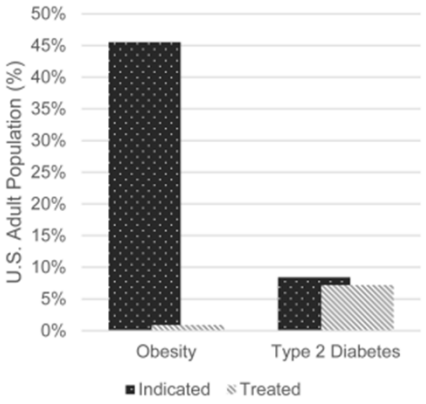
Objectives

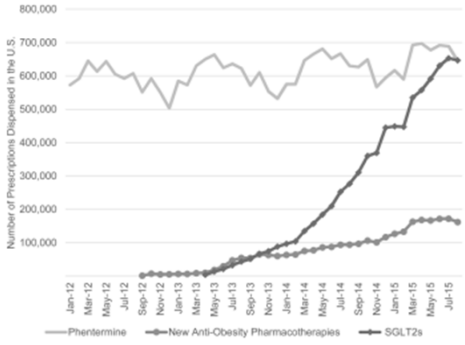
- 1. Review the history of weight loss medications.
- 2. Consider reasons for provider bias against using weight loss medications.
- 3. Discuss clinical insights gained from using weight loss medications.
- 4. Understand the role and efficacy of weight loss medications and how to discuss this with patients.

Low adoption of weight loss medications: A comparison of prescribing patterns of antiobesity and antidiabetes pharmacotherapies



Thomas et al. Obesity, 2016; 24(9):1955-61.

Low adoption of weight loss medications: A comparison of prescribing patterns of antiobesity pharmacotherapies and SGLT2s



Mean increases in prescriptions/month:
25,259 for SGLT2s
5,154 for new antiobesity medications
2,718 for phentermine

Thomas et al. Obesity, 2016; 24(9):1955-61.

Low adoption of weight loss medications

- Cost/lack of insurance coverage
- High discontinuation rate: most common reasons are noncompliance, lost to follow-up, lack of efficacy, and adverse events
  - 33% for phentermine
  - 38% for phentermine + topiramate
  - 44% for lorcaserin
  - 46% for naltrexone + bupropion
  - (vs 9-14% for SGLT2s)
- Unrealistic effectiveness expectations
  - % weight loss
  - Cardiovascular outcomes
- Concern that patients will be "stuck" taking the medications despite lack of efficacy
- History of antiobesity medications being removed from market for safety concerns

History of weight loss medications

	Drug	Serious adverse events
1893/1949	Thyroid hormone	Hyperthyroidism
1933/1935	Dinitrophenol	Cataracts, neuropathy
1937/1971	Amfetamine	Addiction, psychosis
1965/1972	Aminorex	Pulmonary hypertension
1973/1997	Fenfluramine plus phentermine	Cardiac valvular insufficiency
1960/2000 (USA)*	Phenylpropanolamine	Haemorrhagic stroke
2006/2009	Rimonabant	Depression, suicidal ideation
1997/2010	Sibutramine	Cardiovascular disease

*Phenylpropanolamine is still available in some European countries. Modified and updated from reference 1.

Table: **History of drug treatments for obesity, by date of approval/withdrawal**

Astrup. Lancet, 2010;376:567-68.

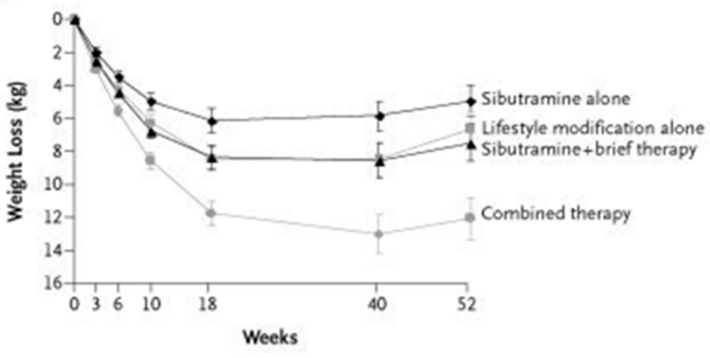
New perspective #1: (most) medications for weight loss have been around for a long time

