OBESITY MANAGEMENT IN PRIMARY CARE TRAINING AND CERTIFICATE PROGRAM

Pharmacotherapy for Obesity

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SCOPE Certified
OMA Advanced Certificate of Education in Obesity Medicine

AAPA THE OBESITY SOCIETY NACE

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Commercial Support

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

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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. She is also a Fellow of the Obesity Medicine Association.

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.

Disclosures:

- **Consultant:** Novo Nordisk
- **Advisor:** Gilesis Biotechnology, Currax Pharmaceuticals, Eli Lilly and Company, Vivus
- **Speaker's Bureau:** Currax Pharmaceuticals, Novo Nordisk, Vivus

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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.

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Treatment Overview

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Case Study

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Meet Ellen: History

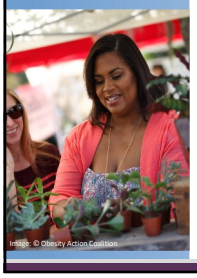

Image: © Obesity Action Coalition

- 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.

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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.

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Check Your Knowledge - 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

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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-Q, 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.

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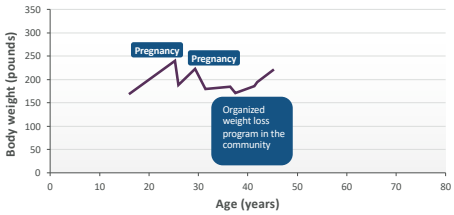
Body Weight Graph

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



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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, GERD
- Obesity comorbidities: OSA; depression
- Obesogenic medication: β blocker
- Staging of obesity
  - WHO – obesity class II
  - EOSS – stage 2
  - AACE/ACE – stage 2

Image © iStock/Adobe Stock/Getty

AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOSS, Edmonton Obesity Staging System; GERD, gastroesophageal reflux disease; 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.

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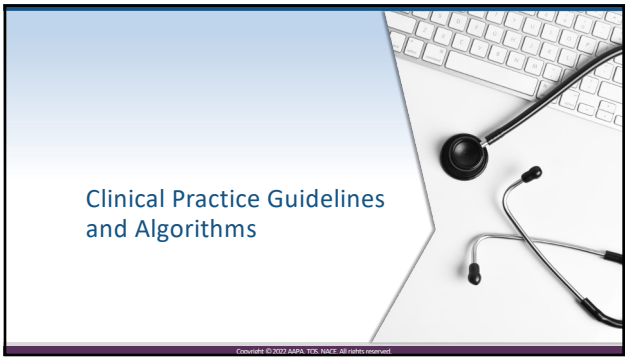

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Guideline Recommendations

Similarities	Differences
• 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	**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.

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Current Guidelines/Algorithm

Endocrine Society (ES)
- Clinical Practice Guideline

American Association Clinical Endocrinologists (AACE)
- Clinical Practice Guideline

Obesity Medicine Association (OMA)
- Obesity Algorithm
- Clinical Practice Statement on obesity history, physical exam, laboratory, body composition, and energy expenditure

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

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Current Guidelines/Algorithm Comparison

ES	AACE/ACE	OMA	OC
• Mention of nutrition, activity, behavioral intervention • Details on available pharmacology for antiobesity medications • Obesogenic medications with options of other choices	• Complication-specific treatment guideline • Prevention reviewed • Staged recommendations for treatment • ORC-centric obesity treatment based on pharmacology	• Annually updated clinician tool • Review of bias and stigma implications • Podcast companions • Top 10 messages of each section • Obesity myths section	• 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.

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Pharmacologic Therapy

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

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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.

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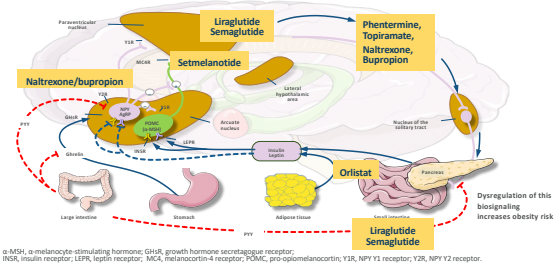
Components of Appetite Regulation



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.

