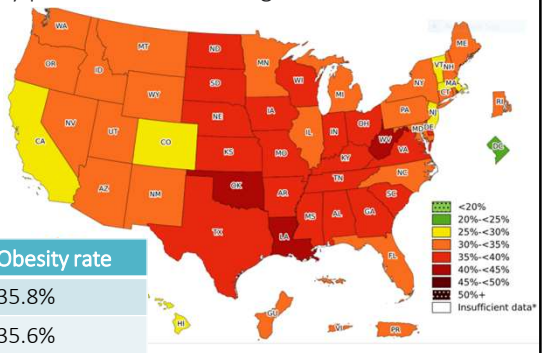
Obesity Epidemiology – CDC 2022 Data

- The majority US has an obesity prevalence greater than 20% (more than a in 5 adults have obesity)
- From 2017- 2020, the prevalence of obesity among US children and adolescents was 19.7%
- Three states (Louisiana, Oklahoma, and West Virginia) had obesity prevalence of 40% or greater
- FL Department of Health – 2024 data:
  -- Overweight rate 36%
  -- Obese rate 28%
- Excess weight has been associated with an increased risk of other medical conditions



US Region o	Obesity rate
Midwest	35.8%
South	35.6%
West	29.5%

Centers for Disease Control – Obesity. [Accessed Aug 12,2024] https://www.cdc.gov/obesity/php/data-research/adult-obesity-prevalence-maps.html

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Pediatric Obesity Epidemiology CDC 2022 Data

- Approximately 1 in 5 US children and adolescents have obesity
- The prevalence of pediatric obesity increased with age from 2017 to March 2020

Age	Prevalence of Obesity
2-5 years old	12.7%
6-11 years old	20.7%
12-19 years old	22.2%

- Wording is IMPORTANT when discussing obesity as a chronic diseases with children
- Talk about "children WITH obesity" instead of "obese children"

https://www.cdc.gov/obesity/php/data-research/childhood-obesity-facts.html

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Obesity is a Medical Problem

- Health risks associated with individuals having obesity or overweight
  - Type 2 diabetes
  - High blood pressure
  - Stroke
  - Metabolic Syndrome
  - Fatty Liver Disease
  - Some cancers → esophagus, colon, rectum and breast
  - Breathing problems
  - Osteoarthritis
  - Gout
  - Gallbladder disease
  - Kidney disease
  - Pregnancy problems
  - Fertility problems
  - Mental Health problems

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Body Mass Index (BMI)

- Body Mass Index (BMI) is the tool use in US to determine healthy weight in US
- To calculate BMI = Height (Kg) / Height (m) 2 → for adult women and men
- Inaccuracies of BMI
  - Weight → Does not distinguish between muscle mass and fat or location of fat
  - Not account for differences among ethnic groups

Weight Classification	Adults
Underweight	< 18.5
Healthy Weight	18.5 - 24.9
Overweight	25 – 29.9
Obesity	≥ 30

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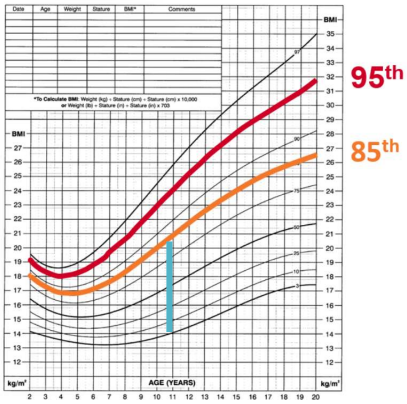
Pediatric Obesity Epidemiology CDC 2022 Data

- BMI is used to determine whether a child's weight fits the criteria of overweight or obese
- Children are overweight if they fall above 85% and below 95% or obese if they fall above 95% in weight/height for their age group
- Obesity in children often coexist with psychiatric disorders mainly depression – obesity rates have risen by 6%, while rates of psychiatric disorders have risen by 12%



BMI Category	BMI Range
Underweight	Less than the 5th percentile
Healthy Weight	5th percentile to less than the 85th percentile
Overweight	85th percentile to less than the 95th percentile
Obesity	95th percentile or greater
Severe Obesity	120% of the 95th percentile or greater, or 35 kg/m^2 or greater

Kokka I et al. Psychiatric disorders and obesity in Childhood and Adolescents- A systematic review of cross-sectional studies. Children (Basrel) 2023;10(2):285

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Inaccuracies of BMI

- Weight factor used in calculating BMI introduces inaccuracies →It does not account for muscle mass differences bone density