Current weight loss medications

Drug	FDA approval
Phentermine (Adipex)	5/1959
Orlistat (Alli, Xenical)	4/1999
Lorcaserin (Belviq)	6/2012
Phentermine plus topiramate (Qsymia)	7/2012
Topiramate	1996
Bupropion plus naltrexone (Contrave)	9/2014
Bupropion	1985/1989
Naltrexone	1984
Liraglutide (Saxenda)	12/2014
Liraglutide (Victoza)	2010

New perspective #2: weight loss medications should be used in combination with efforts at lifestyle modification

Mean weight loss: combined therapy vs medical therapy or lifestyle modification

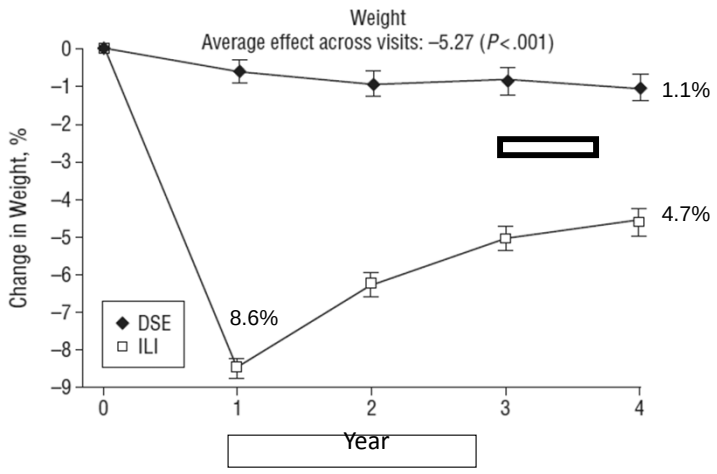


Wadden et al. NEJM, 2005;353:2111-2120.

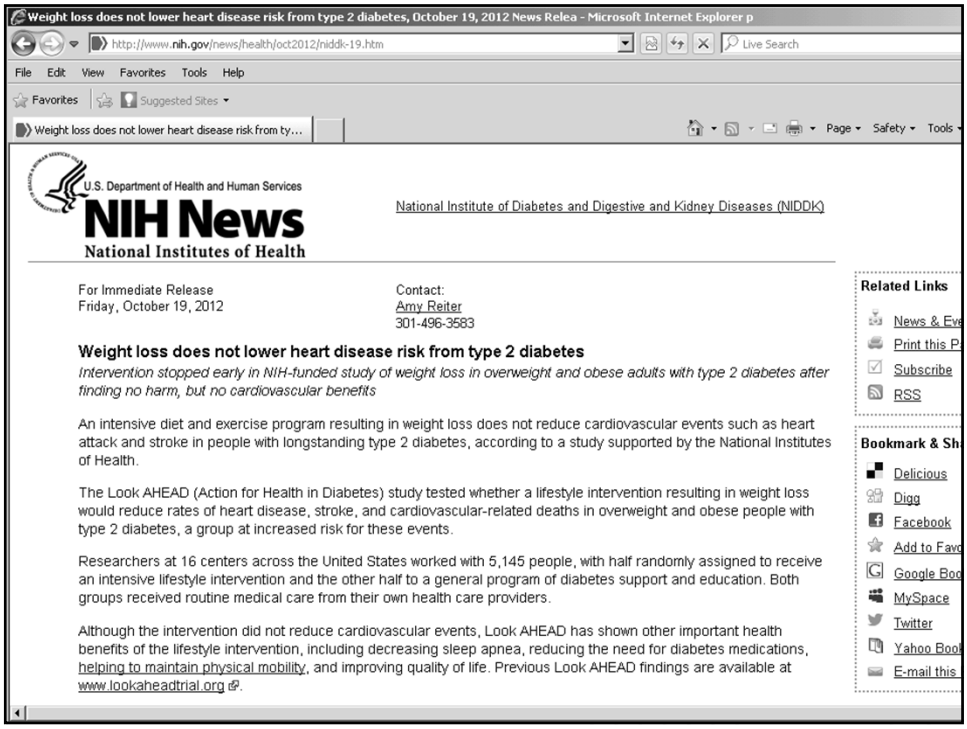
New perspective #3: obesity is a disease and pharmacotherapy is recommended

- 1995, Institute of Medicine
- 1997, World Health organization
- 1998, National Institutes of Health
- 2005, American College of Physicians
- 2012, American Association of Clinical Endocrinologists, American College of Endocrinologists
- 2013, American Medical Association
- 2013, American Heart Association, American College of Cardiology, Obesity Society
- 2015, Endocrine Society

Look AHEAD



Arch Intern Med, 2010.



