Medical of Obesity

Benjamin O'Donnell, MD
Associate Professor - Clinical
Fellowship Program Director
Division of Endocrinology, Diabetes, and Metabolism
The Ohio State University Wexner Medical Center

MedNet21
Center for Continuing Medical Education

The Ohio State University
Wexner Medical Center

Objectives

- Background
- Control of Energy Homeostasis
- Approach to Diet and Exercise
- Medications
- FDA Approved Endoscopic Therapies

Background

Overweight and Obesity

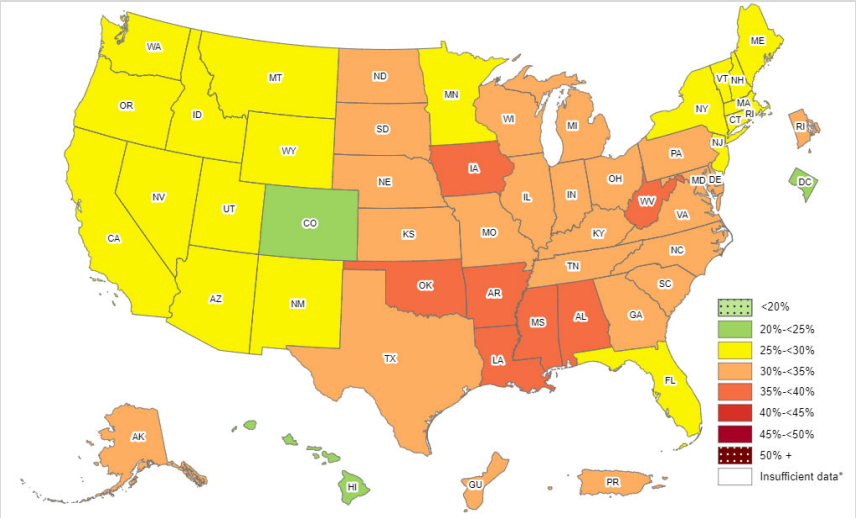
- Defined by BMI
  - Measure of weight (kg) per height (m^2)
- Overweight
  - BMI – 25-29.9 kg/m^2
- Obese (by BMI category)
  - Class 1 – 30-34.9 kg/m^2
  - Class 2 – 35-39.9 kg/m^2
  - Class 3 (severe) – $\geq$ 40 kg/m^2

https://www.cdc.gov/obesity/adult/defining.html

- In Asian populations, BMI cut offs are lower
  - BMI 23-27.49 = overweight
  - BMI $\geq$ 27.5 = obesity
- Severity is determined by presence of comorbid conditions: DM2, HTN, Hyperlipidemia, sleep apnea, PCOS, arthritis, infertility

Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2017

¶ Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.



*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.

https://www.cdc.gov/obesity/data/prevalence-maps.html

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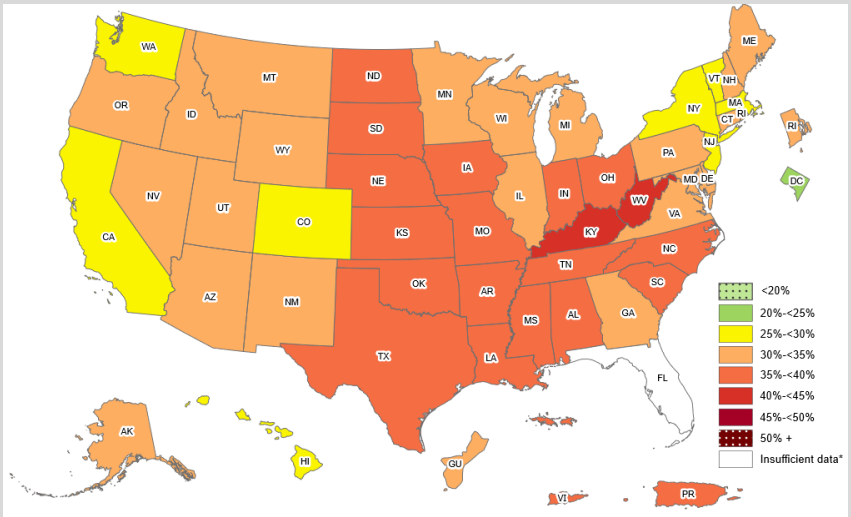

