Obesity Basics: Adjunctive Therapy – Medications and Surgery

Donna H. Ryan, MD, FACP

You have a 33-year-old patient with a BMI of 40 kg/m^2 who has diabetes and hypertension. What should you require before prescribing medications along with her lifestyle program?

1. I would like to see her try to lose weight with a program, and if she fails, I will prescribe
2. She needs to show me she can lose at least 3% before I will prescribe
3. She needs to have a history of trying lifestyle intervention in the past, *and succeeding,* before I will prescribe for this weight-loss effort
4. She needs a history of trying lifestyle intervention in the past *with or without* success
5. I do not care about her past attempts. She just needs to know she needs help and share in the decision to choose a medication and lifestyle program

Messages From Obesity Guidelines on Pharmacotherapy

- For patients who struggle, intensification is appropriate (E; 1|⊕⊕⊕⊕)
- Medications as adjuncts to lifestyle intervention are appropriate for patients with (E; 1|⊕⊕⊕⊕) :
  - BMI >30 kg/m^2
  - BMI >27 kg/m^2 with a comorbidity, who have a history of lack of success

Apovian CM, et al. *J Clin Endocrinol Metab*. 2015;100:342-362. Garvey WT, et al. *Endocr Pract*. 2014;20:977-989. Jensen MD, et al. *Obesity*. 2014;22:S1-S410. ANPF. http://international.aanp.org/Content/docs/ObesityWhitePaper.pdf. Accessed September 24, 2015.

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Why Do Patients Struggle to Lose Weight?

- Weight loss drives biologic and physiologic adaptations that increase hunger and reduce metabolic rate
  - These changes are persistent and only abate with weight regain
- Weight loss is more difficult when patients are on concomitant medications that drive weight gain, have poorly controlled chronic diseases (ie, T2DM, OSA), have episodic hypoglycemia, are sleep deprived, and are under stress
- **Medications work through biology to reinforce adherence to dietary intentions and also to thwart adherence**

OSA, obstructive sleep apnea.

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Weight Gain Associated With Medications – From the ENDO Guidelines

- When prescribing for patients with chronic medical conditions, who are overweight or obese:
  - Whenever possible, prescribe a medication that is weight neutral or associated with weight loss
  - Counsel patients on the weight effects of prescription medications

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

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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) (SGLT2 inhibitors)

* (2|⊕⊕⊕○)

*, levels of evidence
?, denotes where evidence is mixed or reports are of few cases
Apovian CM, et al. *J Clin Endocrinol Metab*. 2015;100:342-362.

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Cardiology Medications and Weight

	Weight Gain Associated With Use	Alternatives (weight reducing in parentheses)
Hypertension medications	α-blocker? β-blocker?	ACE inhibitors? Calcium channel blockers? Angiotensin-2 receptor antagonists

*(1|⊕⊕⊕⊕)

*, levels of evidence
?, denotes where evidence is mixed or reports are of few cases
Apovian CM, et al. *J Clin Endocrinol Metab*. 2015;100:342-362.

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Antipsychotic and Anticonvulsant Medications and Weight

	Weight Gain Associated With Use	Alternatives (weight reducing in parentheses)
Antipsychotics	Clozapine Risperidone Olanzapine Quetiapine Haloperidol Perphenazine Quetiapine	Ziprasidone Aripiprazole
Anticonvulsants	Carbamazepine Gabapentin Valproate	Lamotrigine? (Topiramate) (Zonisamide)

* (1|⊕⊕⊕o)

*, levels of evidence
?, denotes where evidence is mixed or reports are of few cases
Apovian CM, et al. *J Clin Endocrinol Metab*. 2015;100:342-362.

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Gynecologic Medications and Weight

	Weight Gain Associated With Use	Alternatives (weight reducing in parentheses)
Oral contraceptives	Progestational steroids Hormonal contraceptives containing progestational steroids	Barrier methods IUDs
Endometriosis treatment	Depot leuprolide acetate	Surgical treatment

* (2|⊕○○○)

*, levels of evidence
IUD, intrauterine device.
Apovian CM, et al. *J Clin Endocrinol Metab*. 2015;100:342-362.

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Prescribing Medications to Aid in Lifestyle Adherence

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Does Adding Medications Approved for Chronic Weight Management Produce More Weight Loss Than Lifestyle Alone?

- FDA efficacy benchmarks for approval
  - ≥5% difference in mean weight loss between the drug-treated and placebo-treated groups (with statistical significance)
  - Proportion of subjects who achieve ≥5% weight loss in the drug-treated group is at least 35% and is twice as many as in the placebo-treated group (with statistical significance)

All approved medications have approximated or exceeded these benchmarks.

FDA. Guidance for Industry: Developing products for weight management. February 2007. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071612.pdf. Accessed September 25, 2015.

