Weight Lost?
Pharmacotherapy Update On Weight Management

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October 28, 2023

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No actual or potential conflicts of interest in relation to this presentation

Objectives

- Characterize the increasing rate of obesity in the United States
- Describe obesity-related complications
- Review evidence-based recommendations for the treatment of obesity in adults
- Identify prominent adverse effects and monitoring parameters for these medications

Background

- Obesity is a disease state that occurs when body weight is higher than what is considered a healthy weight

- Prevalence of children and adults with obesity has increased dramatically over the past few decades

- Despite previous guidelines for management of overweight and obesity, prevalence rates continue to increase

Background

- Highly stigmatized as a result of personal choice and energy imbalance
- Other factors that may impact weight gain:
  - Genetics
  - Illness and medications
  - Sleep quality
  - Socioeconomic contributors
  - Increasing obesogenic environment

Complications of Obesity

- Obesity is associated with an increased risk for many diseases and health conditions when compared to those with a healthy weight
  - Heart disease
  - Stroke
  - Type II diabetes
  - Osteoarthritis
  - Metabolic dysfunction associated steatohepatitis
  - Obstructive sleep apnea
  - Certain cancers
- Obesity-related medical costs in the United States were estimated to be $173 billion in 2019

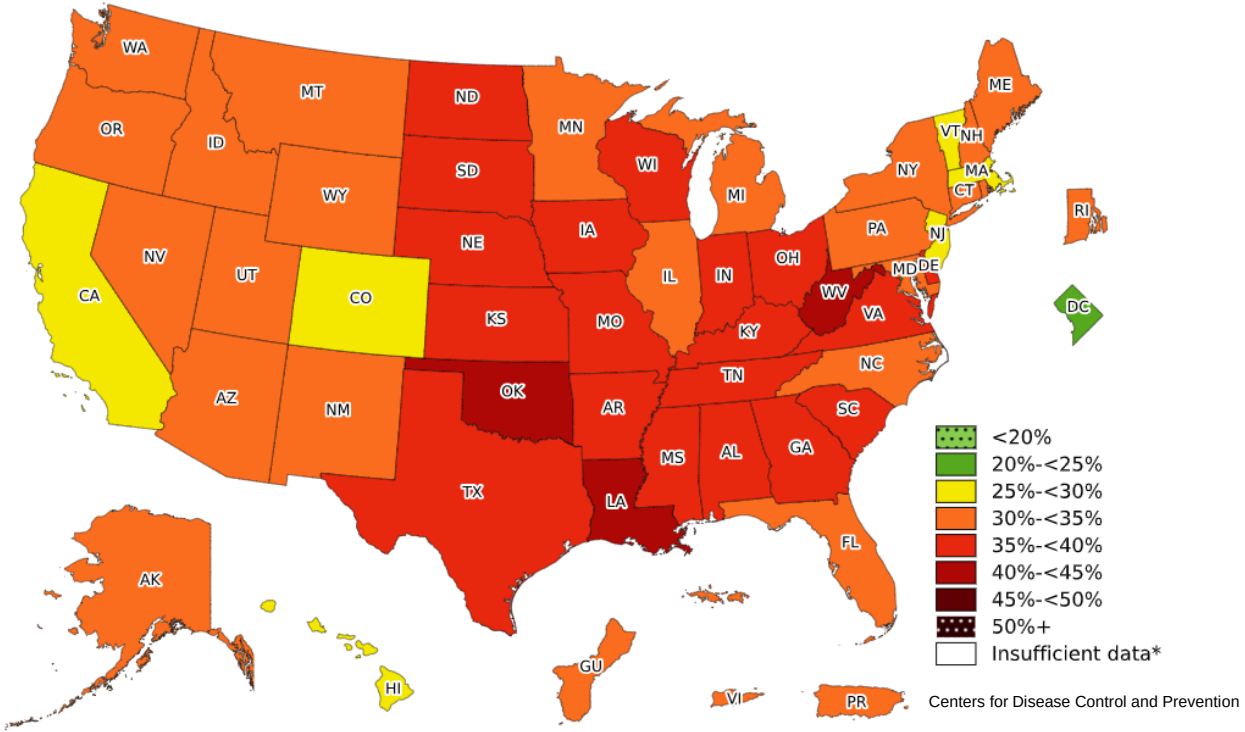
Classification

Body Mass Index kg/m^2 (BMI)	Category
<18.5	Underweight
18.5-24.9	Healthy weight
25-29.9	Overweight
≥30	Obese

