Review of Weight Management Drugs

NATALIE ABOUBECHARA, PHARMD, BCPS

PHARMACIST EVIDENCE ANALYST AND STRATEGIST

KAISER PERMANENTE

DISCLOSURE

The speaker has no financial conflicts of interest to disclose.

Learning Objectives

- Explain why the FDA requested the withdrawal of lorcaserin
- Differentiate between FDA-approved chronic and short-term weight management drugs
- Summarize obesity guideline recommendations
- Recommend appropriate pharmacotherapy for weight management

TEST QUESTIONS

1. Why did the FDA request the withdrawal of lorcaserin from the U.S. market?

   a) Cardiovascular risk b) Cancer risk c) Drug interaction

2. How long should short-term weight management drugs be used for?

   a) Up to 12 weeks b) Up to 6 months c) Up to 1 year

TEST QUESTIONS

3. Which FDA-approved drug for weight management is available over-the-counter?

   a) Liraglutide b) Orlistat c) Phentermine

4. A generalizable hierarchical pharmacotherapy algorithm is applicable to all patients requiring weight management.

   TRUE or FALSE?

February 2020

MedWatch - The FDA Safety Information and Adverse Event Reporting Program

A *MedWatch* Safety Alert was added to the FDA *MedWatch* webpage

TOPIC: Belviq, Belviq XR (lorcaserin) by Eisai: Drug Safety Communication – FDA Requests Withdrawal of Weight-Loss Drug

1. US FDA. MedWatch 2020.

LORCASERIN CARDIOVASCULAR SAFETY STUDY[1,2]

- CAMELLIA-TIMI 61 was required by the FDA at approval to evaluate the risk of cardiovascular problems
- 5-year study uncovered a possible ↑ risk of cancer in patients treated with lorcaserin:
  - 7.7% of patients on lorcaserin vs. 7.1% of patients on placebo
  - Different types of cancers including pancreatic, lung and colorectal

1. US FDA. MedWatch 2020. 2. US FDA. Drug Safety Communications 2020.

Alternatives?

Efficacy?

Safety?

Guidelines?

Health Professionals

Health professionals should stop prescribing and dispensing lorcaserin to patients. Contact patients currently taking lorcaserin, inform them of th[illegible] in the clinical trial, and ask them to stop taking the m[illegible]

Discuss alternative weight-loss medicines or strategies with your patients.

FDA is not recommending special screening for patients who have taken lorcaserin. As with any individual patient, regardless of prior lorcaserin treatment, standard screening recommendations for cancer should be implemented.

Health professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

- Complete and submit the report online.
- Download form or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the form, or submit by fax to 1-800-FDA-0178.

1. US FDA. MedWatch 2020.

FDA-Approved Drugs for Weight Management[3]

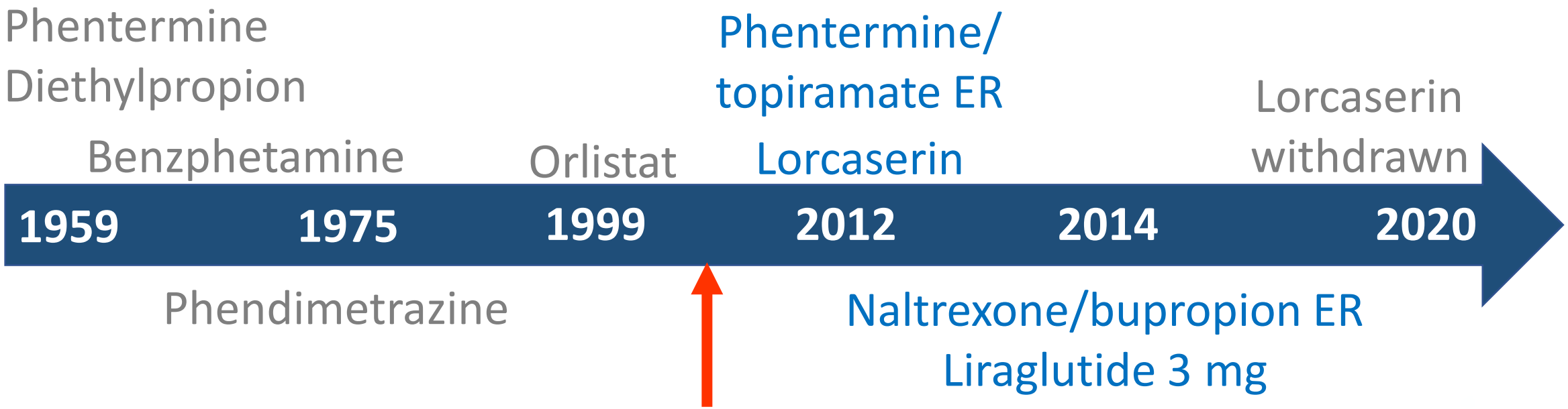
Timeline not to scale

ER = extended release. Purple color = drugs approved for short-term use. Blue color = drugs approved for chronic use.

3. US FDA. Drugs@FDA.

FDA-Approved Drugs for Weight Management[3,4]

Timeline not to scale



ER = extended release.

3. US FDA. Drugs@FDA.
4. US FDA. Guidance for Industry Developing Products for Weight Management. 2007

DRUGS FOR CHRONIC WEIGHT MANAGEMENT

FDA Efficacy Benchmarks for Chronic Drugs[4]

- Difference in mean body weight loss between the active- & placebo-treated groups is ≥5% *AND* the difference is statistically significant.
- Proportion of subjects who lose ≥5% of baseline body weight in the active group is ≥35%,

  Is approximately double the proportion in the placebo group,

  AND the difference between groups is statistically significant.