- BMI suffers from:
  -- Overclassification → individuals with high muscle mass (bodybuilders) will weight more than less muscular individuals may be classified as overweight or obese → labelling them if a condition they "do not" have

  -- Underclassification → Individuals of Asian descent tend to have more adipose tissue than white individuals of the same weight their risk of metabolic and cardiovascular disease may be overlooked

- Unfortunately, BMI is the parameter use to determine if patients qualify for drug therapies or procedures

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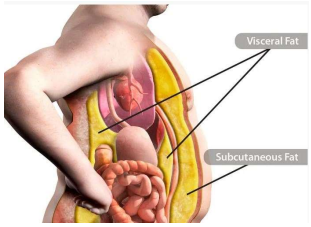
Adipose Tissue Distribution

- Adipose tissue distribution may be a better indicator of long-term "Health Risk" than BMI

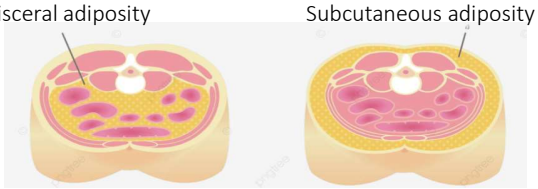
- Location, Location, Location of adiposity
  - Subcutaneous fat – associated with lower levels of inflammation
  - Visceral fat – associated with "higher inflammation"

- Numerous studies indicate that loss of visceral fat occurs first than loss of subcutaneous fat independently of weight loss strategies used

- Increased amounts of visceral fat is associated with increased risk of developing heart disease, type 2 diabetes, fatty liver disease and sleep apnea



Visceral adiposity Subcutaneous adiposity



Merlotti c et al. Subcutaneous fat loss is greater than visceral fat loss with diet and exercise, weight-loss promoting drugs and bariatric surgery: a critical review and meta-analysis. Intern J Obesity2017;(41):672-682.

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Waist-to-Hip Ratio versus BMI

- Waist-to-hip ratio may be a better indicator of long term "Health Risk" than BMI
- Waist-to-Hip Ratio (in cm or inches)= waist measurement /hip circumference

Health risk	Women	Men
low	0.80 or lower	0.95 or lower
moderate	0.81-0.85	0.96-1.0
high	0.86 or higher	1.0 or higher

Alser Met al. Mechanism of body fat distribution and gluteal-femoral fat protection against metabolic disorders. Front Nutr 2024; (11) https://doi.org/10.3389/fnut.2024.1368966

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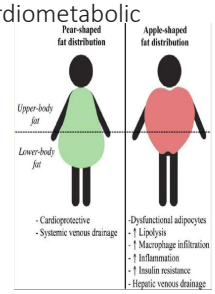
Cardiometabolic Syndrome

- NCEP-ATP III defined Cardiometabolic Syndrome as a cluster of objective measures that associated with an increased risk of cardiovascular risk
- To be diagnosed with the Cardiometabolic Syndrome patients had to fulfilled 3 of the 5 Cardiometabolic Syndrome risk factors:
  - -- Waist circumference for women ≥ 35 in (88 cm) or males ≥ 40 in (102 cm) **
  - -- BP ≥ 135/ 85 mm Hg or on anti-hypertensive medication(s)
  - -- Fasting blood Glucose > 100 mg/dL
  - -- Triglycerides > 150 mg/dL
  - -- HDL < 50 mg/dL in women and < 40 mg/dL in men



- The Waist circumference measurements stated in the NCEP-ATP III used most white population
  - -- ** Individuals of Asian or Indican descents the waist circumference to qualify as having metabolic syndrome → Waist circumference for women ≥31.5 in (80 com) and for men≥ 35.4 in (90 cm)

Grandinetti A et al. Detecting Cardiometabolic Syndrome Using World Health Organization Public Health. Ethn Dis 2010;20(2):123-128.

