Clinical Pharmacy Services - MTM

Pharmacotherapy for Weight Loss

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Objectives

- Provide an overview for weight loss and obesity
- Cover pharmaceutical weight loss agents
  - Mechanisms of action
  - Adverse effects
  - Agent benefits
- Summarize the information for use in clinical applications

Overview

Epidemiology

- **In 2013, the American Medical Association (AMA) designated obesity as a chronic disease**
- The prevalence of obesity in the United States has dramatically increased
  - 30.5% in 1999–2000 to 41.9% in 2019–2020

- Prevalence of obesity for young adults also increased
  - 6.2% in 1976–1980 to 33% in 2017–2018

- In adults the prevalence of obesity-related complications has also increased
  - Cardiovascular disease, stroke, type 2 diabetes mellitus (T2DM), nonalcoholic steatohepatitis, obstructive sleep apnea, osteoarthritis, and certain types of cancer
  - Contributing to high morbidity and mortality rates

Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. CMAJ. 2020;192(31):E875-E891. doi:10.1503/cmaj.191707

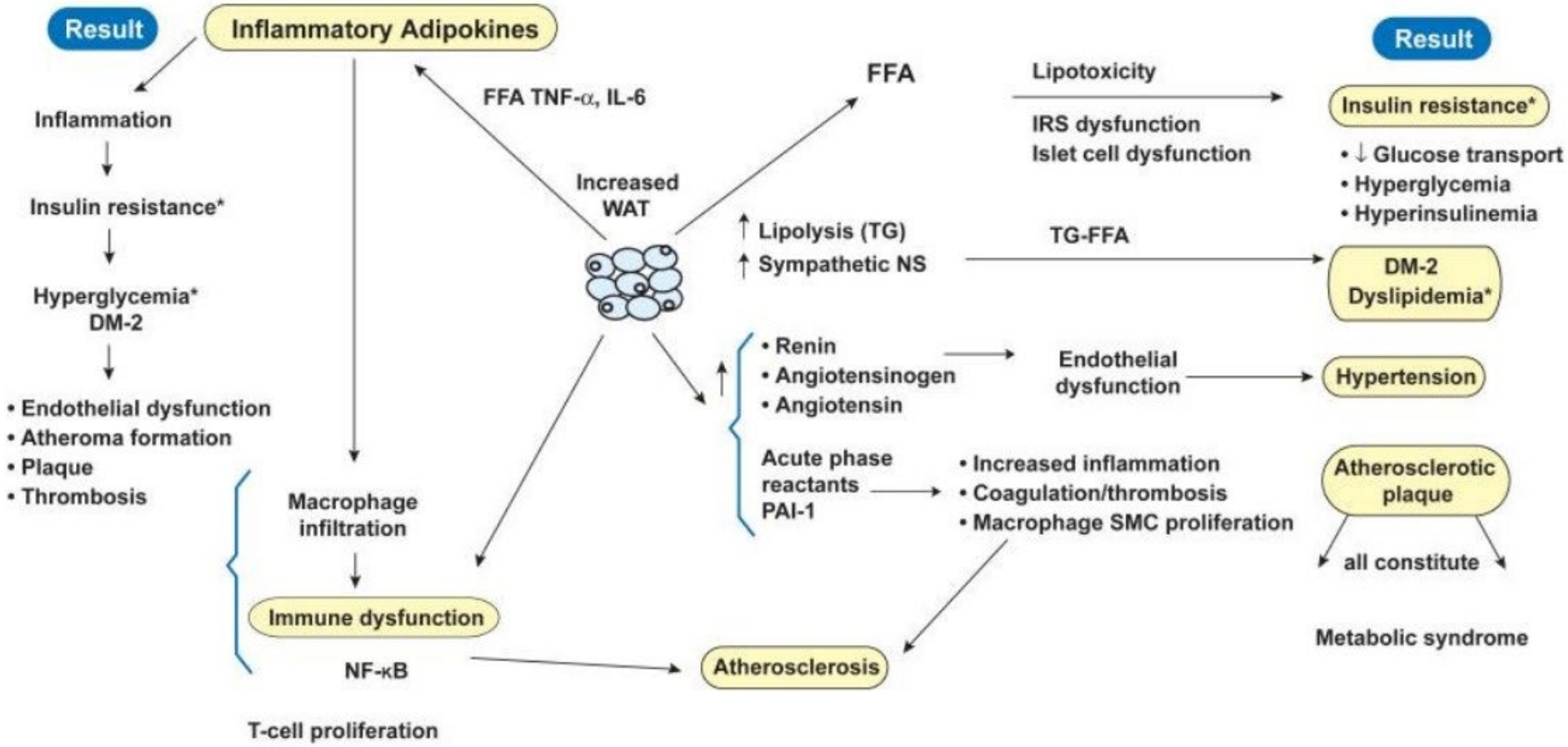
Physiology

- During starvation states adequate adipose and triacylglyceride storage is necessary for survival
  - However, excessive consumption of macronutrient-dense foods leads to excessive storage of fat, resulting in obesity

- Hyperlipidemia is caused by the liver's conversion of glucose to palmitate
  - This palmitate gets transported on VLDLs
    - VLDLs eventually become LDLs that are difficult for the body to metabolize
      - This feeds forward atherosclerosis, and other metabolic syndrome effects

Veiraiah A. Hyperglycemia, lipoprotein glycation, and vascular disease. Angiology. 2005;56(4):431-438. doi:10.1177/000331970505600411

The Pathophysiology of Obesity



Redinger RN. The pathophysiology of obesity and its clinical manifestations. Gastroenterol Hepatol (N Y). 2007;3(11):856-863.

Classifications

$$\text{BMI} = \frac{\text{Weight (in kilograms)}}{\text{Height}^2 \text{ (in meters)}}$$

- Weight classifications are based on BMI
  - BMI of less than 18.5 falls within the underweight range