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Medications Approved for Chronic Weight Management and How They Work

Agent	Action	Approved	Scheduled Drug
Orlistat	• Peripheral pancreatic lipase inhibitor - Blocks ingested fat absorption	1999	No
Lorcaserin	• 5-HT_{2C} serotonin agonist • Little affinity for other serotonergic receptors	2012	Yes
Phentermine/ topiramate ER	• Sympathomimetic amine • Anticonvulsant (GABA receptor modulator, carbonic anhydrase inhibitor, glutamate antagonist)	2012	Yes
NaltrexoneSR/ bupropion SR	• Opioid receptor antagonist • Dopamine/noradrenaline reuptake inhibitor	2014	No
Liraglutide 3.0 mg	• GLP-1 receptor agonist	2014	No

ER, extended release; SR: sustained release; 5-HT, serotonin; GABA, gamma aminobutyric acid; GLP-1, glucagon-like peptide 1.

FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed on September 25, 2015.

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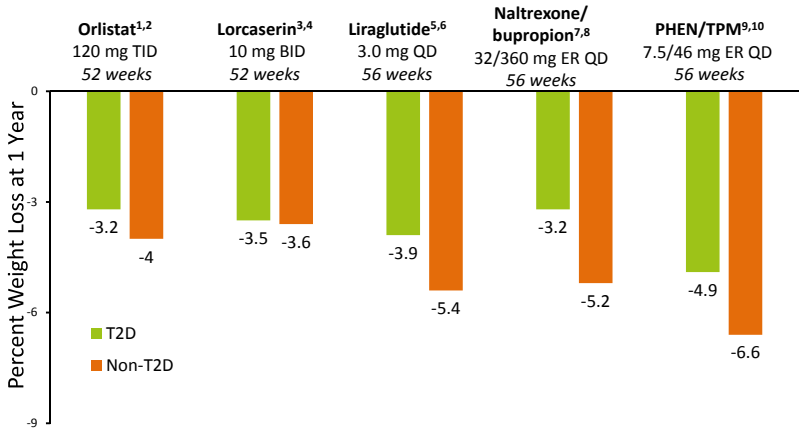
Placebo-Subtracted Mean Weight Loss in Patients With and Without T2DM

(NOT head-to-head comparisons)



Values are placebo-subtracted and approximated from kg weight reductions where applicable.
PHEN/TPM, Phentermine/topiramate ER.

1. Torgerson JS, et al. *Diabetes Care.* 2004;27:155-161. 2. Berne C, et al. *Diabet Med.* 2005;22:612-618. 3. Smith SR, et al. *N Engl J Med.* 2010;363:245-256. 4. O'Neil PM, et al. *Obesity.* 2012;20:1426-1436. 5. Pi-Sunyer, et al. *Diabetologia.* 2014;57 (suppl 1):73-OR. 6. Davies, et al. *Diabetologia.* 2014;57 (suppl 1):39-OR. 7. Apovian CM, et al. *Obesity (Silver Spring).* 2013;21:935-943. 8. Hollander P, et al. *Diabetes Care.* 2013;36:4022-4029. 9. Gadde KM, et al. *Lancet.* 2011;377:1341-1352. 10. Garvey WT et al. Diabetes Care. 2014;37:3309-3316.

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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
  - All have stopping rules
- The intensity of lifestyle intervention greatly affects total weight loss
- Medications can have targeted effects on outcomes independent of weight loss

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How Do Available Drugs Compare in Safety and Tolerability?

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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

HTN, hypertension; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.

FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed on September 25, 2015.

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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.

FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed on September 25, 2015.

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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

FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed on September 25, 2015.

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The patient asks, "Which drug is the best drug for me?"

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Medications for Chronic Weight Management and the Patient…

Who could become pregnant	Do NOT prescribe weight loss! 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.

NB, naltrexone SR/bupropion SR.
FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed on September 25, 2015.

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Medications for Chronic Weight Management and the Patient…(cont.)

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

FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed on September 25, 2015.

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Medications for Chronic Weight Management: Contraindications

Personal or family history of medullary thyroid cancer	liraglutide
Chronic malabsorption	orlistat
Cholestatis	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

FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed on September 25, 2015.

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How Long Should Medications Be Used? From the ENDO Guidelines…

- **Suggestion:** For eligible patients, use medications to promote long-term weight loss maintenance (2|⨁⨁◯◯)

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

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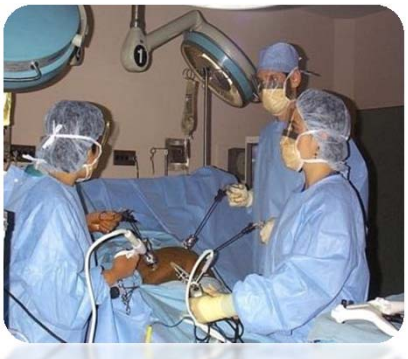
ACC/AHA/TOS Obesity Guidelines: Recommendation 5 Grade A (Strong)

- Advise your patients with BMI >35 kg/m^2 and a comorbidity or those with BMI >40 kg/m^2 that bariatric surgery may be an appropriate option to improve health
- **Offer referral to an experienced bariatric surgeon for consultation and evaluation**



Jensen MD, et al. *Obesity*. 2014;22:S1-S410.

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Questions???

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