Pharmacotherapy for Obesity

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SCOPE Certified
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OBESITY MANAGEMENT IN PRIMARY CARE CERTIFICATE PROGRAM:

A Practice Management & Leadership Training Program for PAs and NPs

Commercial Support

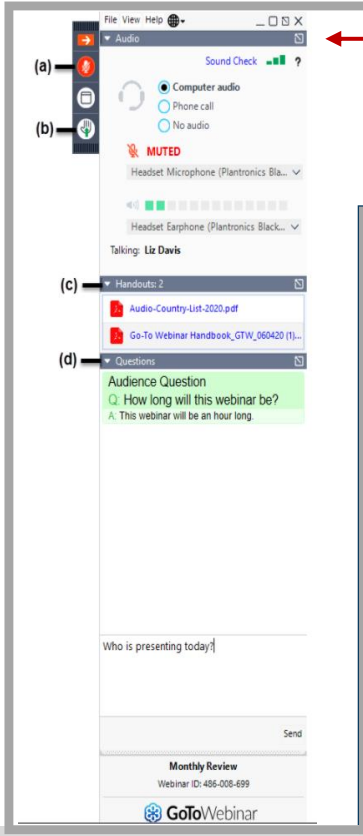
This activity was sponsored by an educational grant from Novo Nordisk, Inc.

Accreditation Statement

- This activity has been reviewed by **the AAPA Review Panel** and is compliant with AAPA CME criteria. **This activity is designated for 1.5 AAPA Category 1 CME** credits. Participants should only claim credit commensurate with the extent of their participation.
- This activity was planned in accordance with AAPA's CME Standards for Commercial Support of Enduring Activities.
- **This activity is approved for 1.5 contact hour(s) of continuing education by the American Association of Nurse Practitioners**. Activity ID 21034782. This activity was planned in accordance with AANP Accreditation Standards and Policies

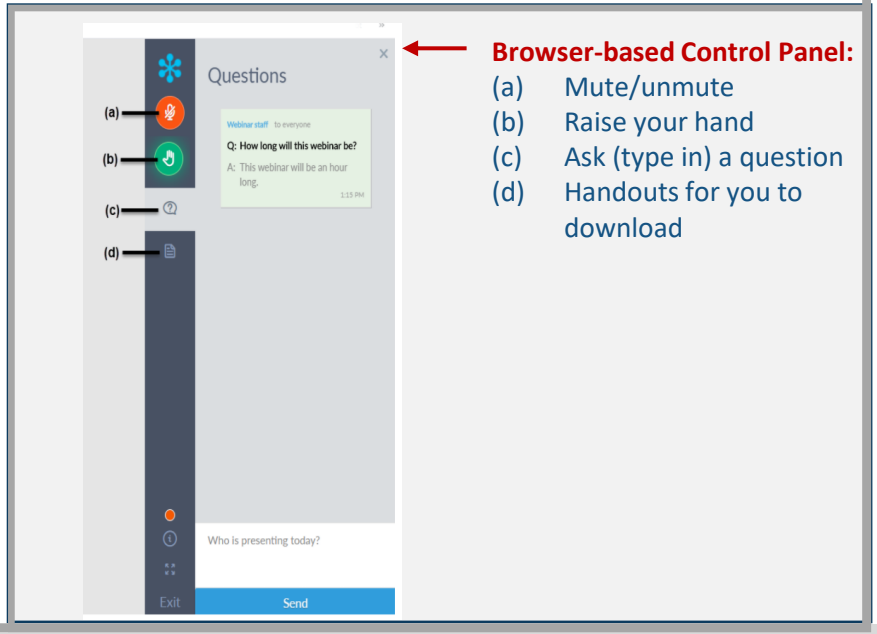
House Keeping

Using Your GTW Control Panel and Reminders



Desktop App Control Panel:

(a) Mute/unmute
(b) Raise your hand
(c) Handouts for you to download
(d) Ask (type in) a question



Browser-based Control Panel:

(a) Mute/unmute
(b) Raise your hand
(c) Ask (type in) a question
(d) Handouts for you to download

Questions

- Please post questions throughout the webinar via the **Questions / (?)** section in your GTW control panel (CP)
  - In the Desktop app click on the 'triangle' to open the Questions bar.
  - In the browser CP, click on the "?" icon.
- Your questions will be addressed during the Q&A section at the end of the webinar.

Handouts

- The faculty selected handouts for you to review, use in practice, and/or to follow along with during this session.
  - In the Desktop app CP click on the 'triangle' to open the Handouts bar.
  - In the browser CP, click on the "document" icon
- To download the handouts double click on the PDF links

Polling Questions

- There are audience response-like questions that I'll refer to as "polling questions" in this presentation.
- Please be sure to respond to each polling question accordingly. You'll have 10 seconds to submit your responses.

POLLING PRACTICE

In what time zone are you located?

A. Eastern (ET)

B. Central (CT)

C. Mountain (MT)

D. Pacific (PT)

E. Island/Alaska Time

AAPA Learning Central: Module 5

Posttest and Evaluation

- After completion of this webinar, please go to Module 5 of the course in AAPA's Learning Central to complete the **posttest** and **evaluation** to obtain credit for this activity.

Faculty and Disclosure Statement

- Angela is a current fellow and past president of the American Association of Nurse Practitioners (AANP). Her tenure as the president of the AANP gives her a unique and overarching perspective of the multifunctional role of the Nurse Practitioner.
- Angela has her own primary care practice, NP from Home, LLC, and NP Obesity Treatment Clinic where she provides clinical services as a family nurse practitioner. Angela has a great deal of experience as a consultant in the development of patient education materials. She has given interviews on obesity treatment and authored several peer-reviewed articles and book chapters related to obesity as well as other topics for advanced practice nursing.
- Angie has recently published a book, *Treating Obesity in Primary Care*, through Springer Publishing. She presents nationally and internationally on advanced practice with an emphasis on health policy, leadership and clinical care.

- Novo Nordisk: Speakers' bureau and consultant for obesity
- Unjury: Consultant for nutrition

Objectives

Initiate — Initiate appropriate pharmacotherapy early in the obesity management plan according to clinical practice guidelines.

Summarize — Summarize the mechanisms of action, safety, efficacy, and dosing of anti-obesity medications.

Select — Select an appropriate medication based on patient characteristics and comorbid conditions.

Treatment Overview

Eating Plans

Activity

Behavioral Intervention

Medication

Surgery

Case Study

Meet Ellen: History


Image: © Obesity Action Coalition

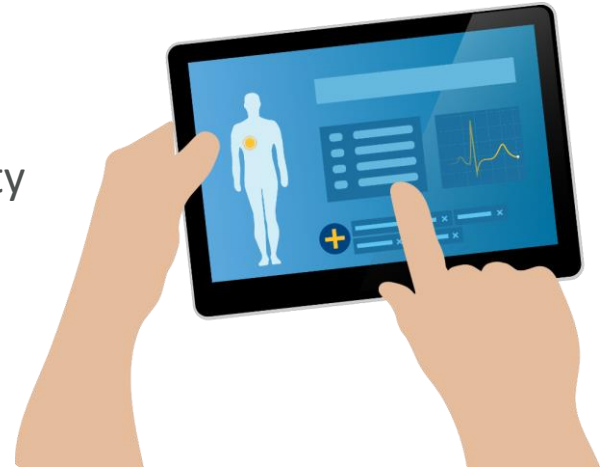
- Obesity history: has been “heavy” since she was a teenager but has gained 40-lbs over the past 4 years
  - Has never seen a healthcare provider for weight/obesity treatment
  - Has tried lots of OTC remedies (eg, raspberry ketones)
- Social: ETOH 1x/week, married with two teenagers at home, works outside the house as a nurse
- Family: father, mother, sister with HTN, diabetes, and all are “heavy”; no history of thyroid cancer
- Personal: no history of alcohol or drug abuse; no personal history of pancreatitis
- Nutrition: tries to be careful most days; craves sweets at night
- Activity: nothing specific right now

ETOH, alcohol; HTN, hypertension; OTC, over the counter.

Ellen: Medical History and Medications

Medical History

- Obstructive sleep apnea (OSA) – on BiPAP
- Gastroesophageal reflux disease (GERD)
- Hypertension
- Depression
- Stage 2 obesity



Medications

- Metoprolol 20 mg/day
- Omeprazole OTC once daily
- Vortioxetine 20 mg/day
- Multivitamin once daily
- Pregnancy prevention: IUD
- NKDA

BiPAP, bilevel positive airway pressure; IUD, intrauterine device; NKDA, no known drug allergies.

