From Behavior Modification through Pharmacotherapy to Surgery – an Emphasis on the Team Approach

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- Understand the physician's role in obesity management using a multidisciplinary team approach
- Learn how to choose an initial management strategy for the patient with overweight or obesity
- Learn how to modify the treatment approach based on available resources

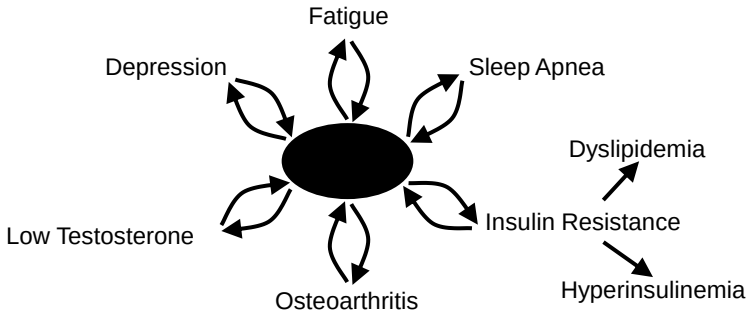
Management of obesity

- Step therapy:
  - Energy deficit meal plan
  - Increased physical activity
  - Behavioral modification
  - Antiobesity medications
  - Devices
  - Surgery
- Therapeutic lifestyle changes combined with any treatment modality enhances weight loss

The Team

- Endocrinologist
- PCP
- Bariatric surgeons
- Psychiatrists and psychologists
- Specialists (cardiologist, gastroenterologist, orthopedist)
- HCPs
- Nurses
- Dietitians
- Exercise physiologist and trainers
- Health coach or health educator
- Pharmacist
- Office staff (front and back)
- Family and friends

Complications of obesity: Obstacles to weight loss



Gonzalez-Campoy et al. *Int. J. Endocrinology,* May, 2014

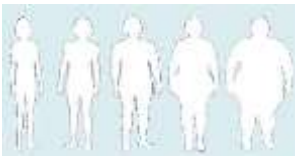
Stigma: Obesity is not a disease because it is behavior induced:

Behavior induced diseases:

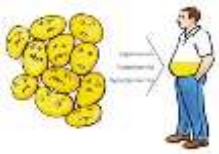
- Alcoholic liver disease
- Sexually transmitted disease
- Lung cancer
- Addiction

Why is Obesity a disease?

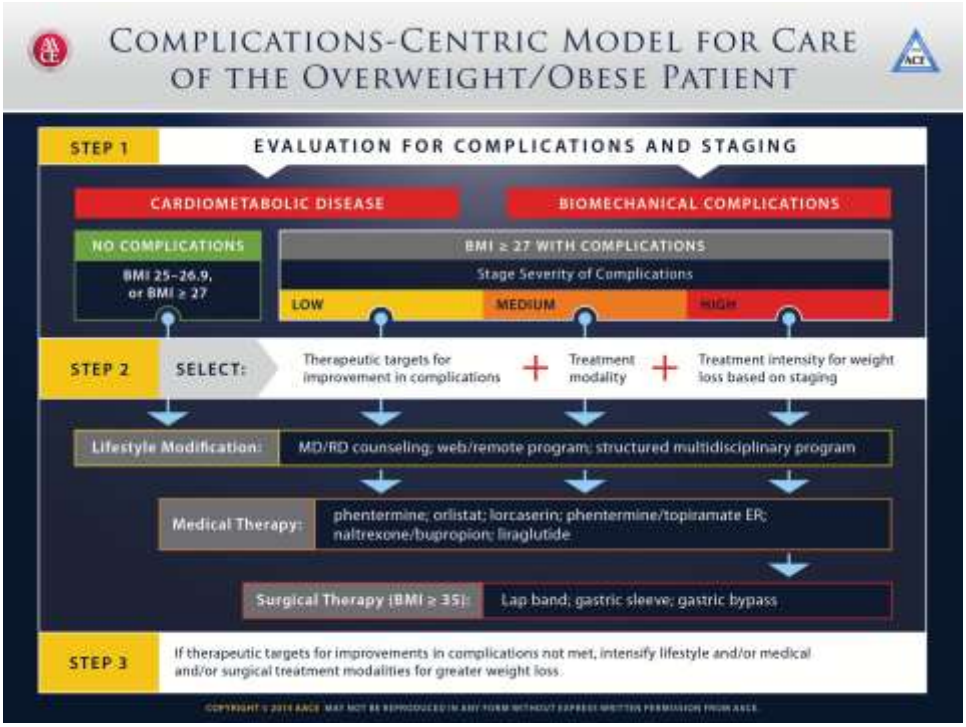
- Physical changes (adiposity)



