Riding the GLP1 Wave: Pharmacological Weight Management & The Role of the Pharmacist

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COI/ Disclosure Statement

- Dr. Amering and Dr. Cabral have no conflicts to disclose

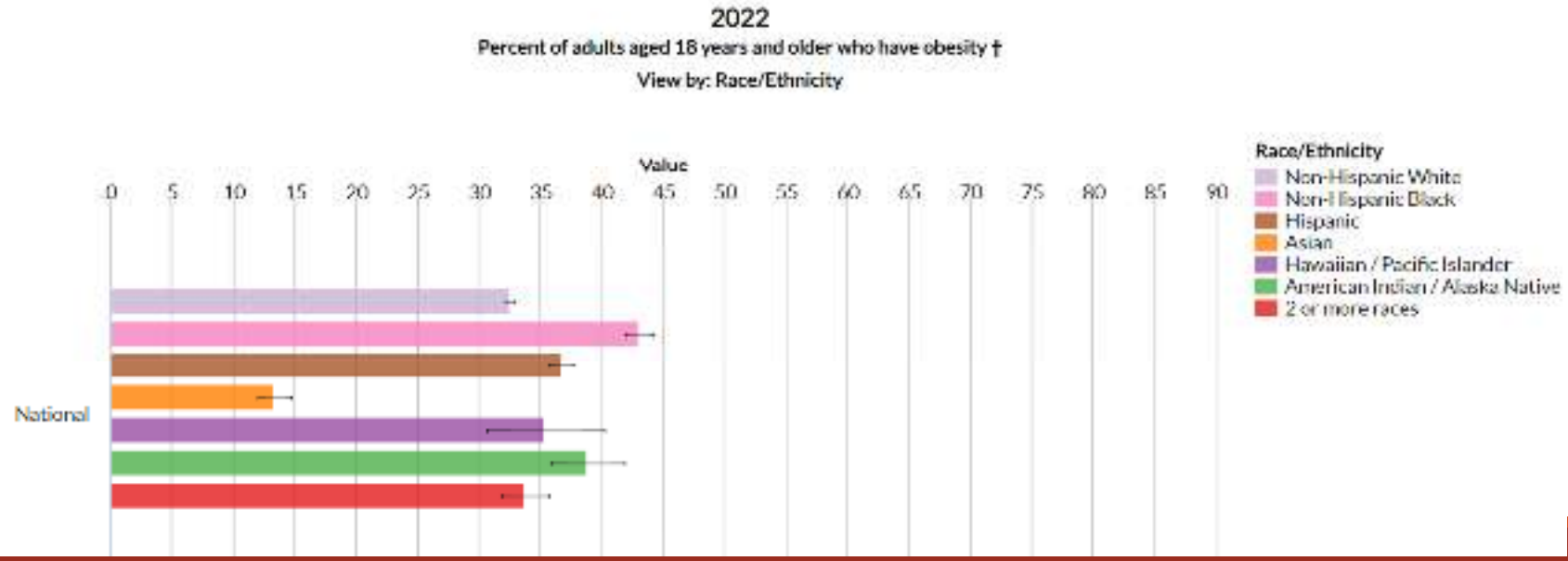
Objectives

1. Summarize pathophysiology & epidemiology related to obesity
2. Evaluate the evidence of glucagon-like peptide 1 (GLP-1) agonists in the management of obesity and its associated comorbidities
3. Examine case examples and management of GLP-1 agonist related adverse effects
4. Describe the role of the pharmacist in obesity management and the integration of pharmacy interventions as part of Comprehensive Medication Management service

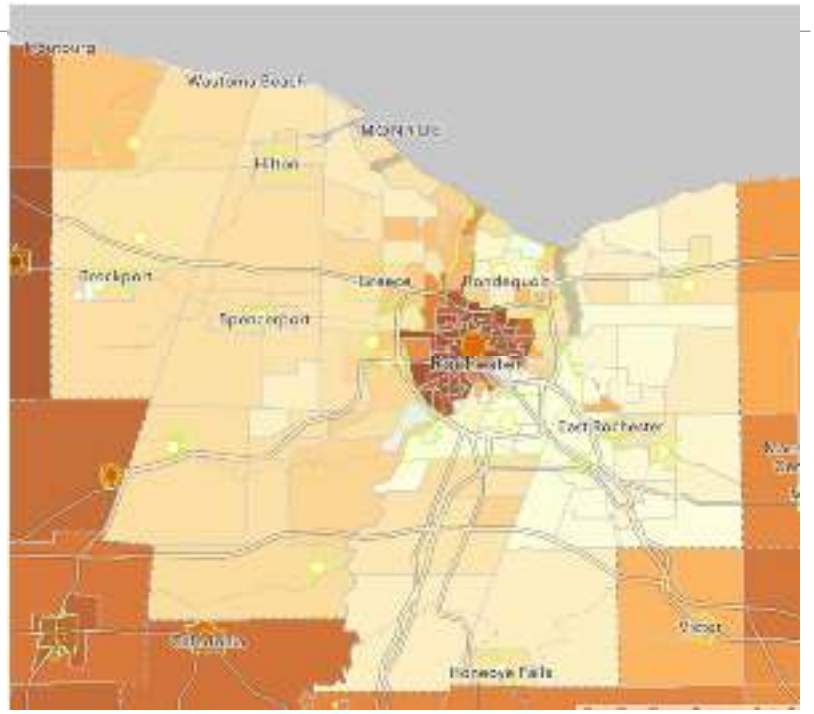
Obesity: Stats

CDC

- Prevalence of obesity 2017-March 2020 was 41.9% (up from 30.5%)
- Severe obesity from 4.7% to 9.2%