4. US FDA. Guidance for Industry Developing Products for Weight Management. 2007

Drugs for Chronic Weight Management

Generic Name	Drug Class/MOA
Orlistat (Rx, OTC)[5,6]	Lipase inhibitor
Phentermine/topiramate ER[7]	Sympathomimetic/GABA
Naltrexone/bupropion ER[8]	Opioid antagonist/antidepressant
Liraglutide 3 mg[9]	GLP-1 receptor agonist
Lorcaserin (withdrawn)[10]	*Serotonin receptor agonist*

ER = extended release, MOA = mechanism of action. Rx = prescription, OTC = over-the-counter.

5. Xenical package insert. 6. Alli package insert. 7. Qsymia package insert. 8. Contrave package insert. 9. Saxenda package insert. 10. Belviq package insert.

	FDA-approved Indications & Limitations		
Orlistat[5]	Adults with BMI ≥30 kg/m^2 - *OR* - ≥27 kg/m^2 + ≥1 weight-related comorbidity[a]	- In conjunction with reduced-calorie diet - To reduce risk for weight regain after prior weight loss	None in labeling
Phentermine/ topiramate ER[7]		Adjunct to a reduced-calorie diet and ↑ physical activity	CV morbidity/ mortality unknown
Naltrexone/ bupropion ER[8]			CV morbidity/ mortality unknown
Liraglutide 3 mg[9]			Not indicated in T2D, do not combine with other GLP-1RA

Safety/efficacy with other weight loss products (Rx, OTC, herbal) have not been established[b]

a) E.g., hypertension, type 2 diabetes, or dyslipidemia. b) Not stated in orlistat labeling. BMI = body mass index, CV = cardiovascular, ER = extended release, T2D = type 2 diabetes, RA = receptor agonist, RX = prescription, OTC = over-the-counter.

5. Xenical package insert. 7. Qsymia package insert. 8. Contrave package insert. 9. Saxenda package insert

ORLISTAT CAPSULE

- Prescription (120 mg TID)[5] or over-the-counter (60 mg TID)[6]
- MOA: inhibits pancreatic lipase - 30% of ingested fat is not digested[5]
- Should be taken with a meal or up to 1 hour after a meal[5]
- No renal or hepatic dosing adjustment[5]
- Meta-analysis: 12 orlistat trials over 24-36 months + behavioral modifications.[11]
  - Weight loss with orlistat = 5-10 kg (11-22 lb; 8% of baseline weight)
  - Weight loss with placebo = 3-6 kg (7-13 lb; 5% of baseline weight)

TID = three times a day, MOA = mechanism of action.

5. Xenical package insert. 6. Alli package insert. 11. Leblanc et al. *Ann Int Med*. 2011.

ORLISTAT CAPSULE

XENDOS (4-year study, n=3,305)[12]: Compared orlistat 120 mg TID vs. placebo in adults with BMI ≥30 kg/m^2 and normal (79%) or impaired (21%) glucose tolerance

Results at Year 4	orlistat (n=1,650)	placebo (n=1,655)
T2D cumulative incidence, n%	6.2%	9%
	HR=0.627 [0.455-0.863], 37.3% RRR, p=0.0032	
Mean weight change, kg	-5.8 kg	-3 kg
	difference of 2.7 kg, p <0.001	

TID = three times a day, BMI = body mass index, T2D = type 2 diabetes.

12. Torgerson et al. *Diabetes Care*. 2004

ORLISTAT CAPSULE

Safety[5]

- GI events: cramps, flatus, fecal incontinence, oily spotting
- Decreased absorption/interaction with medications and vitamins
- May increase risk of cholelithiasis due to weight loss
- *Rare* liver injury (hepatocellular necrosis or acute hepatic failure)
- *Rare* urinary oxalate induced kidney injury
- Good cardiovascular (CV) safety profile (improvement in BP, LDL, TChol)
- Category X in pregnancy

BP = blood pressure, LDL = low density lipoprotein, Tchol = total cholesterol.

5. Xenical package insert

PHENTERMINE/TOPIRAMATE EXTENDED RELEASE CAPSULE[7]

- Dosed once in AM with or without food
- Dosing must be titrated from starting dose 3.75 mg/23 mg up to the max dose of 15 mg/92 mg[a]
- DEA Schedule CIV due to potential for abuse or dependence[b]
- Qsymia REMS Program: requires pregnancy test prior to initiation & monthly thereafter; effective contraception needed[13]
  - Provider training, patient consultation, med guide & brochure
  - Only certified pharmacies may dispense drug

a) Capsules available in four strengths: 3.75/23 mg, 7.5/46 mg, 11.25/69 mg, 15/92 mg. b) Boxed warning and subject to CURES. AM = morning, REMS = Risk Evaluation and Mitigation Strategy.

7. Qsymia package insert. 13. Qsymia REMS www.qsymiarems.com

PHENTERMINE/TOPIRAMATE EXTENDED RELEASE CAPSULE

CONQUER (1-year study, n=2,487)[14]

- Different doses of PHN/TPM vs. placebo in adults, BMI 27-45 kg/m^2 with ≥2 comorbidities[a]

Results at 1 year	PHN/TPM 7.5/46 mg	PHN/TPM 15/92 mg	Placebo
Mean weight change, kg (%)	-8.1 kg (-7.8%)	-10.2 kg (-9.8%)	-1.3 kg (-1.2%)
PBO-adjusted % weight loss	-6.6%	-8.6%	--
Pts with ≥5% weight loss	62%	70%	21%
Pts with ≥10% weight loss	37%	48%	7%

PHN/TPM = phentermine/topiramate extended release, Pts = patients, PBO = placebo.
a) hypertension, dyslipidemia, diabetes, prediabetes, or abdominal obesity.
14. Gadde et al. *Lancet* 2011.