- Metabolic changes (adiposopathy)



- Psychological changes



Treatment of Obesity

- Balance efficacy, safety, and cost
- Optimize benefit: risk ratio
- Achieve best outcomes
- Cost-effectiveness of care

Lifestyle intervention

Surgery & Devices

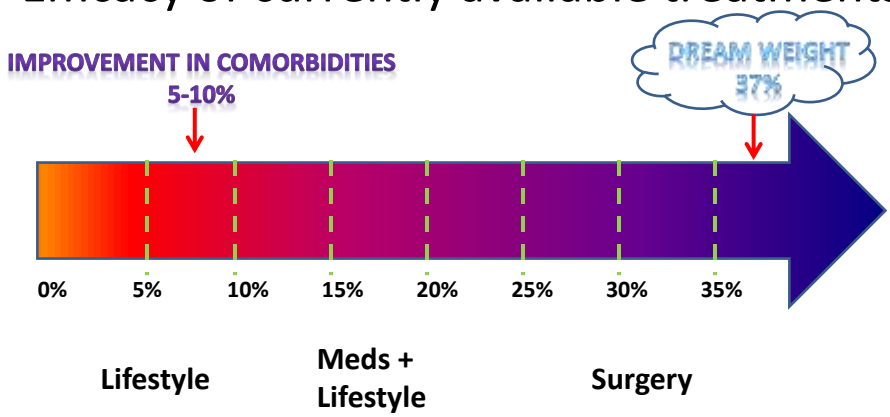
Antiobesity medications

Patient expectations for weight loss

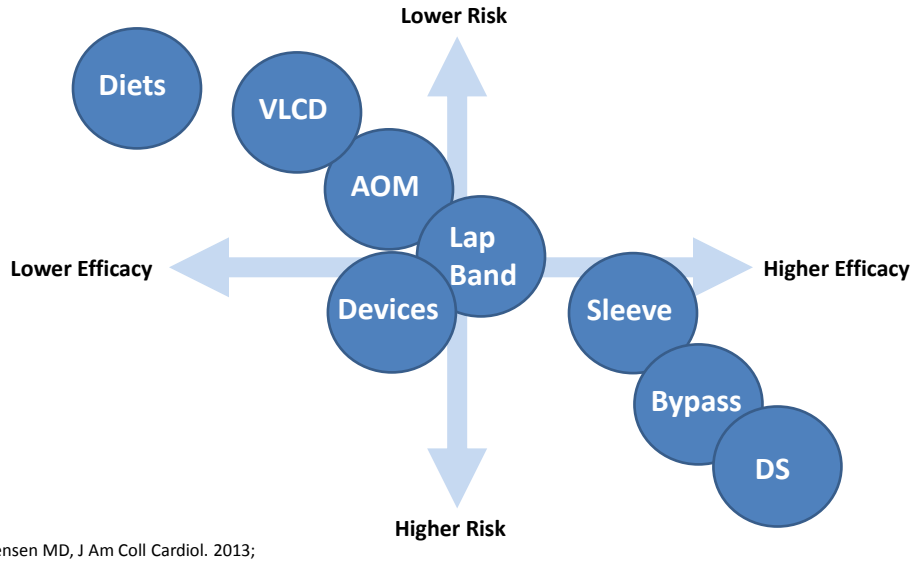
Dream weight	-37%
Happy weight	-31%
Acceptable weight	-24%
Disappointed weight	-15%

Foster & Wadden et al. J Consult Clin Psychol. 1997 Feb;65(1):79-85.