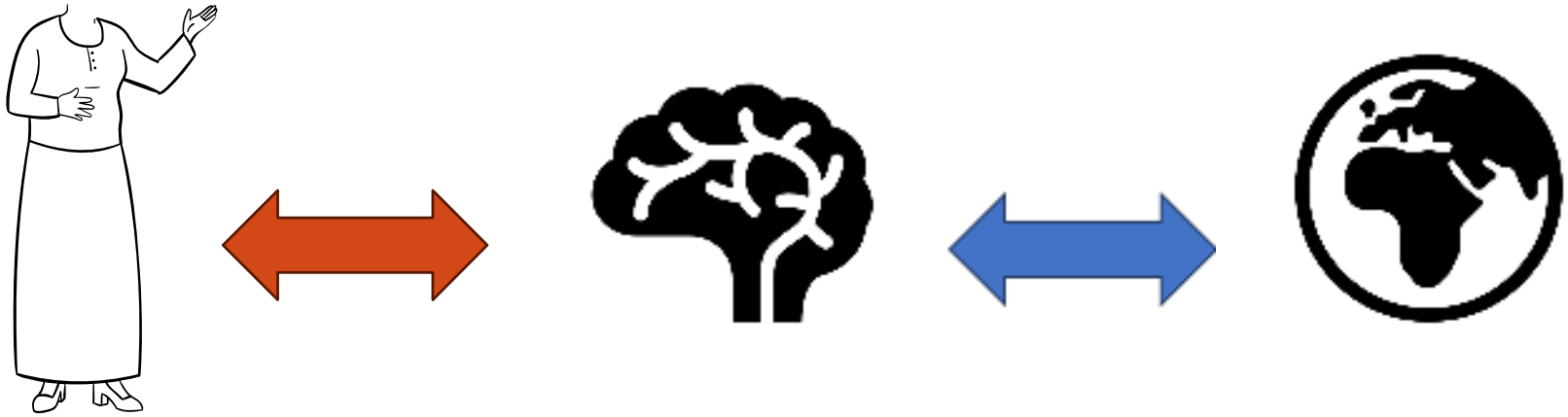


Stats



CDC PLACES https://arcg.is/185bTG0 . Accessed 3/21/2024

Bio-Psycho-Social model



Biological

Calories in > calories out = weight gain

Right?