PHENTERMINE/TOPIRAMATE EXTENDED RELEASE CAPSULE

EQUIP (1-year study, n=498)[15]

- PHN/TPM ER vs. placebo in adults ≥BMI 35 kg/m^2 without diabetes

Results at 1 year	PHNTPM 3.75/23 mg	PHN/TPM 15/92 mg	Placebo
Mean % weight change	-5.1%	-10.9%	-1.6%
PBO-adjusted % weight loss	-3.5%	-9.4%	--
Pts with ≥5% weight loss	45%	67%	17%
Pts with ≥10% weight loss	19%	47%	7%

PHN/TPM ER = phentermine/topiramate extended release. Pts = patients, PBO = placebo.

15. Allison et al. *Obesity* 2012.

PHENTERMINE/TOPIRAMATE EXTENDED RELEASE CAPSULE[7]

Safety precautions (selected)

- Fetal toxicity (cleft palate)
- Increased heart rate
- Suicidal behavior and ideation
- Acute myopia and secondary angle closure glaucoma
- Mood and sleep disorders
- Metabolic acidosis
- Elevated creatinine, kidney stones
- Increased risk of hypoglycemia with glucose lowering drugs
- Dose adjustment for renal and hepatic impairment (7.5/46 mg/d)
- Pregnancy category X

Most common adverse events: paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth

7. Qsymia package insert.

PHENTERMINE/TOPIRAMATE EXTENDED RELEASE CAPSULE

Drug interactions[7]

- MAOI use during or within 14 days of phentermine is contraindicated
- Oral contraceptives: irregular bleeding
- Central nervous system depressants including alcohol
- Non-potassium sparing diuretics
- Antiepileptic drugs
- Carbonic anhydrase inhibitors: may increase risk of kidney stones

MAOI = monoamine oxidase inhibitor.

7. Qsymia package insert.

NALTREXONE/BUPROPION EXTENDED RELEASE TABLET[8]

- Fixed dose combination tablet available in one strength (8 mg/90 mg) taken with food
- Dosed according to escalation schedule:
  - Week 1: 1 tab in AM;
  - Week 2: 1 tab BID (AM & PM);
  - Week 3: 2 tabs in AM & 1 tab in PM;
  - Week 4: 2 tabs BID (AM & PM):

  Usual/max dosage = NAL 32 mg/BUP 360 mg

AM = morning, PM = evening, BID = twice daily, NAL = naltrexone, BUP = bupropion.

8. Contrave package insert

NALTREXONE/BUPROPION EXTENDED RELEASE TABLET

Study 56-week results	Treatment Arms	Mean % weight change	Pts with ≥5% weight loss
COR-I [16] n=1742	NAL 32 mg/BUP 360 mg	-6.1%*	48%*
	NAL 16 mg/BUP 360 mg	-5%*	39%*
	placebo	-1.3%	16%

*p <0.0001 vs. placebo. **p <0.001 vs. placebo. NAL = naltrexone, BUP = bupropion. Results from published trials are based on modified intent-to-treat (miTT) population which differ from the results in the labeling.

16. Greenway et al. *Lancet* 2010.

NALTREXONE/BUPROPION EXTENDED RELEASE TABLET

Study 56-week results	Treatment Arms	Mean % weight change	Pts with ≥5% weight loss
COR-II [17] n=1496	NAL 32 mg/BUP 360 mg	-6.4%**	50.5%**
	placebo	-1.2%	17.1%
COR-BMOD [18] n=793	NAL 32 mg/BUP 360 mg	-9.3%**	66.4%**
	placebo	-5.1%	42.5%

*p <0.0001 vs. placebo. **p <0.001 vs. placebo. NAL = naltrexone, BUP = bupropion. Results from published trials are based on modified intent-to-treat (miTT) population which differ from the results in the labeling.

17. Apovian et al. *Obesity* 2013. 18. Wadden et al. *Obesity* 2011.

NALTREXONE/BUPROPION EXTENDED RELEASE TABLET

Study 56-week results	Treatment Arms	Mean % weight change	Pts with ≥5% weight loss
COR-Diabetes [19] n=1496	NAL 32 mg/BUP 360 mg	-5%*	44.5*
	placebo	-1.8%	18.9

- Patients in the study had a mean baseline A1c of 8%
- Mean change in A1c was greater in treatment arm (-0.6%) vs. (-0.1%) in placebo arm
- More patients in the treatment arm (44.1%) achieved A1c <7% compared to those in the placebo arm (26.3%)

*p <0.001 vs. placebo. NAL = naltrexone, BUP = bupropion. Results from published trial are based on modified intent-to-treat (miTT) population which differ from the results in the labeling.

19. Hollander et al. *Diabetes Care* 2014.

NALTREXONE/BUPROPION EXTENDED RELEASE TABLET

BOXED WARNING: SUICIDAL THOUGHTS AND BEHAVIORS [8,20]

- Increased risk of suicidal thoughts & behaviors in children, adolescents/ young adults taking antidepressants for major depression & other psychiatric disorders.
- Monitor for worsening and emergence of suicidal thoughts & behaviors
- Serious neuropsychiatric reactions in patients taking bupropion for smoking cessation have been reported.

Not indicated for the treatment of pediatric patients, depression, or smoking cessation

8. Contrave package insert 20. Contrave Medication Guide.

NALTREXONE/BUPROPION EXTENDED RELEASE TABLET[8]

Contraindications

- Pregnancy (Category X)
- Concomitant use of other bupropion-containing products
- Chronic opioid, opiate agonist or partial agonist use, or acute opiate withdrawal
- Known allergy to components
- Abrupt discontinuation of alcohol, benzodiazepines, barbiturate, & antiepileptic drugs
- Uncontrolled hypertension
- Seizure disorder
- Eating disorders
- MAOIs: concurrent use or use within 14 days

MAOI = monoamine oxidase inhibitors.