Body Mass Index kg/m^2 (BMI)	Obesity Category
30-34.9	Class 1
35-39.9	Class 2
≥40	Class 3

Prevalence

- National obesity prevalence 42%
- Ohio obesity prevalence 38%
- In the last 20 years, obesity prevalence has increased 11%



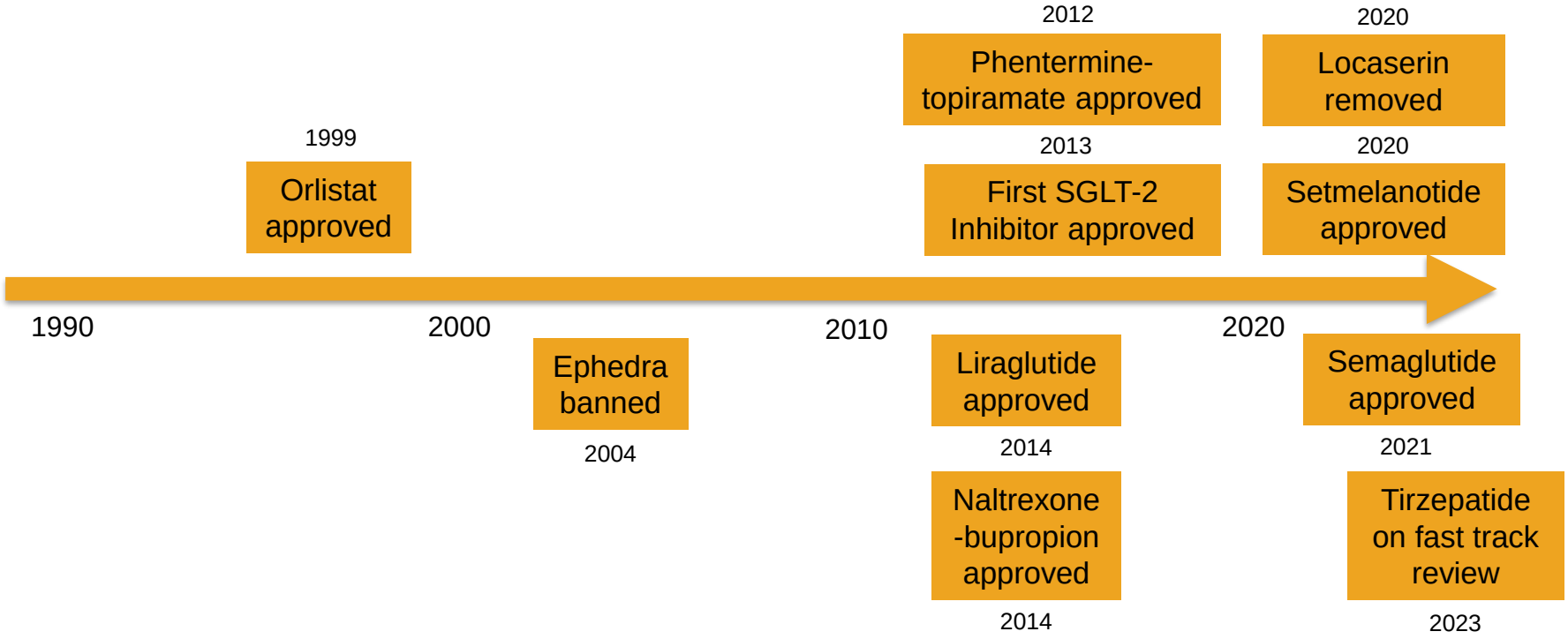
Response

- In 2004 and 2011, the *WHO Global Strategy on Diet, Physical Activity and Health* detailed actions to support healthy diets and regular exercise
- In 2015, The United Nations met to adopt the *2030 Agenda for Sustainable Development* aiming to reduce mortality from non-communicable diseases by one-third
- In 2018, the *WHO Global action plan on physical activity 2018–2030: more active people for a healthier world* detailed policies to increase physical activity