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Check Your Knowledge - 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

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Therapeutic Goals

Weight reduction of 5-10% of body weight → Reduce obesity-associated complications within 6 months → Improve patient health and quality of life

- Reduces CVD risk factors, prevents/delays T2DM, improves osteoarthritis
- Reduces sleep apnea, depression, improves physical functioning

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.

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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.

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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.

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Phentermine

Study of Interest

PORTAL Electronic Health Records (EHR) Analysis

- EHR from 13,972 patients
- Phentermine 37.5 mg for at least 12 months of continuous enrollment

Conclusions:

- Longer duration of phentermine use (≥3 months) is associated with greater weight loss up to 2 years after initiating treatment
- Patients prescribed phentermine for ≤ 3 months (current label direction) did not experience durable, clinically significant weight loss
- Phentermine is effective and safe for longer-term use in low-risk individuals

Lewis KH, et al. *Obesity (Silver Spring)*. 2019;27(4):591-602.

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FDA-Approved Chronic 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
Semaglutide (subcutaneous injection)	GLP-1 receptor agonist

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.

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Long-Term Efficacy for Anti-obesity Medications

Therapy (listed alphabetically)	Length of Trial	Mean Weight Loss (Placebo-subtracted)
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)
Semaglutide	≥1 year	-14.9%

Bray GA, et al. *Lancet* 2016;387(10031):1947-1956. Wilding JPH, et al. *N Engl J Med.* 2021;384(11):989-1002.

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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 and lactation
  - 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.

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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.

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Orlistat

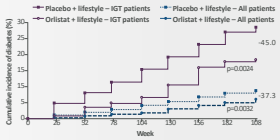
Study of Interest

XENDOS

- Randomized study for prevention of T2DM in patients with obesity
- 4-year study of 3,305 patients with BMI >30 kg/m² 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.

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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
- 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.

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Phentermine/Topiramate ER

Study of Interest

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.

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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 • 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.

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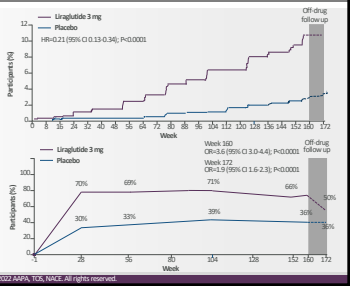
Liraglutide

Study of Interest

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.

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Semaglutide

Dose Frequency	Efficacy	Contraindications/ Precautions/Warnings	Side Effects
Weekly dose titration beginning at 0.25 mg once weekly and increased every 4 weeks to target dose of 2.4 mg by week 16	• Mean weight loss 14.9% at 68 weeks • Reduced waist circumference, BMI, and systolic/diastolic BP	Personal or family history of medullary thyroid cancer history or multiple endocrine neoplasia type 2; history of pancreatitis, diabetic retinopathy; pregnancy; breastfeeding	Nausea, diarrhea, vomiting, constipation, nasopharyngitis, headache, dyspepsia, abdominal pain, upper respiratory tract infection

Practical Considerations

- Pre-filled once-weekly injectable administration
- FDA approved for use in adults with BMI ≥30kg/m² or ≥27 kg/m² with at least one weight-related condition
- Nausea most common side effect – slow titration

Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989-1002.

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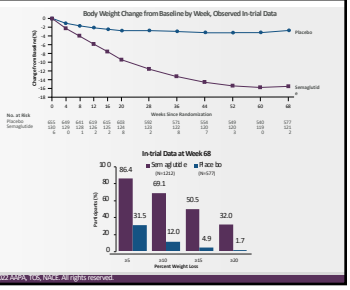
Semaglutide

Study of Interest

STEP 1 (2021)

Randomized, double-blind, controlled trial of 1,961 patients with BMI ≥30 kg/m² or ≥27 kg/m² with comorbidities

- Mean change in body weight was -14.9% in semaglutide group
- 86% had ≥5% reduction in weight, and 69% had ≥10% reduction in weight
- Semaglutide-treated patients had greater improvement in cardiometabolic risk factors



Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989-1002.

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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.

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Naltrexone/Bupropion ER

Study of Interest

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.

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Rare Genetic Cause of Obesity Treatment

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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.

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Setmelanotide

- 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.

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Setmelanotide

Study of Interest

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.

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Device or Medication?

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Nonsystemic Oral Hydrogel

- 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.