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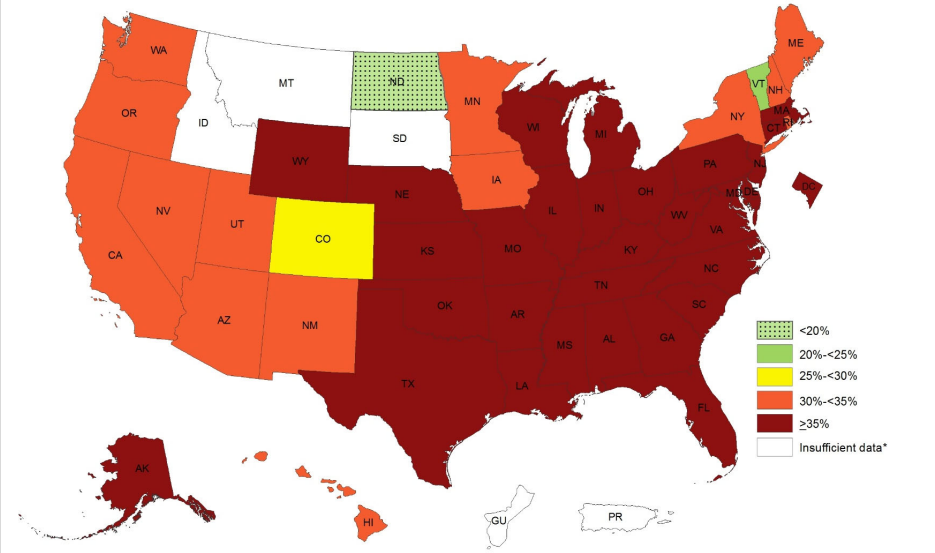
https://www.cdc.gov/obesity/data/prevalence-maps.html

Impact of Obesity

- According to CDC:
  - 2017-2021 estimated prevalence of adults who are obese is **41.9%**.
  - The estimated annual medical cost of obesity in the U.S. was $173 billion in 2019 U.S. dollars.
  - The per capita medical costs for people who are obese were $1,861 higher than those of normal weight.

https://www.cdc.gov/obesity/data/adult.html

Prevalence of Self-Reported Obesity Among Non-Hispanic Black Adults, by State and Territory, BRFSS, 2014-2016



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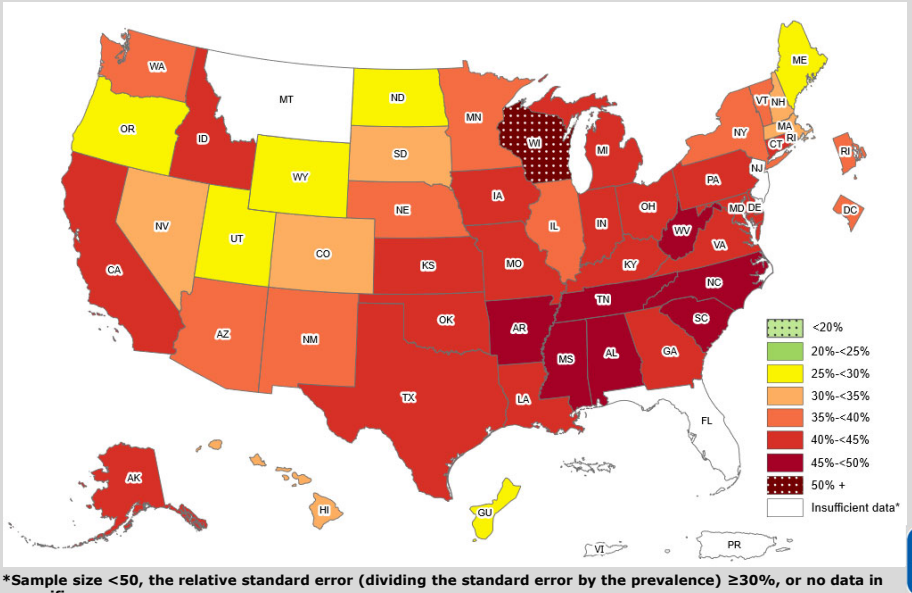
Prevalence of Self-Reported Obesity Among Non-Hispanic Black Adults, by State and Territory, BRFSS, 2019–2021



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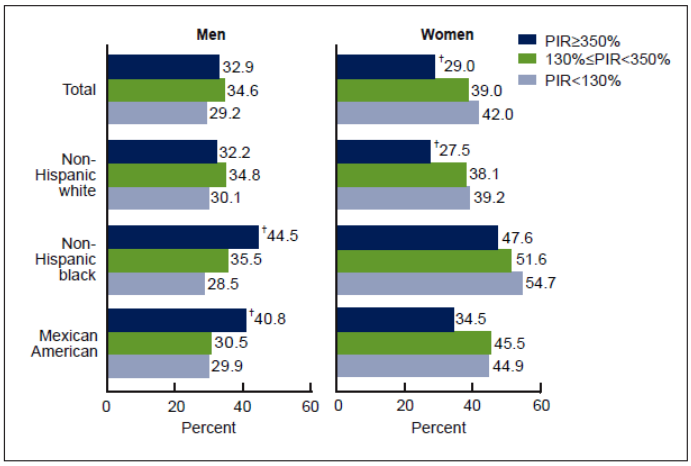
https://www.cdc.gov/obesity/data/prevalence-maps.html

Population data

Figure 1. Prevalence of obesity among adults aged 20 years and over, by poverty income ratio, sex, and race and ethnicity: United States 2005–2008



†Significant trend.