8. Contrave package insert.

NALTREXONE/BUPROPION EXTENDED RELEASE TABLET[8]

Warnings/Precautions

- Suicidal behavior and ideation / neuropsychiatric adverse events and suicide risk in smoking cessation treatment
- Risk of seizure
- Vulnerability to opioid overdose, opioid withdrawal
- Increase in blood pressure and heart rate
- Hepatotoxicity
- Angle-closure glaucoma
- Hypoglycemia in patients taking glucose lowering drugs
- Allergic reactions
- Activation of mania

8. Contrave package insert.

.

NALTREXONE/BUPROPION EXTENDED RELEASE TABLET[8]

Most common adverse reactions:

- Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth & diarrhea

Other adverse reactions (selected):

- Psychiatric and sleep disorders
- Neurocognitive adverse reactions
- Increases in serum creatinine

Drug interactions:

- MAOIs
- Opioid analgesics, alcohol
- Digoxin
- Substrates, inhibitors and inducers of CYP2D6
- Drugs that lower seizure threshold
- Dopaminergic drugs
- False-positive labs

MAOIs: monoamine oxidase inhibitors

8. Contrave package insert.

LIRAGLUTIDE 3 MG INJECTION[9]

- Available in disposable, pre-filled pen
- Subcutaneous injection in abdomen, thigh, or upper arm
- 3 mg once daily, any time of day, without regard to meals
  - Initiate at 0.6 mg/day for 1 week.
  - Increase dose weekly by 0.6 mg/day until a dose of 3 mg/day is reached (week 5)
- Discontinue if 3 mg not tolerated; efficacy not established at lower doses

9. Saxenda package insert

LIRAGLUTIDE 3 MG INJECTION

Study 56-week results	Treatment Arms	Mean % weight change	Pts with ≥5% weight loss
SCALE-obesity & pre-diabetes [21] n=3731	Liraglutide 3 mg	-8*	63.2*
	Placebo	-2.6	27.1
SCALE-diabetes [22] n=846	Liraglutide 3 mg	-6*	54.3*
	Liraglutide 1.8 mg	-4.7*	40.4*
	placebo	-2	21.4

*p <0.001 vs. placebo. Sponsor's primary analysis: modified last available observation carried forward imputation using only on-treatment measurements.The FDA-approved labeling reports the results from the intent-to-treat analysis.

21. Pi-Sunyer et al. *N Engl J Med* 2015. 22. Davies et al. *JAMA* 2015.

LIRAGLUTIDE 3 MG INJECTION

Study 56-week results	Treatment Arms	Mean % weight change	Pts with ≥5% weight loss
SCALE-maintenance [23] n=422	Liraglutide 3 mg	-6.2**	81.4**
	Placebo	-0.2	48.9

**p <0.001 vs. placebo. Sponsor's primary analysis: modified last available observation carried forward imputation using only on-treatment measurements.The FDA-approved labeling reports the results from the intent-to-treat analysis.

23. Wadden et al. *Int J Obes (Lond)* 2013..

LIRAGLUTIDE 3 MG INJECTION

BOXED WARNING: RISK OF THYROID C-CELL TUMORS [9,24]

- Thyroid C-cell tumors at clinically relevant exposures in rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans (relevance of this rodent data has not been determined)
- Contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)

9. Saxenda package insert. 24. Saxenda medication guide.

LIRAGLUTIDE 3 MG INJECTION[9]

Contraindications:

- Personal or family history of MTC or MEN2
- Hypersensitivity to liraglutide or any product components
- Pregnancy (Category not listed)

Other warnings/precautions:

- Acute pancreatitis, acute gallbladder disease
- Serious hypoglycemia (with insulin/insulin secretagogue)
- Increase in heart rate
- Renal impairment
- Hypersensitivity
- Suicidal behavior and ideation

9. Saxenda package insert

LIRAGLUTIDE 3 MG INJECTION[9]

Drug interactions:

- Delayed gastric emptying may impact absorption of oral medications (unclear if clinically relevant)

Most common adverse reactions:

- Nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase

9. Saxenda package insert.

Drugs for Short-term Weight Management

Drugs Short-Term Weight Management (≤ 3 months)

Drug [3,25-28]	Indication
Phentermine[a]	Short-term adjunct (a few weeks) + exercise behavioral modification and caloric restriction in pts BMI ≥30 or ≥27 with risk factors (e.g., controlled HTN, diabetes, hyperlipidemia)
Diethylpropion[a,b]	Short-term adjunct (a few weeks) + caloric restriction in pts BMI ≥30 who have not responded to appropriate weight reducing regimen (diet and/or exercise) alone
Phendimetrazine[b]	
Benzphetamine[b]	

a) Limited usefulness of agents of this class should be measured against possible risk factors. b) Indicated for use as monotherapy only.

3. US FDA. Drugs@FDA. 25. Phentermine package insert 26. Diethylpropion package insert. 27. Phendimetrazine package insert 28. Benzphetamine package insert.

Drugs Short-Term Weight Management (≤ 3 months)

Controlled medications – subject to CURES

Drug[25-30]	MOA[29-30]	Mean short-term weight change (dif. from placebo)[31]
Phentermine 15-37.5 mg *CIV*	Noradrenergic causing appetite suppression	3.6 kg
Diethylpropion 25 or 75 mg *CIV*		3 kg
Phendimetrazine 17.5-70 mg *CIII*		n/a
Benzphetamine 25-50 mg *CIII*		3.3 kg

MOA = mechanism of action. dif = difference.

25. Phentermine package insert 26. Diethylpropion package insert. 27. Phendimetrazine package insert 28. Benzphetamine package insert. 29. Yanovski et al. *JAMA* 2014. 30. Saxon et al. *ENDO online* 2020. 31. Haddock et al. *Int J Obes Relat Metab Disord* 2002.

