



Medicating the Patient with Obesity... Guidance from AACE 2014 Advanced Framework

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Disclosure

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Objectives



1. Identify principles for medicating the obese patient, chiefly, when to employ medications and how long to use them;
2. Identify differences in mechanism of action of medications used for chronic weight management;
3. Recognize differences in safety, tolerability and efficacy profiles for the five medications used for chronic weight management so as to match medication profiles to patient profiles.

- Carmella Z. 47 year old nurse anesthetist, history of HTN; referred by boss for weight loss; job performance is suffering
- CC: "tired all the time" and "I am almost dropping off at work"
- History: weighed 130 pounds when she finished college
 - gained about 15 pounds when she quit smoking
 - gained ~40 pounds with each of her three pregnancies and "had to fight to lose the most of the extra weight afterwards"
 - divorced five years ago, experienced depression, took paroxetine and gained 30 pounds.
 - Lost 25 pounds with Jenny Craig and 15 pounds with Weight Watchers – with regain.
 - "I know how to diet, but have a hard time with appetite. I go to water aerobics at the Y once a week. My knees give me problems when walking or jogging."
- Physical Examination: Height 63 inches, weight 175 pounds, BMI 31, waist circumference 45 inches. Blood pressure 145/90. The physical examination is normal. Pap smear obtained and mammogram ordered.
- Meds: depot progesterone for contraception, propranolol and hydrodiuril for HTN, acetaminophen PM for sleep, oxybutinin for incontinence
- Labs: Chem profile: Fasting glucose 117, A1c 5.9% TG 170 mg/dL, otherwise chem survey, lipid panel normal.

Which one of the patient's medications (present and past) is not likely to have contributed to her weight gain?

1. Oxybutinin
2. Paroxetine
3. Depot progesterone
4. Propanolol
5. Acetaminophen PM

Which aspect of the patient's history is not likely to have contributed to her weight gain?

1. Smoking cessation
2. Shift work and sleep deprivation
3. Post-partal weight retention
4. Sedentary lifestyle
5. Jenny Craig and Weight Watchers

What additional information is most important to obtain before undertaking a treatment plan?

1. Liver biopsy
2. Sleep study
3. Beck Depression Inventory
4. X rays of knees and orthopedic evaluation
5. Repeat lipid profile and fasting glucose

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How would you stage this patient according to the AACE Advanced Framework ?

1. Stage 0; she has BMI >30, but no complications
2. Stage 1; she has BMI >30 and mild/moderate complications
3. Stage 3; she has BMI >30 and at least one severe complication

AACE Advanced framework. <https://www.aace.com/files/2014-advanced-framework-for-a-new-diagnosis-of-obesity-as-a-chronic-disease.pdf>.

Evidence for Stage 2 diagnosis

Prediabetes, Metabolic Syndrome, and Type 2 Diabetes.

- Stage 0 (none) No risk factors related to insulin resistance (WC, BP, HDL, TG, fasting Glucose). This is equivalent to Cardiometabolic Disease Stage 0 (CMDS) (9)
- Stage 1 (mild-moderate) 1 or 2 risk factors (WC, BP, HDL, TG; CMDS stage 1)
- **Stage 2 (severe) Prediabetes, Metabolic Syndrome, or Type 2 Diabetes (CMDS stages 2-4)**

AACE Advanced framework. <https://www.aace.com/files/2014-advanced-framework-for-a-new-diagnosis-of-obesity-as-a-chronic-disease.pdf>.

Evidence for Stage 2 diagnosis

Hypertension

- Stage 0 (none) Blood Pressure < 130/85 mm/Hg
- Stage 1 (mild-moderate) BP \geq 130/85 mm/Hg in absence of other risk factors
- Stage 2 (severe complication) BP target not met despite use of anti-hypertensive medication(s)
BP \geq 130/85 mm/Hg in high risk individual: CMDS 2-4, smoking, African American, congestive heart failure

AACE Advanced framework. <https://www.aace.com/files/2014-advanced-framework-for-a-new-diagnosis-of-obesity-as-a-chronic-disease.pdf>.