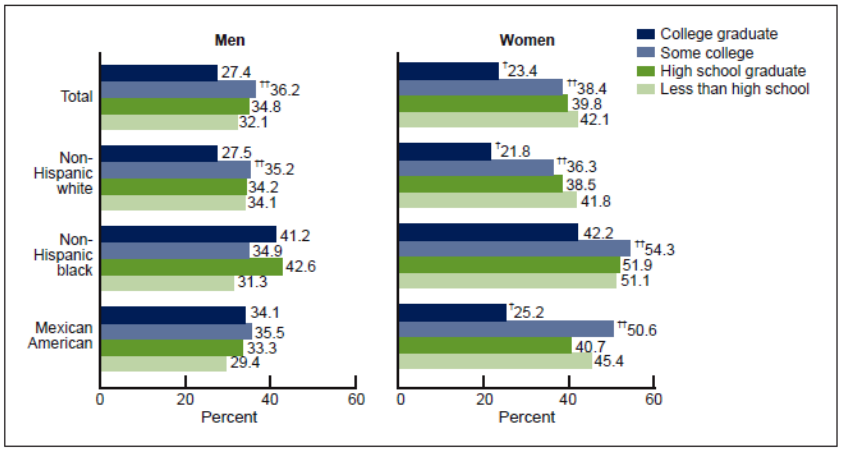
NOTES: PIR is poverty income ratio. Persons of other race and ethnicity included in total.

SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2005–2008.

Ogden CL, Lamb MM, Carroll MD, Flegal KM. Obesity and socioeconomic status in adults: United States 1988–1994 and 2005–2008. NCHS data brief no 50. Hyattsville, MD: National Center for Health Statistics. 2010.

Population data

Figure 3. Prevalence of obesity among adults aged 20 years and over, by education, sex, and race and ethnicity: United States 2005–2008



†Significant trend.
††Significantly different from college graduates.
NOTE: Persons of other race and ethnicity included in total.
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2005–2008.

Ogden CL, Lamb MM, Carroll MD, Flegal KM. Obesity and socioeconomic status in adults: United States 1988–1994 and 2005–2008. NCHS data brief no 50. Hyattsville, MD: National Center for Health Statistics. 2010.

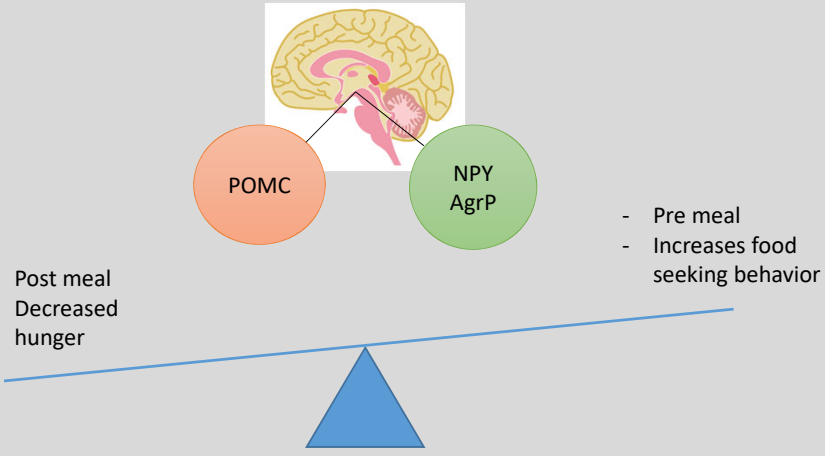
Pathophysiology

Physiology

- Food is a basic need.
- Caloric restriction leads to decreased metabolic rate.
- Overfeeding leads to a temporary increase in metabolic rate.
- The body will defend a higher set point (overweight) – patients often refer to this as yo-yo dieting.

Stephan J. Guyenet and Michael W. Schwartz; *Regulation of Food Intake, Energy Balance, and Body Fat Mass: Implications for the Pathogenesis and Treatment of Obesity J Clin Endocrinol Metab* 97: 745–755, 2012.