Polling Question

What (if any) medication is Ellen taking that could be obesogenic?

A. Metoprolol

B. Omeprazole

C. Vortioxetine

D. More than 1 medication is obesogenic

E. None are obesogenic

Ellen's First Visit for Obesity

- Vital signs:
  - 5'4"; 212 lbs; BP 142/88 mmHg; HR 78 bpm; RR 16 breaths/min; pOx 98%
- BMI: 36.30 kg/m^2
- Waist circumference: 42"
- Neck circumference: 15"
- Screening tools: PHQ-9 (4), BED7 (neg), PAR-7, STOP-BANG negative

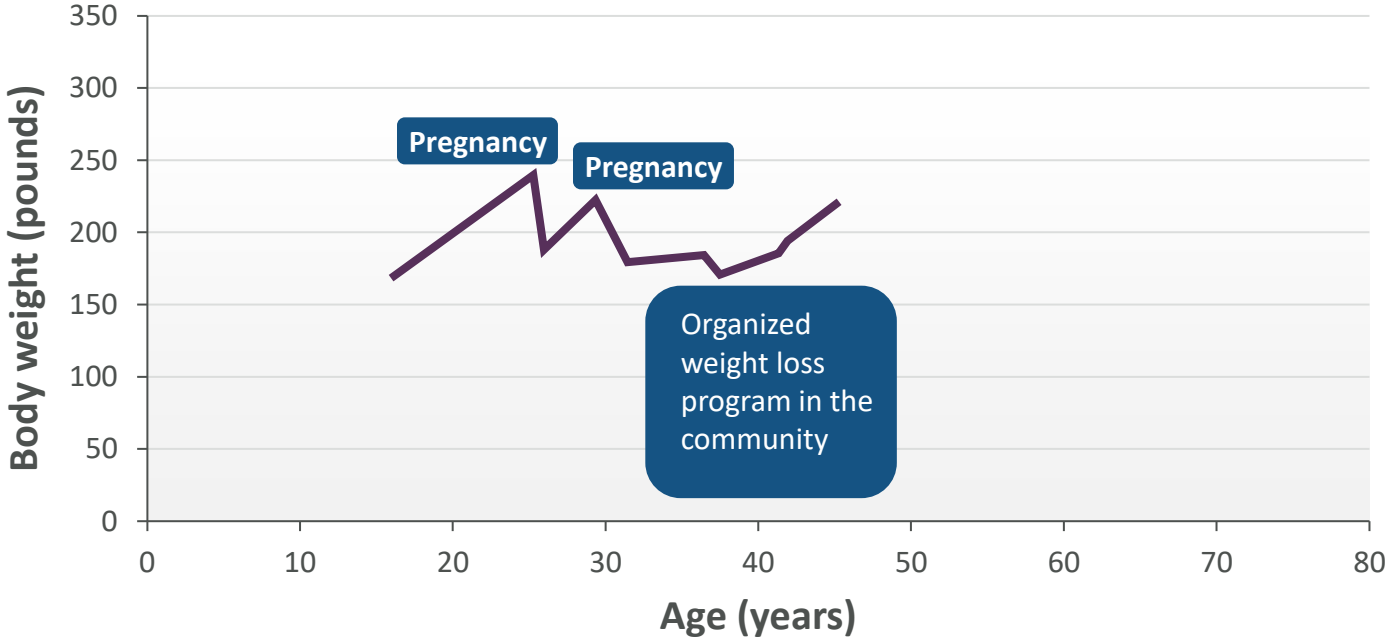
	Yes	No
Has your NP or healthcare provider said you have a heart condition or high blood pressure?	X	
Do you feel pain in your chest at rest, during your daily activities of living or when you do physical activity?		X
Do you lose balance because of dizziness or have you lost consciousness in the last 12 months (answer no if your dizziness was associated with over-breathing, including during vigorous exercise)?		X
Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)? Please list conditions here: Depression, Sleep apnea	X	
Are you currently taking prescribed medications for a chronic medical condition? Please list conditions and medications here:_____		X
Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please answer no if you had a problem in the past, but it does not limit your current ability to be physically active. Please list conditions here: _____		X
Has your healthcare provider ever said that you should only do medically supervised physical activity?		X

Form adapted from PAR 7 by Angela Golden for use at NP Obesity Treatment Center.

BED7, Binge Eating Disorder; BMI, body mass index; BP, blood pressure; bpm, beats per minute; HR, heart rate; PAR-7, Physical Activity Readiness. PHQ, Patient Health Questionnaire; pOx, pulse oximetry; RR, respiratory rate; STOP-BANG, snoring, tiredness, observed apnea, pressure, BMI, age, neck circumference, and gender.

Body Weight Graph

- Use this graph to chart live events, health conditions, times of stress, and other factors that have influenced your weight



Ellen's First Visit for Obesity (cont'd)

- Most recent labs: triglycerides 174 mg/dL; TC 236 mg/dL; LDL 134 mg/dL; HDL 48 mg/dL; AST 67 u/L; ALT 102 u/L; vitamin D 34 ng/mL
- Fasting insulin 18 mIU/L; glucose 94 mg/dL; HOMA IR 4.17; QUICKI 0.31
- Obesity-related complications: elevated liver enzymes, hyperlipidemia, HTN
- Obesity comorbidities: OSA; depression
- Obesogenic medication: β blocker
- Staging of obesity
  - WHO – obesity class II
  - EOSS – stage 2
  - AACE/ACE – stage 2


Image: © Obesity Action Coalition

AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOSS, Edmonton Obesity Staging System; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; QUICKI, quantitative insulin sensitivity check index; TC, total cholesterol; WHO, World Health Organization.

Clinical Practice Guidelines and Algorithms

Guideline Recommendations

Similarities

- Focused on adults with obesity
- Individualized eating plans
- Counseling patients to increase physical activity
- Behavioral interventions
- Medication may be appropriate for some patients
- Referral to an obesity specialist or surgery may be appropriate

Differences

Endocrine Society paradigm shift toward pharmacologic therapy over no therapy for patients:

- With a history of unsuccessful weight loss and maintenance
- Who meet label indications
- Obesogenic medications

Apovian CM, et al. *J Clin Endocrinol Metab.* 2015;100(2):342-362. Bays HE, et al. 2020. https://obesitymedicine.org/obesity-algorithm/ Accessed February 12, 2020. Garvey WT, et al. *Endocr Pract.* 2016;22(Suppl 3):1-203. Wharton S, et al. *CMAJ.* 2020;192(31):E875-E891.

Current Guidelines

Endocrine Society (ES)
- Clinical Practice Guideline

American Association Clinical Endocrinologists (AACE)
- Clinical Practice Guideline

Obesity Medicine Association (OMA)
- Obesity Algorithm

Obesity Canada (OC)
- Obesity in Adults Clinical Practice Guideline

Current Guidelines/Algorithm Comparison

ES

- Mention of nutrition, activity, behavioral intervention
- Details on available pharmacology for antiobesity medications
- Obesogenic medications with options of other choices

AACE/ACE

- Complication-specific treatment guideline
- Prevention reviewed
- Staged recommendations for treatment
- ORC-centric obesity treatment based on pharmacology

OMA

- Annually updated clinician tool
- Review of bias and stigma implications
- Podcast companions
- Top 10 messages of each section
- Obesity myths section

OC

- Living document updated with emerging evidence
- Created with sections for primary care professions, persons living with obesity, and policy holders
- Prevention and treatment
- Only 3 medications approved in Canada

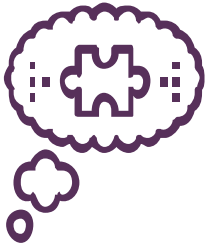
ORC, obesity-related complications and comorbidities.

Apovian CM, et al. *J Clin Endocrinol Metab*. 2015;100(2):342-362. Bays HE, et al. 2020. https://obesitymedicine.org/obesity-algorithm/ Accessed February 12, 2020. Garvey WT, et al. *Endocr Pract*. 2016;22(Suppl 3):1-203. Wharton S, et al. *CMAJ*. 2020;192(31):E875-E891.