DRUGS SHORT-TERM WEIGHT MANAGEMENT[3,25-29]

Contraindications:

- Cardiovascular disease/ uncontrolled hypertension
- MAOI use
- Hyperthyroidism
- Glaucoma
- Hypersensitivity
- History of drug abuse
- Pregnancy / Nursing
- Diethylpropion & phendimetrazine: Combination with other anorectic drugs
- Agitated states

Pregnancy categories:

- Category X: phentermine, benzphetamine
- Category C: phendimetrazine
- Category B: diethylpropion

3. US FDA. Drugs@FDA. 25. Phentermine package insert 26. Diethylpropion package insert. 27. Phendimetrazine package insert 28. Benzphetamine package insert. 29. Yanovski et al. *JAMA* 2014.

DRUGS SHORT-TERM WEIGHT MANAGEMENT[3,25-28]

Warnings / Precautions:

- + other weight loss drugs
- Primary pulmonary hypertension
- Valvular heart disease
- Tolerance
- Ability to engage in hazardous tasks
- Abuse and dependence
- Usage with alcohol
- Hypertension
- Glucose lowering drugs
- Risk of allergic reaction

3. US FDA. Drugs@FDA. 25. Phentermine package insert. 26. Diethylpropion package insert. 27. Phendimetrazine package insert. 28. Benzphetamine package insert.

Drugs Short-Term Weight Management[3,25-28]

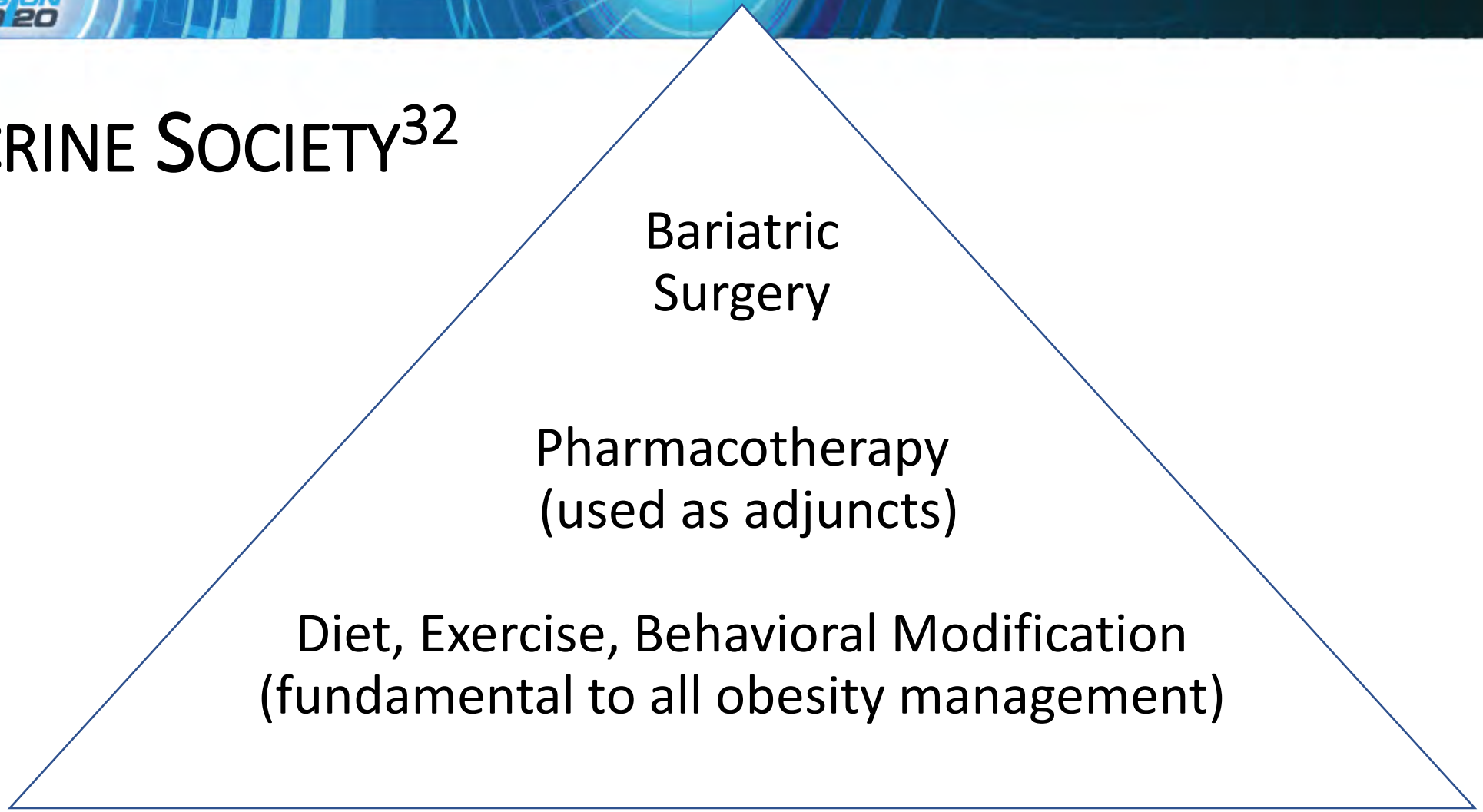
- Common adverse reactions (selected): insomnia, ↑heart rate, dry mouth, altered taste, dizziness, tremors, headache, diarrhea, constipation, vomiting, GI distress, anxiety, restlessness, urticaria, rash, changes in libido
- Drug interactions*: MAOIs, alcohol, glucose lowering drugs, adrenergic central nervous system stimulants, neuron blocking drugs
  diethylpropion only: general anesthetics, antihypertensives (e.g., guanethidine, methyldopa), phenothiazines

GI = gastrointestinal, MAOIs = monoamine oxidase inhibitors. *no drug interactions reported for phendimetrazine.

3. US FDA. Drugs@FDA. 25. Phentermine package insert. 26. Diethylpropion package insert. 27. Phendimetrazine package insert. 28. Benzphetamine package insert.