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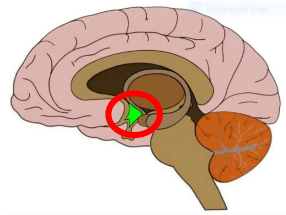
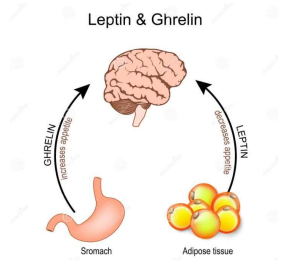
Obesity Pathophysiology

- Early studies believed that obesity was all about increasing size and number of adipocytes, recent studies indicate Obesity causes complex METABOLIC DYSFUNCTION of peripheral hormones and central nervous system signaling



- The Hypothalamus is the main "HUNGER CONTROL" center in the brain

- Two peripheral hormones, leptin and ghrelin, secreted peripherally activate different pathways in the hypothalamus leading to changes in food intake and weight control



- Both Leptin and Ghrelin pathways are disrupted in the presence of obesity

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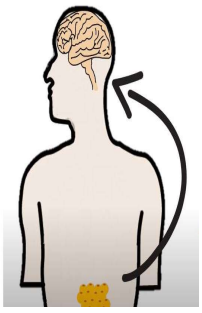
Leptin Pathway in Obesity

- Leptin is hormone secreted by adipocytes into the bloodstream, crosses the Blood-Brain-Barrier and provides feedback to the brain about the amount of energy stored in the body → Long-term energy storage



- L eptin → L OWERS appetite
- If high levels of adipose tissue are present → LOW LEPTIN and vice versa
- As adiposity increases MORE leptin is produced → However, obese individuals become "leptin resistant" → creating a "metabolic dysfunction" as obese individuals DO NOT experienced decrease appetite
- A proposed theory for "Leptin Resistance" → over-eating and increase weight causes: Increase adipocytes → Increase leptin levels → Hypothalamus exposure to Increased levels leptin → causes leptin resistance

Klok MD et al. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Reviews;2006⊗8):21-34

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Leptin Pathway in Obesity

- Factors affecting Leptin levels

	Effects on Levels Plasma Leptin
Energy stores – adipocytes	↑ with increase in BMI and increase in % body fat
Gender	↑ in females compared to males
With increase Age	↓
Exercise	↓
Decrease Sleep	↑
Glucose intake	↑

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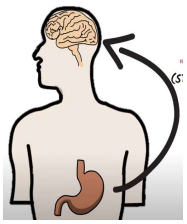
Obesity Ghrelin Pathway

- Ghrelin acts as an appetite stimulator GHRELIN → GROWS appetite
- Ghrelin is a hormone secreted mainly by the Parietal cells of stomach – and to a lesser amount by neurons in the pituitary and the neurons in the Arcuate Nucleolus of the hypothalamus
- Ghrelin plays a role in short-term food intake regulation
- Ghrelin plasma levels show increase pre-prandial and decrease plasma levels post-prandial
- Plasma levels of ghrelin are inverse related to BMI – ghrelin levels increased when obese people loss weight and ghrelin decrease when anorexic individuals gain weight → Ghrelin acts to maintain body weight



Delporte C. Structue and physiological Actions of Ghrelin.Scientifica 2013;2013:518909.

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Acknowledge # 1

TRUE or FALSE – Obesity is a complex, relapsing chronic disease that can lead to multiple other medical complications such as – type 2 diabetes, fatty liver disease, hypertension and sleep apnea among them

TRUE

FALSE

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Acknowledge # 2

TRUE or FALSE

Subcutaneous adipose tissue deposition is associated with higher health risks that visceral adipose tissue deposition

TRUE

FALSE

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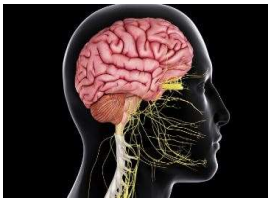
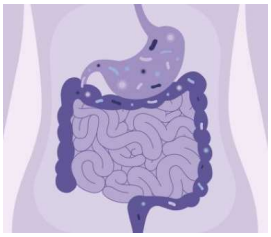
Anti-Obesity Medications

- Early Anti-Obesity Medications target CNS



- Newer Anti-Obesity Medications target both CNS and GI



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Amphetamines

- In the 1940's amphetamines gained popularity for their appetite suppressant properties -
  -- Well known street name as crystal meth
- Mechanism of action → stimulate the synthesis and release of catecholamines – particularly dopamine
- High incidence of addiction
- Physiological effects has two faces:
  -- Suppresses food intake
  -- Either "Stimulates" the CNS (potential for abuse) or "Calms the CNS" in individuals with Attention Deficit disorder

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Amphetamines a solution for Obesity

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Fenfluoramine - Amphetamine Family

- Fenfluramine

  -- Despite federal restrictions on amphetamines given addiction associated with amphetamine use interest in amphetamine modified molecules regained popularity in early 1970's

  -- Fenfluramine decreased appetite by stimulating the release of serotonin (potent vasoconstrictor) and inhibiting its reuptake

  -- Had limited popularity → as the weight loss was only temporary

  -- User developed serious health issues → valvular heart disease and pulmonary arterial hypertension