Pharmacologic Therapy

Therapy Options, Factors to Consider When Selecting Therapy, and Efficacy/Safety Evidence

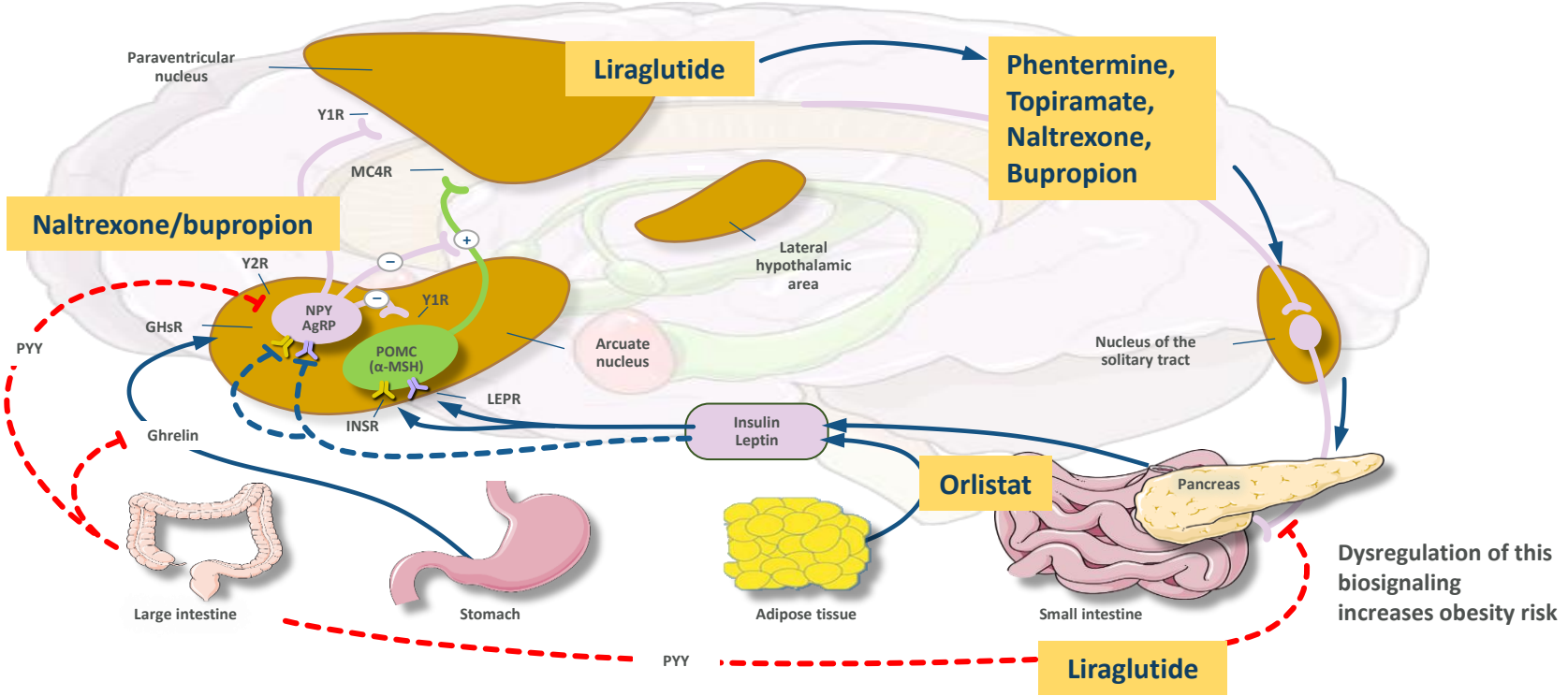
Why Use Medication With Obesity Treatment?



- Weight loss evokes a complex set of neuroendocrine physiologic adaptations that become more intense with greater weight loss
  - These work to slow, then eventually halt weight loss, and eventually may induce weight gain
- Patients who have lost weight find it very difficult to resist neuroendocrine physiology with diet and behavior modification alone
- Anti-obesity medications help offset the physiologic adaptations that resist weight loss and promote weight regain

Greenway FL. *Int J Obes (Lond).* 2015;39(8):1188–1196.

Components of Appetite Regulation



α-MSH, α-melanocyte-stimulating hormone; GHsR, growth hormone secretagogue receptor; INSR, insulin receptor; LEPR, leptin receptor; MC4, melanocortin-4 receptor; POMC, pro-opiomelanocortin; Y1R, NPY Y1 receptor; Y2R, NPY Y2 receptor.

Apovian CM, et al. *J Clin Endocrinol Metab.* 2015;100(2):342-362.

Polling Question

What percentage of weight reduction should be the first therapeutic goal?

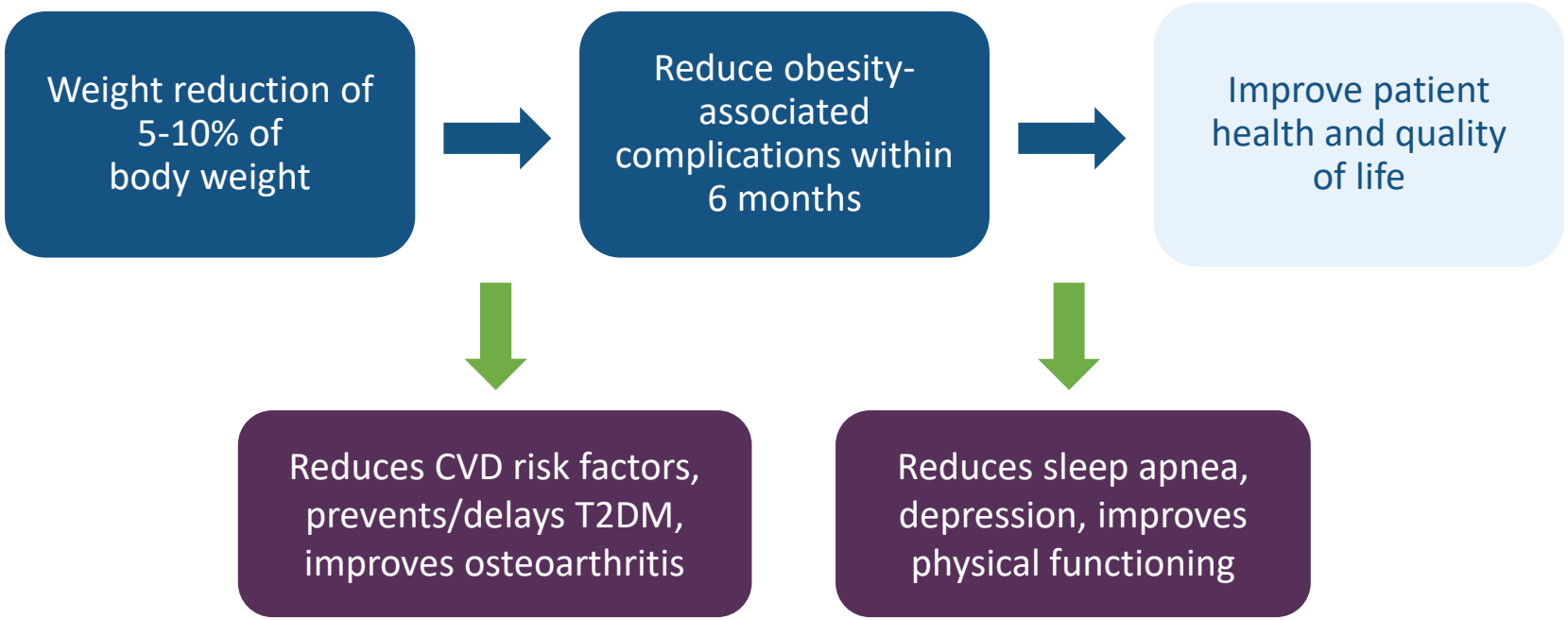
A. <5%

B. 5-10%

C. 11-15%

D. Depends on the individual's baseline BMI

Therapeutic Goals



CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.

Jensen MD, et al. *Circulation*. 2014;129:S102-S138. Garvey WT, et al. *Endocr Pract.* 2016;22 Suppl 3:1-203. Yanovski SZ, et al. *JAMA.* 2014;311:74-86. Apovian CM, et al. *J Clin Endocrinol Metab.* 2015;100(2):342-362.

FDA-Approved Short-Term (Anti) Obesity Therapies

Generic Drug*	Dose	Contraindications	Side Effects
Phentermine	8-37.5 mg	Anxiety disorder, CVD, hypertension, MAO inhibitors, glaucoma, hyperthyroidism, seizures, pregnancy/ breastfeeding, drug abuse history	Insomnia, palpitations, tachycardia, dry mouth, taste alterations, dizziness, tremors, headache, diarrhea, constipation, vomiting, gastrointestinal distress, anxiety, restlessness, increased blood pressure
Diethylpropion	25 mg or 75 mg, SR		
Phendimetrazine	17.5-70 mg or 105 mg, SR		
Benzphetamine	25-50 mg		

*Mechanism of action = sympathomimetic-noradrenergic causing appetite suppression.
MAO, monoamine oxidase; SR, sustained release.
DailyMed. https://dailymed.nlm.nih.gov/dailymed/index.cfm. Accessed February 23, 2021. Bray GA, et al. *Circulation*. 2012;125(13):1695-1703. Apovian CM, et al. *J Clin Endocrinol Metab*. 2015;100(2):342-362.