Weight loss does not lower heart disease risk from type 2 diabetes, October 19, 2012 News Relea - Microsoft Internet Explorer p

http://www.nih.gov/news/health/oct2012/niddk-19.htm

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National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

For Immediate Release
Friday, October 19, 2012

Contact:
Amy Reiter
301-496-3583

Weight loss does not lower heart disease risk from type 2 diabetes

Intervention stopped early in NIH-funded study of weight loss in overweight and obese adults with type 2 diabetes after finding no harm, but no cardiovascular benefits

An intensive diet and exercise program resulting in weight loss does not reduce cardiovascular events such as heart attack and stroke in people with longstanding type 2 diabetes, according to a study supported by the National Institutes of Health.

The Look AHEAD (Action for Health in Diabetes) study tested whether a lifestyle intervention resulting in weight loss would reduce rates of heart disease, stroke, and cardiovascular-related deaths in overweight and obese people with type 2 diabetes, a group at increased risk for these events.

Researchers at 16 centers across the United States worked with 5,145 people, with half randomly assigned to receive an intensive lifestyle intervention and the other half to a general program of diabetes support and education. Both groups received routine medical care from their own health care providers.

Although the intervention did not reduce cardiovascular events, Look AHEAD has shown other important health benefits of the lifestyle intervention, including decreasing sleep apnea, reducing the need for diabetes medications, helping to maintain physical mobility, and improving quality of life. Previous Look AHEAD findings are available at www.lookaheadtrial.org.

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New perspective #4: weight loss is an important target

- Look AHEAD
  - Post-hoc analysis: weight loss ≥10% in first year vs <2%
  - Adjusted hazard ratio primary outcome: 0.79 (0.64-0.98), p= 0.034
  - Adjusted hazard ratio secondary outcome: 0.76 (0.63-0.91), p= 0.003

    Lancet Diabetes Endocrinol, 2016;4:913-21.

- Swedish Obese Subjects (SOS) study (20 year data)
  - Adjusted hazard ratio for cardiovascular death: 0.47 (0.29-0.76), p= 0.002
  - First time fatal or nonfatal cardiovascular events: 0.67 (0.54-0.83), p= 0.001

    Sjostrom et al. JAMA, 2012;307(1):56-65.

New perspective #5: there is [some] evidence that weight loss medications reduce CV disease

The NEW ENGLAND JOURNAL of MEDICINE

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Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

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ABSTRACT

BACKGROUND

The cardiovascular effect of liraglutide, a glucagon-like peptide 1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown.

METHODS

In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.

RESULTS

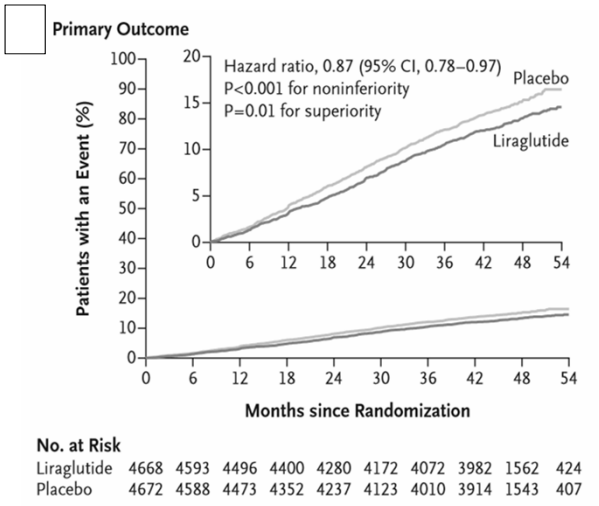
A total of 9340 patients underwent randomization. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85;