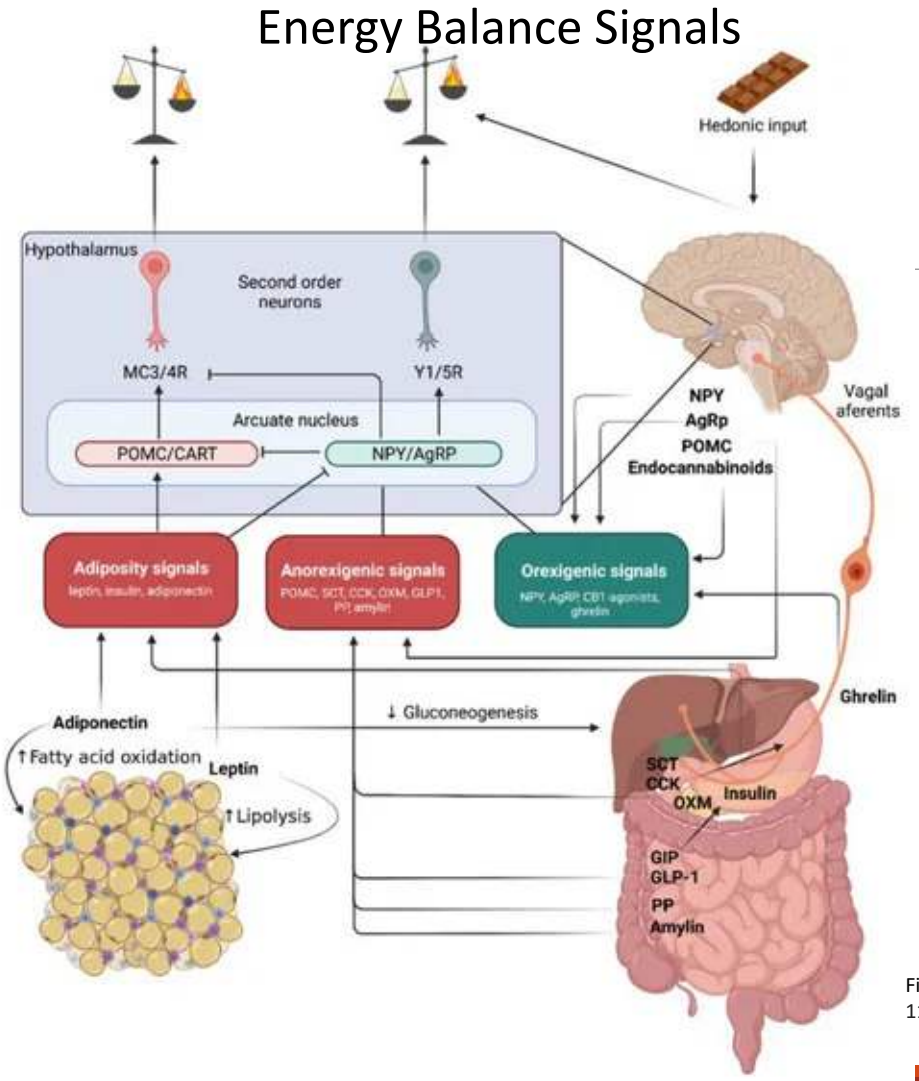


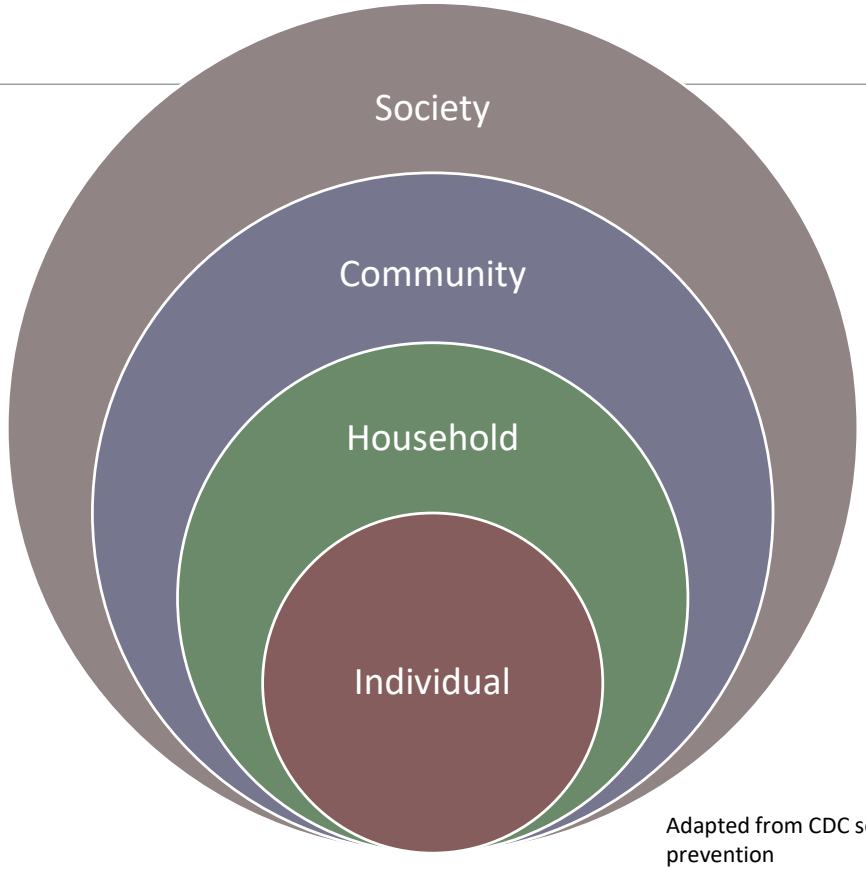
Figure 1. Biomolecules. 2021; 11(10):1426

Psychological

Trauma	• Systemic inflammation • Higher HOMA-IR
Mental health conditions	• Impaired self-care abilities • Side effect of medications
Emotions	• Family cues • Relationship with foods

Experimental Neurology. May 2019. Volume 315: 15-20, Psychiatry Research 142 (2006) 31–37, Nutr J 17, 93 (2018), Food Quality and Preference. Jan 2009. 20(1):62-68, New York Acadmy of Medicine. November 1957. 33(11): 771-782

Social



Adapted from CDC social-ecological model framework for prevention

Kious B. UCLA Nutrition Noteworthy. 2002. 5(1), Mackenback JD. Social, Economic, Physical Environmental Contributors to Obesity Among Adults. Handbook of Obesity Treatment, second edition.

Audience Question

Which of the following contribute to increase weight and disordered metabolism in those with obesity?

a) Decreased response to leptin
b) Increase in adreno-cortisol response in those with history of trauma
c) Decrease in caloric expenditure related to shifting evolutionary responsibilities
d) All of the above

Treatment

Multi-factorial

- Diet changes
  - Nutrient restriction
  - Time restriction
  - Portion restriction
- Physical activity
  - Minimum of 30 minutes of moderate physical activity 5 days per week
  - Strength training 2 to 3 times per week
- Pharmacotherapy
  - BMI ≥ 27 kg/m^2 and comorbidities
  - BMI ≥ 30 kg/m^2
- Surgery

GLP-1 Mechanism of Action

Glucagon-like Peptide 1(GLP1) and Glucose-dependent insulinotropic polypeptide (GIP)

- GLP1
  - Increase insulin section postprandially
  - Suppression of glucagon secretion
  - Released from L cells in small intestine
    - Slows gastric emptying
- GIP
  - Increase glucagon secretion in low glucose concentrations
  - Increased insulin-stimulated glucose transport and fatty acid synthesis