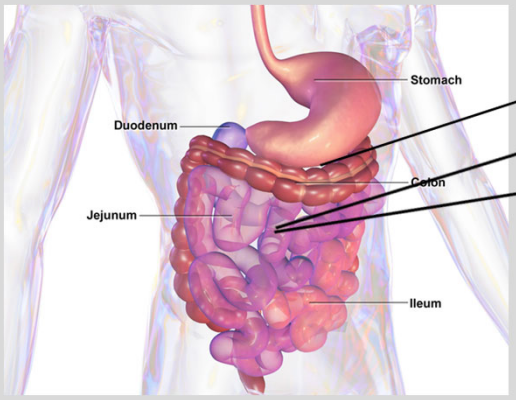
Control of Energy Homeostasis



G. J. Morton, D. E. Cummings, D. G. Baskin, G. S. Barsh & M. W. Schwartz. *Central nervous system control of food intake and body weight.* Vol 443: 21 September 2006. doi:10.1038/nature05026

https://freesvg.org/human-brain-drawing

Physiology



- Leptin
- Insulin
- GLP-1
- CCK
- PYY

POMC

- Gut Bacteria
  - SCFAs

NPY
AgrP

- Inflammation

https://commons.wikimedia.org/wiki/File:Blausen_0432_GastroIntestinalSystem.png; https://creativecommons.org/licenses/by/3.0/

P. V. Bauer et al. Regulation of energy balance by a gut–brain axis and involvement of the gut microbiota. Cell. Mol. Life Sci. (2016) 73:737–755

Management of Obesity

Management

- Multiple modes of therapy
  - Dietary – Medical Nutrition Therapy
  - Exercise/Activity
  - Behavioral therapy
  - Combination Therapy
  - Pharmacotherapy
  - Endoscopic Therapy
  - Surgery

Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. [No authors listed]. Obes Res. 1998 Sep;6 Suppl 2:51S-209S. Review. Erratum in: Obes Res 1998 Nov;6(6):464.

Nutrition

- Low calorie diet
  - Men 1500-1800 kcal/day
  - Women 1200-1500 kcal/day
- 500 kcal/day deficit should produce roughly 1 lbs per week of weight loss
- No one diet is most effective – rather go with patient preference
- Maintain appropriate balance of nutrients
- Dietary intake should not be lower than 800 calories per day
- Initial goal of 10% decrease in body weight

Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. [No authors listed]. Obes Res. 1998 Sep;6 Suppl 2:51S-209S. Review. Erratum in: Obes Res 1998 Nov;6(6):464.

Activity

TABLE IV-5:

DURATION OF VARIOUS ACTIVITIES TO EXPEND 150 KILOCALORIES FOR AN AVERAGE 70 KG (154 LB) ADULT

Intensity	Activity	Approximate duration in minutes
Moderate	Volleyball, noncompetitive	43
Moderate	Walking, moderate pace (3mph, 20 min/mile)	37
Moderate	Walking, brisk pace (4mph, 15 min/mile)	32
Moderate	Table tennis	32
Moderate	Raking leaves	32
Moderate	Social dancing	29
Moderate	Lawn mowing (powered push mower)	29
Hard	Jogging (5 mph, 12 min/mile)	18
Hard	Field hockey	16
Very Hard	Running (6 mph, 10 min/mile)	13

Source: Surgeon General's Report on Physical Activity and Health

Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. [No authors listed]. Obes Res. 1998 Sep;6 Suppl 2:51S-209S. Review. Erratum in: Obes Res 1998 Nov;6(6):464.

Activity – a caveat

- Exercise (especially at higher intensity) leads to calorie expenditure
- As the body perceives the calorie loss, hunger signals increase
- In fact, it is possible for people to gain weight while increasing exercise due to overeating in response[1]

- A survey-study performed in 1997 of 784 people who were able to maintain 30 lbs of weight loss for > 1 year, only 1% achieved this with exercise alone[2]

1. Church TS, Martin CK, Thompson AM, Earnest CP, Mikus CR, et al. (2009) Changes in Weight, Waist Circumference and Compensatory Responses with Different Doses of Exercise among Sedentary, Overweight Postmenopausal Women. PLoS ONE 4(2): e4515.

2. Mary Klem et al. A descriptive study of individuals successful at long-term maintenance of substantial weight loss. *Am J Clin Nutr* 1997;66:239-46.

Motivational Interviewing

- Directive – patient centered counseling that helps explore and resolve issues related to complex behaviors.
- Initially developed for addictive behaviors
- Main difference between motivational interviewing and education sessions is that the motivation is elicited FROM the patient, rather than imparted from the healthcare provider

Motivational interviewing for weight loss. M. J. Armstrong et al. Obesity reviews (2011) 12, 709–723.