Guidelines

- 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults
- 2016 AACE/ACE Comprehensive Clinical Practice Guidelines For Medical Care of Patients with Obesity
- 2022 AGA Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity
- 2023 AAP Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity

Anti-Obesity Medications Timeline



2022 AGA Guideline Recommendations

- In adults with obesity (≥30 kg/m^2) or overweight (≥27 kg/m^2) with at least 1 weight-related complications, with inadequate response to lifestyle intervention
  - Adding pharmacological agents to lifestyle intervention is **strongly** recommended over lifestyle alone
- The AGA recommends semaglutide, liraglutide, phentermine-topiramate ER, and naltrexone-bupropion ER as they have the most robust evidence to support their safety and efficacy
- The AGA recognized orlistat as an alternative in patients that highly value low weight loss and place low value on gastrointestinal side effects

2022 AGA Guideline Recommendations

- Monotherapy phentermine and monotherapy diethylpropion were conditionally recommend
  - These are only approved for 12 weeks of treatment
- The AGA recognized a knowledge gap for the use of the Gelesis100 oral superabsorbent hydrogel and has no recommendations on use

Pharmacological Interventions for Adults with Obesity

Top Guideline Recommendations

In adults with overweight (BMI ≥ 27 kg/m²and weight-related complications) or obesity (BMI ≥ 30 kg/m²), with inadequate response to lifestyle interventions, add pharmacological therapy*

(strong recommendation, moderate certainty)

Anti-obesity medications

aga

	Semaglutide	Liraglutide	Phenetermine-topiramate ER	Naltrexone-bupropion ER
AGA recommendation	Suggest using			
Mean difference % total body weight loss achieved (drug vs. placebo)	10.8%	4.8%	8.5%	3.0%

American Gastroenterological Association

2023 AAP Guidelines Recommendations

- The American Academy of Pediatrics 2023 guidelines strongly encourages a multifaceted approach to the care of children and adolescents with overweight or obesity
- AAP details the use of metformin in patients 10 years and older with type II diabetes, but weight loss in trials is inconsistent
- Orlistat is approved for patients 12 years and older for treatment of obesity
- Liraglutide and semaglutide are approved for patients 12 years and older

2023 AAP Guidelines Recommendations

- Melanocortin 4 receptor (MC4R) agonist, setmelanotide, is approved for patients 6 years and older with specific disorders of appetite regulation related to the MC4R pathway
- Phentermine is approved for short-course therapy of 12 weeks in patients 16 years and older
- Phentermine-topiramate ER is approved for patients 12 to 18 years old for chronic obesity treatment

General Considerations When Considering AOMs

- Use of anti-obesity medication (AOM) is generally chronic
- Selection of medication should be personalized to the patient and their needs
- Factors such as comorbidities, patient preferences, costs, and access to therapy must be considered

General Considerations When Considering AOMs

- AOMs should not used in pregnant women
- Use of AOMs in patients with diabetes may increase the risk of hypoglycemia
- Use of AOMs in patients on anti-hypertensive therapy may increase the risk of hypotension
- Must be used with caution in those with eating disorders, such as active bulimia nervosa or binge eating disorder

Semaglutide (Wegovy®)

Liraglutide (Saxenda®)

Phentermine-topiramate (Qsymia®)

Naltrexone-bupropion (Contrave®)

Orlistat (Alli OTC®; Xenical®)

Semaglutide (Wegovy®)

- Glucagon-like peptide-1 (GLP-1) receptor agonist which increases glucose-dependent insulin secretion, suppresses inappropriate glucagon release, slows gastric emptying and regulates appetite

Semaglutide (Wegovy®)

- GLP-1 agonists have been associated with increased risk of pancreatitis, gallbladder disease, and thyroid C-cell tumors in rodents
- Delayed gastric emptying may cause significant nausea and vomiting
- Side effects include abdominal pain, constipation, diarrhea, headache, and fatigue