From the University of Texas Southwestern Medical Center, Dallas (S.P.M.); Massachusetts General Hospital, Boston (G.H.D.); Novo Nordisk, Bagsvaerd, Denmark (K.B.-F., P.K., L.S.R., M.S.); Friedrich Alexander University of Erlangen, Erlangen (J.F.E.M.), and St. Josef Hospital, Ruhr University, Bochum (M.A.N.) — both in Germany; Cleveland Clinic, Cleveland (S.E.N.); London School of Hygiene and Tropical Medicine Medical Statistics Unit (S.P.) and Imperial College London (N.R.P.), London; George Washington University Medical Center, Washington, DC (W.M.S.); Lunenfeld–Tanenbaum Research Institute, Mt. Sinai Hospital, University of Toronto, Toronto (B.Z.); International Diabetes Center at Park Nicollet, Minneapolis (R.M.B.); and the University of North Carolina School of Medicine, Chapel Hill (J.B.B.). Address reprint requests to Dr. Buse at the University of North Carolina School of Medicine, CB7172, Chapel Hill, NC 27599, or at john_buse@med.unc.edu.

*A complete list of the investigators in the Liraglutide Effect and Action in Dia-

New perspective #5: there is [some] evidence that weight loss medications reduce CV disease

- Leader trial

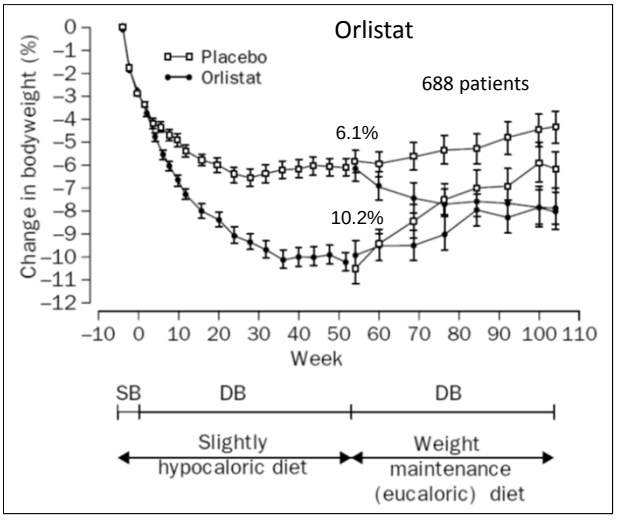


Marso. NEJM, 2016;375(4):311-22.

New perspective #6: CV disease is *not* the only meaningful outcome for weight loss

- 3-5% weight loss
  - ↓ Triglycerides
  - ↓ Glucose, HgbA1c
  - ↓ Risk developing diabetes mellitus
- >5% weight loss
  - ↓ BP
  - ↓ LDL
  - ↑ HDL
  - ↓ Need for medications to control BP, glucose, lipids
- Other benefits
  - ↑ Physical fitness and physical function
  - ↓ Kidney disease
  - ↓ Retinopathy
  - ↓ Sleep apnea
  - ↓ Incontinence
  - ↑ Quality of life
  - ↓ Depression
  - ↓ Joint pain
  - ↓ Antihypertensives, insulin, statins

New perspective #7: obesity is a chronic disease, so medications for weight loss should be used long term



Reduced at 2 years
- Total cholesterol
- LDL cholesterol
- LDL/HDL ratio
- [glucose]
- [insulin]

GI symptoms (3-5%)

Sjostrom. Lancet, 1998;352:167.

New perspective #8: medications are effective at causing weight loss

- Unrealistic effectiveness expectations
  - 0.77% drop in hemoglobin A1c (7.86 to 7.09%) is 9.8%.
  - 9.8 mm Hg drop in systolic BP (146.2 to 136.4 mm Hg) is 6.7%.
  - mean weight loss after 1 year of phentermine/topiramate is 10.9%.
- Multivariable analysis of data from obese adult (BMI ≥30) participants in the 2001–2006 NHANES.
  - Identify strategies associated with losing 5% and 10% of body weight.
    - 63% reported trying to lose weight in the previous year.
    - Among those attempting weight loss, 40% lost 5% and 20% lost 10% weight.
  - Although least utilized strategy (3.5%), antiobesity pharmacotherapy was most associated with self-reported body weight loss of ≥10% in the prior year (OR 2.05).