Motivational Interviewing

- Examples:
  - "What have you found to be helpful so far?"
    - Is it keeping a journal? Has it been engaging a friend/coworker?
    - This can be a good jumping off point to set short term goals.
  - "How many days have you been able to add in activity?"
    - If a person truly has limited time during the week, suggest focusing more on the weekends for leisure activity
  - "Have you noticed any changes since you've started exercising?"
    - Hopefully the answer is yes – then reflect on things like stamina, better energy, sleep quality, and potentially better blood pressure

Pharmacotherapy

Use of medications

- Medications do not work on their own; they must be part of a comprehensive approach
- Candidates:
  - BMI > 27 with comorbid conditions
  - BMI > 30
- History of unsuccessful attempts at weight loss OR inability to maintain weight loss
- Comorbid conditions include
  - DM II, HTN, Hyperlipidemia, and OSA
- Guideline states that medications may *amplify adherence* to diet and exercise
  - Potentially help to make exercise easier after initial weight loss

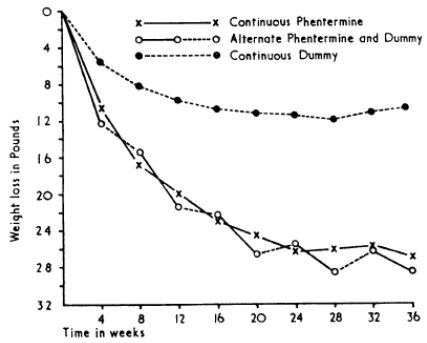
J Clin Endocrinol Metab, February 2015, 100(2):342–362

Phentermine - Adipex

Comparison of Continuous and Intermittent Anorectic Therapy in Obesity

J. F. MUNRO,* M.B., M.R.C.P.ED. ; A. C. MACCUISH,* M.B., CH.B.
ELIZABETH M. WILSON,* S.R.D. ; L. J. P. DUNCAN,* M.B., B.SC., F.R.C.P.ED.

Brit. med. J., 1968, **1**, 352–354



Mean weight loss in each group during the study.

- Phentermine works via release of norepinephrine
- Prescribed as intermittent therapy based on this trial from 1968
- Definition of intermittent varies, but in Ohio this is 3 months on 6 months off.
- Caution with glaucoma, MAOIs, cardiac disease, hyperthyroidism.

Orlistat –Xenical (Rx), Alli (OTC)

- Pancreatic lipase inhibitor, reduces absorption of dietary fats, must be taken three times a day with meals.
- Available in prescription (120mg) and OTC (60mg) doses.
- Mean weight loss after 1 year on full dose compared with placebo about 3%.
- Approved for long term use.
- Significant GI side effects.
- May be a good option for patients with prior cardiac disease.

Robert F. Kushner, Caroline M. Apovian and Ken Fujioka; Obesity Consults—Comprehensive Obesity Management in 2013: Understanding the Shifting Paradigm. Obesity (2013) 21, S3–S13. doi:10.1002/oby.20627

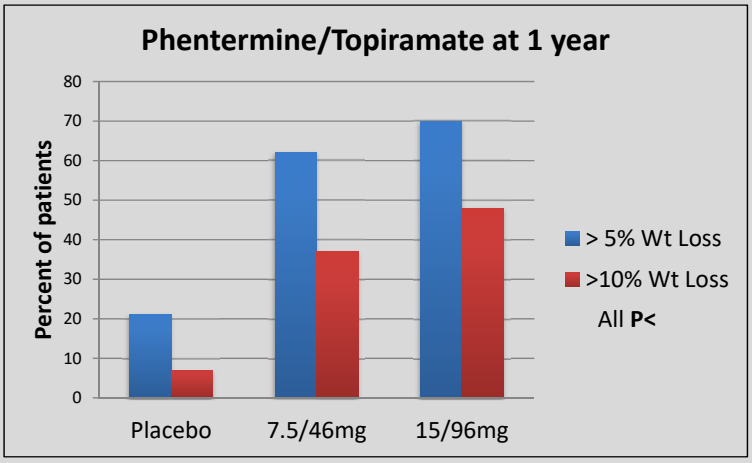
Lorcaserin - Belviq

- 5HT2-C serotonin receptor agonist
- FDA recommended voluntary removal in Feb 2020
- In the CVOT CAMELLIA-TIMI 61 a slight difference in incidence of cancer was reported in the treatment group vs placebo
- 7.7% vs 7.1%
- Cancers included lung, pancreatic, and colon