Semaglutide (Wegovy®) Considerations

- May preference semaglutide over other AOMs due to the magnitude of weight loss
- Semaglutide is also used in the treatment of type II diabetes
- Manufacturer recommends discontinuing therapy if target dose of 2.4 mg cannot be tolerated
- Consider discontinuation if at least 5% of baseline body weight loss is not achieved within 12 weeks

Liraglutide (Saxenda®)

- Glucagon-like peptide-1 (GLP-1) receptor agonist which increases glucose-dependent insulin secretion, suppresses inappropriate glucagon release, slows gastric emptying and regulates appetite

Liraglutide (Saxenda®)

- GLP-1 agonists have been associated with increased risk of pancreatitis, gallbladder disease, and thyroid C-cell tumors in rodents
- Delayed gastric emptying may cause significant nausea and vomiting
- Side effects include constipation, diarrhea, headache, gastroenteritis, hypoglycemia, and increased heart rate

Liraglutide (Saxenda®) Considerations

- Liraglutide is also used in the treatment of type II diabetes
- Dose escalation may be extended to 2 weeks if patient is not tolerating dose increases
- Consider discontinuation if at least 4-5% of baseline body weight loss is not achieved within 12 weeks at maximally tolerated dose or 16 weeks from initiation of therapy

Missed Doses of GLP-1 Agonists

- Semaglutide: administer missed dose as soon as possible within 5 days
  - If more than 5 days have elapsed, skip the missed dose and resume at the normal schedule
- Liraglutide: continue at next dosing interval
  - Do not give extra or a higher dose the next day
- If 2 doses of either medication are missed, consider continuing at same dose if patient has been tolerating or lowering the dose
- If 3 doses of either medication are missed, consider restarting the titration schedule

Phentermine-Topiramate Extended Release (Qsymia®)

- Phentermine is a sympathomimetic amine that reduces appetite secondary to CNS effects
- Topiramate promotes appetite suppression and satiety enhancement through multiple potential mechanisms

Week 1-2	Week 3-12	<3% weight loss	Week 13-14	Week 15 and after
3.75 mg/ 23 mg once daily	7.5 mg/ 46 mg once daily		11.25 mg/ 69 mg once daily	15 mg/ 92 mg once daily

Phentermine-Topiramate Extended Release (Qsymia®)

- Consider discontinuing therapy if <3% of baseline body weight loss is not achieved at week 12 or if <5% is not achieved at week 15
  - Must discontinue therapy with a gradual taper to prevent inducing a seizure
  - One capsule every other day for 1 week is recommended prior to discontinuation
- Avoid in patients with cardiovascular disease or uncontrolled hypertension
- Side effects include cognitive impairment, constipation, dry mouth, palpitations, and paresthesias

Phentermine-Topiramate Extended Release (Qsymia®) Considerations

- Recommend taking in AM due to risk of insomnia
- May be preferential agent for patients with comorbid migraines
- In females of childbearing potential, a pregnancy test should be completed prior to initiation and monthly thereafter (REMS)
- Renal dosing
  - If CrCl <50 ml/min, max dose is 7.5 mg/46 mg once daily
  - Avoid in end-stage renal disease
- Avoid use with monoamine oxidase inhibitors due to risk of hypertension

Off-Label Use

- Topiramate is not FDA approved as a monotherapy AOM though off-label use is common
  - 50-200mg split into one or two doses per day is typical
- Use of topiramate as a single agent is usually due to the cost of phentermine-topiramate ER
- Zonisamide may also be used off-label for weight loss due to its pharmacological similarity to topiramate
  - 100-400mg split into one or two doses per day is typical

Naltrexone-Bupropion Extended Release (Contrave®)

- Naltrexone is a pure opioid antagonist
- Bupropion is a weak inhibitor of neuronal dopamine and norepinephrine uptake

Week 1	Week 2	Week 3	Week 4
8 mg/90 mg once daily	8 mg/90 mg twice daily	16 mg/180 mg AM 8 mg/90mg PM	16 mg/ 180 mg twice daily

Naltrexone-Bupropion Extended Release (Contrave®)