Efficacy of currently available treatments



Current Treatments: Efficacy and Risks



Jensen MD, J Am Coll Cardiol. 2013;
http://formularyjournal.modernmedicine.com/print/368664

Office Readiness

- Welcoming front desk staff
- Avoid “obese” or “overweight” as adjectives
- Appropriately sized furniture (steel-framed)
- Accurate platform scale (capacity to 800 pounds)
- Blood pressure cuffs and measuring tapes
- Examination gowns
- Exam tables with hydraulic lifts
- Trained, experienced nursing staff

Therapeutic Lifestyle Change
(Behavior Modification)

- Set realistic achievable goals
- Individualized
- 5-10% of body weight in 4-6 months
- Specific behavior goals (e.g. I will walk at lunch 3 times a week)
- Help patients gradually make changes to dietary patterns that are harmful to their health
- Communication should focus on a healthy lifestyle
- Encourage "physical activity" over "exercise"

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/m^2 or BMI 27 <30 kg/m^2 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 REDUCTING 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	
Antidepressants/mood stabilizers: MAO Inhibitors	Phenylzine Tranylcypromine	
Lithium		

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

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

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

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/m^2 or BMI 27 <30 kg/m^2 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

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

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

Rationale for treatment of obesity with medications

- Obesity is a chronic disease.
- Most chronic diseases are treated with medications (ie. diabetes, HTN, hyperlipidemia).
- The biochemistry of obese people is different than that of lean people.
- When obese people lose weight their biochemistry does not become the same as lean people.
- Medications change biochemistry.

Criteria for using antiobesity medications

BMI $\geq$ 27 kg/m^2 with at least one comorbidity

BMI $\geq$ 30 kg/m^2 with or without comorbidity

Always as an adjunct to an energy-deficit meal plan, increased physical activity and behavior modification.

Role of medications in weight loss

- They do not work on their own.
- Medications amplify the effects of behavioral changes to produce consumption of fewer calories.
- Addition of a medication of a comprehensive weight loss program produces and additive effect.

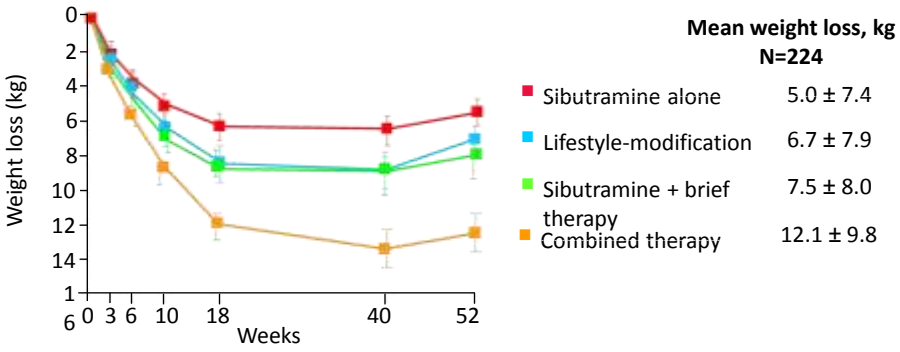
Should pharmacotherapy be used as an adjunct to lifestyle intervention?

- 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?*"

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.

Medication follow up

- Best weight loss outcomes come with frequent face to face visits.
- More frequent visits for the first 3 months.
- Monthly x 3 months or at month 1 & 3, then every 3 months.
- Use a team approach for follow up appointments.
- Reinforce behavior modification, nutrition and physical activity.
- Assess medication efficacy and/or adverse effects and make changes as appropriate.

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.