Phentermine

- US Drug Enforcement Agency scheduled IV drug
  - Risk for addiction
- Not indicated for long-term use
  - 13 weeks by label

Endocrine Society allows for possible long-term use:

- No CVD
- No psychiatric/substance abuse history
- Has been informed about therapies that are approved for long-term use
- Document off-label use in patient's medical record
- No clinically significant increase in pulse/BP when taking phentermine
- Demonstrates significant weight loss with phentermine
- Start at 7.5 or 15 mg/d—dose escalate if not achieving significant weight loss
- Monitor monthly during dose escalation

Apovian CM, et al. *J Clin Endocrinol Metab.* 2015;100(2):342-362.

Study of Interest

Phentermine

PC-II

- 269 participants
- Phentermine 37.5 mg for more than 2 years with abrupt withdrawal

Conclusions:

- Phentermine abuse or psychological dependence (addiction) does not occur in patients treated with phentermine for obesity
- Amphetamine-like withdrawal does not occur upon abrupt treatment cessation even at doses much higher than commonly recommended and after treatment durations of up to 21 years

Hendricks EJ, et al. *Am J Ther*. 2011;18(4):292-299.

FDA-Approved (Anti) Obesity Therapies

Generic (listed alphabetically)	Mechanism of Action
Liraglutide (subcutaneous injection)	GLP-1 receptor agonist
Naltrexone/bupropion ER (oral)	Opioid receptor antagonist; dopamine and noradrenaline reuptake inhibitor
Orlistat (oral)	Pancreatic lipase inhibitor—impairs gastrointestinal energy absorption, causing excretion of approximately 30% of ingested triglycerides in stool
Phentermine/topiramate-ER (oral)	Noradrenergic + GABA-receptor activator, kainite/AMPA glutamate receptor inhibitor causing appetite suppression

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ER, extended release; GABA, gamma-aminobutyric acid; GLP, glucagon-like peptide.

DailyMed. https://dailymed.nlm.nih.gov/dailymed/index.cfm. Accessed February 23, 2021.

Long-Term Efficacy for (Anti) Obesity Medications

Therapy (listed alphabetically)	Length of Trial	Mean Weight Loss
Liraglutide	≥1 year	-7.4% (full dose)
Naltrexone/bupropion	≥1 year	-5.4%
Orlistat	≥1 year	-6.1%
Phentermine/topiramate	≥1 year	- 9.8% (full dose)

Bray GA, et al. *Lancet* 2016;387(10031):1947-1956.

General Considerations in Pharmacologic Initiation

Pharmacologic interventions may be helpful as adjuvant therapy with lifestyle interventions for patients 18 years and older* with BMI ≥30 kg/m^2 or ≥27 kg/m^2 with comorbidities.

- Different patients respond to different medications
  - If one option does not work, consider others
- Discontinue medication in patients who do not respond with weight loss of at least 5% at 12 weeks after maximum dose†
- Avoid in pregnancy
  - Pregnancy tests at baseline
  - Consider a disclosure signature

*December 2020: liraglutide label change to include 12–17-year-olds with body weight of >60 kg and initial BMI corresponding to 30 kg/m^2 or greater for adults.
†Liraglutide label suggests only 4% weight loss at 12 weeks after maximum dose.
Apovian CM, et al. *J Clin Endocrinol Metab* 2015;100(2):342-362.

Orlistat

Dose Frequency	Efficacy	Contraindications/ Precautions/Warnings	Side Effects
60 mg OTC 120 mg TID within 1 h of fat-containing meal	• Mean weight loss ranged from 3.9-10.2% at Year 1 in 17 RCTs (120 mg TID) • ↓ BP, TC, LDL-C, fasting glucose at 1 year • Slows risk of progression to T2DM	Chronic malabsorption syndrome, pregnancy, breastfeeding, cholestasis, some medications (eg, warfarin, antiepileptic agents, levothyroxine, cyclosporine)	Oily spotting, cramps, flatus with discharge, fecal urgency, fatty oily stool, increased defecation, fecal incontinence

Practical Considerations

- Consider fat-soluble multivitamin
- Limit fat intake to 30% of calories
- Counsel on risk of GI adverse events

BP, blood pressure; GI, gastrointestinal. RCT, randomized controlled trial; TID, three times daily.

Bragg R, et al. *J Am Assoc Nurse Pract* 2016;28(2):107-115. Kahan S. *Am J Manag Care*. 2016;22(7 Suppl):S186-S196.

Study of Interest

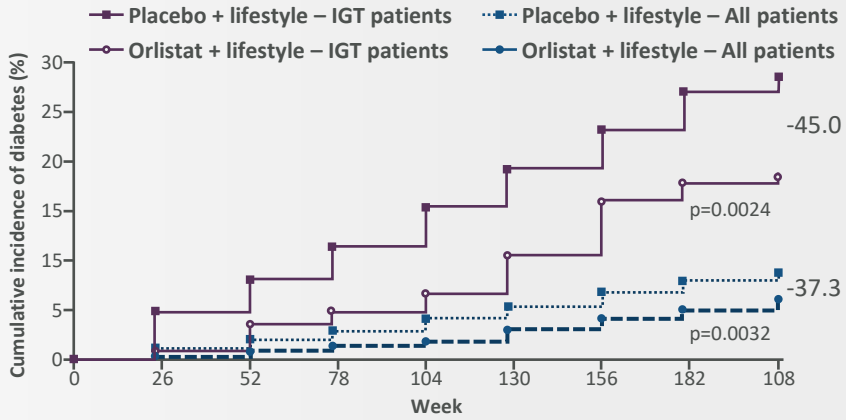
Orlistat

XENDOS

- Randomized study for prevention of T2DM in patients with obesity
- 4-year study of 3,305 patients with BMI >30 kg/m^2 and normal or impaired glucose tolerance (IGT)

Conclusion: Compared with lifestyle changes alone, orlistat plus lifestyle changes resulted in a greater reduction in the incidence of T2DM over 4 years and produced greater weight reduction in a clinically representative population with obesity

- Difference in diabetes incidence was detectable only in the IGT subgroup
- Weight reduction was similar in subjects with IGT or normal glucose tolerance
- T2DM: 9% in placebo group and 6.2% in orlistat group, corresponding to risk reduction of 37.3%



Torgerson J. *Diabetes Care*. 2004;27(1):155-161.

Phentermine/Topiramate ER

Dose Frequency	Efficacy	Contraindications/ Precautions/Warnings	Side Effects
• Initiate treatment at 3.75 mg/23 mg for 2 weeks • Increase to 7.5 mg/ 46 mg • Escalate to 11.25 mg/ 69 mg for 2 weeks then to max 15 mg/92 mg	• 10% weight loss with treatment vs 2% with placebo • Improved cardiometabolic markers • Reduced progression to T2DM	Pregnancy and breastfeeding, hyperthyroidism, glaucoma, use of MAO inhibitors	Paresthesias, dizziness, taste alterations, insomnia, constipation, dry mouth, elevation in heart rate, memory or cognitive changes

Practical Considerations

- Titrate dose at initiation and discontinuation
- Drug Enforcement Agency Schedule IV drug
- Risk evaluation and mitigation strategy
- Counsel about risk for mood disorders, suicidal thoughts
- Taper highest dose every other day for 1 week if discontinuation is necessary
- Women of childbearing age: pregnancy prevention plan and monthly pregnancy testing

Bragg R, et al. *J Am Assoc Nurse Pract* 2016;28(2):107-115. Kahan S. *Am J Manag Care*. 2016;22(7 Suppl):S186-S196.

Study of Interest

Phentermine/Topiramate ER

Qsymia as an Adjunct to Surgical Therapy in the Super Obese

- Open-label trial of 13 patients with BMI ≥50 kg/m^2 who planned to undergo laparoscopic sleeve gastrectomy (LSG)
- Participants received phentermine/topiramate ER 7.5/46 mg/day or 15/92 mg/day for 3 months preoperatively and 2 years postoperatively
- LSG + phentermine/topiramate ER had 39.3% weight reduction vs 31.4% for LSG historical controls at 12 months (P=0.018)

Conclusion: There was a significant increase in the odds of achieving BMI <40 kg/m^2 for the experimental group compared with controls at 6 months

Ard JD, et al. *Surg Obes Relat Dis*. 2019;15(7):1039-1043.