- May be preferential agent for patients who are attempting smoking cessation or with depression
- Avoid in patients with seizure disorders
- Should not be used concomitantly with opioid medications
- Avoid use with monoamine oxidase inhibitors due to risk of hypertension
- Side effects include nausea, constipation, vomiting, headache, and sleep disturbances

Naltrexone-Bupropion Extended Release (Contrave®) Considerations

- Blood pressure and heart rate monitoring is recommended especially in the first 12 weeks of therapy
- Consider discontinuation if at least 4-5% of baseline body weight loss is not achieved 12 weeks
- Naltrexone-bupropion ER should be discontinued prior to any procedure requiring opiates
- Renal dosing
  - If moderate to severe impairment, max dose is 8 mg/90 mg twice daily
  - Avoid in end-stage renal disease

Orlistat (Alli OTC®; Xenical®)

- Orlistat is an inhibitor of gastric and pancreatic lipases which reduces the amount of fat absorption
- Orlistat is available as an over-the-counter and prescription product

Alli OTC®

60 mg three times daily

Xenical®

120 mg three times daily

Orlistat (Alli OTC®; Xenical®)

- AGA recommends that orlistat may be more beneficial in patients who place high value on small weight loss and low value on gastrointestinal side effects
- Compared to newer AOMs, cost of orlistat is lower
- Orlistat acts locally within the gastrointestinal tract and has lower neuropsychiatric adverse effects
- Side effects include significant gastrointestinal effects, abdominal distress/pain, bowel urgency, flatulence with discharge, oily evacuation, steatorrhea, vitamin deficiency, influenza, upper respiratory tract infections, and headaches

Orlistat (Alli OTC®; Xenical®) Considerations

- Patient using orlistat should take a multivitamin that contains vitamins A, D, E, and K and separate by 2 hours
- Consider discontinuation if at least 4-5% of baseline body weight loss is not achieved in 12 weeks
- Advise patients to take this within 1 hour of fat containing meals
  - Doses can be held if meal is low in fat
- Avoid orlistat in patients with chronic malabsorption disorders such as chronic diarrhea, celiac disease, inflammatory bowel disease or who have had bariatric surgery

Setmalanotide (Imcivree®)

SGLT-2 Inhibitors

Gelesis100

Tirzepatide (Mounjaro®)

Ephedra, Lorcaserin

Setmalanotide (Imcivree®)

- Setmalanotide is a peptide analog of endogenous melanocortin peptide alpha-melanocyte stimulating hormone that acts as a MC4R agonist
- Only approved for obesity due to Bardet-Biedl syndrome or pro-opiomelanocortin, proprotein convertase subtilisin/kexin type 1, or leptin receptor deficiency

Week 1-2	Week 3 and after
2 mg once daily	1.2 mg once daily

Setmalanotide (Imcivree®)

- Duration of therapy will depend on the specific genetic cause of obesity
- Consider discontinuation if weight loss from baseline is <5%
- Side effects include new or worsening depression or suicidal ideation, disturbances in sexual arousal, skin hyperpigmentation, gastrointestinal effects

Sodium-Glucose Cotransporter-2 Inhibitors

- SGLT-2 inhibitors prevent the reabsorption of glucose in the renal tubular lumen and promote urinary excretion of glucose
- Initially approved for treatment of diabetes, but empagliflozin and dapagliflozin have approval for chronic kidney disease and heart failure
- Weight loss tends to be minimal with these agents, and is listed as intermediate efficacy for weight loss in the ADA 2023 guidelines

Sodium-Glucose Cotransporter-2 Inhibitors

- May be used an adjunctive agent if patient has diabetes, heart failure or chronic kidney disease
- Associated with increased risk of genital mycotic infections
  - Rare reports of Fournier gangrene
- Monitor volume status and blood pressure
- Side effects include euglycemic diabetic ketoacidoisis, urinary tract infections, increased thirst, and nausea

Gelesis100 (Plenity®)

- Gelesis100 is technically classified as a medical device
- A capsule containing cellulose and citric acid which forms a matrix in the stomach
  - Occupies volume in the stomach and promote a sense of fullness and satiety

Plenity®

2.25 g twice daily before meals

Gelesis100 (Plenity®)