Nicklas et al. Am J Prev Med, 2012;42(5):481-5.

New perspective #8: medications are effective at causing weight loss

- Lorcaserin (Belviq)- 2012
  - 7794 participants (3 trials; 52 weeks each)
- Phentermine/topiramate (Qsymia)- 2012
  - 4430 participants (3 trials; 56 weeks for 2, 2 years for 1)
- Bupropion/naltrexone (Contrave)- 2014
  - 4536 participants (4 trials; 56 weeks each)
- Liraglutide (Saxenda)- 2014
  - 4999 participants (3 trials; 56 weeks each)

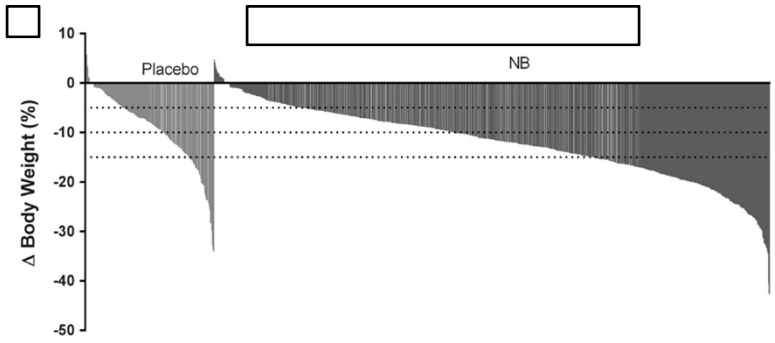
Pharmacotherapy for Obesity

- FDA approved for:
  - BMI of 27 to 29.9 kg/m^2 with comorbidity
  - All patients with BMI ≥30 kg/m^2

Pharmacotherapy for Obesity

- FDA approved for:
  - BMI of 27 to 29.9 kg/m^2 with comorbidity
  - All patients with BMI ≥30 kg/m^2
- Stop medications if the patient does not lose ≥5% of their weight.

Contrave: individual weight loss at week 56



- Four phase 3, randomized, placebo-controlled, 56 week clinical trials of naltrexone/bupropion 32/360 mg
- 80% identified correctly who lost ≥5% at week 56 that had lost ≥5% at week 16.

Fujioka et al. Int J of Obesity, 2016; 40:1369–1375.

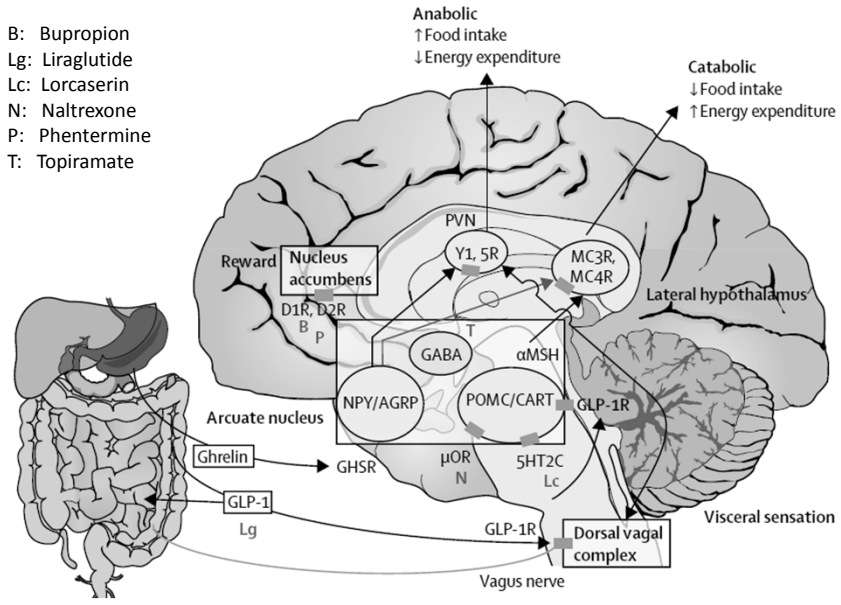
Contrave: look for the responders

- Weight loss ≥5% at Week 16 associated with mean weight loss ≈12% at Week 56
  - Average weight loss= 6.7%
- 85% had a Week 56 weight loss of ≥5%
  - 52.4% lost ≥5%
- 57% had a Week 56 weight loss of ≥10%
  - 28.3% lost ≥10%

Fujioka et al. Int J of Obesity, 2016; 40:1369–1375.