Evidence for Stage 2 diagnosis

Hypertriglyceridemia/Dyslipidemia

- Stage 0 (none) TG < 150 and HDL-c \geq 40 in male and \geq 50 in female
- Stage 1 (mild-moderate) TG 150-399 and/or HDL-c < 40 in male and < 50 in female in absence of other risk factors
- Stage 2 (severe) TG \geq 400 in absence of other risk factors; TG \geq 150 and HDL-c < 40 in male and < 50 in female in high risk individual: CMDS stage 2-4

AACE Advanced framework. <https://www.aace.com/files/2014-advanced-framework-for-a-new-diagnosis-of-obesity-as-a-chronic-disease.pdf>.

Staging other diagnoses

Sleep Apnea

- Stage 0 (none) No symptoms, Apnea Hypopnea Index (AHI) < 5
- Stage 1 (mild-moderate) AHI 5-29 with no or mild symptoms
- Stage 2 (severe) AHI \geq 30; AHI 5-29 with severe symptoms and/or clinical consequences

AACE Advanced framework. <https://www.aace.com/files/2014-advanced-framework-for-a-new-diagnosis-of-obesity-as-a-chronic-disease.pdf>.

Staging Other Diagnoses

Osteoarthritis

- Stage 0 (none) No symptoms and no radiographic joint changes
- Stage 1 (mild-moderate) Mild-moderate symptoms and functional impairment (e.g., validated questionnaire) and/or mild-moderate anatomical joint changes
- Stage 2 (severe) Moderate-severe symptoms and functional impairment (e.g., validated questionnaire) and/or moderate-severe anatomical joint changes; S/P knee or hip replacement surgery

Stress and Urge Urinary Incontinence

- Stage 0 (none) No symptoms and/or normal urodynamics
- Stage 1 (mild-moderate) Mild-moderate symptom severity score
- Stage 2 (severe) Severe symptom severity score

AACE Advanced framework. <https://www.aace.com/files/2014-advanced-framework-for-a-new-diagnosis-of-obesity-as-a-chronic-disease.pdf>.

Should pharmacotherapy be used as an adjunct to lifestyle intervention?

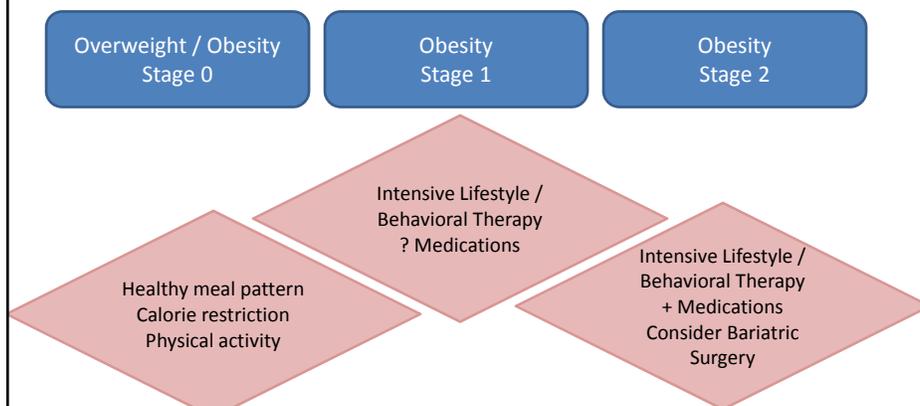
- Yes, if patients have a history of struggling to achieve and sustain weight loss.
- Yes, if patients meet indications.
- Yes, always with lifestyle intervention, because the medications don't work on their own.



"Hundreds of years of medical progress, and all you can tell me to do is *eat less?*"

What does the Advanced Framework Say?

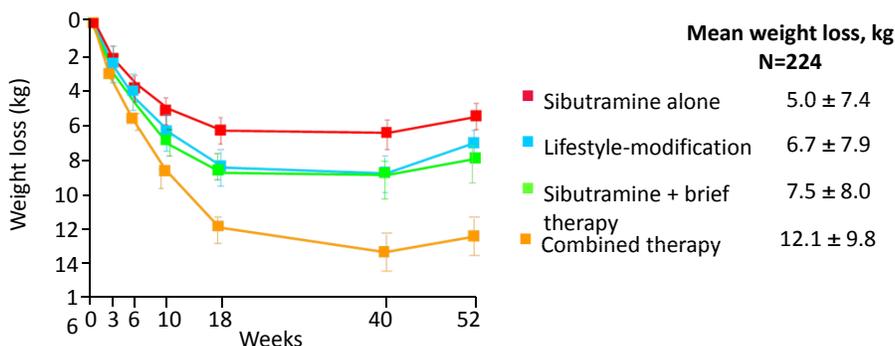
Treatment based on clinical judgment



AACE Advanced framework. <https://www.aace.com/files/2014-advanced-framework-for-a-new-diagnosis-of-obesity-as-a-chronic-disease.pdf>.