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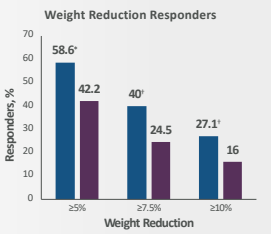
Nonsystemic Oral Hydrogel

Study of Interest

- 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.

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Considerations for Selecting an Anti-obesity Medication

R	Reimbursement/cost
X	eXcluded for contraindications or side effects
A	Additional reason to use anti-obesity medicine, such as complications or patient history
O	Off-label options if not able to use on-label medication
M	Medication selection with patient (shared decision-making)

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Considerations for Selecting an Anti-obesity Medication

R	Patient checking insurance
X	Orlistat (had SE), no allergies, no contraindications (seizures, thyroid cancer, glaucoma, uncontrolled HTN), no pancreatitis
A	Insulin resistance, cravings, depression, controlled HTN
O	Won't be necessary at this point
M	Leaves all medications as options

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Ellen: Shared Decision-making

AOM	Additional Benefit	Relative Contraindication
Naltrexone/bupropion ER (oral)	+ craving of sweets in the evening	None
Orlistat (oral)	None	GI side effects with OTC in past
Phentermine (oral)	Cost (least expensive)	HTN
Phentermine/topiramate ER (oral)	Improved efficacy vs phentermine alone	HTN
~~Liraglutide or semaglutide (subcutaneous injection)~~	~~Insulin resistance, NAFLD treatment~~	~~None~~

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Check Your Knowledge - Question

Which medication would you recommend for Ellen?

A. Semaglutide
B. Naltrexone/bupropion ER
C. Orlistat
D. Phentermine
E. Phentermine/topiramate ER

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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

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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

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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

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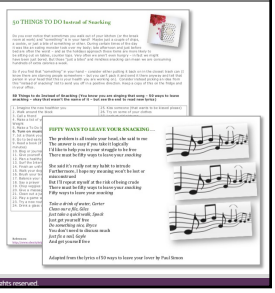
Ellen's Visit in 3-4 Weeks

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



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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

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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

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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.

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Ellen: Shared Decision-making

Liraglutide (subcutaneous injection) Semaglutide (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

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Considerations for Switching Ellen's Therapy

Liraglutide?
Semaglutide?

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

Phentermine/ topiramate ER?

- More weight loss on average
- No history of seizures

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Ellen: Shared Decision-making

Liraglutide (subcutaneous injection) Semaglutide (subcutaneous injection)	No contraindications; benefit on insulin resistance; no history of pancreatitis or family history of thyroid cancer
~~Naltrexone/bupropion ER (oral)~~	Patient already on bupropion, so would have to manipulate the dosing to prevent too high a dose; no complaint of cravings
~~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

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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 https://www.novocare.com/saxenda/savings-card.html
- Wegovy (if covered for AOMs) has a savings card https://www.novocare.com/wegovy/savings-card.html
- https://www.myplenity.com/healthcare-professionals/prescribing-plenity

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Maintaining Weight Loss

Weight regain typically occurs when medication is stopped[1]

Successful obesity treatment includes:[2]

- Self-monitoring
- Weight loss of >2kg in 4 weeks
- Frequent/regular attendance at weight loss program
- Self-belief that weight can be controlled

Maintaining weight loss is made difficult by the reduction in energy expenditure that weight loss induces

Continue the medical treatment program

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

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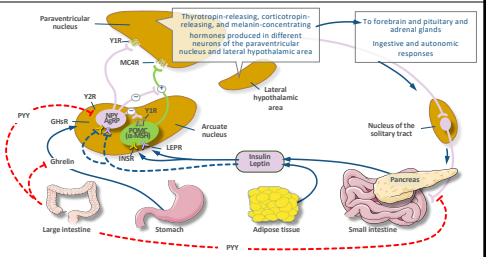
Physiology of Weight Regain

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

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Future of AOMs

Medication name	Description
Tirzepatide	GIP/GLP-1 agonist Phase 3 trial Improved beta cell function and insulin sensitivity; 11% weight loss
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 receptors; 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.

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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.

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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.

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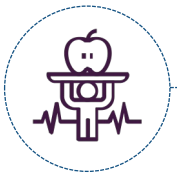
Key Take-aways



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**

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For an additional Obesity Resource: https://BookHip.com/RCPMFK

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