  -- Fenfluramine (Fintepla®) currently FDA for control of seizure disorders in Dravet or Lenox-Gastaut Syndrome in patients ≥ 2yo

Fintepla®
(fenfluramine)
2.2 mg/mL oral solution

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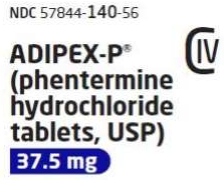
Phentermine – Amphetamine Family



- Marketed as Adipex-P® is FDA approved for up to 12 weeks for weight loss
- Phentermine is C-IV → theoretically less potential for abuse
- Approved for short term use up to 12 weeks → Is obesity a chronic, relapsing disease??
- A study of over 900 people from Mexico showed that about 80% of people with obesity lost at least 5% of their body weight after 6 months of phentermine treatment
- One small study from South Korea showed that almost 86% of people taking phentermine for 14 weeks lost 5% of their body weight. And more than 50% of people lost 10% or more of their body weight. This study included people considered either overweight or obese

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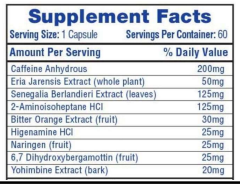
Phentermine – Fenfluramine

- Fenfluramine - Phentermine → was NEVER FDA approved as a combination product
  - -- Fenfluramine (Redux® -dexfenflouramine) and Phentermine (Adipex®) were separately FDA approved
  - -- Study done in 1984 at the University of Rochester Medical Center showed:

    121 obese patients treated for 34 weeks with a combination of Phentermine 15 mg and Fenfluramine 60 mg daily (Phen-Fen) lost an average of 14.2% body weight compared to 4.6% loss in placebo-treated patients and most common adverse event was dry-mouth which subsided after 4 weeks

  - -- Two subsequent studies using Phen-Fen submitted to NEJM showed that approximately 33% of study subjects exhibited heart abnormalities – cardiac valvular disease, pulmonary hypertension and pulmonary fibrosis



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Acknowledge # 3

The use of amphetamines or amphetamines modified agents was associated with _____
.

Select all answers that apply.

A) Increase incidence of addiction

B) Approved for long-term use of weight loss

C) Associated with heart valvular disease, pulmonary hypertension or pulmonary fibrosis

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Sibutramine – Meridia®

- Sibutramine (Meridia®) was FDA approved in 1997
- A serotonin and norepinephrine reuptake inhibitor – acts by inhibiting food intake and stimulation of energy expenditure
- Sibutramine was associated with ~ 3% weight loss and improvement in triglycerides and high-density lipoprotein
- Sibutramine use was associated with increased blood pressure and increase in cardiac arrythmias
- In 2010 FDA recommended against prescribing Meridia® and Abbott voluntarily withdrew Meridia® from the market

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Phentermine and Topiramate – Qsymia®

- In 2012 FDA approved Qsymia® as adjunct to lifestyle modifications in adults with a BMI ≥ 30 or BMI ≥ 27with an additional medical condition and pediatric patients ≥ 12 years old with a BMI equal to ≥ 95th percentile standardized according to sex and age

- Topiramate is FDA approved in the treatment of epilepsy and migraine selectively decreasing CNS neuronal activity when used as monotherapy it causes weight loss ranging from 3.8% to 6.5% from baseline in a dose-dependent manner – it is not understood how topiramate causes weight loss

- When topiramate is used as adjunct to phentermine the weight loss seen is greater than the weight loss achieved with either agent as monotherapy

- Use of Qsymia typically results in a placebo-subtracted weight loss of 5.9% to 9.0% from baseline

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Orlistat – Alli® or Xenical®

- Orlistat is a lipase inhibitor which inhibits the absorption of fatty acids from the intestine tract

- Absorption of fat decreases calories leading to a placebo-subtracted weight loss in the range of ~ 2.6%

- An undesirable side effect of this agent is spontaneous defecation – this side effect increases with increase fat food content

- Alli was FDA approved in 1999 in 120 mg capsules dose. In 2007, Alli became available over-the-counter in 60 mg for adults ≥ 18 yo for weight loss

- In 2010 FDA review orlistat due to serious liver injury cases, these cases were not confirmed to be associated with orlistat use