GUIDELINES

ENDOCRINE SOCIETY[32]



GRADE: Strong recommendation, high quality evidence

32. Apovian et al. *J Clin Endocrinol Metab* 2015.

ENDOCRINE SOCIETY[32]

Indications for pharmacotherapy:

- BMI ≥ 30 kg/m^2
- BMI ≥27 kg/m^2 with ≥1 comorbidity
  - hypertension, diabetes, dyslipidemia, obstructive sleep apnea

GRADE: Weak recommendation, low quality evidence

Monitoring/Assessment

- Assess efficacy, safety at least monthly for first 3 months then at least every 3 months

GRADE: Strong recommendation; high quality evidence

32. Apovian et al. *J Clin Endocrinol Metab* 2015.

ENDOCRINE SOCIETY[32]

When to discontinue?

- Effective: weight loss ≥5% of body weight at 3 month = continue medication
- Ineffective: weight loss <5% body weight at 3 months or if there are safety or tolerability issues at any time = discontinue medication

GRADE: Strong recommendation; high quality evidence

32. Apovian et al. *J Clin Endocrinol Metab* 2015.

WHEN TO DISCONTINUE DUE TO LACK OF EFFICACY?

Drug	FDA recommendation
Orlistat[5]	no recommendation made in labeling
Phentermine/ topiramate ER[7]	7.5/46 mg: if pt has not lost ≥3% of BW after 12 wks 15/92 mg (max): if pt has not lost ≥5% of BW after 12 wks
Naltrexone/ bupropion ER[8]	if patient has not lost ≥5% of BW after 12 wks
Liraglutide 3 mg[9]	if 3 mg not tolerated, or if patient has not lost ≥4% of BW after 16 wks

pt = patient, BW = body weight, wks = weeks.

5. Xenical package insert. 7. Qsymia package insert. 8. Contrave package insert. 9. Saxenda package insert

American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE)[33]

- Pharmacotherapy as an adjunct to lifestyle therapy
- Consider in patients with weight-related complications that can be ameliorated by weight loss
- Consider in patients with obesity, when potential benefits outweigh risks, for chronic treatment
- Short-term treatment (3 to 6 months) using weight-loss medications has not been demonstrated to produce longer-term health benefits

33. Garvey et al. *Endocrine Practice* 2016.

AACE/ACE Guideline[33]

Choice of Weight-Loss Agent

- Consider efficacy, side effects, cautions, & warnings
- Consider presence of weight-related complications and medical history
- Access to all approved medications

"A generalizable hierarchical algorithm for medication preferences that would be applicable to all patients cannot currently be scientifically justified."

33. Garvey et al. *Endocrine Practice* 2016.

AACE/ACE – Individualization of Therapy[33]

preferred drug use with caution avoid

Condition*		Orlistat	Phen/Top ER	Nal/Bup ER	Lira 3 mg
Diabetes prevention				Insufficient data for T2D prevention	
T2D					
Hypertension			Monitor HR	Monitor BP & HR	Monitor HR
				CI: uncontrolled HTN	
CVD	CAD		Monitor HR	Monitor HR, BP	Monitor HR
	Arrhythmia		Monitor HR, rhythm	Monitor HR, rhythm, BP	Monitor HR, rhythm,
	CHF	Insufficient data	Insufficient data	Insufficient data	Insufficient data

*clinical characteristics or coexisting diseases. Phen = phentermine, Top = topiramate, Nal = naltrexone, Bup = bupropion, Lira = liraglutide, ER = extended release, T2D = type 2 diabetes, CVD = cardiovascular disease, CAD = coronary artery disease, CHF =chronic heart failure, BP = blood pressure, HR = heart rate, CI = contraindicated. 33. Garvey et al. *Endocrine Practice* 2016

CS

AACE/ACE – Individualization of Therapy[33]

preferred drug use with caution avoid

Condition*		Orlistat	Phen/Top ER	Nal/Bup ER	Lira 3 mg
CKD	Mild (≥50 ml/min)				
	Moderate (30-49 mL/min)		DNE 7.5 mg/46 mg/d	DNE 8 mg/90 mg BID	
	Severe (<30 mL/min)	Watch for oxalate nephropathy	Urinary clearance of drug	Urinary clearance of drug	Avoid vomiting, volume depletion
Nephrolithiasis		Calcium oxalate stones	Calcium phosphate stones		
Hepatic impairment	Mild-moderate (Child-Pugh 5-9)	Watch for cholelithiasis	DNE 7.5 mg/46 mg/d	DNE 8 mg/90 mg AM	Watch for cholelithiasis
	Severe (Child-Pugh >9)	Not recommended	Not recommended	Not recommended	Not recommended

*clinical characteristics or coexisting diseases. BID = twice daily, AM = morning, DNE = do not exceed.

33. Garvey et al. *Endocrine Practice* 2016

AACE/ACE – Individualization of Therapy

■ preferred drug ■ use with caution ■ avoid

Condition*		Orlistat	Phen/Top ER	Nal/Bup ER	Lira 3 mg
CKD	Mild (≥50 ml/min)				
	Moderate (30-49 ml/min)		DNE 7.5 mg/46 mg/d	DNE 8 mg/90 mg BID	
	Se (<3				Avoid vomiting, volume depletion
Nephrolithia					
Hepatic impairment	Mild-moderate (Child-Pugh 5-9)	Watch for cholelithiasis	DNE 7.5 mg/46 mg/d	DNE 8 mg/90 mg AM	Watch for cholelithiasis
	Severe (Child-Pugh >9)	Not recommended	Not recommended	Not recommended	Not recommended

Additional conditions covered in AACE/ACE guideline

*clinical characteristics or coexisting diseases. Phen = phentermine, Top = topiramate, Nal = naltrexone, BUP = Bupropion, Lira = liraglutide, ER = extended release, BID = twice daily, AM = morning, DNE = do not exceed. 1. Garvey et al. *Endocrine Practice* 2016