The meds don't work on their own

It is important to use medication as an adjunct to lifestyle counseling: here's why



Wadden TA, et al. N Engl J Med 2005;353:2111–2120.

The patient asks, “Do you think a weight loss medication is right for me?” You say, “I’m glad you are thinking about taking some steps to lose weight. It’s the single best thing you can do to improve your overall health. But...”

1. “You would need to show me that you are committed to losing weight before I will prescribe one for you. Lose 10 pounds first.”
2. “You would need to show me you can’t lose weight on your own. Go on a diet and exercise for 6 months. If you have trouble, I will prescribe.”
3. “We need to adjust some of your current medications that are producing weight gain and get your blood pressure under better control. Let’s do that. I also suspect you have sleep apnea and we need to investigate that. I’ll see you back in a month and we will talk about which medication to try and what lifestyle program you’ll use. If you can lose just 10% you can dramatically reduce your chances of progressing to diabetes.”
4. “Your blood pressure is too high. I need to add a medication for your blood pressure. Your blood sugar is in prediabetes range. I am prescribing metformin. That will reduce your blood sugar and metformin also produces weight loss.”

Medications for Diabetes and Weight

WEIGHT GAIN ASSOCIATED WITH USE	ALTERNATIVES (WEIGHT REDUCING IN PARENTHESES)*
Insulin (weight gain differs with type and regimen used) Sulfonylureas Thiazolidinediones Sitagliptin? Metiglinide	(Metformin) (Acarbose) (Miglitol) (Pramlintide) (Exenatide) (Liraglutide) (SGLT 2 inhibitors)

* Only liraglutide 3.0 is FDA-approved for chronic weight management in patients with BMI 30+ kg/m² or BMI 27 <30 kg/m² with one or more comorbidities.

Apovian CM, Aronne LJ, Bessesen DH et al. Pharmacologic Management of obesity: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015
doi:10.1210/jc.2014-3415

Antidepressant Medications and Weight

	WEIGHT GAIN ASSOCIATED WITH USE	ALTERNATIVES (WEIGHT REDUCING IN PARENTHESES)*
Antidepressants/mood stabilizers: tricyclic antidepressants	Amytriptyline Doxepin Imipramine Nortriptyline Trimipramine Mirtazapine	(Bupropion) Nefazodone Fluoxetine (short term) Sertraline (< 1 yr)
Antidepressants/mood stabilizers: SSRIs	Fluoxetine? Sertraline? Paroxetine Fluvoxamine	* Only naltrexone SR/ bupropion SR combination is FDA-approved for chronic weight management in patients with BMI 30+ kg/m ² or BMI 27 <30 kg/m ² with one or more comorbidities
Antidepressants/mood stabilizers: MAO Inhibitors	Phenylzine Tranylcypromine	
Lithium		

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doi:10.1210/jc.2014-3415

Cardiologic Medications and Weight

	WEIGHT GAIN ASSOCIATED WITH USE	ALTERNATIVES (WEIGHT REDUCTING IN PARENTHESES)
Hypertension medications	α -blocker? β -blocker?	ACE inhibitors? Calcium channel blockers ? Angiotensin-2 receptor antagonists

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Antipsychotic and Anticonvulsant Medications and Weight

	WEIGHT GAIN ASSOCIATED WITH USE	ALTERNATIVES (WEIGHT REDUCTING IN PARENTHESES)*
Antipsychotics	Clozapine Risperidone Olanzapine Quetiapine Haloperidol Perphenazine Quetiapine	Ziprasidone Aripiprizole
Anticonvulsants	Carbamazepine Gabapentin Valproate	Lamotrigine? (Topiramate) (Zonisamide)

* Only phentermine/topiramate ER is FDA-approved for chronic weight management in patients with BMI 30+ kg/m² or BMI 27 <30 kg/m² with one or more comorbidities