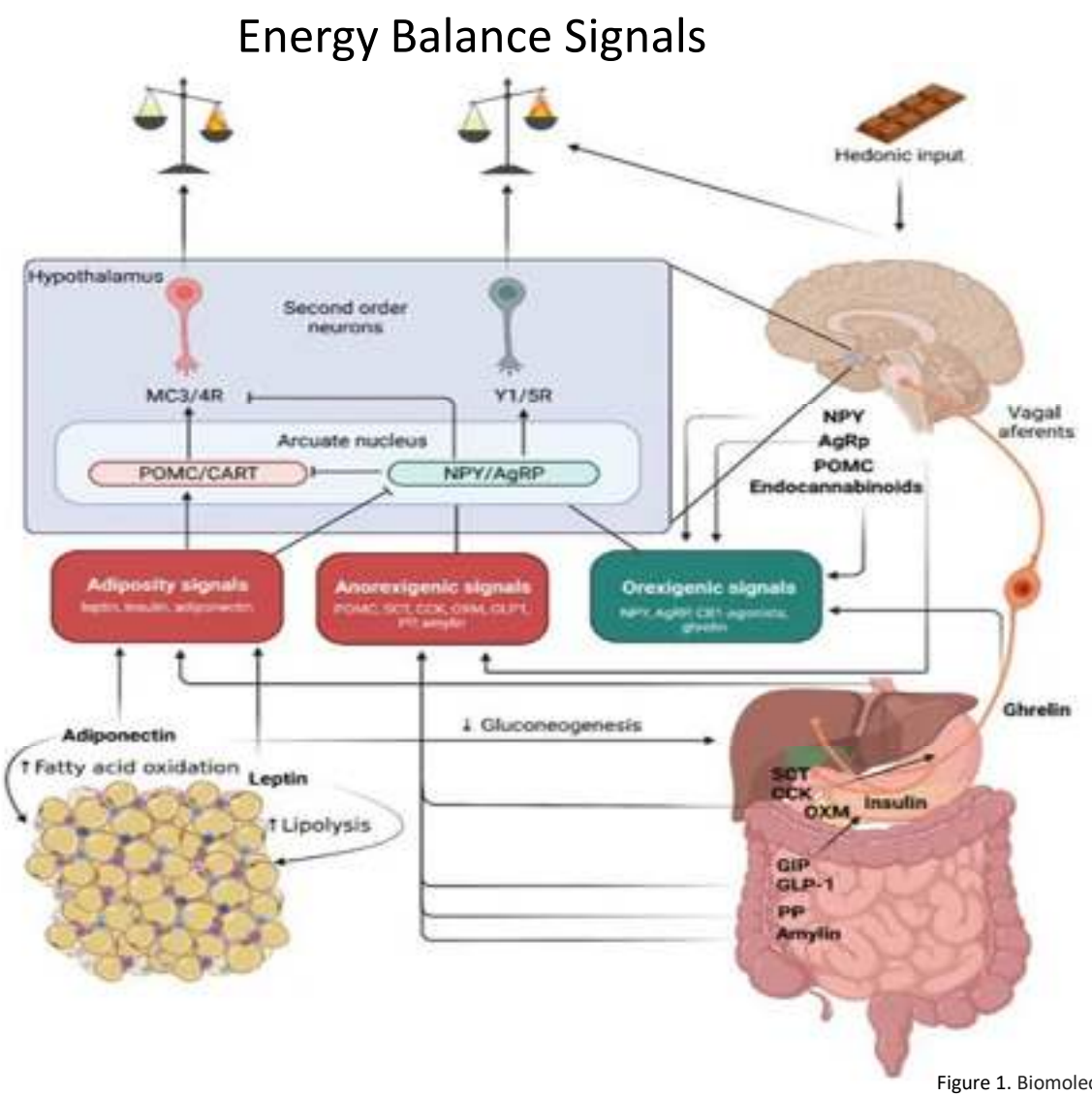


Figure 1. Biomolecules. 2021; 11(10):1426

Receptor effects

- GLP1
  - Hypothalamus
    - Binds to specific receptors in arcuate nucleus that result in increase satiety and decreased hunger
  - Hindbrain
    - Activates certain glutaminergic and GABAergic neurons resulting in decreased food intake
  - Hippocampus
    - Reduction in hunger/desire for food

Adv Ther 38, 2821–2839 (2021)

Figure 1. Representative targets for GLP-1 action and sites of GLP1R expression within the nervous system, and consequences of GLP-1 therapy in people with obesity

Audience Question

GLP1 activation in the hippocampus induces the anorexic response.

a. True

b. False

Clinical Effects

Trial	Intervention	Population	Results
SCALE Pi-Sunyer 2015	Liraglutide 3 mg (n= 2487) vs placebo (n = 1244) for 56 weeks	Prediabetes + BMI > 30 or 27 and untreated dyslipidemia or HTN	Mean weight loss from baseline: -8.0% vs -2.6% For liraglutide: 27.1% lost 5% TBW 10.6% lost 10% TBW
STEP 3 Wadden 2021	Semaglutide 2.4 mg (n = 407) vs placebo (n = 204) for 68 weeks	BMI > 30 or 27 and at least 1 comorbidity	Mean weight loss from baseline: -16.0% vs -5.7% 86.6% lost 5% TBW vs 47.6%
STEP 5 Garvey 2022	Semaglutide 2.4 mg (n = 152) vs placebo (n = 152) for 104 weeks	BMI > 30 or 27 and at least 1 comorbidity	Mean weight loss from baseline: -15.2% vs -2.6% 77.1% lost 5% TBW vs 34.4%
SURMOUNT-1 Jastreboff 2022	Tirzepatide 5, 10, 15 mg vs placebo for 72 weeks (n= 2539)	BMI > 30 or 27 and at least 1 comorbidity	Mean weight loss from baseline: 5 mg: -15.0% 10 mg: -19.5% 15 mg: - 20.9% Placebo -3.1% Those achieving 20% TBW loss: 10 mg: 50% 15 mg: 57% Placebo: 3%
Surmount-4 Aronne 2023	N = 783 completed 36 week lead-in period on tirzepatide 10 or 15 mg Then randomized to Tirzepatide (n = 335) vs placebo (n = 335) for 52 weeks	BMI > 30 or 27 and at least 1 comorbidity	36 week lead in period: Total mean weight loss 20.9% Weeks 36 to 88 mean percent change in weight Tirzepatide: -5.5 % Placebo 14.0% 80% of those receiving tirzepatide for 88 weeks maintained weight loss vs 16.6% of placebo