  - BMI of 18.5 to <25 falls within the healthy weight range
  - BMI of 25.0 to <30 falls within the overweight range
  - **BMI of 30.0 or higher falls within the obesity range**

Defining adult overweight & obesity. Centers for Disease Control and Prevention. June 3, 2022. Accessed July 14, 2023. https://www.cdc.gov/obesity/basics/adult-defining.html

Obesity

- Obesity is subdivided into three categories:
  - Class 1: BMI of 30 to < 35
  - Class 2: BMI of 35 to < 40
  - Class 3: BMI of 40 or higher
    - Class 3 obesity can be categorized as “severe” obesity

Defining adult overweight & obesity. Centers for Disease Control and Prevention. June 3, 2022. Accessed July 14, 2023. https://www.cdc.gov/obesity/basics/adult-defining.html

Weight Related Comorbidities

- A high BMI or weight has a known relation to many comorbidities:
  - Cardiovascular diseases
    - HTN
    - Dyslipidemia
    - Stroke
    - Heart Failure
  - Type 2 Diabetes
  - Osteoarthritis
  - Obstructive Sleep Apnea

Cornier MA. A review of current guidelines for the treatment of obesity. Am J Manag Care. 2022;28(15 Suppl):S288-S296. doi:10.37765/ajmc.2022.89292

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TREATMENT

Treatment Goals

- Lower BMI to the acceptable range
  - Weight loss between 5% and 10% is enough to induce clinically relevant improvements in health risk factors

- Obesity is chronic in nature
  - Treatment plan must be long term
    - Personalized action plan
      - Practical and sustainable and addresses the drivers of weight gain

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Treatment Options

- Pharmaceutical weight loss agents

- Non-pharmacologic treatment
  - Nutrition and exercise
  - Psychological and behavioural interventions
  - Bariatric surgery

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General Requirements for Covered Treatment

- Drugs approved for weight management
  - BMI of ≥30
  - BMI ≥27 in the presence of weight-related comorbidities

- Surgery is only recommended when
  - BMI is ≥ 40
  - BMI ≥ 35 in the presence of weight-related comorbidities