N Engl J Med 2010;363:245-56

NEJM 2020 Sep 10;383(11):1000-1002

Phentermine/Topiramate - Qsymia

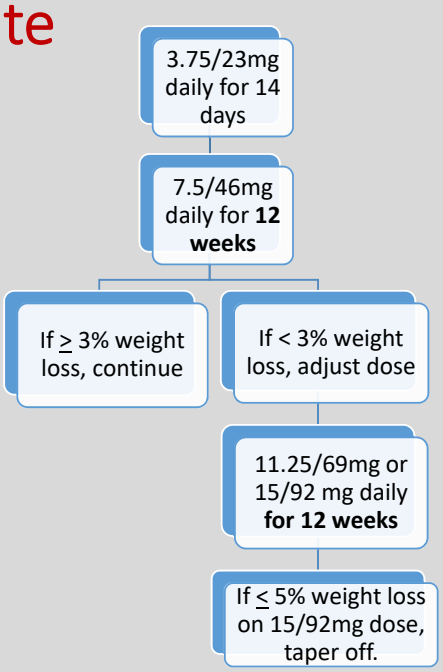


- Phentermine acts centrally via norepinephrine, Topiramate works via GABA receptors
- Can titrate dose based on response

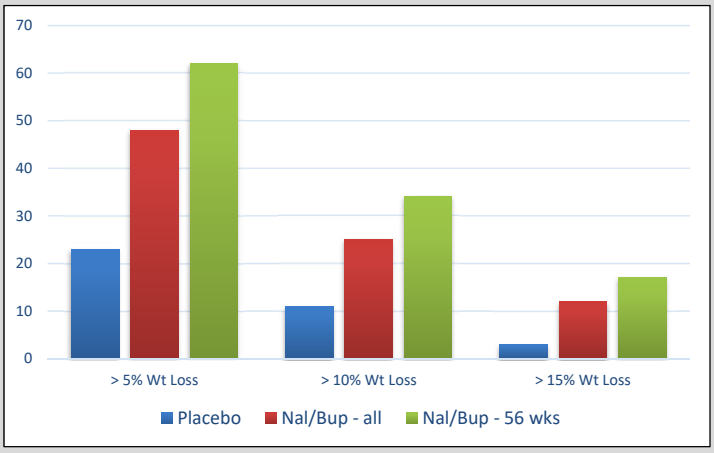
Lancet 2011; 377: 1341–52

Phentermine/Topiramate

- Caution use in patients with uncontrolled hyperthyroidism, cardiac disease, kidney stones, glaucoma, or if on MAOIs
- Contraindicated in pregnancy – topiramate is teratogenic
- Renal dose adjustment, not to increase above 7.5/46mg dose



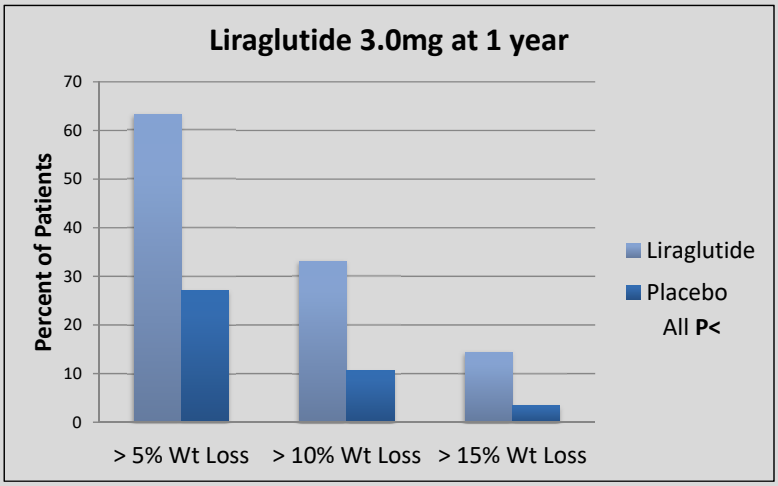
Bupropion/Naltrexone - Contrave



Lancet 2010; 376: 595–605 – correction published Oct 10, 2010 at Lancet.com

- Bupropion has combined effects on appetite (mild) and cravings. Naltrexone acts centrally on hypothalamus to potentiate appetite reduction.
- Dose is titrated weekly until week 4 (final dose is 2 pills twice a day)
- Caution in patients with history of seizure, substance use (alcohol or opioids), anorexia or bulimia, uncontrolled HTN, glaucoma or on MAOIs