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Gynecologic Medications and Weight

	WEIGHT GAIN ASSOCIATED WITH USE	ALTERNATIVES (WEIGHT REDUCTING IN PARENTHESES)
Oral contraceptives	Progestational steroids Hormonal contraceptives containing progestational steroids	Barrier methods IUDs
Endometriosis treatment	Depot leuprolide acetate	Surgical treatment

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Ms. Z comes back in a month. You have stopped propranolol and acetaminophen PM and the patient has seen her OBGYN and will stop depot progesterone and use a diaphragm. She is on CPAP for sleep apnea and reports better work performance. She has a plan to start back at Weight Watchers and join a class with stationary bikes. She has researched medications for weight management on the web.

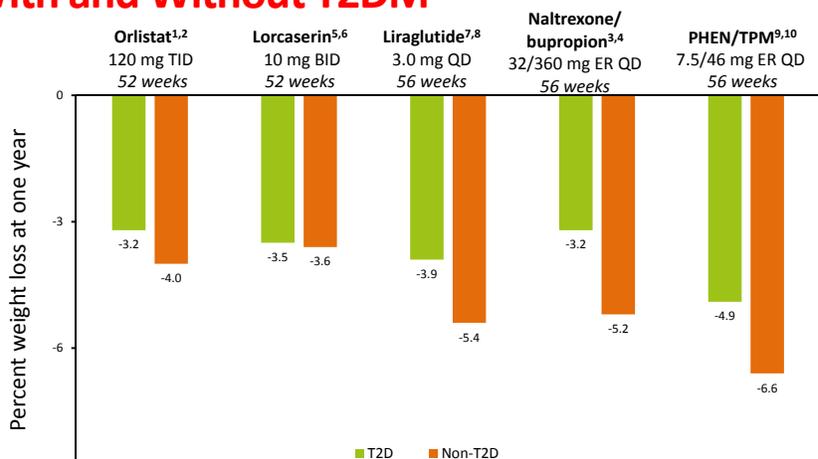
- She asks, “will I lose more weight if I take a medication?”
- “Which one do you think produces the most weight loss, doctor?”

Does adding medications produce more weight loss than lifestyle alone?

- FDA efficacy bench marks for approval:
 - ≥5% weight loss than placebo
 - at least 35% of those on medications achieve 5% weight loss and twice as many as on placebo

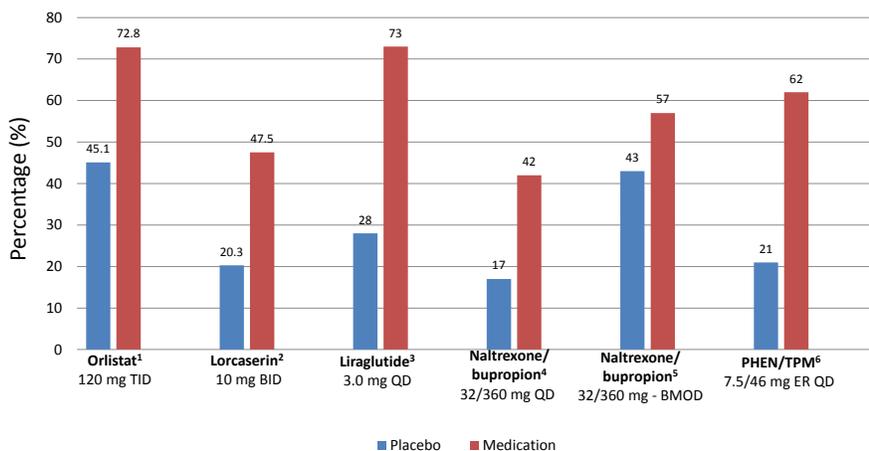
All approved medications have approximated these bench marks.