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®**	• Peripheral pancreatic lipase inhibitor - blocks ingested fat absorption	Approved 1997	• No
Lorcaserin **Belviq®**	• 5-HT_{2C} serotonin agonist • Little affinity for other serotonergic receptors	Approved 2012	• YES
Phentermine/ Topiramate ER **Qsymia™**	• Sympathomimetic • Anticonvulsant (GABA receptor modulator carbonic anhydrase inhibitor, glutamate antagonist)	Approved 2012	• YES
Naltrexone SR/ Bupropion SR **Contrave®**	• Opioid receptor antagonist • Dopamine/noradrenaline reuptake inhibitor	Approved 2014	• NO
Liraglutide 3.0 mg **Saxenda®**	• GLP-1 receptor agonist	Approved 2014	• No

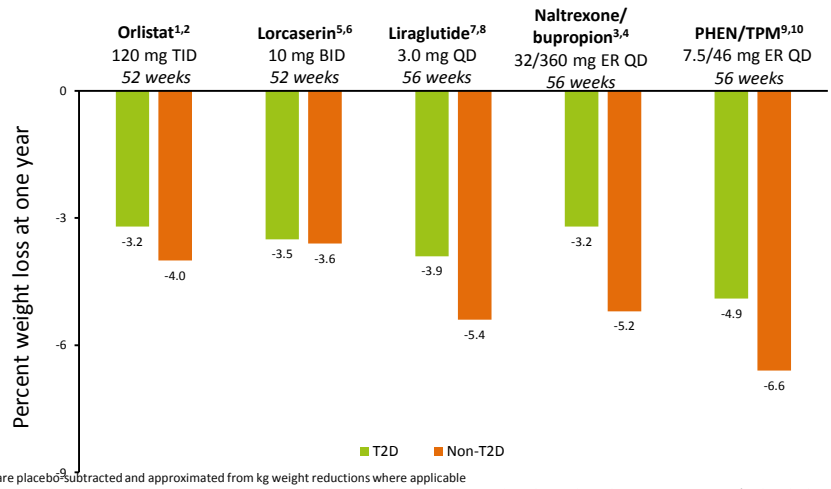
ER: extended release; SR: sustained release. 5HT: serotonin. GABA: Gamma aminobutyric acid. GLP-1: Glucagon-like peptide 1.

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

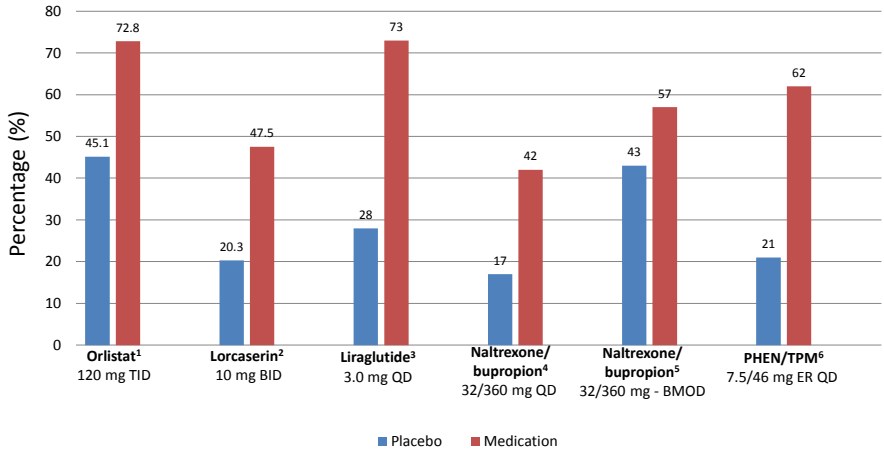
Placebo-subtracted Weight Loss in Patients With and Without T2DM



Values are placebo-subtracted and approximated from kg weight reductions where applicable