Evidence in Comorbidities

Trial	Intervention	Population	Results
SCALE Sleep Apnea Blackman 2016	Change in AHI scores in adults with moderate to severe OSA treated with liraglutide (n=180) vs placebo (n=179) over 32 weeks	Non-diabetic with moderate to severe apnea-hypoapnea index (AHI) scores	Reduction from baseline: -12.2 events/h vs -6.1 events/h (95%CI -11.0 to -1.2)
NN9931-4296 Newsome PN 2021	72 week phase 2 study comparing once daily SQ semaglutide doses 0.1, 0.2, or 0.4 mg vs placebo to evaluate resolution of NASH without worsening of fibrosis	320 patients with biopsy confirmed NASH and liver fibrosis 230 had fibrosis stage 2 or 3)	Primary outcome: 0.1 mg – 40% 0.2 mg – 36% 0.4 mg – 59% Placebo – 17% ($p<0.001$ for 0.4 mg).

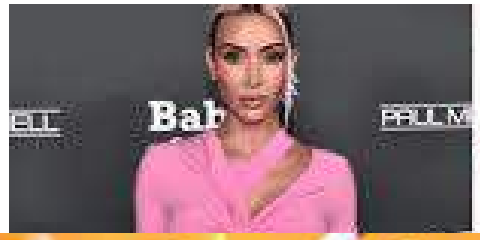
The SELECT Trial

Intervention	Population	Primary outcome	Secondary outcomes and adverse events
• Event driven superiority trial • 1:1 semaglutide 2.4 mg (n = 8803) vs placebo (n = 8801) • Primary outcome: composite of death from cardiovascular causes, nonfatal MI, nonfatal CVA • Secondary: hierarchical order 1. death from cardiovascular causes 2. composite heart failure 3. death from any cause	• 61 y/o • 72% male • 84% white • BMI 33.3 kg/m2 • 67% had A1C > 5.7% • 67% MI only • 17% stroke only • 2 or more 8.2%	Mean duration of exposure for semaglutide 34 months and placebo 39 months Semaglutide: 569/8803 (6.5%) Placebo: 701/8801 (8.0%) HR 0.80; 95%CI 0.72 to 0.90) NNT 67	Death from cardiovascular causes: 2.5% vs 3.0%; HR 0.85 (95% CI 0.71 to 1.01) Leading to discontinuation of product: GI 10% vs 2% Metabolism and nutrition 1.2% vs 0.3% General disorders and administration site conditions 1.2% vs 0.5%

N Engl J Med 2023;389:2221-32. DOI: 10.1056/NEJMoa2307563

Real World Application

Who Do We Prescribe These Meds For?



Who To Initiate GLP1-Agonists in?

- Adjunct to reduced calorie diet & increased physical activity for chronic weight management in adults with:
  - BMI ≥ 30 kg/m^2 OR
  - BMI ≥ 27 kg/m^2 in the presence of at least one weight-related comorbid condition (e.g. hypertension, type 2 diabetes or hyperlipidemia)