Placebo-subtracted Weight Loss in Patients With and Without T2DM



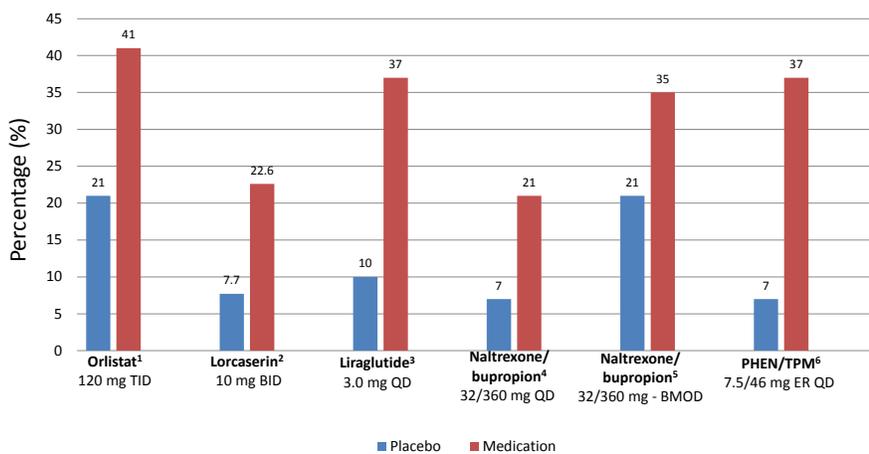
Values are placebo-subtracted and approximated from kg weight reductions where applicable
 1. Torgerson et al. *Diabetes Care* 2004;27:155-61; 2. Berne et al. *Diabet Med* 2005;22:612-8; 3. Smith et al. *N Engl J Med* 2010;363:245-56; 4. O'Neil et al. *Obesity* 2012;20:1426-36; 5. Apovian et al. *Obesity (Silver Spring)* 2013;21:935-43; 6. Hollander et al. *Diabetes Care* 2013;36:4022-9; 7. Pi-Sunyer et al. *Diabetologia* 2014;57:73-OR; 8. Davies et al. *Diabetologia* 2014;57:39-OR; 9. Gadde et al. *Lancet* 2011;377:1341-52; 10. Garvey et al. *Diabetes Care* online September, 2014

Proportion (%) achieving 5% weight loss after 52 weeks at top dose



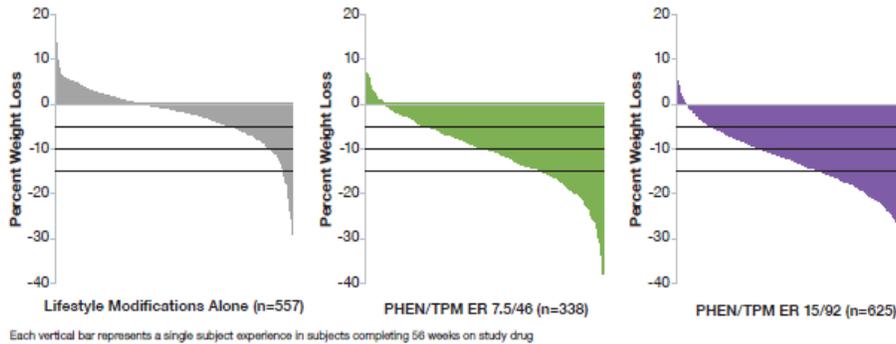
1. Torgerson et al. *Diabetes Care* 2004;27:155-61; 2. Smith et al. *N Engl J Med* 2010;363:245-56; 3 Astrup, et al. *Lancet* 2009; 1606-1616 . 4. Greenway, et al. *Lancet* 2010; 595-605. 5. Wadden , et al. *Obesity* (2011) 19, 110-120. 6. Gadde et al. *Lancet* 2011;377:1341-52;

Proportion (%) achieving 10% weight loss after 52 weeks at top dose



1. Torgerson et al. *Diabetes Care* 2004;27:155-61; 2. Smith et al. *N Engl J Med* 2010;363:245-56; 3 Astrup, et al. *Lancet* 2009; 1606-1616 . 4. Greenway, et al. *Lancet* 2010; 595-605. 5. Wadden , et al. *Obesity* (2011) 19, 110-120. 6. Gadde et al. *Lancet* 2011;377:1341-52;

When individual weight loss is displayed, it looks like this:



McCullough PA, et al. Poster AANP 2013.

Medications approved for chronic weight management and how they work

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>.