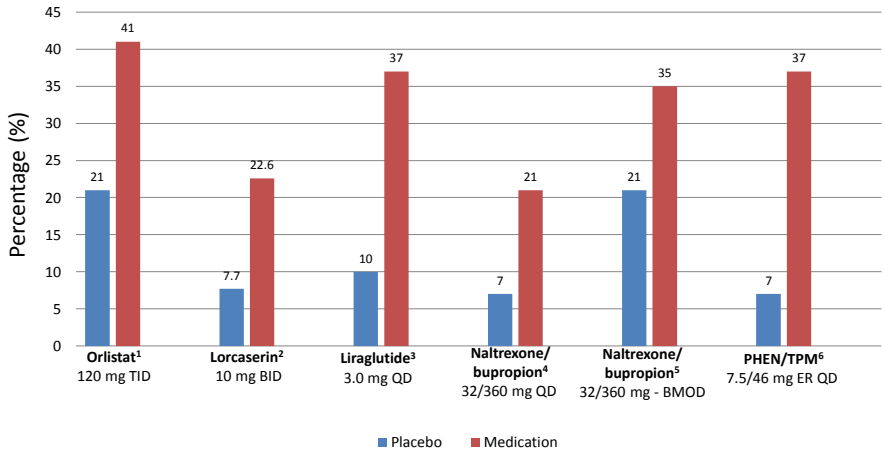
1. Torgerson *et al. Diabetes Care* 2004;27:155–61; 2. Berne *et al. Diabet Med* 2005;22:612–8; 3. Smith *et al. N Engl J Med* 2010;363:245–56; 4. O'Neil *et al. Obesity* 2012;20:1426–36; 5. Apovian *et al. Obesity (Silver Spring)* 2013;21:935–43; 6. Hollander *et al. Diabetes Care* 2013;36:4022–9; 7. 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



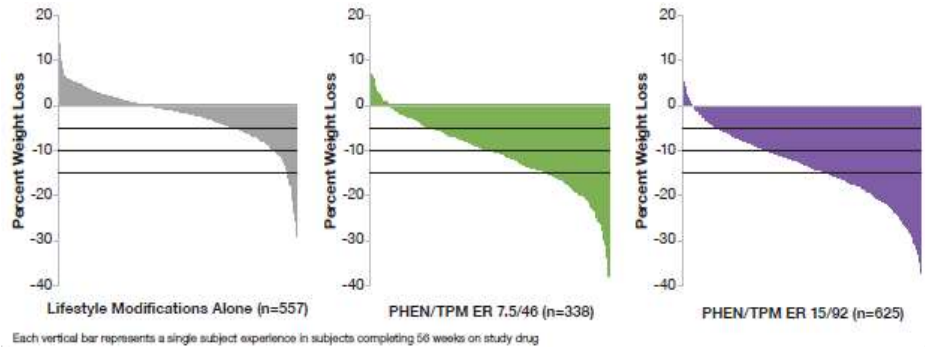
1. Torgerson *et al. Diabetes Care* 2004;27:155–61; 2. Smith *et al. N Engl J Med* 2010;363:245–56; 3 Astrup, et al. *Lancet* 2009; 1606-1616 . 4. Greenway, et al. Lancet 2010; 595-605. 5.Wadden , et al. *Obesity* (2011) 19, 110–120. 6Gadde *et al. Lancet* 2011;377:1341–52;

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. 6Gadde *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 – 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

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
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

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

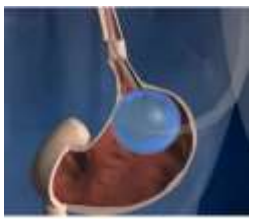
Remember

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.

Intragastric Balloons

- Endoscopic outpatient procedure
- Relatively easy to perform
- Removed after 6 months
- Modest weight loss (~10%)

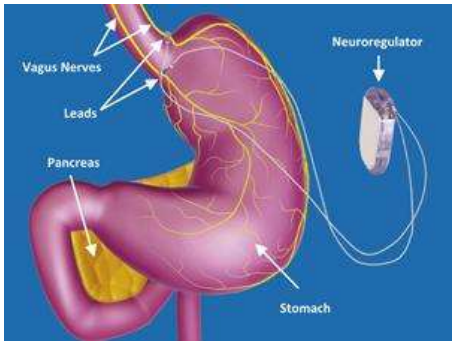
Orbera



Reshape

Vagal blockade (VBLOC)

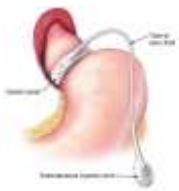
- "Pacemaker" for the stomach
- Difficult surgery, need expertise
- Neuroregulator implanted subcutaneously
- Modest weight loss



Bariatric Surgery Procedures

(Indication BMI ≥40 or BMI ≥35 with comorbidity)