Liraglutide

Dose Frequency	Efficacy	Contraindications/ Precautions/Warnings	Side Effects
Weekly titration by 0.6 mg over 5 weeks to target dose of 3.0 mg	• Mean weight loss 9% at 1 year • Reduced progression to T2DM in patients with prediabetes • Reduced risk of weight regain at 1 year	Medullary thyroid cancer history, multiple endocrine neoplasia type 2 history, history of pancreatitis, pregnancy, breastfeeding	Nausea, vomiting, diarrhea, constipation, hypoglycemia in patients with T2DM, increased lipase, increased heart rate, pancreatitis

Practical Considerations

- Injectable administration
- FDA approved for use in adults with BMI ≥30kg/m^2 or ≥27 kg/m^2 with at least one complication
- Risk evaluation and mitigation strategy (medullary thyroid carcinoma, acute pancreatitis)
- Approved 12/2020 label change: treatment of obesity in adolescents aged 12 to 17 years with a body weight of at least 60 kg and an initial BMI corresponding to 30 kg/m^2 or greater for adults

Bragg R, et al. *J Am Assoc Nurse Pract* 2016;28(2):107-115. Kahan S. *Am J Manag Care*. 2016;22(7 Suppl):S186-S196.

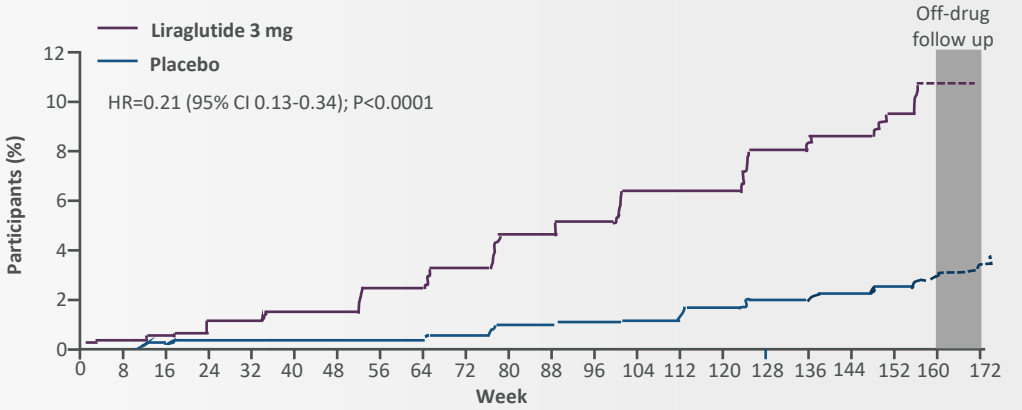
Study of Interest

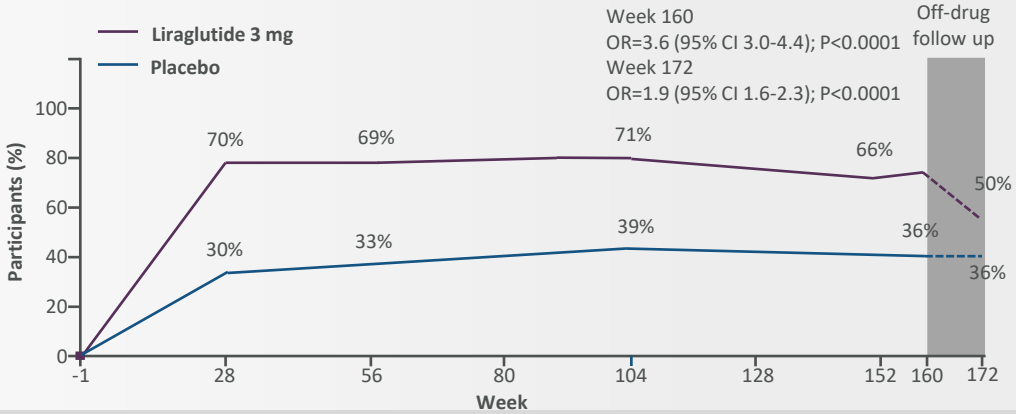
Liraglutide

SCALE Obesity and Prediabetes trial (2017)

Randomized, double-blind, controlled trial of 2,254 patients with prediabetes and BMI ≥30 kg/m^2 or ≥27 kg/m^2 with comorbidities

- 80% less likely to develop diabetes vs placebo group
- 60% reverted to normoglycemia
- Of those that did go on to T2DM – took 2-7 times longer





CI, confidence interval; HR, hazard ratio; OR, odds ratio.
LeRoux C, et al. *Lancet*. 2017;389(10077):1399-1409.

Naltrexone/Bupropion ER

Dose Frequency	Efficacy	Contraindications/ Precautions/Warnings	Side Effects
• Initiate 8 mg/90 mg x 1 week • Weekly escalation to target dose of 32 mg/360 mg (2 tablets BID)	• Weight loss of 8.2% vs 1.4% (placebo) • Improved cardiometabolic parameters • Fewer cravings • Lowered HbA1c in patients with T2DM	Uncontrolled hypertension, seizure disorder, anorexia or bulimia, drug or alcohol withdrawal, chronic opioid use, MAO inhibitors, caution with renal/ hepatic impairment	Nausea, constipation, headache, dizziness, vomiting, insomnia, dry mouth Transient increase in BP

Practical Considerations

- Titrate dose on initiation
- Monitor BP
- Monitor closely for depression

BID, twice daily.

Bragg R, et al. *J Am Assoc Nurse Pract* 2016;28(2):107-115. Kahan S. *Am J Manag Care*. 2016;22(7 Suppl):S186-S196.

Study of Interest

Naltrexone/Bupropion ER

COR-I and -II

- COR-II 1496 participants
- COR-I 1742 participants
  - Active treatment in the COR-I and COR-II trials was associated with significant improvements in eating control

LIGHT

- Cardiovascular outcome study with 8,900 participants
  - Data released through a patent and securities filing without knowledge from the study's clinical trial leaders
  - Interim analysis was agreed on by the FDA but was intended only to show the medication did not double the risk of cardiovascular events due to the reports of increased blood pressure
  - DSMB performed an analysis of data that included 50% of the enrolled patients; investigators found no reduction in cardiovascular events

DSMB, data and safety monitoring board.

Greenway F, et al. *Lancet*. 2010;376(9741):595-605. Apovian C, et al. *Obesity (Silver Spring).* 2013;21(5):935-943. Nissen SE, et al. *JAMA*. 2016;315(10):990-1004.

Rare Genetic Cause of Obesity Treatment

Uncommon Obesity

>20 rare genetic disorders

Common symptoms

- Early onset of severe obesity, often less than one year of age
- Insatiable hunger (hyperphagia)

Genetic testing is critical (free)

Patient eligibility criteria:

- ≤18 years of age, BMI ≥97th percentile or
- ≥19 years of age, BMI ≥40 kg/m^2, and a history of childhood obesity before age 10

Uncommon Obesity. https://www.uncommonobesity.com/. Accessed February 23, 2021. Rhythm Pharmaceuticals. https://www.rhythmtx.com/science-overview/. Accessed February 23, 2021.

Setmelanotide – Imcivree™

- Approved in November 2020 for patients with obesity due to POMC, PCSK1, or LEPR deficiency
  - Impaired MC4 receptor pathway
  - Adults and pediatric patients 6 years of age and older with deficiency confirmed by genetic testing
- Action: MC4 receptor agonist
  - Restore impaired MC4 receptor pathway activity arising due to genetic deficits upstream of the MC4 receptor
- Rare pediatric disease priority review voucher, breakthrough therapy designation, orphan drug designation

PCSK1, proprotein convertase subtilisin/kexin type 1.

Uncommon Obesity. https://www.uncommonobesity.com/. Accessed February 23, 2021. Rhythm Pharmaceuticals. https://www.rhythmtx.com/science-overview/. Accessed February 23, 2021.

Study of Interest

Setmelanotide

Setmelanotide for the Treatment of LEPR Deficiency Obesity

- 11 participants
- Open-label, one-year trial in patients with early-onset, LEPR-deficiency obesity due to bi-allelic loss-of-function LEPR genetic mutation

Results

- 45% (5) had at least 10% weight loss

Clement, K. et al. *Lancet Diabetes Endocrinol*. 2020;8(12):960-970.