Grunvald E, Shah R, Hernaez R, et al. AGA Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity. Gastroenterology. 2022;163(5):1198-1225. doi:10.1053/j.gastro.2022.08.045

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PHARMACEUTICAL AGENTS

Pharmaceutical Weight Loss Classes

- GLP-1 Agonists
- SGLT-2 Inhibitors
- Lipase Inhibitor
- Norepinephrine and dopamine reuptake inhibitor
  - May be used with an opiate antagonist
- Anorexiant
  - May be used with an anti-seizure agent

Aaseth J, Ellefsen S, Alehagen U, Sundfør TM, Alexander J. Diets and drugs for weight loss and health in obesity - An update. Biomed Pharmacother. 2021;140:111789. doi:10.1016/j.biopha.2021.111789

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Glucagon-like Peptide-1

GLP-1

GLP-1 Agonists

- Dulaglutide (Trulicity)
- Exenatide Extended Release (Bydureon BCise)
- Exenatide (Byetta)
- Tirzepatide (Mounjaro)
- Liraglutide (Victoza, Saxenda)
- Lixisenatide (Adlyxin)
- Semaglutide
  - Ozempic
  - Wegovy
  - Rybelsus

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Pharmacokinetics and Pharmacodynamics

- Mechanism of action: GLP-1 receptor agonists increase glucose-dependent insulin secretion
  - Decreases inappropriate glucagon secretion and slows gastric emptying
    - Also acts on regulation of appetite and caloric intake

- Side effects: severe nausea, vomiting, abdominal pain, diarrhea, and injection site reactions

Ard J, Fitch A, Fruh S, Herman L. Weight Loss and Maintenance Related to the Mechanism of Action of Glucagon-Like Peptide 1 Receptor Agonists. Adv Ther. 2021;38(6):2821-2839. doi:10.1007/s12325-021-01710-0

GLP-1s Approved for Weight Loss

- Semaglutide
  - Ozempic, Wegovy
    - Weeks 1 through 4: 0.25 mg once weekly
    - Weeks 5 through 8: 0.5 mg once weekly
    - Weeks 9 through 12: 1 mg once weekly
    - Weeks 13 through 16: 1.7 mg once weekly
    - Week 17 and beyond: 2.4 mg weekly

- Liraglutide
  - Victoza, Saxenda
    - Inject 0.6 mg once daily for 1 week
    - Increase by 0.6 mg daily at weekly intervals to a target dose of 3 mg once daily
    - Use maximum tolerated dose (< 3 mg/day) if goal weight loss is achieved on that dose

- Lixisenatide (Adlyxin)
  - Inject 0.6 mg once daily for 1 week
  - Increase by 0.6 mg daily at weekly intervals to a target dose of 3 mg once daily
  - Use maximum tolerated dose (< 3 mg/day) if goal weight loss is achieved on that dose

Smits MM, Van Raalte DH. Safety of Semaglutide [published correction appears in Front Endocrinol (Lausanne). 2021 Nov 10;12:786732]. Front Endocrinol (Lausanne). 2021;12:645563. Published 2021 Jul 7. doi:10.3389/fendo.2021.645563
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Weekly Injectables

- Dulaglutide (Trulicity)
  - Inject 0.75 mg once weekly
  - Increase to 1.5 mg once weekly after 4 to 8 weeks
  - Increase to 3 mg once weekly after at least 4 weeks on the 1.5 mg weekly dose
  - Maximum of 4.5 mg once weekly after at least 4 weeks on the 3 mg weekly dose

- Exenatide ER (Bydureon BCise)
  - Inject 2 mg weekly irrespective of meals

- Tirzepatide (Mounjaro)
  - 2.5 mg once weekly for 4 weeks, then increase to 5 mg once weekly
  - May increase dose in 2.5 mg/week increments every 4 weeks if needed to achieve glycemic goals
  - Maximum weekly dose of 15 mg