Pharmacotherapy for Obesity

- FDA approved for:
  - BMI of 27 to 29.9 kg/m^2 with comorbidity
  - All patients with BMI ≥30 kg/m^2
- Stop medications if the patient does not lose ≥5% of their weight.
- Advise patients: medications work in the brain to suppress appetite and help maintain calorie goal- they do not increase metabolism, burn fat, or give energy.

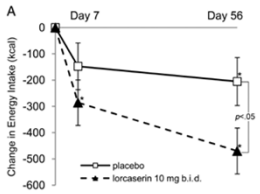


Bessesen et al. Lancet Diabetes Endocrinol, 2017.

Lorcaserin reduces body weight by decreasing energy intake without influencing energy expenditure

Change in body weight, percent body fat, EE, substrate oxidation, and activity by group

	Placebo		10 mg twice-daily lorcaserin		*P* value	
	wk 1[a] – baseline	wk 8[a] – baseline	wk 1 – baseline	wk 8 – baseline	wk 1	wk 8
Body weight (kg)		−2.2 ± 0.5[b]		−3.8 ± 0.4[b]		0.01
Total body fat (%)		−1.2 ± 0.2[b]		−0.9 ± 0.2[b]		0.39
24-h EE from respiratory chamber (kcal/d)	−57 ± 20[b]	−103 ± 21[b]	−96 ± 20[b]	−162 ± 20[b]	0.17	0.05
24-h EE adjusted for body composition (kcal/d)		−86 ± 20[b]		−106 ± 27[b]		0.56
24-h RQ from respiratory chamber	0.00 ± 0.00	0.01 ± 0.00[b]	0.01 ± 0.00[b]	0.01 ± 0.00	0.10	0.61
SMR from respiratory chamber (kcal/d)	−50 ± 17[b]	−72 ± 18[b]	−97 ± 17[b]	−137 ± 17[b]	0.06	0.01
SMR adjusted for body composition (kcal/d)		−76 ± 28[b]		−78 ± 26[b]		0.95
RMR, ventilated hood (kcal/d)	−2 ± 22	1 ± 22	−50 ± 21[b]	−84 ± 21[b]	0.12	<0.01
RMR adjusted for body composition (kcal/d)		−43 ± 24		−106 ± 33[b]		0.13
Average METs (armband accelerometer)	0.03 ± 0.05	0.23 ± 0.06[b]	0.14 ± 0.05[b]	0.16 ± 0.05[b]	0.13	0.38



Martin et al. JCEM, 2011;96:837:45.

Pharmacotherapy for Obesity

- FDA approved for:
  - BMI of 27 to 29.9 kg/m^2 with comorbidity
  - All patients with BMI ≥30 kg/m^2
- Stop medications if the patient does not lose ≥5% of their weight.
- Advise patients: medications work in the brain to suppress appetite and help maintain calorie goal- they do not increase metabolism, burn fat, or give energy.
- Counsel patients on risks, costs, and potential benefits of weight loss medications including likelihood of achieving meaningful weight loss.

Lorcaserin (Belviq)

- 3 phase 3 clinical trials (BLOOM, BLOSSOM, BLOOM-DM)
- Average weight loss= 5.8% (2.2% placebo)
- 44.1% lost ≥5% (20.5% placebo)
- 20.5% lost ≥10% (7.3% placebo)
- Cost: $250/month ($90-100 with coupon)

- Contraindications
  - concomitant use with other serotonergic and dopaminergic drugs
  - pregnancy (category X)

- Adverse effects
  - nausea
  - dizziness
  - headache
  - fatigue
  - mood effects

Phentermine/topiramate (Qsymia)