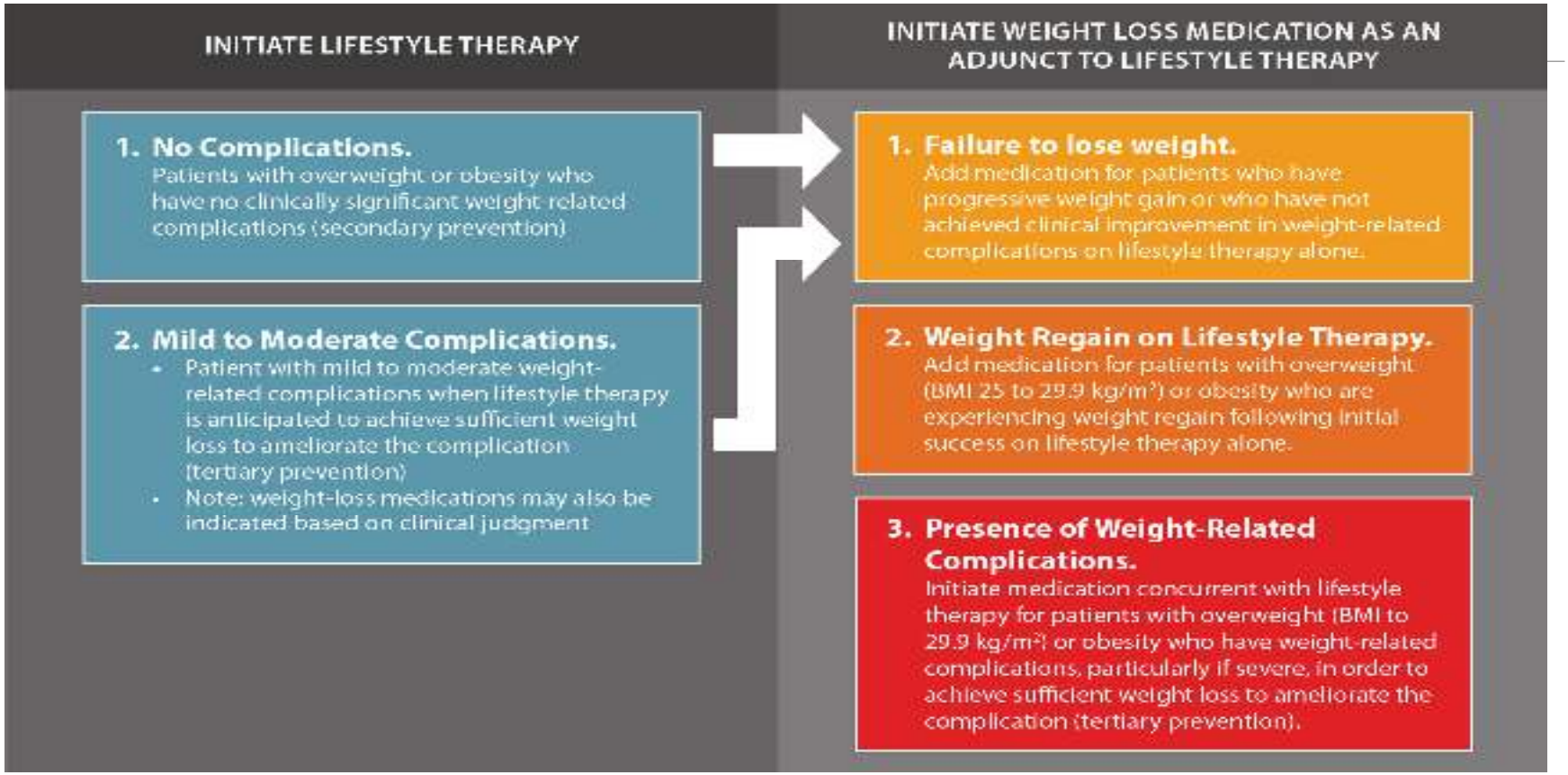
- *Wegovy (semaglutide) specific:*
  - *in combination with a reduced calorie diet & increased physical activity: to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight*
  - *pediatric patients ≥ 12 years of age with an initial BMI at the 95th percentile or greater for age and sex*

Weight Loss Goals of Pharmacologic Therapy

Medical Comorbidity	Weight-loss goal
Metabolic Syndrome	10%
Prediabetes	10%
T2DM	5-15%
Dyslipidemia	5-15%
Hypertension	5-15%
Obstructive sleep apnea	7-11%
Polycystic ovary syndrome	5-15%

Garvey WT, et al. AACE/ACE Obesity Clinical Practice Guidelines. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR MEDICAL CARE OF PATIENTS WITH OBESITY. Endocr Pract. 2016 Jul;22 Suppl 3:1-203. doi: 10.4158/EP161365.GL.

Who To Initiate GLP1-Agonists in?



Garvey WT, et al. AACE/ACE Obesity Clinical Practice Guidelines. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR MEDICAL CARE OF PATIENTS WITH OBESITY. Endocr Pract. 2016 Jul;22 Suppl 3:1-203. doi: 10.4158/EP161365.GL.

Lifestyle Interventions

Low Calorie Diets

- WOMEN
  - 1200-1500 kcal/day
- MEN
  - 1500-1800 kcal/day

Physical Activity

- Aerobic activity: goal of ≥ 150 min/week of moderate exercise over 3 – 5 daily sessions/week
- Resistance/muscle training: goal >2 days per week
- NEAT (non-exercise activity thermogenesis)
  - Important component of total daily energy expenditure

FDA-Approved GLP-1 Agonists for Weight Management

Drug	FDA Approval Year	Administration	Supply Shortage?
Saxenda (liraglutide)	2014	Subcutaneous, once daily	Yes!
Wegovy (semaglutide)	2021	Subcutaneous, once weekly	Yes!
Zepbound (tirzepatide)	2023	Subcutaneous, once weekly	Yes!

GLP1-Agonist: Contraindications

- Personal or familial history of medullary thyroid carcinoma
- Multiple Endocrine Neoplasia syndrome (MENS) type 2
- Pregnancy (may cause fetal harm, discontinue once pregnancy recognized)

GLP1-Agonist: Warnings

- History of pancreatitis
- History of gallstones
- Reduced efficacy of oral hormonal contraception*

Lisco G, De Tullio A, Disoteo O, Piazzolla G, Guastamacchia E, Sabbà C, De Geronimo V, Papini E, Triggiani V. Glucagon-like peptide 1 receptor agonists and thyroid cancer: is it the time to be concerned? Endocr Connect. 2023 Sep 27;12(11):e230257. doi: 10.1530/EC-23-0257.