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Lorcaserin – Belviq®

- Lorcaserin –Belviq® was FDA approved in 2012 for the treatment of chronic weight management in adults with a body mass index (BMI) of 30 or greater (obese) as an addition to a reduced-calorie diet and exercise
- Lorcasein is a selective serotonin 2C agonist (3rd generation 5-HT-based anti-obesity drugs) resulting in a 3.2% placebo-subtracted weight loss in overweight or obese adults
- In February 2020 FDA asked manufacturer of Belviq to withdrawal Belviq® from the market due to increased rates of cancer associated with its use

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Naltrexone–Bupropion XR – Contrave®

- Its mechanism combines an opiod receptor antagonist (naltrexone) with a dopamine and norepinephrine reuptake inhibitor (bupropion) as extended-release formulation
- FDA approved in 2014 as an adjunct to increased physical activity and a reduced-calorie diet for chronic weight management in adults who have a body mass index (BMI) ≥ 30 kg per m^2 or those with a BMI ≥ 27 kg per m^2 with one or more weight-related comorbidities such as type 2 diabetes mellitus, hyperlipidemia, or hypertension
- Clinical trials showed that use Contrave® as adjunct to diet showed that about 40% of adults lost ~ 5% of their body weight after taking Contrave for 1 year, while over 15% of adults loss ~ 10% of their body weight after taking Contrave after 1 year

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Setmelanotide - Imcivree®

- FDA approved 2020 for chronic weight management in patients ≥ 6 yo with obesity due to a rare genetic condition suffering from Bardet-Biedl syndrome
- Bardel-Biedel genetic disorders occurs in 1/ 140,000 to 160,000 newborns is an autosomal recessive inherited disease characterized by childhood obesity and serious eye pathologies
- Children with Bardel-Biedel are constantly eating
  - -- Parents have to lock foods
  - -- Is very difficult to go to school, is difficult to concentrate

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Acknowledge # 3

Select all answers that apply. Multiple early Anti-Obesity Medications FDA approved have been removed from the market due to following safety concerns:

A) Increased incidence of addiction

B) Increase incidence of seizures disorders

C) Increase incidence of cardiovascular disorders

D) Increase incidence of cancer

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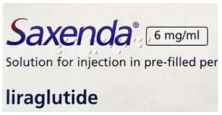
Liraglutide (Saxenda®)



- Saxenda – liraglutide - is a Glucagon-like peptide-1 receptor agonist (GLP1RA) which promotes weight loss by stimulating GLP1 receptor in the hindbrain and hypothalamus areas of the brain and decreases GI motility
- FDA approved in 2010 liraglutide (Victoza®) for type 2 diabetes management

- FDA approved in 2014 liraglutide as - Saxenda® for the chronic weight management in adults with a BMI ≥ 30 kg/m2 or BMI ≥ 27 Kg/m2 with at least one weight-related condition in conjunction with a reduced calorie diet and physical activity
- The LEADER trial lasting 56 weeks enrolled >3,700 patients with BMI ≥ 30, patients in the liraglutide arm lost an average of 8.4Kg versus 2.8 Kg in the placebo arm

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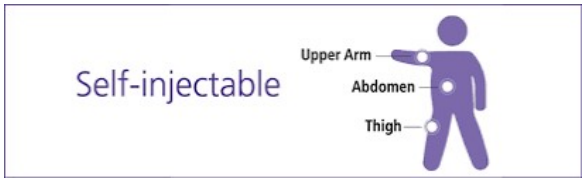
Liraglutide (Saxenda®)

- FDA approved since 2020 under the name Saxenda® for chronic weight management of pediatric patients ≥ 12 yo who are obese as defined by BMI cutoffs according to their age and sex
- The SCALE Teens study was conducted in patients 12 to < 18 years old and showed that at least 43.3% of liraglutide users had a 5% reduction in their BMI, compared to 18% in the placebo arm
- Dosing → Daily sq injection – Most common side effects nausea, vomiting, diarrhea or constipation

Week	Saxenda dose (mg)
1	0.6
2	1.2
3	1.8
4	2.4
5	3



Pi-Sunyer X et al. A randomized, Controlled Trial of 3.0 mg of liraglutide in weight management. NEJM 2015;373:11_11-22.