Device or Medication?

Nonsystemic Oral Hydrogel (Plenity™)

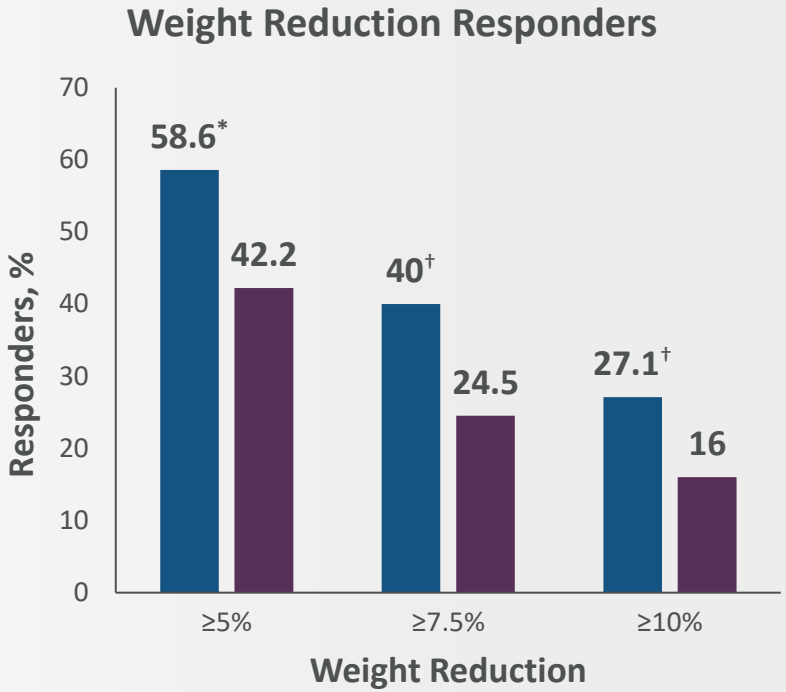
- Hydrogel matrix – cellulose and citric acid
- Mechanism of action: capsule releases non-aggregating particles that absorb water
  - Increases the volume and elasticity of stomach and small intestines
- Dosing: three capsules taken before lunch and dinner with 16-20 ounces of water
- Indication: BMI >25 kg/m^2 to <40 kg/m^2
- Side effects: GI – diarrhea, abdominal distension, constipation, nausea, abdominal pain
- Caution: patients with severe reflux or ulcers
- NO RESTRICTION on how long it can be used

Gelesis, Inc. Plenity. https://www.myplenity.com/static/pdfs/hcp-isi.pdf. Accessed February 23, 2021.

Study of Interest

Nonsystemic Oral Hydrogel

- Gelesis Loss of Weight (GLOW) study
- 52 patients
  - With or without diabetes
  - 300 kcal/d calorie deficit
  - 30 minutes of walking/day
  - Aged 22 to 65 years
- Amount of loss:
  - 59% lost at least 5%
  - 27% lost at least 10%



*P=0.001. †P=0.05.

Greenway FL, et al. *Obesity (Silver Spring).* 2019;27(2):205-216.

Change in Availability

Lorcaserin

February 13th FDA requested Eisai withdraw lorcaserin

- FDA – small increase in cancer
- CAMILLA-TIMI study 12,000 patients
  - CVOT not cancer risk study
  - No increase in CV risk
  - Reduction in risk of diabetes
  - NEJM: signaled no difference in cancer risk
  - 3 years of data: cancer observed in 3.59% of patients receiving lorcaserin vs 3.50% receiving placebo
  - FDA reported cancer in 7.7% of patients receiving lorcaserin vs 7.1% receiving placebo
- No hearing, no publication

CVOT, cardiovascular outcomes trial.

ConscienHealth. https://conscienhealth.org/2020/02/fda-requests-lorcaserin-withdrawal-scant-disclosure/. February 14, 2020. Accessed February 23, 2021. United States FDA. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market. February 13, 2020. Accessed February 23, 2021. PR Newswire. https://www.prnewswire.com/news-releases/eisai-to-voluntarily-withdraw-belviqbelviq-xr-in-the-us-301004885.html. February 13, 2020. Accessed February 23, 2021. Bohula E, et al. *N Engl J Med.* 2018;379(12):1107-1117.

5-Step Strategy for Therapy Selection

- Safety
- Complications/ Co-morbidities
- Patient history
- Cost + insurance
- Side effects

Ellen and Pharmacology

SAFETY	COMPLICATIONS AND/OR COMORBIDITIES	PATIENT HISTORY	COST AND INSURANCE	SIDE EFFECTS
Patient has no allergies to medications	HTN, depression, and insulin resistance; HTN and depression are controlled	No history of pancreatitis, seizures or family history of thyroid cancer Has tried OTC orlistat and could not tolerate the side effects	Patient has good insurance, but will require prior authorization	Has depression so will need close monitoring for all medications but orlistat; patient states she cannot be fatigued

Which medication would you recommend for Ellen?

A. Liraglutide

B. Naltrexone/bupropion ER

C. Orlistat

D. Phentermine

E. Phentermine/topiramate ER

Ellen: Measuring Success

Begin therapy with naltrexone/bupropion	**Initiate 8 mg-90 mg tablet once/day, moving up weekly until 4 tablets/day**
Effective response to therapy	**>5% weight loss from baseline 12 weeks after maximum dose**
Improvement in CV risk markers	**Improvement in BP and insulin resistance**

Ellen's Visit in 2-3 Weeks

2-3 weeks

- Review eating and activity tracking
- Evaluate BP with medication change
- Evaluate if still taking omeprazole
- Review any side effects from medication
- Intensive behavioral therapy (IBT) – Related to physical activity

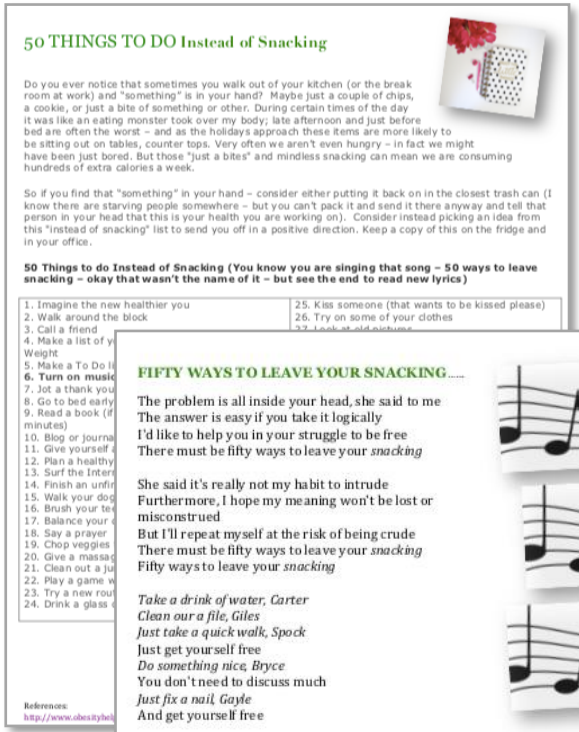
Visit Goals

- Increased medication to 4 tablets (2 in am and 2 in pm)
  - No side effects
  - Continues pregnancy prevention plan
- Now, 95% of eating is plant-based, whole food
- Ready to increase activity
  - Jujitsu 60-minute class three days/week – Monday, Wednesday, Friday right after work
  - Continuing steps, which are up to 7,000 average per day; listening to a book so enjoying this

Ellen’s Visit in 3-4 Weeks

3-4 weeks

- Weight 198 lbs, BP 122/64 mmHg
- No side effects noted
- Continues to track food and is now at 100% plant-based, whole food
- Enjoying jujitsu and walking
- Disappointed about not losing weight; she is still snacking in the evening but realizes she isn’t as hungry, just eating
- IBT – how to avoid snacking



50 THINGS TO DO Instead of Snacking

Do you ever notice that sometimes you walk out of your kitchen (or the break room at work) and "something" is in your hand? Maybe just a couple of chips, a cookie, or just a bite of something or other. During certain times of the day it was like an eating monster took over my body; late afternoon and just before bed are often the worst – and as the holidays approach these items are more likely to be sitting out on tables, counter tops. Very often we aren't even hungry – in fact we might have been just bored. But those "just a bites" and mindless snacking can mean we are consuming hundreds of extra calories a week.