Agent	Action	Approval	Scheduled Drug
Orlistat Xenical®	<ul style="list-style-type: none"> Peripheral pancreatic lipase inhibitor - blocks ingested fat absorption 	Approved 1997	<ul style="list-style-type: none"> No
Lorcaserin Belviq®	<ul style="list-style-type: none"> 5-HT_{2C} serotonin agonist Little affinity for other serotonergic receptors 	Approved 2012	<ul style="list-style-type: none"> YES
Phentermine/Topiramate ER Qsymia™	<ul style="list-style-type: none"> Sympathomimetic Anticonvulsant (GABA receptor modulator carbonic anhydrase inhibitor, glutamate antagonist) 	Approved 2012	<ul style="list-style-type: none"> YES
Naltrexone SR/Bupropion SR Contrave®	<ul style="list-style-type: none"> Opioid receptor antagonist Dopamine/noradrenaline reuptake inhibitor 	Approved 2014	<ul style="list-style-type: none"> NO
Liraglutide 3.0 mg Saxenda®	<ul style="list-style-type: none"> GLP-1 receptor agonist 	Approved 2014	<ul style="list-style-type: none"> No

ER: extended release; SR: sustained release. 5HT: serotonin. GABA: Gamma aminobutyric acid. GLP-1: Glucagon-like peptide 1.

Medications approved for chronic weight management – Dosing and Response Evaluation		
Agent	Dosing	Response Evaluation
Orlistat	120 mg orally with each meal	Not addressed in label
Lorcaserin	10 mg orally twice daily	Stop if <5% loss at 12 weeks
Phentermine/ Topiramate ER	Orally in am; 3.75 mg/23 mg × 14 days; Then, 7.5/46 mg ×14 days.	At 12 weeks, option to ↑ to 11.25 mg/69 mg × 14 days, then 15 mg/96 mg; Stop if <5% loss at 12 weeks on top dose
Naltrexone SR/ Bupropion SR	Orally; Wk 1 -1 tab (8 mg/90 mg) in am ; Wk 2 - 1 in am 1 in pm; Wk 3 - 2 in am 1 in pm; Wk 4 - 2 in am 2 in pm.	Stop if <5% loss at 12 weeks
Liraglutide 3 mg	Inject subcutaneously (any time of day); Wk 1 - 0.6 mg; increase dose by 0.6 mg weekly until dose is 3.0 mg (Wk 5)	Stop if <4% weight loss at 16 weeks
All data from product label		

How do available drugs compare in efficacy?

- The mean weight loss greater than placebo varies somewhat.
- Each medication is associated with variation in response... none produces excellent weight loss in every patient; every one has example of lack of response.
- The intensity of lifestyle intervention greatly affects total weight loss.
- Medications can have targeted effects on outcomes independent of weight loss.

Weight loss Effects and Effects Independent of weight loss – data from prescribing information

Agent	Weight loss-related	Weight loss independent Positive	Weight loss independent Negative
Orlistat	Expected	Independent effect on ↓ LDL cholesterol	Reduction in fat soluble vitamin levels
Lorcaserin	Expected	? Independent effect on glycemia	-
Phentermine/ Topiramate ER	Expected	-	-
Naltrexone SR/ Bupropion SR	Expected Except less than expected reduction in pulse, BP	-	Less than expected decrease in BP and pulse -
Liraglutide 3 mg	Expected Except increased pulse	Independent effect on glycemia	Increase in lipase, uncertain significance

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>.

Should we use combinations not approved by the FDA?

- NO!
- No evidence to support off-label combinations
- Labels have specific language that this not be done
- However, prescribing for other chronic conditions should be weight-centric

How do available drugs compare in safety and tolerability?

Medications Approved for Chronic Weight Management – Safety and Contraindications

Agent	Safety	Contraindications
Orlistat	Warning: ↑ cyclosporine exposure; rare liver failure; multivit advised	Chronic malabsorption; gall bladder disease
Lorcaserin	Warnings: serotonin syndrome; valvular heart disease; cognitive impairment; depression; hypoglycemia; priapism	Do not use with MAOIs. Use with “extreme caution” with serotonergic drugs (SSRIs, SNRIs); Pregnancy
Phentermine/Topiramate ER	Warning: fetal toxicity; acute myopia; cognitive dysfunction; metabolic acidosis; hypoglycemia	Glaucoma; hyperthyroidism; MAOIs; Pregnancy
Naltrexone SR/Bupropion SR	Boxed warning: suicidality; Warning: BP, HR; ↑ seizure risk; glaucoma; hepatotoxicity	Seizure disorder; uncontrolled HTN; chronic opioid use; MAOIs; Pregnancy
Liraglutide 3.0 mg	Boxed warning: rodent thyroid c-cell tumors. Warnings: acute pancreatitis, acute gallbladder disease, hypoglycemia, heart rate increase; renal impairment; suicidal behavior	Patients with a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia.; Pregnancy