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Semaglutide (Wegovy®)

- Wegovy is a Glucagon-like peptide-1 receptor agonist (GLP1RA) which promotes weight loss by stimulating GLP1 receptor in the brain (hypothalamus and hindbrain)

- FDA approved in 2021 for the chronic weight management in adults with a BMI ≥ 30 kg/m2 or BMI ≥ 27 Kg/m2 with at least one weight-related condition in conjunction with a reduced calorie diet and physical activity and FDA approved in 2022 for pediatric patients ≥ 12 yo who are obese as defined by BMI cutoffs according to their age and sex

- The STEP1 study enrolling 1,961 patients overweight or obese without diabetes for 68 weeks demonstrated that individuals receiving Wegovy® loss 15.3 Kg versus 2.6 Kg individuals on the placebo arm

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Semaglutide (Wegovy®)

- Step 1 study also showed that 86.4% of individuals on Wegovy® loss at least 5% of their baseline BMI versus 31% of those on placebo. Those losing at least at 10% of their baseline BMI were 69.1% used Wegovy® versus 12% used placebo. Those losing at least 15% of their baseline BMI were 50.5% used Wegovy® versus 4.9% on placebo

- In the SELECT study weight loss continued at 65 weeks and was sustained data on 208 weeks weight was a 10.2% weight reduction from baseline for those on semaglutide versus 1.5% for those on placebo, waist circumference was also reduced by 7.7 cm in the semaglutide arm versus 1.3 cm in the placebo arm

- The cardiovascular outcome trial SUSTAIN-6 showed a 20% RRR in 3-POINT MACE (cardiovascular death, non-fatal stroke, non –fatal MI) compared to those on the placebo arm

- Semaglutide has shown to lower plasma hsCRP

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Semaglutide (Wegovy®)

➢ Dosing for Wegovy®

Week	Wegovy® (mg)
Week 1 through Week 4	0.25
Week 4 through Week 8	0.5
Weeks 9 through Week 12	1.0
Week 13 through Week 16	1.7
Week 17 through Week 20	2.4

➢ Administration

Wilding JP, Batterham RL, Calanna S et al. Once-weekly semaglutide in adults with overweight or obesity. NEJM 2021;384:989-1002.

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Tirzepatide (Zepbound®)

➢Tirzepatide is a dual -acting Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP1) receptor agonist

➢Tirzepatide was first FDA approved in 2022 under the name Mounjaro® for the management of adults with type 2 diabetes

➢ Tirzepatide was FDA approved in 2023 under the name of Zepbound® was FDA for the management of individuals ≥ 18yo with obesity BMI ≥ 30 or overweight with BMI ≥ 27 with at least one weight-related condition for use in addition to reduced calorie diet and increased physical activity

➢ There are ongoing cardiovascular outcome trials to assess the effect of tirzepatide on 3-point MACE ??

Jastreboff AM, Aronne LJ, Ahmad NN et al. Tirzepatide Once Weekly for the Treatment of Obesity. NEJM 2022;387:205-216.

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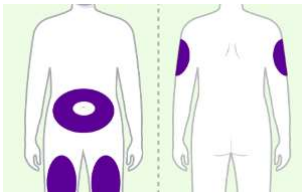
Tirzepatide (Zepbound®)

- Dosing

Weeks	Zepbonud dose (mg)
Week 1 through Week 4	2.5
Week 5 through Week 8	5
Week 9 through Week 12	7.5
Week 13 through Week 16	10
Week 17 through Week 20	12.5
Week 21 through Week 24	15.7

- Administration



Jastreboff AM, Aronne LJ, Ahmad NN et al. Tirzepatide Once Weekly for the Treatment of Obesity. NEJM 2022;387:205-216.

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Tirzepatide (Zepbound®)

- Results from the SURMONT-1 study enrolled 2,539 patients with BMI at least 30 and one or more weight-related complications over a 72-week period, the mean BMI was 38 (with 94.5% patients having a BMI of > 30
- At 72 weeks the mean % change in body weight was 15% (5 mg), 19.5% (10 mg) and 20.9% (15 mg)
- Individuals that had a weight loss of 5% or more was 85% (5 mg), 89% (10 mg), 91% (15mg) compared with a 35% weight loss for the placebo arm
- Individuals that has a weight loss of 20% or more was 50% (10 mg) and 57% (10 mg) as compared to 3% in the placebo arm

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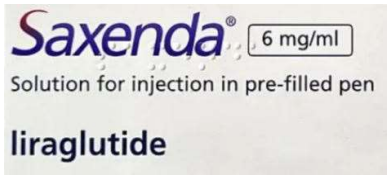
Boxed Warnings with Saxenda®, Wegovy®, and Zepbound®

➢ All GLP1RA and double agonist GIP/GLP1RA have similar packet label information:

-- BOXED WARNINGS

- Thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether --------- causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of ------- -induced rodent thyroid C-cell tumors has not been determined. --------- is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors .



chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.novo-pi.com/saxenda.pdf [Accessed Aug 18,2024].