- 2 phase 3 clinical trials (EQUIP, CONQUER)
- Average weight loss= 5.1-10.9%
- 66.7-70.0% lost ≥5%
- 47.2-48% lost ≥10%
- Cost: $200/month ($140-150 with coupon)

- Contraindications
  - known vascular disease
  - uncontrolled hypertension
  - glaucoma
  - MAO-I
  - hyperthyroidism
  - pregnancy (category X)

- Adverse effects
  - constipation
  - altered taste
  - dry mouth
  - insomnia
  - paresthesias
  - fatigue
  - metabolic acidosis, nephrolithiasis
  - mood changes

Bupropion/naltrexone (Contrave)

- 4 phase 3 clinical trials (COR-I, COR-II, COR-BMOD, COR-Diabetes)
- Average weight loss= 6.7% (2.4% placebo)
- 52.4% lost ≥5% (23.6% placebo)
- 28.3% lost ≥10% (9.7% placebo)
- Cost: $240/month ($90 with coupon)

- Contraindications
  - seizure history/alcohol abuse
  - opiate therapy
  - uncontrolled hypertension
  - severe depression/suicidality
  - pregnancy (category X)
  - MAO-I

- Adverse Effects
  - nausea
  - headache
  - constipation
  - dizziness
  - vomiting
  - dry mouth
  - mood changes
  - blood pressure: ↑1.5 mm Hg then ↓1 mm Hg
  - pulse: ↑1.5-2.5 bpm

Liraglutide (Saxenda)

- 4 phase 3 clinical trials (SCALE-Diabetes, SCALE-Obesity and Prediabetes, SCALE-Maintenance)
- Average weight loss= 6.5% (1.6% placebo)
- 56% lost ≥5% (23.4% placebo)
- 28% lost ≥10% (7.9% placebo)
- Cost: $1200/month (variable with coupon)

- Contraindications/Warnings
  - personal or FH of MTC/MEN
  - pregnancy (category X)
  - pancreatitis

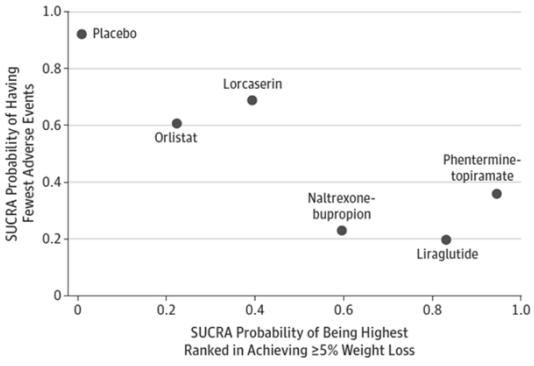
- Adverse Effects
  - Nausea/vomiting
  - Diarhea, constipation
  - Headache
  - Dyspepsia, abdominal pain
  - Dizziness
  - Fatigue

Weight loss summary: new obesity medications

Medication	Ave wt loss	5% wt loss	10% wt loss
Belviq	5.8%	44.1%	20.5%
Qsymia	5.1-10.9%	66.7-70.0%	47.2-48%
Contrave	6.7%	52.4%	28.3%
Saxenda	6.5%	56%	28%

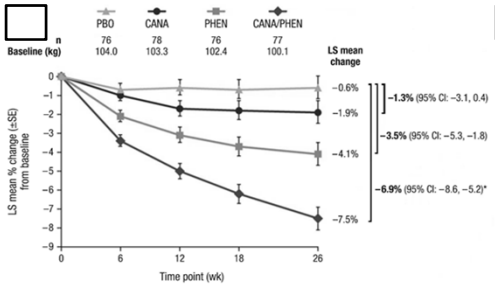
Comparison of antiobesity medications

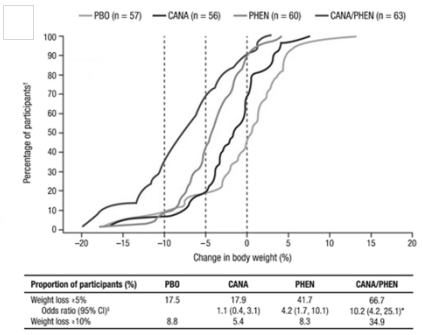
- SUCRAs forWeight Loss and Adverse Event Outcomes



Khera et al. JAMA, 2016;315(22):2424-34.