Gastric Restriction Procedures



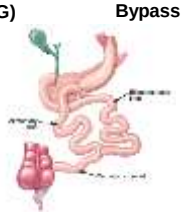
Laparoscopic Adjustable Gastric Band (LABG)

Gastric Plication (Experimental)

Metabolic Procedures

Laparoscopic Sleeve Gastrectomy (LSG)

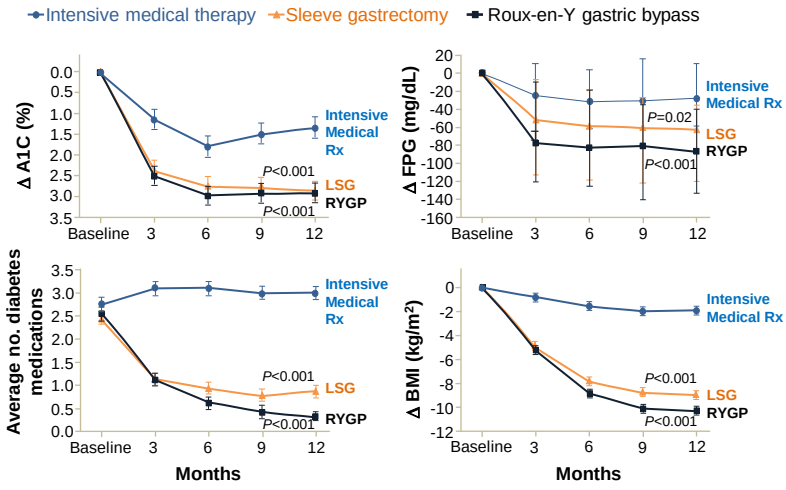
Roux-en-Y Gastric Bypass (RYGB)



Biliopancreatic Diversion (BPD)

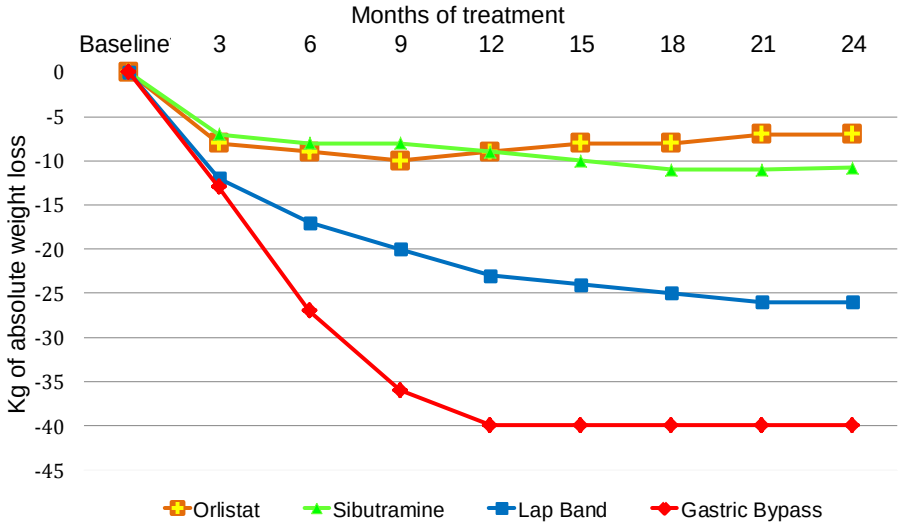
Bariatric Surgery Outcomes

Patients With Type 2 Diabetes



Schauer PR, et al. *N Engl J Med*. 2012;366:1567-1576.

Pharmacotherapy vs Surgery for Obesity (kg of absolute wt loss)



Nutritional deficiencies prior to bariatric surgery

- Vitamin A 12%
- Vitamin B_{12} 13%
- Folate 6%
- Vitamin D 40%
- Zinc 30%
- Iron 16%
- Selenium 58%

Obesity may mask malnutrition

- **Decreased consumption of vegetables and fruits**
- **Increased intake of high calorie nutritionally poor foods**
- **Irreversible sequestration of fat soluble vitamins**

Madan et al. Obes Surg. 2006 May;16(5):603-6.