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Warnings and Precautions with Saxenda®, Wegovy® and Zepbound®

➢ Acute pancreatitis – discontinue promptly is pancreatitis is suspected . DO NOT restart if pancreatitis is confirmed.

➢ Acute Gallbladder disease – If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated

➢ Hypoglycemia can occur when (GLP1RA or GIP/GLP1RA) is used with an insulin secretagogue (e.g. sulfonylurea) or insulin. Risk may be lowered by a reduction or discontinuation of secretagogue

➢ Renal impairment – has been reported post marketing usually associated with nausea, vomiting, diarrhea or dehydration

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Name	Dose	Type	Placebo	Drug
Phentermine	Cap:15-30 mg po daily Lomaira: 8 mg orally TID Adipex 37.5 mg po daily	Sympathomimetic	Not provided in the PI	Not provided in PI
Orlistat	120 mg po TID before meals	Pancreatic lipase inhibitor	- 2.6%	- 6.1%
Phentermine /Topiramate ER	7.5 mg/46 mg or 15mg/92 mg po as rescue (requires titration)	Sympathomimetic anticonvulsant and Glutamine antagonist	- 1.2%	-7.8% - mid-dose -9.8% - full dose
Naltrexone / Bupropion SR	32 mg/360 mg po	Opiod receptor antagonist; dopamine and norepinephrine reuptake inhibitor	-1.3% to -1.7%	- 3.7% to -5.4%
Liraglutide	3 mg sq daily –requires titration	GLP-1 receptor agonist	- 1.7% to – 3.0%	- 5.4%to- 7.4%
Semaglutide	2.4mg sq weekly – requires titration	GLP-1 receptor agonist	- 2.4% to – 3.4%	- 9.6% to – 14.9%
Tirzepatide	5 mg, 10 mg or 15 mg sq-requires titration	Dual GIP and GLP-1 receptor agonist	- 3.1% to – 3.2%	- 14.7% to – 20.9%

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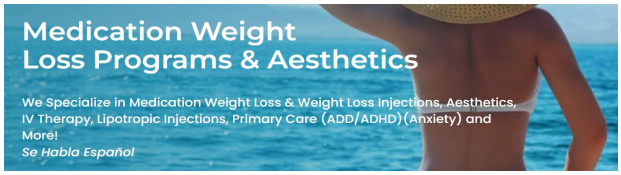
Weight Loss Clinics



Semaglutide or Tirzepatide

bmiMD.com

★★★★☆ (3,266)

~~$568.50~~ **$24.99**

$22.49 with code PROMO, Ends 8/24

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Weight Loss Drugs Supply Crisis

Feature | Article | December 21, 2023 American Journal of Managed Care

An Ongoing Crisis: Semaglutide Shortage Raises Dual Concerns for Obesity and Diabetes Treatment

Some doctors are embracing compounded versions of popular weight loss drugs

During shortages, the FDA allows compounding pharmacies to make versions of drugs that are "essentially a copy" of brand-name medicines.

Poison centers see nearly 1,500% increase in calls related to injected weight-loss drugs as people accidentally overdose

By Brenda Goodman, CNN
6 minute read · Updated 2:32 PM EST, Mon December 18, 2023

Medscape Medical News > News Alerts

Compounded Semaglutide Overdoses Tied to Hospitalizations

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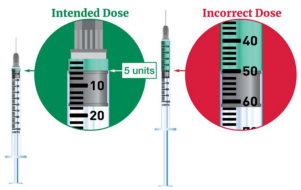
FDA alerts health care providers, compounders and patients of dosing errors associated with compounded injectable semaglutide products

Several reports describe health care providers incorrectly calculating the intended dose when converting from milligrams to units or milliliters, which resulted in patients administering five to 10 times more than the intended dose of semaglutide.

- One provider intended to dose 0.25 milligrams (5 units), but prescribed 25 units instead, leading to a patient receiving five times the intended dose and experiencing severe vomiting.
- Another provider prescribed 20 units instead of 2 units, affecting three patients who, after receiving 10 times the intended dose, experienced nausea and vomiting.
- Additionally, a patient, who is a health care provider, attempted to recalculate their own dose in units and inadvertently self-administered a dose 10 times higher than intended.

Figure 1. **U-100 insulin syringe with fill volume of 5 units and 50 units**



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Case #1

MA is a 44yo HF presenting to her PCP for follow up. Last lab values showed she was pre-diabetes 5.7%. She complain of tiredness (she has 2 active boys), lack of motivation. She was worried about her pre-diabetes and started to do exercises – walking 35 min/ 4 x week. She has been is focusing on eating less take-out food, eating more at home and has increased her vegetables consumption. She reports not seeing much change in weight despite her changes in exercise and food choices.