OTHER GUIDELINES[34]

- Obesity Society
- American Diabetes Association – Obesity Management for the treatment of Type 2 Diabetes
- European Association for the Study of Obesity (EASO)
- National Institute for Health and Care Excellence (NICE)
- Canadian Task Force on Preventative Health Care
- National Health and Medical Research Council (Australian)
- Joint statements of different associations

34. Semlitsch et al. *Obes Rev*. 2019.

RULE OUT IATROGENIC DRUGS[32,35]

Condition	Look out for drugs that may cause weight gain
Diabetes	Insulin, sulfonylureas, meglitinides, TZDs
Hypertension	Propranolol, metoprolol, atenolol
Depression	Amitriptyline, nortriptyline, imipramine, citalopram, paroxetine, mirtazapine
Psychoses	Clozapine, quetiapine, olanzapine, haloperidol, lithium, valproic acid
Epilepsy	Gabapentin, pregabalin, valproic acid
Contraceptives	Depot medroxyprogesterone
Anti-inflammatory	Prednisone, dexamethasone
Antihistamines	Diphenhydramine, cetirizine

TZD = thiazolidinediones. 32. Apovian et al. *JCEM* 2015. 35. Wharton et al. *Diabetes Metabl Syndr Obes* 2018.

So what's the best alternative to lorcaserin?

CONSIDER...

- Likelihood of attaining goal weight/maintaining weight loss
- Safety: contraindications / adverse events
- Concomitant drugs or disease states / pathophysiology
- Dosage form and administration: oral vs. injection
- Frequency (daily vs. more often) / Pill burden?
- Underlying behaviors
- Cost

PATIENT CASE: 39-YEAR-OLD FEMALE, BMI 32, PREVIOUSLY ON LORCASERIN

What alternative treatments to recommend?

- Individualized treatment:
  - Identify realistic weight loss goals
  - Review medical history and current medication list
- Consider patient preferences: side effect profile, administration route, cost/affordability
- Don’t forget emphasis on healthy eating, lifestyle interventions and support system to encourage success

PATIENT CASE: 37-YEAR-OLD FEMALE, BMI 32, PREVIOUSLY ON LORCASERIN

What are alternative options you can recommend to her prescriber?

- Goal weight loss: at least 4-5% of initial body weight
  - e.g., 205 lbs = 8 to 11 lb weight loss after 3 to 4 months of treatment
- No significant medical history; on hormonal contraceptive
- Patient states that she doesn't want to give herself injections
- Patient is motivated and using an app suggested by her prescriber that is based on behavioral strategies to facilitate adherence to diet and activity

PATIENT CASE: 37-YEAR-OLD FEMALE, BMI 32, PREVIOUSLY ON LORCASERIN

Avoid:

- Phen/Top ER: topiramate drug interaction with hormonal contraceptives
- Liraglutide 3 mg: daily injection

Suggest: orlistat or NAL/BUP ER

- Review expected efficacy, potential adverse events, dosing and administration of each drug. Look out for other patient preferences that may come up.

Drug choice should be made on an individual basis

COMPARISON TABLE: WEIGHT CHANGE[3,30]

	Typical maintenance dose	%BW lost	Pts with ≥5% weight loss	Pts with ≥10% weight loss
Lorcaserin	10 mg BID (XR: 20 mg daily)	4-6%	47%	22%
Orlistat[a]	120 mg TID (Rx)	3-4%	21%	12%
Phen/Top ER	7.5-15 mg/46-92 mg daily	8-11%	41-49%	30-41%
Nal/Bup ER	16 mg/180 mg BID	5-6%	35%	20%
Lira 3 mg	3 mg daily	6-7%	36%	23%
Phentermine[b]	15-37.5 mg	5%	nr	nr

a. Also available over-the-counter. b. Short-term use. BID = twice daily, nr = not reported.
b. 3. US FDA. Drugs@FDA. 30 Saxon et al. *ENDO online* 2020.

COMPARISON TABLE: CONTRAINDICATIONS AND SELECT MAJOR PRECAUTIONS

Orlistat	Phen/Top ER	Nal/Bup ER	Lira 3 mg
• Pregnancy • Chronic malabsorption syndrome • Cholestasis	• Pregnancy; fetal toxicity (REMS) • Glaucoma • Hyperthyroidism • MAOIs • Cardiovascular disease (due to increased HR) • Suicidal behavior & ideation	• Pregnancy • Uncontrolled HTN • Seizure disorder; eating disorders, abrupt withdrawal of alcohol, benzodiazepines, barbiturates, antiepileptic drugs • Other bupropion products, chronic opioid use &MAOIs • ESRD • Suicidal behavior & ideation	• Pregnancy • Personal or family history of MTC/MEN2 • Pancreatitis • Suicidal behavior & ideation