- AGA does not make a recommendation for or against the use of this agent
- FDA approved for those with BMI of 25-40 kg/m^2 in addition to diet and exercise
- Must be taken with 16 ounces of water 20 minutes before lunch and dinner
- Side effects include diarrhea, abdominal distention/pain, bloating and flatulence

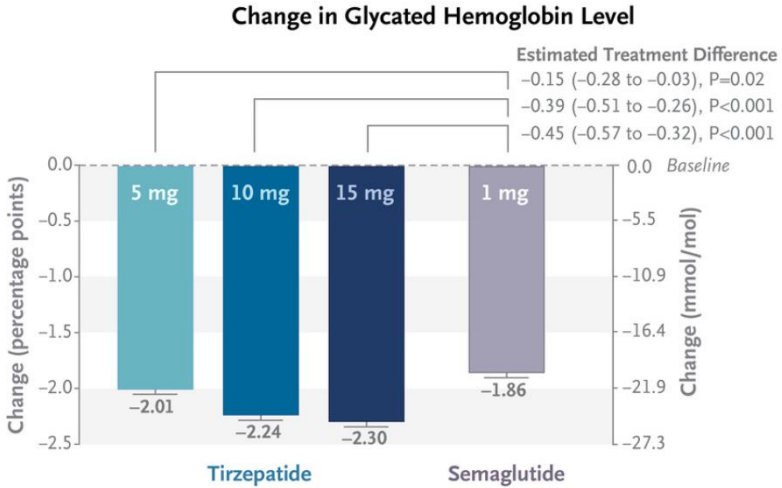
Tirzepatide (Mounjaro®)

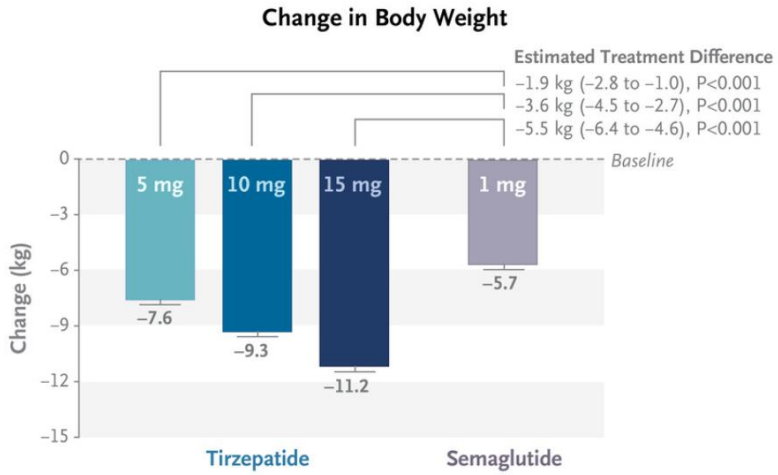
- Unique glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) dual agonist that increases glucose-dependent insulin secretion, decreases glucagon section, and slows gastric emptying
- Currently only approved for diabetes II treatment

Week 1-4	Week 5-8	Week 9-12	Week 13-16	Week 17-20	Week 21 and after
2.5 mg once weekly	0.5 mg once weekly	7.5 mg once weekly	10 mg once weekly	12.5 mg once weekly	15 mg once weekly

Tirzepatide (Mounjaro®)

- Fast track review for FDA approval for use as an AOM
- Has been studied in the SURPASS for diabetes treatment





Tirzepatide (Mounjaro®)

- GLP-1 agonists have been associated with increased risk of pancreatitis, gallbladder disease, and thyroid C-cell tumors in rodents
- Delayed gastric emptying may cause significant nausea and vomiting
- More serious adverse effects were reported in the tirzepatide group
- Side effects include diarrhea, increased amylase/lipase, nausea, and, abdominal distention/pain

Summary

- The prevalence of obesity has continued to increase in the United States due to a multitude of factors
- In adult patients who have not had success with lifestyle modification only, semaglutide, liraglutide, phentermine-topiramate ER, and naltrexone-buproprion ER should be considered in addition to lifestyle modifications
- AOM selection should include patient factors such as comorbidities, patient preferences, costs, and access to therapy

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