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Taken Daily

- Exenatide (Byetta)
  - Immediate release:
    - Inject 5 mcg twice daily
      - Within 60 minutes prior to morning and evening meals (≥ 6 hours apart)
    - Increase to 10 mcg twice daily after 1 month if needed to achieve goals
  - Extended release:
    - Inject 2 mg once weekly without regard to meals
- Semaglutide
  - Rybelsus
    - Administer ≥ 30 minutes before the first food, beverage, or other medication(s)
    - Take 3 mg by mouth once daily for 30 days
    - Increase to 7 mg by mouth once daily
    - Increase to 14 mg once daily after 30 days on the 7 mg dose if needed to achieve glycemic goals.
      - Note: The 3 mg daily dose is intended to reduce GI symptoms; it does not provide effective glycemic control

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The Effects of Liraglutide on Non Diabetic vs. Diabetic Patients

- Liraglutide (Non-Diabetic)
  - Liraglutide resulted in 3.4 to 6.1% difference in mean weight loss vs. placebo.
  - The proportion of subjects who lost ≥ 5% of baseline body weight was 50.5–73%.

- Liraglutide (Diabetic)
  - The difference in mean weight loss between the liraglutide and placebo-treated groups was < 5% after 1 year
  - The proportion of subjects who lost ≥ 5% of baseline body weight in the liraglutide group was > 35%, from 51.8 to 54.3%.

Jensterle M, Rizzo M, Haluzík M, Janež A. Efficacy of GLP-1 RA Approved for Weight Management in Patients With or Without Diabetes: A Narrative Review. Adv Ther. 2022;39(6):2452-2467. doi:10.1007/s12325-022-02153-x

The Effects of Semaglutide on Non Diabetic vs. Diabetic Patients

- Semaglutide (Non-Diabetic)
  - Semaglutide resulted in 10.3–17.4% difference in mean weight vs. placebo treatment.
  - The proportion of subjects who lost ≥ 5% of baseline body weight was 86.4–88.7%.
- Semaglutide (Diabetic)
  - Semaglutide resulted in 6.2% difference in mean weight loss vs. placebo.
  - The proportion of subjects who lost ≥ 5% of baseline body weight with semaglutide was 68.8%.

Jensterle M, Rizzo M, Haluzík M, Janež A. Efficacy of GLP-1 RA Approved for Weight Management in Patients With or Without Diabetes: A Narrative Review. Adv Ther. 2022;39(6):2452-2467. doi:10.1007/s12325-022-02153-x

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Sodium-glucose Co-transporter 2

SGLT-2

SGLT-2 Inhibitors

- Bexagliflozin (Brenzavvy)
  - 20 mg PO qAM, taken with or without food
- Canagliflozin (Invokana)
  - 100 mg PO QD before the first meal of the day
  - May increase to 300 mg PO QD
- Dapagliflozin (Farxiga)
  - 5 mg PO qAM, taken with or without food
- Empagliflozin (Jardiance)
  - 10 mg PO qAM, taken with or without food
  - May increase to 25 mg
- Ertugliflozin (Steglatro)
  - 5 mg PO qAM, taken with or without food
  - May increase to 15 mg once daily

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Pharmacokinetics and Pharmacodynamics

- Mechanism of action: inhibits SGLT-2, the transporter responsible for reabsorption of the majority of glucose from the renal glomerular filtrate in the renal proximal tubule
  - Inhibition reduces the renal reabsorption and renal threshold of glucose
    - Increases urinary glucose excretion
- Side effects: nausea, fatigue, DKA, polyuria, polydipsia, and xerostomia
- Usual Adult Dose for Obesity:
  - Not currently approved for weight loss

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LIPASE INHIBITOR

Orlistat (xenical)

- Mechanism of action: reversibly inhibits gastric and pancreatic lipases
  - The inactivation of lipases prevents the hydrolysis of triglycerides
    - Free fatty acids are not absorbed

- Side effects: pain or tenderness in the upper stomach, pale stools, dark urine; loss of appetite, nausea, unusual itching, unusual tiredness or weakness, or yellow eyes or skin

- Usual Adult Dose for Obesity: 120 mg orally three times a day with each main meal containing fat