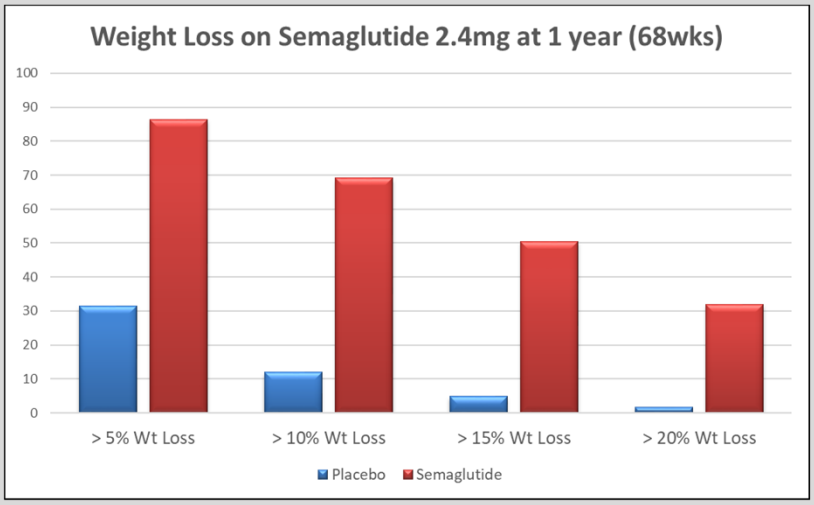
Liraglutide 3.0mg - Saxenda



- GLP-1RA – works in the gut to slow gastric emptying and centrally to reduce appetite
- Dose is given daily, titrated by 0.6mg per week to 3.0mg
- Contraindicated in patients with family history of MEN-2, personal or family history of medullary thyroid cancer, and pregnancy

N Engl J Med 2015;373:11-22.

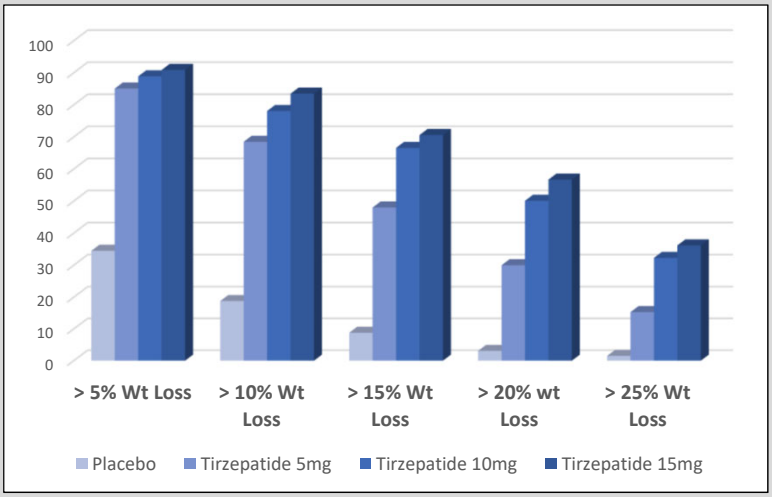
Semaglutide 2.4mg - Wegovy



- GLP-1RA – effects on gut and CNS to reduce appetite and improve satiety
- Dose is given weekly, starts at 0.25mg and increases monthly to 0.5mg, 1mg, 1.7mg, and 2.4mg
- Contraindicated in patients with family history of MEN-2, personal or family history of medullary thyroid cancer, and pregnancy

N Engl J Med 2021;384:989-1002.

Tirzepatide – not yet FDA approved



- New agent, dual GLP-1RA and GIP agonist
- Dosed weekly, begins with 2.5mg, increases monthly 5mg, 7.5, 10, 12.5, and 15mg
- Slightly more pronounced GI side effects
- Very impressive weight loss

N Engl J Med 2022;387:205-16.

Drug	Weight Loss Above Placebo	Pluses	Minuses
Phentermine[1]	3.6 kg (7.9 lbs) in 2-24 weeks	Inexpensive, greater weight loss	No long term data, side effects
Orlistat[1]	2.9-3.4% (6.5-7.5 lbs)	Non-systemic, long term data, inexpensive OTC	Side effects, less weight loss
Phen/Top[1]	14.5 lbs (low dose) 18.9 lbs (high dose)	Robust weight loss, long term data	Teratogenic, cost
Bup/Nal[1]	6.3kg (~13 lbs)	Greater weight loss, food addiction(?)	Side effect profile, cost
Liraglutide[1]	5.6kg (12.3 lbs)	Side effect profile, long term data, CVOT data (?)	Injectable, cost
Semaglutide[2]	12.7 kg (28 lbs)	Side effect profile, long term data, CVOT (?)	Injectable, cost
Tirzepatide[3]	12.5 kg (27.4 lbs) – 5mg 17.2 kg (37.8 lbs) – 10mg 18.7 kg (41 lbs) – 15mg	Significant proportion meeting ≥15% weight loss	NOT FDA APPROVED yet

[1]J Clin Endocrinol Metab, February 2015, 100(2):342–362 [2]N Engl J Med 2021;384:989-1002. [3]N Engl J Med 2022;387:205-16.