GLP1-Agonist: Common Adverse Effects

	Placebo (n= 1261) vs. Wegovy 2.4 mg (n=2116)	Placebo (n=958) vs. Zepbound 15 mg (n=941)
Nausea	16% vs. 44%	8% vs. 28%
Diarrhea	16% vs. 30	8% vs. 23%
Vomiting	6% vs. 24%	2% vs. 13%
Constipation	11% vs. 24%	5% vs. 11%
Abdominal pain	10% vs. 20%	5% vs. 10%
Headache	10% vs. 14%	--
Fatigue	5% vs. 11%	3% vs. 7%
Dyspepsia	3% vs. 9%	4% vs. 10%
Injection site reaction	--	2% vs. 8%

Wegovy [prescribing info]. Plainsboro, NJ: Novo Nordisk Inc. 2024.
Zepbound [prescribing info]. Indianapolis, IN: Eli Lilly Co. 2024

Patient Case #1

- 59 yo F with ASCVD- h/o MI and DES to LAD, HTN, hyperlipidemia, paroxysmal atrial fibrillation, hypothyroidism and obesity- class 2.

- Height 64”, weight 217 lb, BMI 37.2

- She recently started Wegovy and just finished her 3rd dose of 0.25 mg. She calls with complaints of constipation and stomach cramping/bloating. She reports that she has not had a bowel movement in 3 days, which is unusual for her.

Audience Question

What do you recommend for this patient's Wegovy therapy?

a) Discontinue Wegovy
b) Discontinue Wegovy and start Zepbound
c) Continue Wegovy at 0.25 mg once weekly
d) Increase Wegovy to 0.5 mg once weekly

Patient Case #1: Management

1. Treat Constipation

- Eat foods high in fiber: fruits (pears, prunes), cereals, and vegetables
- Drink 2-3 L of non-alcoholic fluids (water, juices) each day; unless told otherwise by your doctor
- Exercise 30 minutes most days of the week, as tolerated
- **OTC Medications may be used***:*
  - Prebiotic Dietary Fiber Supplement (Benefiber®) or Psyllium Fiber Supplement (Metamucil®)
  - Polyethylene Glycol (MiraLAX®)
  - Senna (Senokot®) or Bisacodyl (Dulcolax®)
  - Docusate sodium (Colace®)
  - Glycerin suppository
  - Magnesium hydroxide (Milk of Magnesia®)

2. Determine dosing recommendation

Wegovy (semaglutide) Dosing

Patient Case #2

- 67 yo M HTN, hyperlipidemia, T2DM for 15 years, obstructive sleep apnea and obesity- class 3

- Height 68”, weight 260 lbs, BMI 39.5

- Patient comes in for a follow up appointment while on Zepbound (tirzepatide) 7.5 mg dose; he started therapy 11 weeks ago and has just one more 7. 5 mg dose left.

- He has lost 25 lbs (8.7%) since starting the medication

- Reports that he has a decreased appetite and is not hungry at all. He often will just eat one meal a day and has to force himself to eat. He also notes that at times when he eats his big meal, he has some heartburn and nausea.

Patient Case #2: Management

1. Discuss decreased appetite
   - Ensure adequate caloric/healthy nutrient intake
2. Manage heartburn & nausea
   - H2 blocker, PPI
   - Ondansetron
   - Food in stomach; correlate with foods?
   - Tums, Pepto Bismol, GasX?
3. Determine Dosing recommendation?

Zepbound (tirzepatide) Dosing

GLP-1 Agonists: Adverse Effects Management Considerations

Other side effects:

- Hair loss
- Hypoglycemia

Switching pharmacotherapy agents?

- Another GLP1-RA?
  - Semaglutide?
- Oral options?
  - Contrave (bupropion/naltrexone)
  - Qysmia (Phentermine/Topiramate)
  - Phentermine
  - Orlistat

Weight Re-gain?

STEP-1 Trial Extension	- 327 pts stopped treatment (semaglutide 2.4 mg vs. placebo + lifestyle changes) at 68 weeks and followed until week 120 - Week 0-68: semaglutide mean weight loss 17.3% (SD 9.3%) vs. placebo 2% (SD 6.1%) - Week 120: 11.6% (SD 7.7) (semaglutide) and 1.9% (SD 4.8) (placebo) percentage points of lost weight was regained - Cardiometabolic improvements seen in first 68 weeks reverted towards baseline - 1 year after withdrawal of Wegovy and lifestyle interventions, pts regained 2/3 of their prior weight loss with similar changes in cardio metabolic variables
SURMOUNT-4	- 670 pts on tirzepatide 10 or 15 mg at 36 weeks were randomized to tirzepatide vs. placebo for 52 weeks - In 36 week lead in period, mean weight reduction of 20.9% - Mean % change from week 36-88: -5.5% with tirzepatide vs. 14% with placebo (diff -19.4% (95%CI -21.2% to -17.7%) p<0.001) - 89.5% of pts on tirzepatide at 88 weeks maintained at least 80% of weight loss vs. 16.6% on placebo (p<0.01)

Wilding JPH et al. STEP1 trial extension. Diabetes Obes Metab.2022;24:1553-1564.
Aronne LJ et al. SURMOUNT-4 Randomized Clinical Trial. JAMA 2024;331(!)38-48.