HPM: none FH: mother –alive – has CVD, dad – HTN, hyperlipidemia

Labs 4-28-2024 Glu= 116, all other wnl , A1c 5.7%, Wt 200 BMI= 34.3

Labs 8-12-2024 Glu=118, BUN= 21, SCr= 0.91, NA=140, K= 3.6, HCO3=24, Cl=103, A1C 5.8%

TC 186, TG 164, HDL 30, LDL 123 Ht 5'4" Wt 198 waist circum 39 in

BMI = 34

1) What are your thoughts about MAs health status?
2) What weight loss will provide a health benefit for MA?
2) What actions would you recommend for MA?
3) If you start any medications provide patient counseling.

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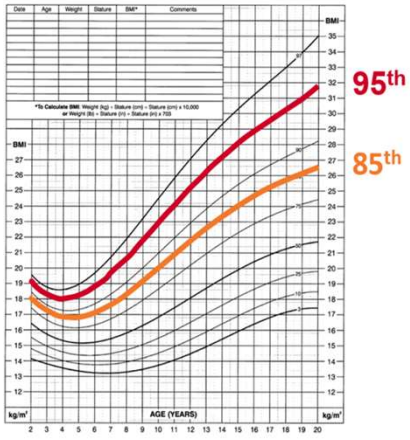
Case #2

Tim is a 15 yo male who has been overweight since he was 10 yo. He goes to the gym with his neighbor and friend Johnny 3-4 times / week for weightlifting and runs 2x/week- 2 miles. Tim has gained muscle (he is very proud of his bigger biceps) but continues to be overweight. He asks his mom if he could get on Ozempic that he sees advertised on TV. His mother has taken him to the pediatrician for a visit.

Ht 5'10" Wt 191 BMI 27.4

TSH 2.6 - wnl

Tim – what checked for hypogonadism- hormones wnl



1) What would you recommend for Tim?

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Pipeline New Weight Loss agents

- Novo Nordisk →
  - -- Subq once weekly → CagriSema → combination of cagrinlitide (Almylin analog) and semaglutide
  - -- Study being conducted is a head-to-head against Zepbound (GIP/GLP1RA) in a Ph3 trial
  - -- In Ph 2 studies showed weight reduction was 15.6% for CagriSema compared to 5.1% for semaglutide only and 8.1% for cagrilintide

- Eli Lilly → Orforglipron → Oral GLP1RA for weight loss

- Viking Therapeutics → VK-2735
  - -- Ph 1 trials showed that 57% of patients on VK-2735 loss at least 5% of baseline body weight compared with placebo
  - -- Ph 2 showed that VK-2735 achieved a 13.1% placebo-adjusted mean weight loss

Miranda K et al. Cannabinoid Receptor 1 Blockade Attenuates Obesity and Adipose Tissue Type 1 Inflammation Through miR-30e-5p Regulation of Delta-Like-4 in Macrophages and Consequently Downregulation of Th1 CellsFront Immunol 2019 https://doi.org/10.3389/fimmu.2019.01049

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Pipeline New Weight Loss agents

- GLP1RA are the rage in this new weight loss space drug development

- They expect the GLP1 market will exceed the $100 Billion by 2030

- The number of clinical trials for weight loss drug development ahs increased by 68% from 2022 to 2023

- The race is to bring to market an effective oral weight loss GLP1RA which will decrease manufacturing cost

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Pipeline New Weight Loss agents

- Survodutide → Boeringher Ingelheim –BI 456906
  -- GLP1RA/GIP/Glucagon receptor triple agonist – Studies are looking at weight loss and reduction of fatty liver disease

- Rimonabant → New mechanism of action targeting → Endocannabinoid Receptor 1 (CB1) blockade

- Novo Nordisk acquired Inversago Pharma INV-202 molecule
  -- Ph 1b results for INV-202 → oral CB1 receptor blocker showed a 7.7 lbs weight loss over a 28-day period compared to 1.2 lbs weight loss by the placebo arm

Miranda K et al. Cannabinoid Receptor 1 Blockade Attenuates Obesity and Adipose Tissue Type 1 Inflammation Through miR-30e-5p Regulation of Delta-Like-4 in Macrophages and Consequently Downregulation of Th1 CellsFront Immunol 2019 https://doi.org/10.3389/fimmu.2019.01049

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Thank You for your kind attention …

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