All data from product label

Medications Approved for Chronic Weight Management – Tolerability

Agent	Tolerability
Orlistat	All the symptoms of steatorrhea (fatty discharge, etc.)
Lorcaserin	Headache, dizziness, fatigue
Phentermine/ Topiramate ER	Paresthesias, dysgeusia; dizziness, dry mouth
Naltrexone SR/ Bupropion SR	Nausea, vomiting, headache, dizziness, insomnia
Liraglutide 3 mg	Nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain.

All data from product label

- The patient asks, “Which drug is the best drug for me?”

Medications for Chronic Weight Management and the Patient

Who could become pregnant	Do NOT prescribe. Obtain negative pregnancy test before prescribing PHEN/TPM and monthly while on therapy.
Who is breast feeding	Do NOT prescribe.
With history of seizure	NB is contraindicated. Taper PHEN/TPM slowly when discontinuing to avoid precipitating seizure .
With history of kidney stones	Avoid: PHEN/TPM, Orlistat.
With glaucoma	Contraindicated: PHEN/TPM. (angle closure glaucoma associated with NB)
With hypertension	NB, PHEN/TPM can increase blood pressure.
With arrhythmia	NB, PHEN/TPM, liraglutide can increase heart rate.

Data from product label. NB: Naltrexone SR/Bupropion SR. PHEN/TPM: Phentermine/Topiramate ER

Medications for Chronic Weight Management and the Patient

With moderate renal impairment	Do not exceed 7.5/46 mg PHEN/TPM Do not exceed 16/180 mg NB Use with caution: Liraglutide, Lorcaserin No information: Orlistat
With moderate hepatic impairment	Do not exceed 7.5/46 mg PHEN/TPM Do not exceed 8/90 mg NB Use with caution: Liraglutide, Lorcaserin No information: Orlistat
With depression receiving SSRIs	Extreme caution: Lorcaserin (PHEN/TPM has been studied in phase III)
With depression	(PHEN/TPM has been studied in phase III)
Age >65 years	Limited experience for NB, PHEN/TPM, Liraglutide, Lorcaserin; none for Orlistat

Data from product label. NB: Naltrexone SR/Bupropion SR. PHEN/TPM: Phentermine/Topiramate ER

Medications for Chronic Weight Management: Contraindications

Personal or family history; medullary thyroid cancer	Liraglutide
Chronic malabsorption	Orlistat
Cholestasis	Orlistat
Chronic opioid use	NB
Seizures	NB
Uncontrolled hypertension	NB
Glaucoma	PHEN/TPM
Hyperthyroidism	PHEN/TPM
Within 14 days of MAOI use	NB, PHEN/TPM

Data from product label

NB: Naltrexone SR/Bupropion SR

PHEN/TPM: Phentermine/Topiramate ER

Ms. Z begins phentermine/topiramate ER and attends Weight Watchers, intensifies her exercise and continues CPAP. After 6 months her blood pressure is 120/65, fasting glucose 70 mg/dl and A1c 5.4%. She reports that she no longer has knee pain and is tapering off CPAP. Her weight is 152 pounds (13% weight loss). She says, "Doctor, I want to thank you for helping me get my life back. I will NEVER go back to the state I was in. How long do I have to stay on this medicine?"

You say,

1. "Forever."
2. "For at least a year."
3. "I don't know."
4. All of the above.

How long should medications be used?

Suggestion: For eligible patients, use medications

- To promote long-term weight loss maintenance.

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All obesity medications....

- Are contraindicated in pregnancy.
- Not every medication profile is right for every patient.
- And not every med will produce weight loss in every patient



Remember



1. Medications for chronic weight management can help patients achieve health benefits,
2. by working through biologic mechanisms to reinforce lifestyle changes.
3. There is no ideal medication because every medication is different and every patient profile is different.
4. Your job is to match the patient profile to the lifestyle and medication plan.

Thank You