So if you find that "something" in your hand – consider either putting it back on in the closest trash can (I know there are starving people somewhere – but you can't pack it and send it there anyway and tell that person in your head that this is your health you are working on). Consider instead picking an idea from this "instead of snacking" list to send you off in a positive direction. Keep a copy of this on the fridge and in your office.

50 Things to do Instead of Snacking (You know you are singing that song – 50 ways to leave snacking – okay that wasn't the name of it – but see the end to read new lyrics)

1. Imagine the new healthier you
2. Walk around the block
3. Call a friend
4. Make a list of y… Weight
5. Make a To Do li…
6. **Turn on music**
7. Jot a thank you…
8. Go to bed early
9. Read a book (if… minutes)
10. Blog or journa…
11. Give yourself …
12. Plan a healthy…
13. Surf the Inter…
14. Finish an unfin…
15. Walk your dog
16. Brush your te…
17. Balance your …
18. Say a prayer
19. Chop veggies
20. Give a massag…
21. Clean out a ju…
22. Play a game w…
23. Try a new rout…
24. Drink a glass …
25. Kiss someone (that wants to be kissed please)
26. Try on some of your clothes
27. Look at old pictures

References:
http://www.obesityhelp…

FIFTY WAYS TO LEAVE YOUR SNACKING……

The problem is all inside your head, she said to me
The answer is easy if you take it logically
I'd like to help you in your struggle to be free
There must be fifty ways to leave your *snacking*

She said it's really not my habit to intrude
Furthermore, I hope my meaning won't be lost or misconstrued
But I'll repeat myself at the risk of being crude
There must be fifty ways to leave your *snacking*
Fifty ways to leave your *snacking*

Take a drink of water, Carter
Clean our a file, Giles
Just take a quick walk, Spock
Just get yourself free
Do something nice, Bryce
You don't need to discuss much
Just fix a nail, Gayle
And get yourself free

Adapted from the lyrics of 50 ways to leave your lover by Paul Simon

Continue to See the Patient Every 2-4 Weeks

IBT

- Can be done by other providers as well, eg, dieticians, physical therapy/exercise physiologist, health coaches

Monitoring: BP, weight

Ellen’s Visit at 16 Weeks

16 weeks

- BP 124/66 mmHg; HR 82 bpm; RR 16 breaths/min; pOx 97%; weight 194 lbs
- Since being at maximum dosing of medication (12 weeks), has lost only 3% of total body weight
- Continues to eat plant-based, whole food
  - Has been able to stop BP medication (has lost 8% of body weight since beginning of treatment, only 3% with medication)
- Continues activity with jujitsu and walking
- Education at this meeting will be related to next medication

Ineffective Response to Therapy

- <4-5% weight loss at 12 weeks of maximum dose
  - Medications with escalating doses could be 16 weeks or longer
  - Unable to tolerate maximum doses
- < ? 3% weight loss but with improvement in ORCs

1. Decrease dose of existing AOM as appropriate
2. Switch to a different AOM

AOM, anti-obesity medication.

Bray GA, et al. *Lancet*. 2016;387(10031):1947-1956. Apovian CM, et al. *J Clin Endocrinol Metab.* 2015;100(2):342-362.

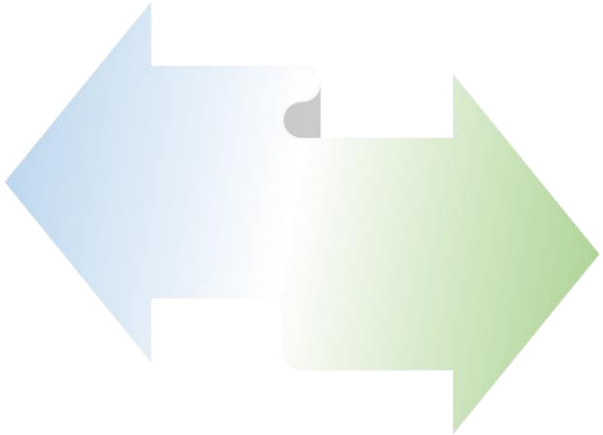
Ellen: Shared Decision-making

Liraglutide (subcutaneous injection)	No contraindications; benefit on insulin resistance; no history of pancreatitis or family history of thyroid cancer
~~Naltrexone/bupropion ER (oral)~~	~~Patient has not met required weight loss~~
~~Orlistat (oral)~~	Patient tried this OTC and was unable to tolerate the GI side effects
Phentermine (oral)	No contraindications but will need to consider low doses for long-term use
Phentermine/topiramate-ER (oral)	No contraindications; BP will need to be monitored closely; Patient has concern with fatigue, which is associated with topiramate

Considerations for Switching Ellen's Therapy

Liraglutide?

- Insulin resistance
- No family history of thyroid cancer or pancreatitis



Phentermine/ topiramate ER?

- More weight loss on average
- No history of seizures

Ellen's Continued 2-4-Week Visits

cont…

- Weight 182 lbs (14% weight loss), BMI 31.24 kg/m^2, waist measurement 38”
- Changed to phentermine/topiramate ER and dose has stabilized at 7.5/46 mg with decreased hunger noted
- No side effects noted and pregnancy prevention plan remains in place
- Continuing to do education and set goals at each meeting

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Coverage for Medications

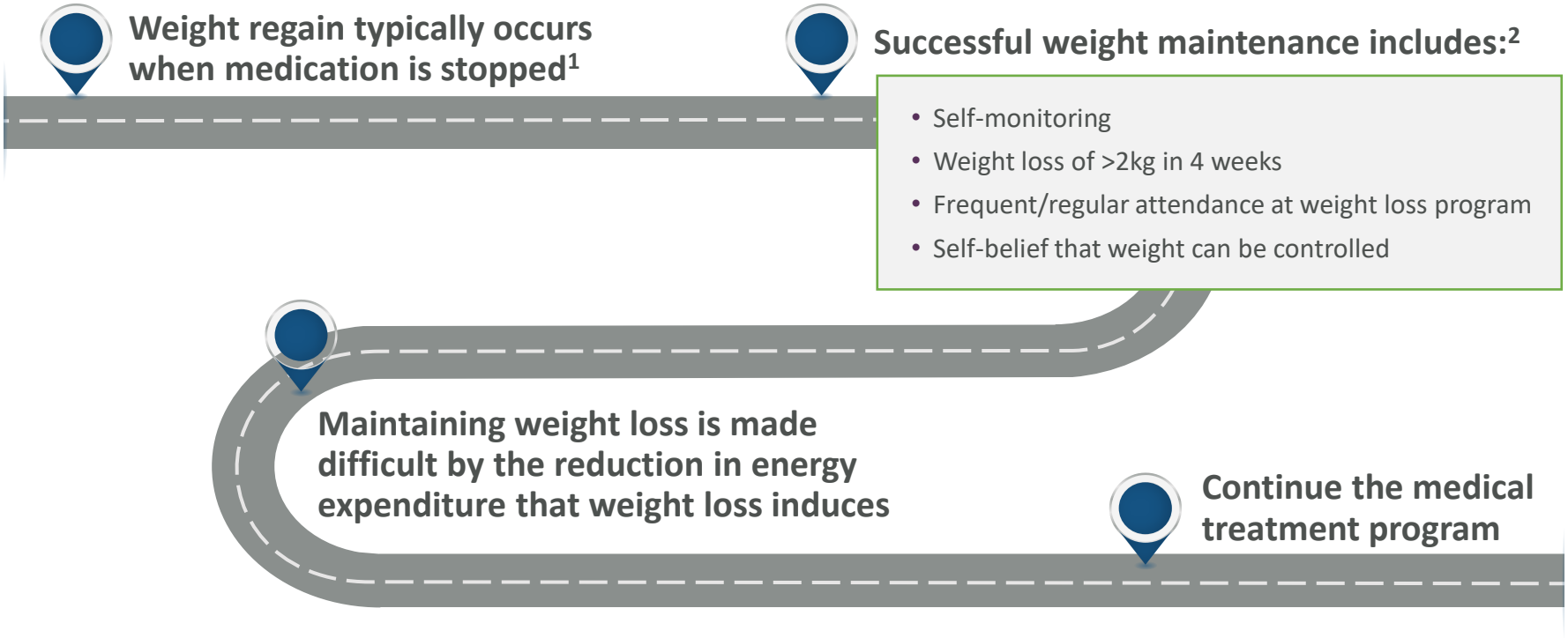
Prior authorization for the majority

- CoverMyMeds

Self-pay with programs from companies

- https://QsymiaEngage.com mail order $98/month
- https://Contrave.com/save/ mail order $99/month
- Saxenda (if covered) has a savings card new.novomedlink.com/obesity-treatment/patient-support/obesity-prescription-savings/card.html