Medications that Can Cause Weight Gain

- Anti-depressants
  - Avoid paroxetine, amitriptyline, nortriptyline, venlafaxine, and duloxetine
  - Better choices are bupropion, fluoxetine, sertraline, citalopram, or escitalopram
- Anti-epileptics
  - Avoid valproate and **gabapentin**
  - Better choice is carbamazepine
- Anti-psychotics
  - Choose aripiprazole or ziprasidone
  - Set expectations with patient, decision to initiate medicine should be shared between doctor and patient.
- Diabetes medicines
  - Insulin, Sulfonylureas, TZDs, glinides
- Recommend concomitant use of Metformin, pramlintide, or GLP-1 agonists/analogs
- Recommend use of ACE-inh, ARBs, and Calcium Channel Blockers over Beta-blockers (non-selective) for HTN
- Choose NSAIDs and DMARDs over glucocorticoids in patients with arthritis.
- **Average weight gain with glucocorticoids approximately 4-8%**

J Clin Endocrinol Metab, February 2015, 100(2):342–362

A note on schedule IV in Ohio

- Phentermine alone and the combination phentermine-topiramate fall under schedule IV
- Prescribing laws exist when it comes to weight loss medications and differ between short term and long term anorexiants
- Prescribers should be familiar with these prescribing laws – which impact timing of prescriptions, follow-up visits, and potential for refills

http://www.justice.gov/dea/druginfo/ds.shtml

Non Pharmacological Therapy

Intragastric Balloons

- Approved for use in patients with **BMI 30-40**

- **Orbera** – in two RCT (66 & 128 enrollees), patients using the IGB for **6 months** achieved weight loss of 14.2% vs. 4.8% in the control (18.2 kg vs 6 kg in the control). In long term follow-up, mean weight regain was about half of the initial weight lost.
- **ReShape Duo** (dual balloon system) – REDUCE trial enrolled 326 subjects, of those eventually 264 opted for balloon placement. Early retrieval occurred in 9.1%. Those with IGB lost 7.6% vs 3.6% in the control group. Approved for use up to **6 months**.
- **Obalon** (ingestible) – can place up to 3 balloons prior to removal (**3-6 months** later). Initial study with 17 subjects with a mean BMI of 31 (44 attempted balloons), treated for 12 weeks – lost median 5kg (no control).

Hurt, et al. Novel Nonsurgical Endoscopic Approaches for the Treatment of Obesity. Nutrition in Clinical Practice. Volume 32 Number 4, August 2017 493–501

Intragastric Balloons

- Contraindicated in patients with documented history of reflux esophagitis, those taking blood thinners, or prior bariatric surgery.
- Most common side effects:
  - Nausea
  - Vomiting
  - Abdominal pain
- Rare side effects:
  - Gastric ulcers
  - Duodenal blockage
  - Pancreatitis

Hurt, et al. Novel Nonsurgical Endoscopic Approaches for the Treatment of Obesity. Nutrition in Clinical Practice. Volume 32 Number 4, August 2017 493–501

Duodenal jejunal bypass sleeve

- Endoscopically placed device consisting of the sleeve that is deployed with an anchor that sits at the duodenal bulb.
- Bile and pancreatic enzymes pass round the sleeve and nutrients then mix and are digested further down similar to a gastric bypass.
- Small studies show 10-12 kg weight loss at 12-24 weeks (can be used up to 1 yr)
- Significant decreases in A1C
- Increases in GLP-1
- Currently investigational approval
- Side effects (3-5%):
  - Pain
  - Nausea/vomiting
  - Potential for migration
  - GI bleeding
  - Sleeve obstruction
- Rare side effects (all < 0.5%):
  - Cholangitis
  - Liver abscesses
  - Acute cholecystitis
  - Esophageal perforation

Hurt, et al. Novel Nonsurgical Endoscopic Approaches for the Treatment of Obesity. Nutrition in Clinical Practice. Volume 32 Number 4, August 2017 493–501

Aspiration Therapy (AT)

- Approved for patients with BMI 35-55 who have failed prior therapy
- Endoscopically placed gastrostomy tube – siphon assembly allows for aspiration of gastric contents 20 minutes post-meal
- Instill 150-200 ml of water and repeat until no food particles are retrieved
- Trial leading to FDA approval included 207 subjects, BMI 35-55 followed for 52 weeks
  - 58.6% of the AT group vs 15.3% of lifestyle group reached >25% excess weight loss (preset goal)

Hurt, et al. Novel Nonsurgical Endoscopic Approaches for the Treatment of Obesity. Nutrition in Clinical Practice. Volume 32 Number 4, August 2017 493–501

Take home points

- Weight loss (meaningful) is a LONG TERM process and requires a multidisciplinary approach.
- Lifestyle modifications are the basis of any successful weight loss program.
- Medications are available to help patients adhere to a diet and exercise program.
- Several non-surgical options have recently been approved.
- Bariatric surgery remains most effective therapy, although new medications are emerging with 20% or higher total body weight loss.

- Good resource: http://obesity.aace.com/obesity-algorithm#/start