Novel combinations: canagliflozin and phentermine





Proportion of participants (%)	PBO	CANA	PHEN	CANA/PHEN
Weight loss ≥5%	17.5	17.9	41.7	66.7
Odds ratio (95% CI)‡		1.1 (0.4, 3.1)	4.2 (1.7, 10.1)	10.2 (4.2, 25.1)*
Weight loss ≥10%	8.8	5.4	8.3	34.9

- Randomized, double-blind, PBO-controlled, multicenter
- N= 335, overweight or obese, without diabetes
- Canagliflozin 300 mg and phentermine 15 mg daily

Hollander et al. Diabetes Care, 2017.

Limitations

- Cost
- Interactions/contraindications
- Lack of really long-term (>2 years) safety data
- Limited data on long-term CV or mortality benefit
- No guidance on which medication would be more effective or better tolerated

Pharmacotherapy: my approach

- Medication approved for long-term use preferred.
  - Lorcaserin (Belviq)
  - Phentermine/topiramate (Qsymia)
  - Bupropion/naltrexone (Contrave)*
  - Liraglutide (Saxenda)*
  - Orlistat (Xenical, Alli)*
- Look for contraindications based on PMH.
- Look for interactions on medication list.
- Patient preference (benefit vs risk vs potential SE).
- Assess progress/tolerability at 1-2 months and at 3 months: ≥5% weight loss?

*Non-scheduled medications

Summary

- Likelihood of losing 5% (~50-70%) or 10% (~30-50%)
- Meant for long-term use (only work when taken)
- Work in the brain to reduce appetite
- Stop after 3 months if no loss of ≥5%
- Risk factor and symptom benefit with all
- Cardiovascular benefit with liraglutide
- CV benefit with all if lose ≥10%?

Drugs that affect weight

Weight Gainers	Weight Losers
Amitriptyline (1.8 kg)	Metformin (1.1 kg)
Mirtazapine (1.5 kg)	Acarbose (0.4 kg)
Olanzapine (2.4 kg)	Pramlintide (2.3 kg)
Quetiapine (1.1 kg)	Liraglutide (1.7 kg)
Risperidone (0.8 kg)	Exenatide (1.2 kg)
Gabapentin (2.2 kg)	Zonisamide (7.7 kg)
Pioglitazone (2.6 kg)	Topiramate (3.8 kg)
Glimepiride (2.1 kg)	Bupropion (1.3 kg)
Glyburide (2.6 kg)	Fluoxetine (1.3 kg)
Glipizide (2.2 kg)	
Sitagliptin (0.55 kg)	

Domecq et al. JCEM, Feb 2015, 100(2):363-370.

Drugs that affect weight

- **Type 2 diabetes mellitus**

Preferred	Less preferred	Least preferred
GLP-1 agonists	Sulfonylureas	Thiazolidinediones
SGLT2 inhibitors	Basal insulin	Premixed and bolus insulins
Metformin		
DPP4 inhibitors		
Pramlintide, α-glucosidase inhibitors		

- **Antihypertensives**
  - Use ACE/ARBs or CCB before β-blockers (carvedilol or nebivolol less associated with weight gain)
- **Antidepressants**

Weight loss	+/-	Weight gain
Bupropion	Citalopram	Paroxetine
Fluoxetine	Escitalopram	Amitriptyline
Sertraline	Venlafaxine	Mirtazapine
	Duloxetine	Nortriptyline

Drugs that affect weight

- **Antipsychotics**

  Aripiprazole, Ziprasidone, Quetiapine, Risperidone, Clozapine, Olanzapine → **+**

- **Antiepileptics**

Weight loss	+/-	Weight gain
Topiramate	Lamotrigine	Gabapentin
Zonisamide	Levetiracetam	Pregabalin
Felbamate	Phenytoin	Valproic acid
		Carbamazepine

- **Contraceptives**
  - Use oral (or IUD) instead of injectable/implants
- **HIV medications**
  - Monitor weight
- **Chronic inflammatory disorders**
  - Use NSAIDs and disease modifying agents rather than glucocorticoids
- **Use antihistamines with less central nervous system activity (less sedation)**