Meds in Pipeline

Drug Name	Manufacturer	Mechanism	Status
Semaglutide oral	Novo Nordisk	GLP-1 RA	Phase III
Cagrilintide Semaglutide	Novo Nordisk	Amylin analog/ GLP 1 RA	Phase III
Retatrutide	Eli Lilly	GLP-1 RA, GIP-RA	Phase III
Orforglipron	Eli Lilly, Chugai	GLP-1 RA	Phase III
Survodutide	Boehringer Ingelheim	GLP-1 RA	Phase III
Danuglipron	Pfizer	GLP-1 RA	Phase II
Maridebart cafraglutide	Amgen	GLP-1RA/ gastric inhib polypeptide receptor	Phase II
Bimagrumab IC	Novartis	Activin receptor antagonist	Phase II

Clinical Pharmacy Services

- Well-established utility in the ambulatory care setting
- Improves medication adherence, decrease medication-related problems, and improve the patient's overall comprehension of their health care
- Collaborative practice models, allowing pharmacists to manage medications based on pre-specified protocols, have shown to contribute to successful disease-state management as evidenced by improvements in clinically meaningful endpoints (e.g., blood glucose, blood pressure, lipids, INR)
- Apply to weight/ obesity management?

Capital Cardiology Associates (CCA) Metabolic Services

- Multidisciplinary approach
  - Dietitians
  - Capital Bariatrics
  - Health Coach
  - Clinical Pharmacy Team
- ‘Pharmacological Weight Loss Per Clinical Pharmacy’ consult
  - Referral in collaboration with cardiologist
  - Developed May 2021
  - Currently managing ~1020 patients

CCA 'Pharmacological Weight Loss Per Clinical Pharmacy'

Initial visit: 45 minutes

- Review cardiac history and medication review/reconciliation
- Introduce services
- Discuss lifestyle interventions & goals
- Discussed pharmacotherapy
- Set up for chronic care management/monitoring

Follow up visit: 15 minutes

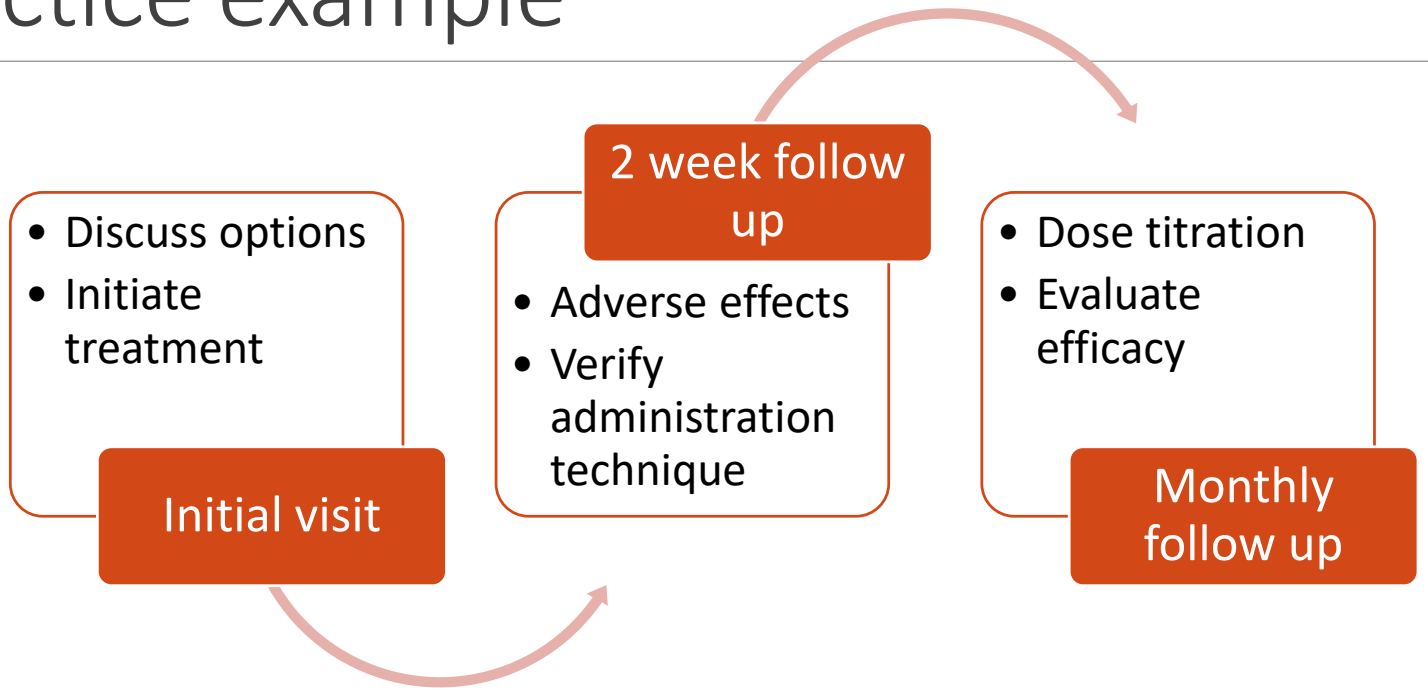
- Every 3-4 weeks per telephone pharmD or RN
- Every ~8 weeks office visit
- Once on maintenance dose every ~12 weeks

Shared decision making

Insurance/third-party assistance in medication access

Monitoring/follow up- labs, tolerability

Manhattan Square Family Medicine practice example




QUESTIONS