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NOREPINEPHRINE AND DOPAMINE REUPTAKE INHIBITOR

OPIATE ANTAGONIST

Bupropion and Bupropion-Naltrexone (Contrave)

- Mechanism of action: bupropion is a relatively weak inhibitor of the neuronal reuptake of dopamine and norepinephrine
  - The exact neurochemical effects of naltrexone/bupropion leading to weight loss are not fully understood
    - Effects may result from action on brain areas involved in regulation of food intake
      - Hypothalamus and the mesolimbic dopamine circuit
  - Naltrexone is a pure opioid antagonist

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Bupropion and Bupropion-Naltrexone (Contrave)

- Side effects: constipation, dizziness, headache, insomnia, nausea, and vomiting

- Usual Adult Dose for Obesity: One tablet once daily in the morning for 1 week
  - Increase as tolerated in weekly intervals:
    - 1 tablet twice daily for 1 week; then 2 tablets in the morning and 1 tablet in the evening for 1 week; and then 2 tablets twice daily
  - Maximum dose: 4 tablets/day (naltrexone 32 mg/bupropion 360 mg per day)

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ANOREXANT

ANTI-SEIZURE AGENT

Phentermine and Phentermine-Topiramate (Qsymia)

- Mechanism of action: A sympathomimetic amine with pharmacologic properties similar to amphetamines
  - Topiramate: Effect on weight management may be due to its effects on appetite suppression and satiety enhancement
    - Based on a combination of potential mechanisms

- Side effects: chest pain, fast, irregular, pounding, or racing heartbeat or pulse, numbness or tingling in the arms or legs, and swelling of the lower extremities

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Phentermine and Phentermine-Topiramate (Qsymia)

- Usual Adult Dose for Obesity:
  - Phentermine 3.75 mg/topiramate 23 mg once daily for 14 days
  - Increase dose as tolerated to 7.5 mg/46 mg once daily for 12 weeks, then evaluate
    - If ≥3% of baseline body weight has not been lost, either discontinue therapy with a gradual taper or escalate the dose based on tolerability and patient preference
    - Dose may be escalated to 11.25 mg/69 mg once daily for 14 days, and then to a maximum dose of 15 mg/92 mg once daily

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Current Treatment Guidelines

- Individuals who are overweight or obese who intend to lose weight should be prescribed:
  - Aerobic exercise and resistance training
  - Reduced-calorie diet
  - Active pursuits should be promoted
  - Sedentary time should be reduced

- Patients should pursue behavioral interventions that foster adherence to physical activity and meal plans such as:
  - Activities conducted by the individual, 1 on 1 sessions with clinicians, and group meetings
    - Behavioral interventions be escalated for patients who do not achieve 2.5% weight loss within 1 month

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NON-PHARMACOLOGIC TREATMENT

Current Treatment Guidelines

- A structured and comprehensive lifestyle intervention program designed for weight loss is recommended for all patients who are overweight or obese seeking to lose weight

  - An in-person, high-intensity program (≥ 14 sessions in 6 months) is recommended as the most effective behavioral treatment for overweight or obesity

    - Participation in high-intensity programs produces on average 5% to 10% body weight loss over 6 months

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Main Treatment Points

- Recommend for obese patients:
  - 30-60 minutes of daily physical activity
  - A balanced diet with a deficit of 1000 calories or higher
  - Cognitive and behavioral therapy
    - Determine root cause of high caloric intake
    - Prevent continual excess caloric intake
  - Maintain a food/diet journal

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PHARMACEUTICAL WEIGHT LOSS

CONCLUSIONS

Summary

- Nonpharmacologic options should be considered first to help manage weight and encourage weight loss before their BMI becomes classified as obese
- If patient is obese and has Type 2 diabetes, Saxenda or Wegovy are recommended
  - SGLT-2 inhibitors may be considered if patient does not respond adequately to GLP-1 agonists
- If patient is not diabetic, Orlistat may be considered in addition to lifestyle modifications
  - Contrave, Phentermine, Qsymia may be considered if Orlistat does not produce any modest weight loss

References

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Questions?

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