Maintaining Weight Loss

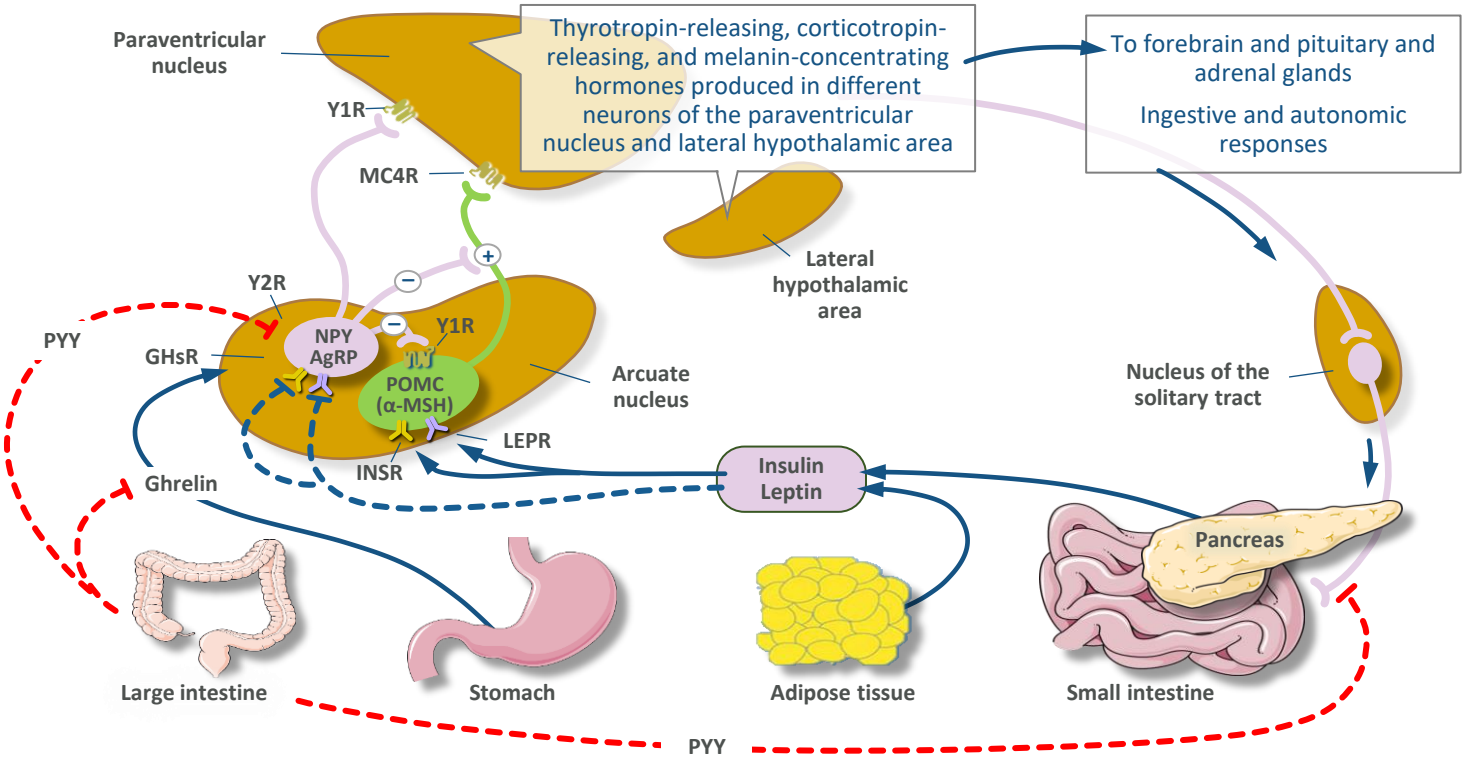


1. Apovian CM, et al. *J Clin Endocrinol Metab* 2015;100(2):342-62.2. Thomas JG, et al. *Am J Prev Med*. 2014;46(1):17-23

Physiology of Weight Regain

Adaptive responses to weight loss promotes weight regain.

- Fall in energy expenditure
- Increase in appetite
- Dysfunctional hormonal system



Apovian CM, et al. *J Clin Endocrinol Metab.* 2015;100(2):342-362

Future of AOMs

Medication name	Description
Tirzepatide	GIP/GLP-1 agonist Phase 3 trial Improved beta cell function and insulin sensitivity; 11% weight loss
Semaglutide	GLP-1 Phase 3a trial Average 17.4% weight loss at 68 weeks (phase 2 trials for NASH show resolution)
Zonisamide/bupropion	Dopamine and norepinephrine reuptake inhibitor Phase IIb trial Average 14% weight loss at 48 weeks
Tesofensine	Presynaptic inhibitor of norepinephrine, dopamine, and serotonin: induces weight loss by promoting the satiety feeling and slightly increasing metabolic rate
Monoclonal antibody	ActRII blockade Phase 2 Fat mass -20.5%; lean mass +3.6%; HbA1C -0.76%

ActRII, actin type II recptors; GIP, glucose-dependent insulinotropic polypeptide.

Srivastava G, et al. *Curr Obes Rep*. 2018;7(2):147-161. Golden A. Springer Nature Switzerland;2020:170-171.

Future of AOMs

Classes	Description
GLP-1/glucagon receptor agonists	Phase 2 trials 5 kg weight loss; improved HbA1C
Amylin/leptin	Pramlintide/metreleptin (showed promise but stopped in 2011)
Cannabinoid-1 receptor (CB1) antagonists	Stimulates anorexigenic signaling
SGLT2i with phentermine	Clinical trial completed in 2016 Demonstrated >5% weight loss with reductions in systolic BP
GLP1 with…..	SGLT2I, PYY3-36, CCK, and setmelanotide in early trials
Glucogon-GIP-GLP1 agonist	Tri-agonist
Ghrelin antagonist or vaccine	Inhibition of ghrelin receptor

CCK, cholecystokinin; SGLT2i, sodium glucose cotransporter-2 inhibitor.

Srivastava G, et al. *Curr Obes Rep*. 2018;7(2):147-161. Golden A. Springer Nature Switzerland;2020:170-171.

Evaluate for Obesogenic Medications

Diabetes		
Weight positive	**Weight neutral**	**Weight negative**
Insulin	DPP-IV	Metformin
Sulfonylurea		Pramlintide
Pioglitazone		GLP1
Rosiglitazone		SGLT2i

Hypertension		
Weight positive	**Weight neutral**	**Weight negative**
Beta blocker	ACEi, ARBs	
	Alpha blockers	
	CCBs	

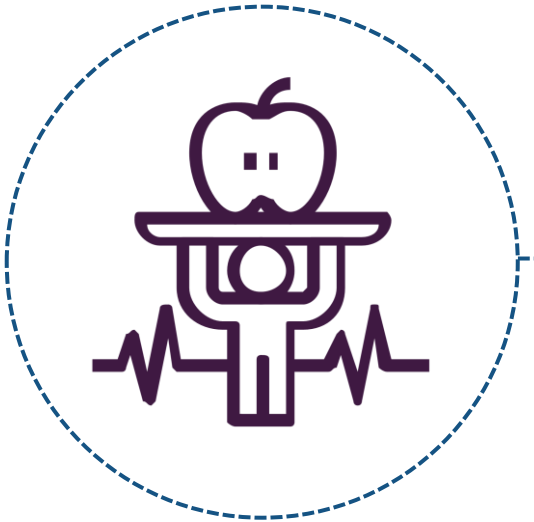
Antidepressants		
Weight positive	**Weight neutral**	**Weight negative**
Mirtazapine	Fluoxetine	Bupropion
Citalopram	Escitalopram	
Paroxetine	Sertraline	
Amitriptyline	Vortioxetine	

Miscellaneous		
Weight positive	**Weight neutral**	**Weight negative**
Corticosteroids		

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DPP, dipeptidyl peptidase.

Wharton S, et al. *Diabetes Metab Syndr Obes.* 2018;11:427-438.

Key Take-aways



01 Obesity is a chronic and often progressive condition

02 Obesity management is not about simply reducing numbers on the scale

03 Intensify treatment with pharmacology

04 Evaluate medication success at 12 weeks

05 If one medication doesn't work, try another

06 With success, continue medical management

Any Questions?

Thank you!

Remember to complete the posttest and evaluation in Module 5 on AAPA's Learning Central to obtain credit and your certificate for this webinar.

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