3. US FDA. Drugs@FDA. 30. Saxon et al. *ENDO online* 2020.

TEST QUESTIONS

1. Why did the FDA request the withdrawal of lorcaserin from the U.S. market?

   a) Cardiovascular risk **b) Cancer risk** c) Drug interaction

2. How long should short-term weight management drugs be used for?

   a) Up to 12 weeks b) Up to 6 months c) Up to 1 year

TEST QUESTIONS

3. Which FDA-approved drug for weight management is available over-the-counter?

   a) Liraglutide **b) Orlistat** c) Phentermine

4. A generalizable hierarchical pharmacotherapy algorithm is applicable to all patients requiring weight management.

   TRUE or **FALSE**

REFERENCE LIST

1. US FDA. Belviq, Belviq XR (lorcaserin) by Eisai: Drug Safety Communication - FDA Requests Withdrawal of Weight-Loss Drug https://www.fda.gov/safety/medical-product-safety-information/belviq-belviq-xr-lorcaserin-eisai-drug-safety-communication-fda-requests-withdrawal-weight-loss-drug. Published February 13, 2020.
2. US FDA. Drug Safety Communications - FDA requests the withdrawal of the weight-loss drug Belviq, Belviq XR (lorcaserin) from the market - Potential risk of cancer outweighs the benefits. https://www.fda.gov/media/135189/download. Published February 13, 2020.
3. US FDA. Drugs@FDA: FDA-Approved Drugs. Database https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
4. U.S. Department of Health and Human Services - Food and Drug Administration - Center for Drug Evaluation and Research (CDER). Guidance for Industry Developing Products for Weight Management. https://www.fda.gov/media/71252/download. Published February 2007.
5. Xenical [package insert]. H2-Pharma, LLC. Montgomery, AL; November 2019.
6. Alli [drug information label]. GSK Consumer Healthcare. Warren, NJ; 2018.
7. Qsymia [package insert]. Vivus, Inc. Campbell, CA; April 2020.
8. Contrave [package insert]. Nalpropion Pharmaceuticals, Inc.. San Diego, CA; April 2019.
9. Saxenda [package insert]. Novo Nordisk Inc. Plainsboro, NJ; March 2020.
10. Belviq [package insert]. Eisai Inc., Woodcliff Lake, NJ; April 2018.
11. Leblanc ES, O'Connor E, Whitlock EP, Patnode CD, Kapka T. Effectiveness of primary care-relevant treatments for obesity in adults: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2011;155(7):434-447. doi:10.7326/0003-4819-155-7-201110040-00006
12. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients [published correction appears in Diabetes Care. 2004 Mar;27(3):856]. *Diabetes Care*. 2004;27(1):155-161. doi:10.2337/diacare.27.1.155
13. Vivus Inc. Qsymia REMS. https://www.qsymiarems.com/ Last updated August 2014.
14. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial [published correction appears in Lancet. 2011 Apr 30;377(9776):1494]. *Lancet*. 2011;377(9774):1341-1352. doi:10.1016/S0140-6736(11)60205-5
15. Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity (Silver Spring)*. 2012;20(2):330-342. doi:10.1038/oby.2011.330
16. Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial [published correction appears in Lancet. 2010 Aug 21;376(9741):594] [published correction appears in Lancet. 2010 Oct 23;376(9750):1392]. *Lancet*. 2010;376(9741):595-605. doi:10.1016/S0140-6736(10)60888-4
17. Apovian CM, Aronne L, Rubino D, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring)*. 2013;21(5):935-943. doi:10.1002/oby.20309
18. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring)*. 2011;19(1):110-120. doi:10.1038/oby.2010.147

REFERENCE LIST (CONTINUED)

19. Hollander P, Gupta AK, Plodkowski R, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes [published correction appears in Diabetes Care. 2014 Feb;37(2):587]. *Diabetes Care*. 2013;36(12):4022-4029. doi:10.2337/dc13-0234
20. Contrave [medication guide]. Nalpropion Pharmaceuticals, Inc. San Diego, CA; April 2019.
21. Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *N Engl J Med.* 2015;373(1):11-22. doi:10.1056/NEJMoa1411892
22. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial [published correction appears in JAMA. 2016 Jan 5;315(1):90]. *JAMA.* 2015;314(7):687-699. doi:10.1001/jama.2015.9676
23. Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study [published correction appears in Int J Obes (Lond). 2013 Nov;37(11):1514] [published correction appears in Int J Obes (Lond). 2015 Jan;39(1):187]. *Int J Obes (Lond)*. 2013;37(11):1443-1451. doi:10.1038/ijo.2013.120
24. Saxenda [medication guide]. Novo Nordisk Inc. Plainsboro, NJ; March 2020.
25. Phentermine hydrochloride capsule [package insert].Aurobindo Pharma USA, Inc. Dayton, NJ; January 2019.
26. Diethylpropion hydrochloride tablets [package insert]. Lannett Company, Inc. Philadelphia, PA; December 2019.
27. Phendimetrazine tartrate tablets [package insert] Elite Laboratories, Inc. Northvale, NJ; January 2019.
28. Benzphetamine hydrochloride tablets. [package insert]. Heritage Pharmaceuticals Inc. East Brunswick, NJ; December 2019.
29. Yanovski SZ and Yanovski JA. Long-term Drug Treatment for Obesity A Systematic and Clinical Review. *JAMA* 2014;311(1):74-86. doi:10.1001/jama.2013.281361
30. Saxon D and Corneir MA. Pharmacotherapy in Obesity. Presented at ENDO Online 2020 on May 19, 2020. https://www.endocrine.org/meetings-and-events/endo-online-2020/schedule-at-a-glance/pharmacotherapy-in-obesity.
31. Haddock CK, Poston WS, Dill PL, Foreyt JP, Ericsson M. Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials. *Int J Obes Relat Metab Disord*. 2002;26(2):262-273. doi:10.1038/sj.ijo.0801889
32. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline [published correction appears in J Clin Endocrinol Metab. 2015 May;100(5):2135-6]. *J Clin Endocrinol Metab*. 2015;100(2):342-362. doi:10.1210/jc.2014-3415
33. Garvey WT, Mechanick JI, Brett EM, et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR MEDICAL CARE OF PATIENTS WITH OBESITY. *Endocr Pract*. 2016;22 Suppl 3:1-203. doi:10.4158/EP161365.GL
34. Semlitsch T, Stigler FL, Jeitler K, Horvath K, Siebenhofer A. Management of overweight and obesity in primary care-A systematic overview of international evidence-based guidelines. *Obes Rev*. 2019;20(9):1218-1230. doi:10.1111/obr.12889
35. Wharton S, Raiber L, Serodio KJ, Lee J, Christensen RA. Medications that cause weight gain and alternatives in Canada: a narrative review. *Diabetes Metab Syndr Obes*. 2018;11:427-438. Published 2018 Aug 21. doi:10.2147/DMSO.S171365

Session Code: