

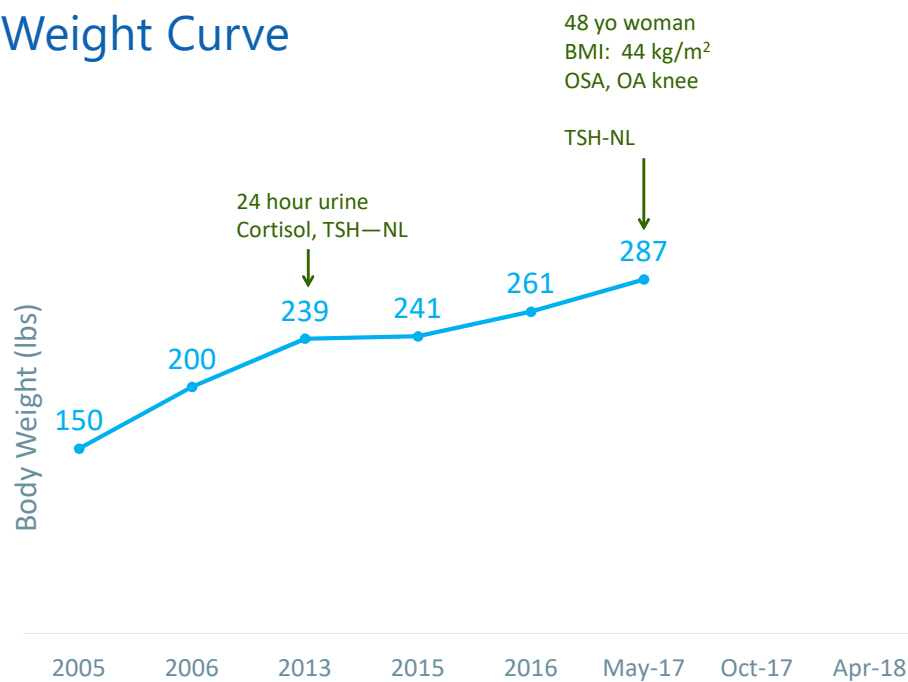
# The Skinny on Pharmacologic Management of Obesity



DATE: 8 Nov 2019 PRESENTED BY: Jonathan Q. Purnell, MD  
Professor, Knight Cardiovascular Institute  
Oregon Health & Science University  
Portland, Oregon

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## Weight Curve



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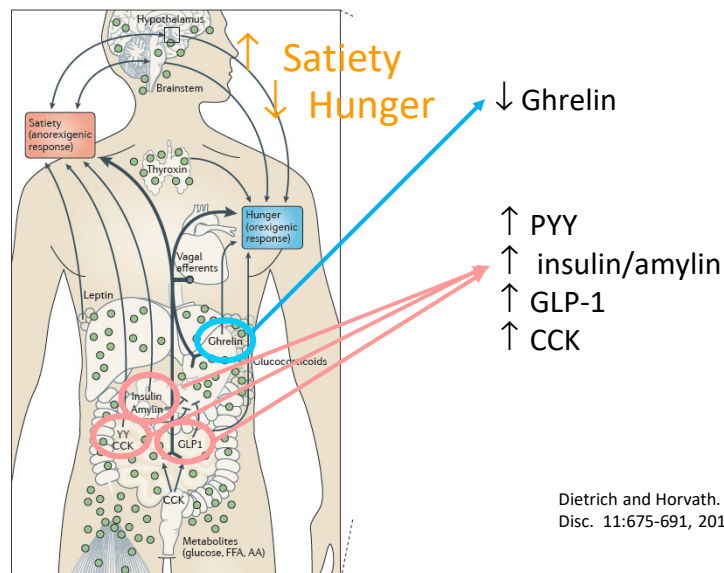
## Weight Management: Chronic Disease Model

- Update on Physiology and of Pathophysiology of Weight Regulation
- Treatment of Overweight and Obesity
  - Lifestyle (diet and exercise)
  - Medications
  - Bariatric Surgery



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## Body Weight Set Point is Receives Signals from Gut Hormones During Meal



Dietrich and Horvath. Nat Rev Drug Disc. 11:675-691, 2012.

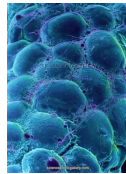
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## CNS Body Weight Regulation Center Receives Adiposity and Meal-related Signals

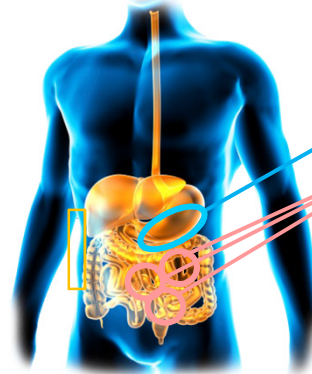
“Are you weighing what I think you should?”



“Are you eating enough (or too much) to maintain that weight?”



Leptin



Ghrelin  
CCK  
Insulin  
Amylin  
PYY  
GLP-1  
..others



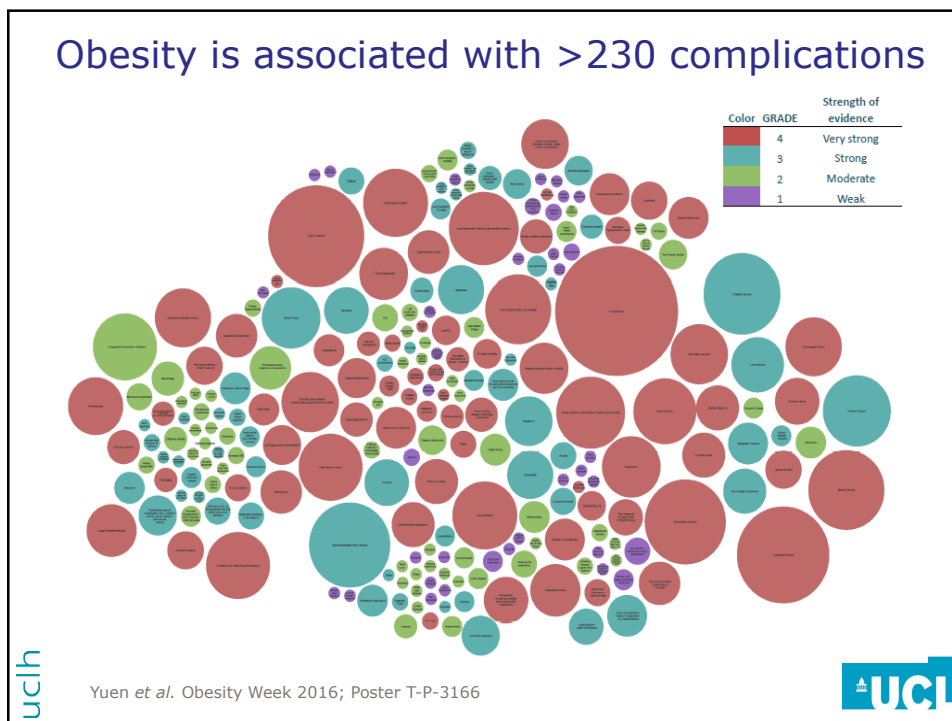
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## Weight Management: Chronic Disease Model

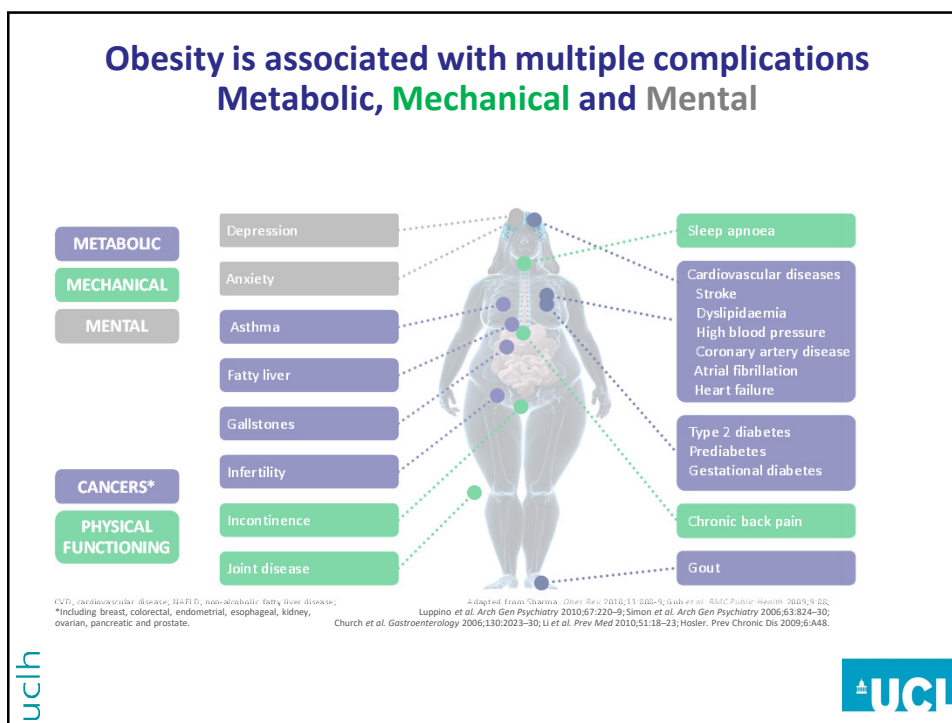
### Weight Management Specific Practice Tips:

- Use “people-first” language: Patients “with obesity” vs. “are obese.”
- Create a “weight history” to identify:
  - Onset of unwanted weight gain
  - Sudden jumps
  - Timing to specific meds, medical diseases
  - Relationship to pregnancy, menopause
  - Lifetime max
  - Any previous strategies that had been successful
  - Current weight
- Identify and code for any obesity-related complication that is covered

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## Weight Management: Chronic Disease Model

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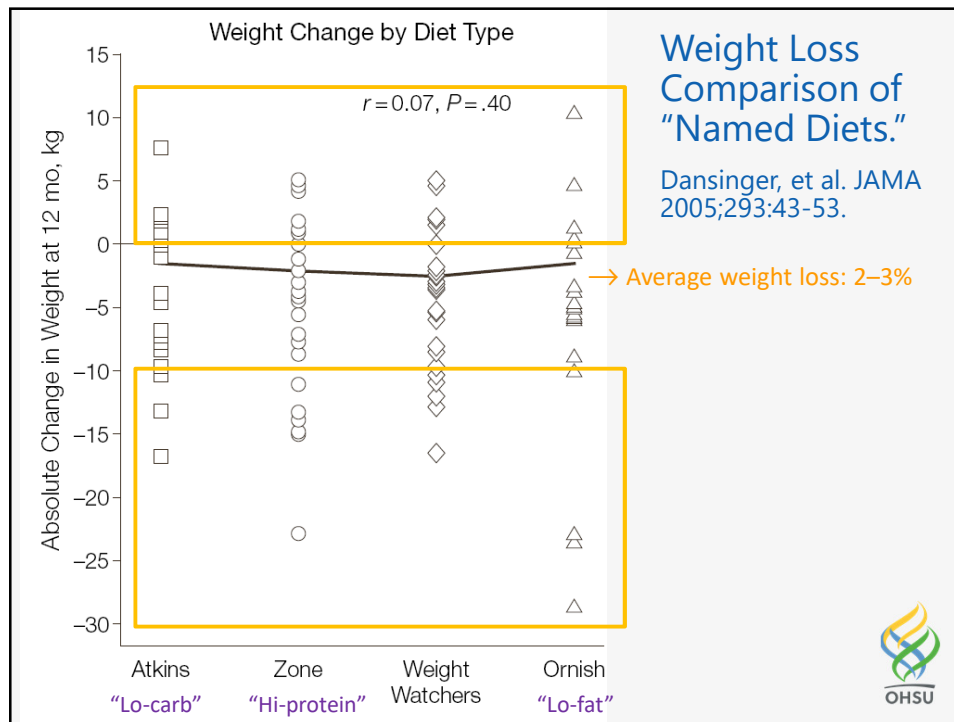
## Question

Which of the following diet and/or diet + exercise approaches is best for weight loss and health?

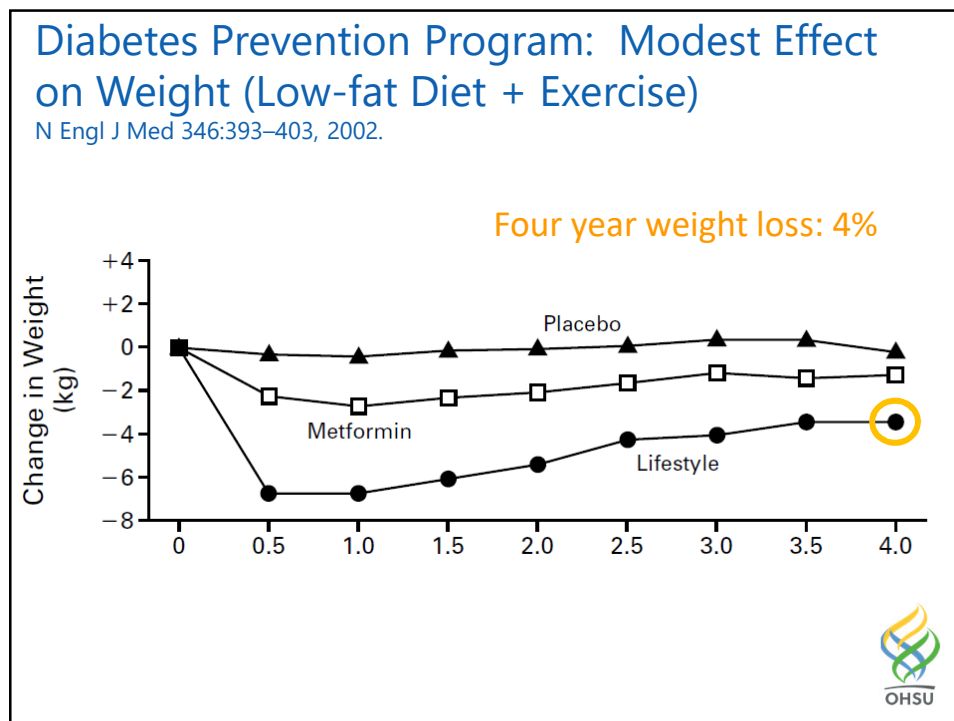
1. Low-carbohydrate diet?
2. Low-fat diet?
3. Keto diet?
4. High-protein diet?
5. Diabetes Prevention Program?



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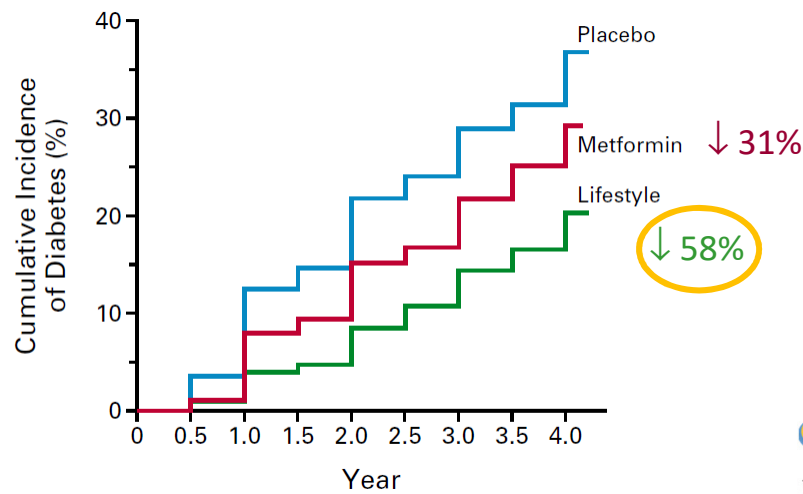
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## Diabetes Incidence Best Lowered by Lifestyle (Low-fat Diet + Exercise)

N Engl J Med 346:393–403, 2002.



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## Question

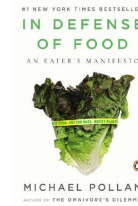
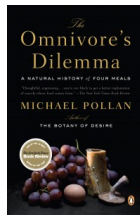
Which of the following diet and/or diet + exercise approaches is best for weight loss and health?

1. Low-carbohydrate diet?
2. Low-fat diet?
3. Keto diet?
4. High-protein diet?
5. Diabetes Prevention Program?



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## Lifestyle Recommendations



Eat food. Mostly plants. Not too much.

Be active. At work. At home.



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## Weight Management: Chronic Disease Model

- Update on Physiology and of Pathophysiology of Weight Regulation
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  - Lifestyle (diet and exercise)
  - Medications
  - Bariatric Surgery



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## Recommendation For Consideration of Pharmacological Weight Management

- BMI 27 - 30 kg/m<sup>2</sup> and a weight-related comorbidity:
    - HTN
    - Dyslipidemia
    - Diabetes
    - Other
- OR
- BMI ≥ 30 kg/m<sup>2</sup>



[https://www.nhlbi.nih.gov/files/docs/guidelines/prctgd\\_c.pdf](https://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf)

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## Pharmacological Weight Management

### The Science of Obesity Management: An Endocrine Society Scientific Statement

(Endocrine Reviews. 39: 79 – 132, 2018)

George A. Bray,<sup>1</sup> William E. Heisel,<sup>2</sup> Ashkan Afshin,<sup>3</sup> Michael D. Jensen,<sup>3</sup> William H. Dietz,<sup>4</sup> Michael Long,<sup>4</sup> Robert F. Kushner,<sup>5</sup> Stephen R. Daniels,<sup>6</sup> Thomas A. Wadden,<sup>7</sup> Adam G. Tsai,<sup>8i</sup> Frank B. Hu,<sup>9</sup> John M. Jakicic,<sup>10</sup> Donna H. Ryan,<sup>1</sup> Bruce M. Wolfe,<sup>11</sup> and Thomas H. Inge<sup>12,13i</sup>

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## Pharmacological Weight Management

### Currently FDA Approved Medications for Weight Loss

- tetrahydrolipstatin (Orlistat) \$\$\$  
     – (now over the counter as “alli”-60 mg dose)
- phentermine (Fastin, Ionamin, Adipex) \$
- phentermine + topiramate (Qsymia) \$ or \$\$\$
- lorcaserin (Belviq) \$\$\$
- bupropion + naltrexone (Contrave) \$\$
- liraglutide 3.0 (Saxenda)



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## Pharmacological Weight Management: Tips

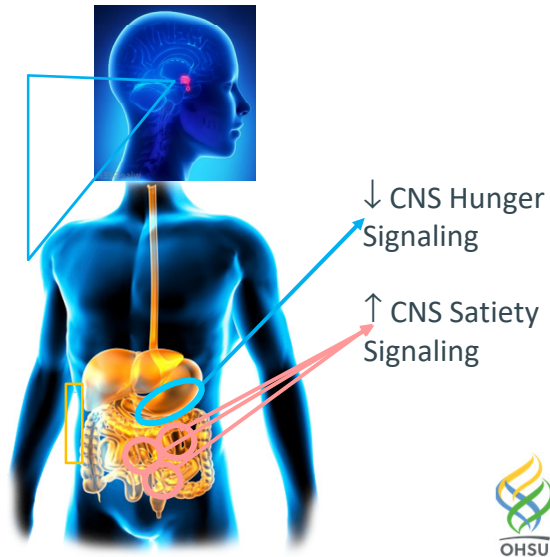
- **Lifestyle** is always attempted **first** and continued during treatment.
- All drugs are **Category X** for Pregnancy and Lactation.
- All drugs have been shown to **improve cardiometabolic risk factors**.
- Weight loss is **variable**.
- Continue treatment long-term (**do not stop**) unless:
  - Patient is a non-responder
  - Side effect(s) emerge
- **Avoid** use of phentermine, phentermine/topiramate ER, and bupropion/naltrexone SR in patients with:
  - Active CAD/CHF
  - Untreated HTN
  - Untreated hyperthyroidism
  - MAO inhibitors
- **Hypoglycemia** is a risk in patients with diabetes treated with oral hypoglycemic med and insulin



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## Weight Loss Medications Enhance CNS Signaling to Meal-related Signals

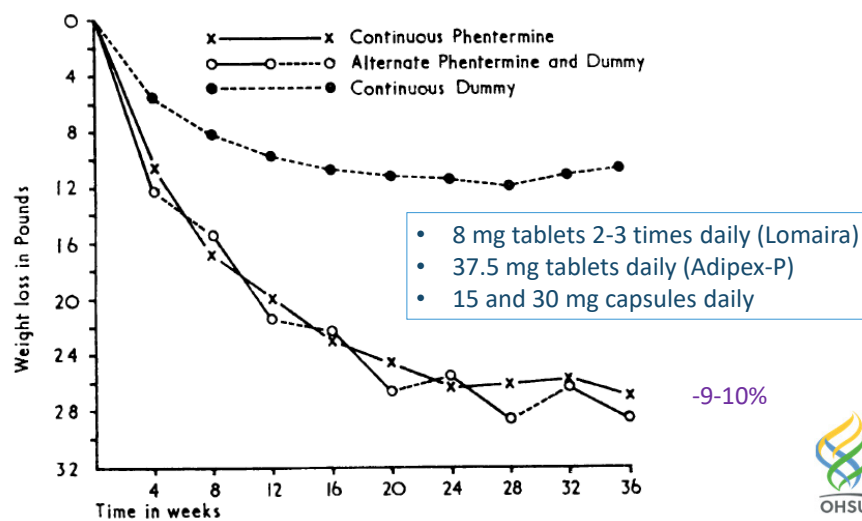
- phentermine
- phentermine + topiramate
- lorcaserin
- bupropion + naltrexone
- liraglutide



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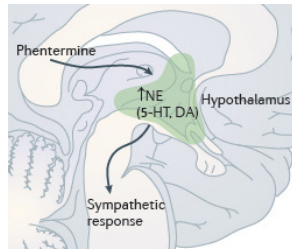
## Weight Loss With Phentermine

Monroe, et al. BMJ. 1:352-54. 1968.



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## Phentermine: Side Effects and Precautions



### Short-Term: Central Adrenergic Agonism

- Insomnia
- Dry mouth
- Increased heart rate and BP
- Anxiety

### Long-term:

- BP stable or reduced with weight loss
- Addictive behaviors not demonstrated
- Can be continued more than 6-12 weeks per Qsymia package insert: "...an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients..."

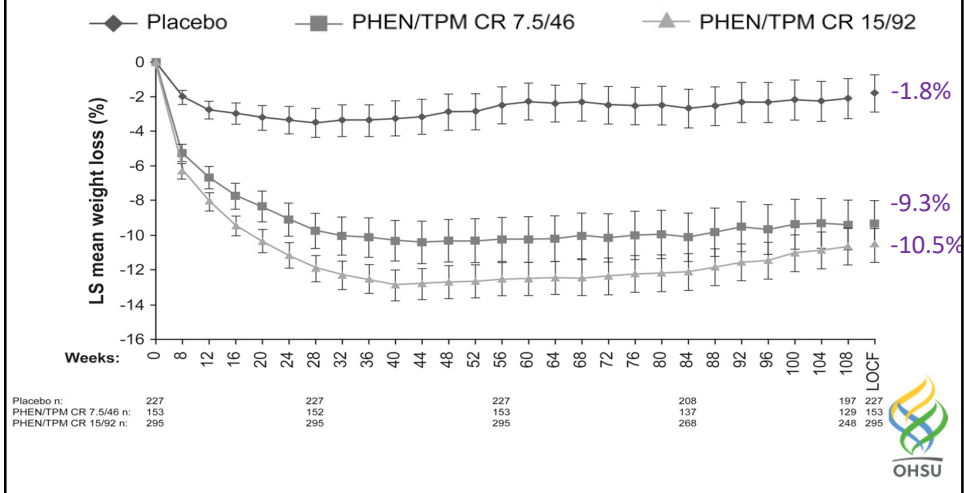
International Journal of Obesity (2014) 38, 292–298.  
Obesity (2011) 19, 2351–2360.  
American Journal of Therapeutics (2011) 18, 292–299



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## Weight Loss with Phentermine + Topiramate (Qsymia)

Garvey WT, et al. Am J Clin Nutr. 2012;95:297-308.



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## Cardiovascular Safety During and After Use of Phentermine and Topiramate

Ritchey ME, et al. J Clin Endocrinol Metab. 2019, 104(2):513–522

**Table 3. Adjusted IRRs and IRDs for MACE and Components of This Outcome**

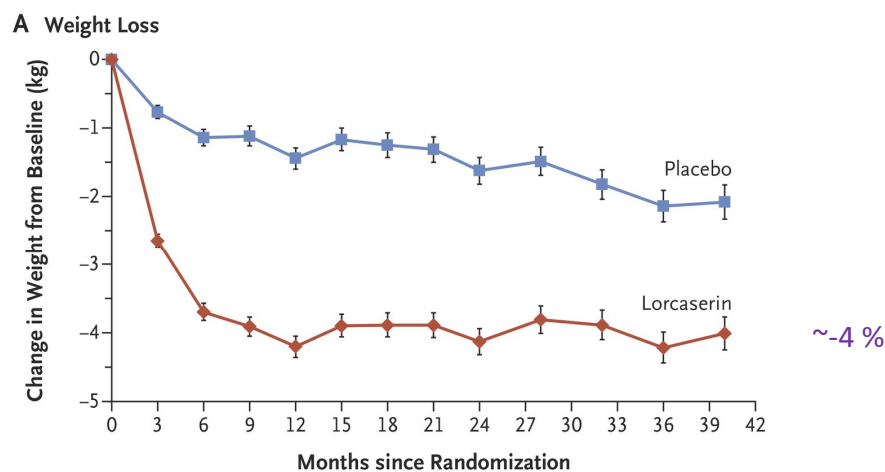
Variable	PHEN/TPM		Fixed-PHEN/TPM		PHEN		TPM	
	Current Use	Unexposed (Reference)	Current Use	Unexposed (Reference)	Current Use	Unexposed (Reference)	Current Use	Unexposed (Reference)
Person-years	2820	232,470	2207	217,665	22,218	251,807	60,889	291,147
MACE								
Events, n	3	424	1	395	17	423	186	539
IRR (95% CI)	0.57 (0.19 to 1.78)		0.24 (0.03 to 1.70)		0.56 (0.34 to 0.91)		1.58 (1.33 to 1.87)	
IRD (95% CI)	-0.79 (-2.05 to 0.44)		-1.45 (-2.37 to -0.50)		-0.62 (-1.02 to -0.22)		1.11 (0.64 to 1.57)	
AMI								
Events, n	1	240	0	225	9	241	51	296
IRR (95% CI)	0.35 (0.05 to 2.52)		0.00 (0.00 to NC)		0.51 (0.26 to 1.00)		0.79 (0.59 to 1.07)	
IRD (95% CI)	-0.66 (-1.37 to 0.06)		-1.02 (-1.20 to -0.85)		-0.39 (-0.68 to -0.10)		-0.22 (-0.48 to 0.04)	
Stroke								
Events, n	2	167	1	154	7	167	133	217
IRR (95% CI)	0.89 (0.22 to 3.53)		0.55 (0.08 to 3.85)		0.58 (0.27 to 1.24)		2.81 (2.26 to 3.50)	
IRD (95% CI)	-0.09 (-1.10 to 0.92)		-0.37 (-1.29 to 0.54)		-0.23 (-0.49 to 0.03)		1.38 (1.01 to 1.76)	
CV-related death								
Events, n	0	17	0	16	1	15	2	26
IRR (95% CI)	0.00 (0.00 to NC)		0.00 (0.00 to NC)		1.03 (0.12 to 8.67)		0.35 (0.08 to 1.45)	
IRD (95% CI)	-0.04 (-0.07 to -0.02)		-0.04 (-0.06 to -0.02)		0.00 (-0.09 to 0.09)		-0.06 (-0.12 to 0.00)	

MACE variables: hospitalization for AMI or stroke and in-hospital CV-related death

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## Weight Loss With Lorcaserin (5-HT<sub>2C</sub> agonist)

Bohula EA et al. N Engl J Med 2018;379:1107-1117

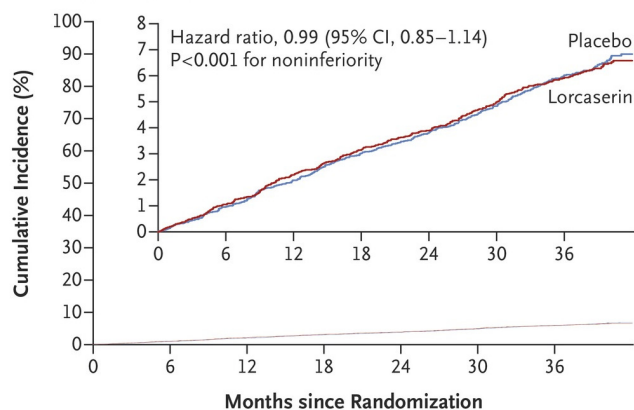


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## Non-inferiority of Lorcaserin (5-HT<sub>2C</sub> agonist) on MACE

Bohula EA et al. N Engl J Med 2018;379:1107-1117

### A Major Cardiovascular Events



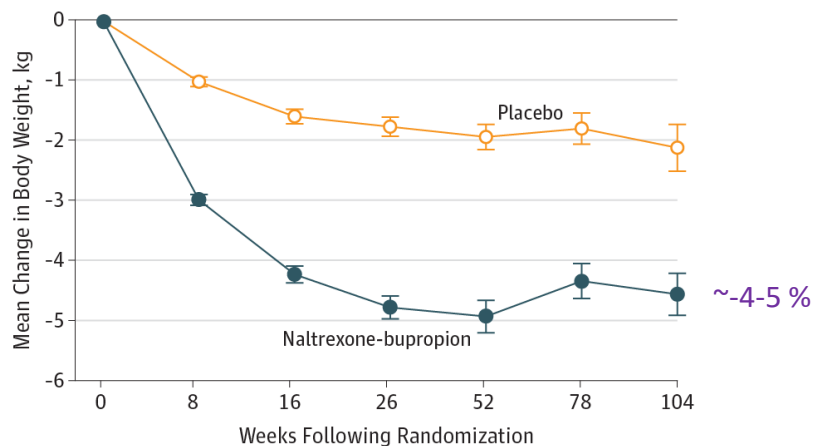
#### No. at Risk

Placebo	6000	5814	5614	4003
Lorcaserin	6000	5816	5623	4041

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## Weight Loss With Bupropion + Naltrexone (Contrave)

Nissen SE, et al. JAMA. 2016;315(10):990-1004.



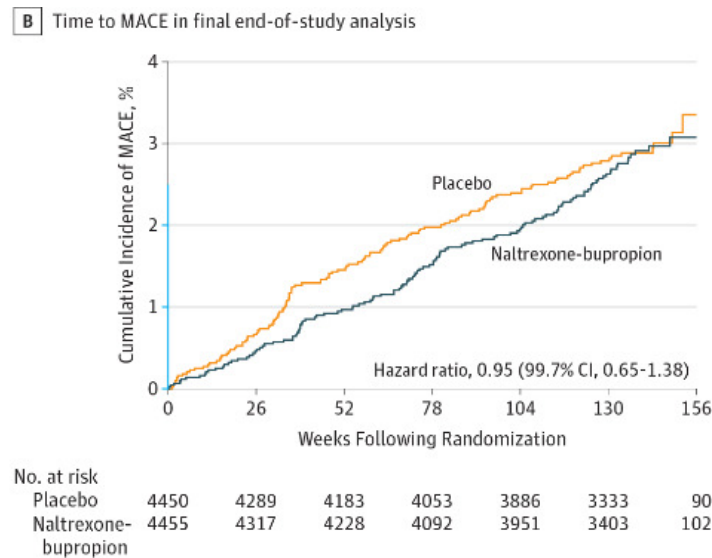
#### No. of patients

Placebo	4450	4042	3738	3297	2848	2507	2264
Naltrexone-bupropion	4455	3977	3677	3404	2995	2690	2408

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## Effect of Bupropion + Naltrexon (Contrave) on MACE

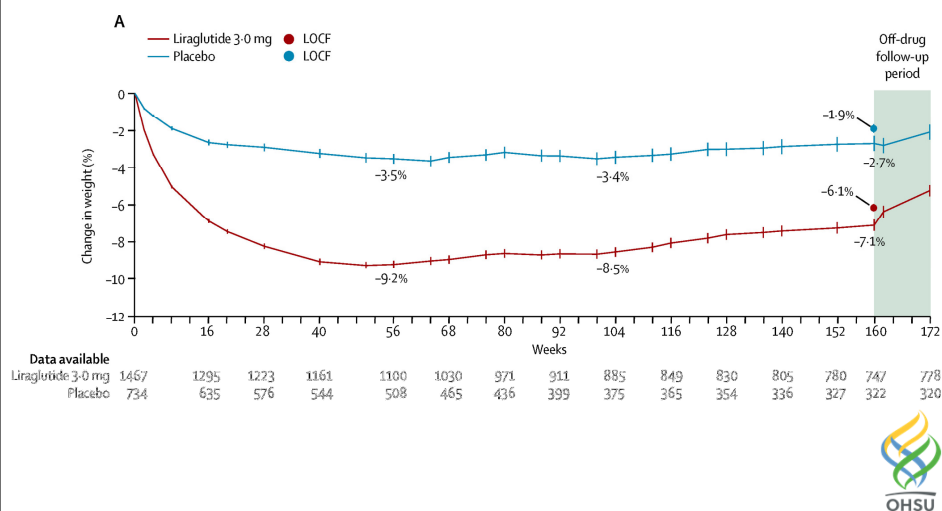
Nissen SE, et al. JAMA. 2016;315(10):990-1004.



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## Liraglutide 3.0 for Weight Management and Type 2 Diabetes Risk Reduction in Pre-diabetes

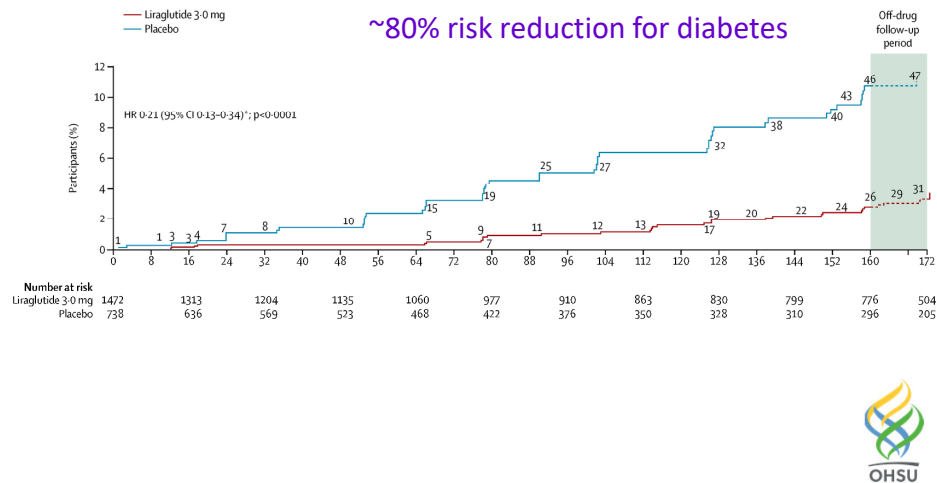
le Roux, et al. Lancet 2017; 389: 1399–409



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## Liraglutide 3.0 for Weight Management and Type 2 Diabetes Risk Reduction in Pre-diabetes

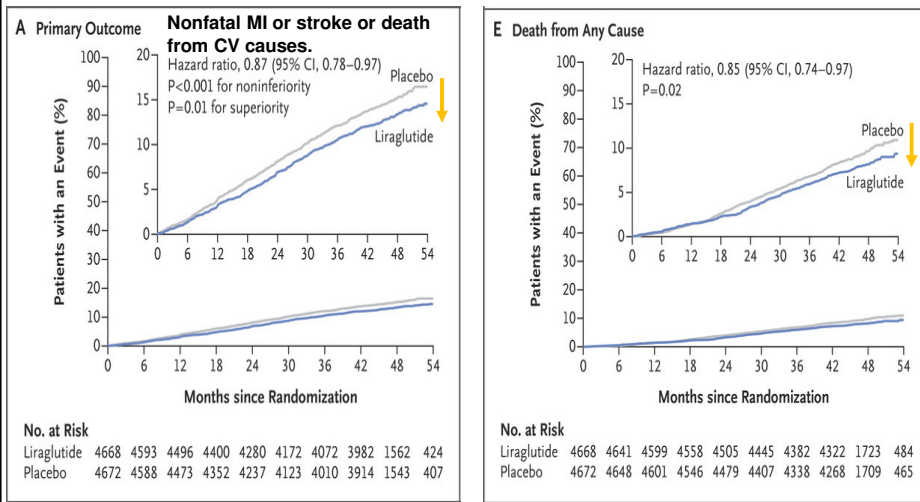
le Roux, et al. Lancet 2017; 389: 1399–409



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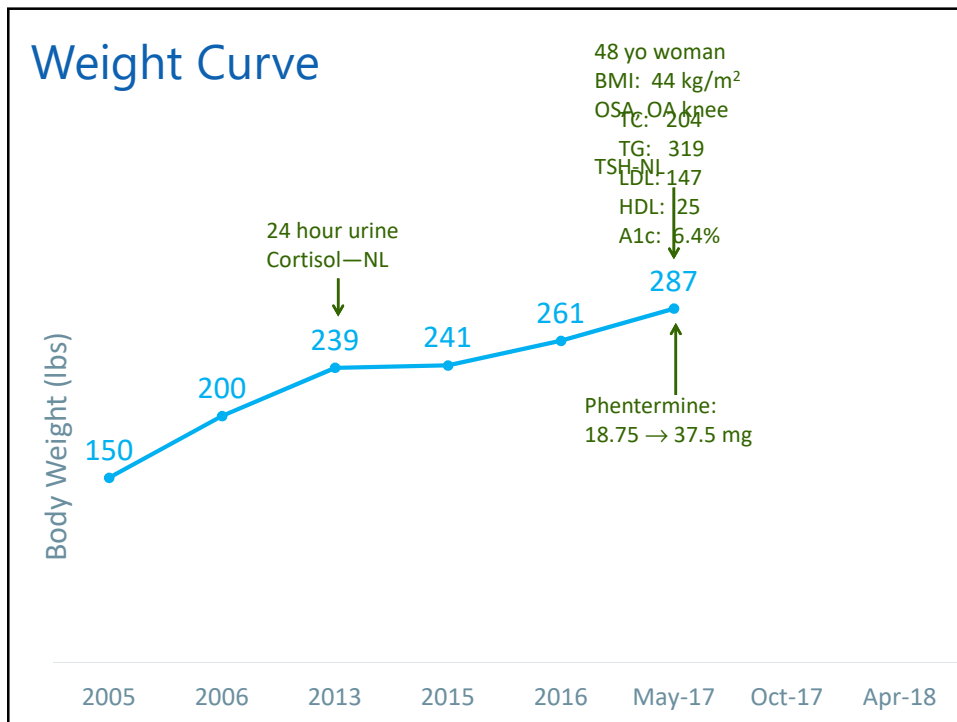
## LEADER: Liraglutide 1.8 mg Improves Cardiovascular Outcomes and All Cause Mortality in Type 2 Diabetes

Marso SP et al. N Engl J Med 2016;375:311-322.

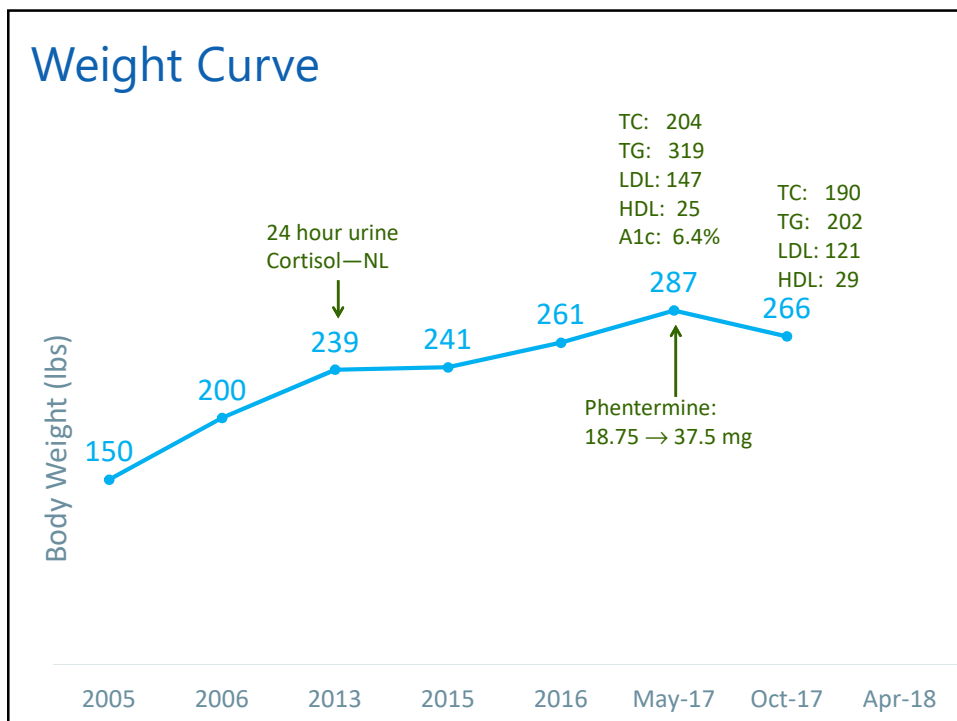


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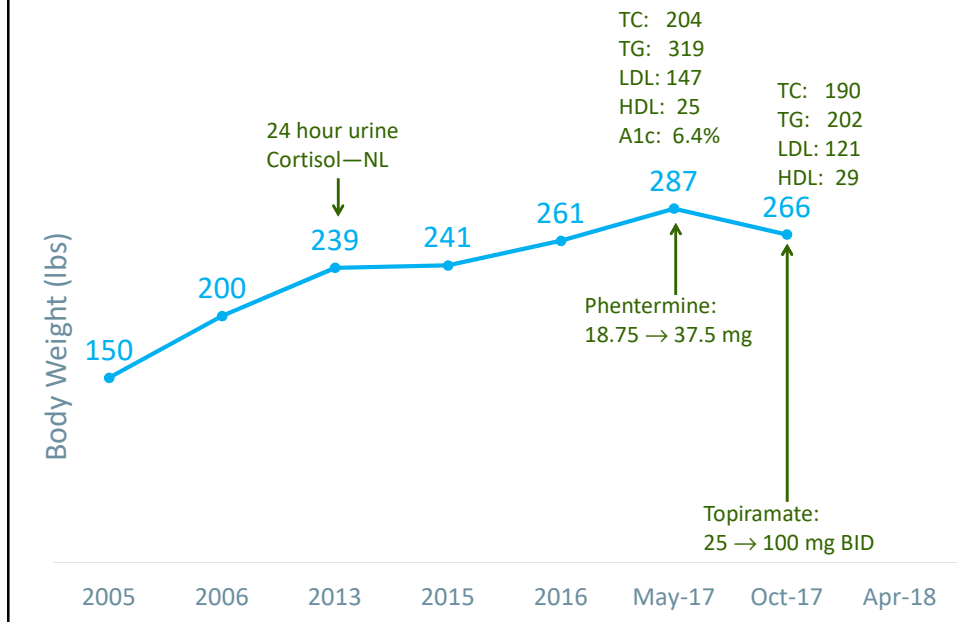


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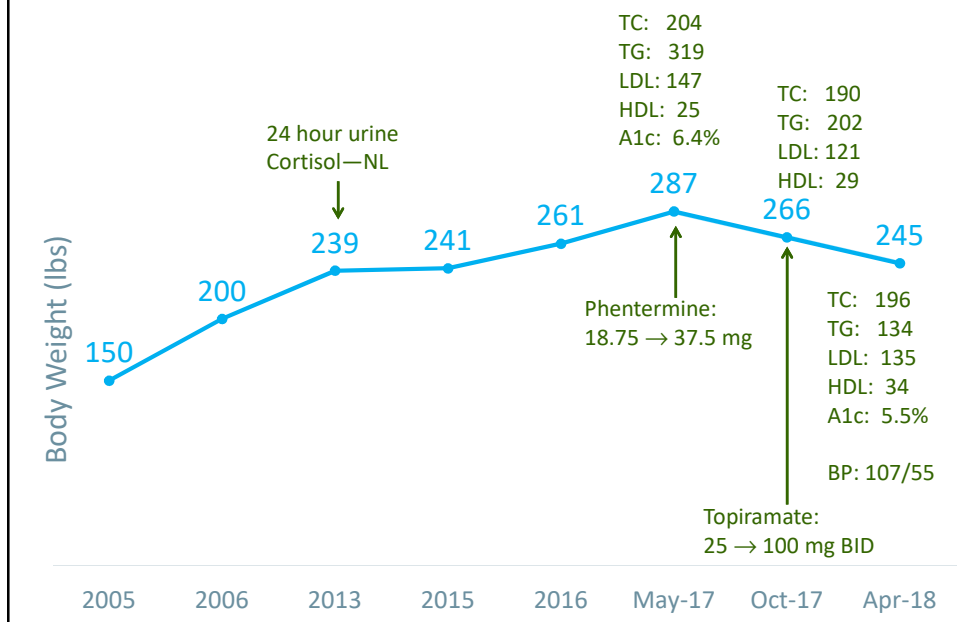
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## Weight Curve: Next Steps



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## Weight Curve: Next Steps



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## Question

What do you recommend next regarding weight loss medications?

1. Continue phentermine for 3 months then stop?
2. Continue both for 1 year then stop and monitor?
3. Continue indefinitely?
4. Begin intermittent therapy (every other month)?



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## Question

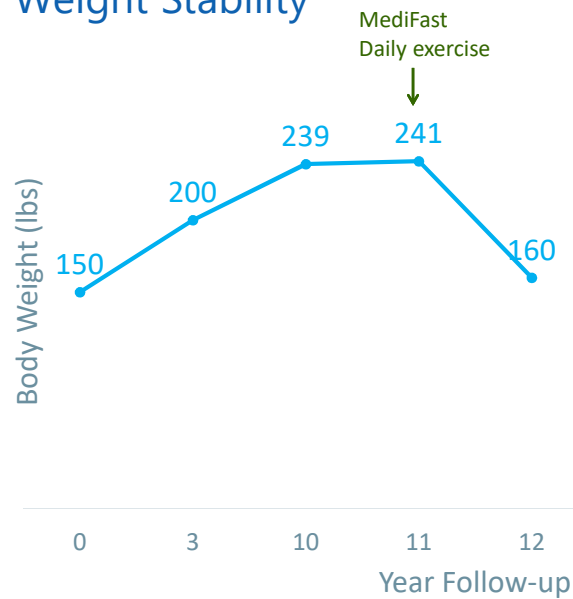
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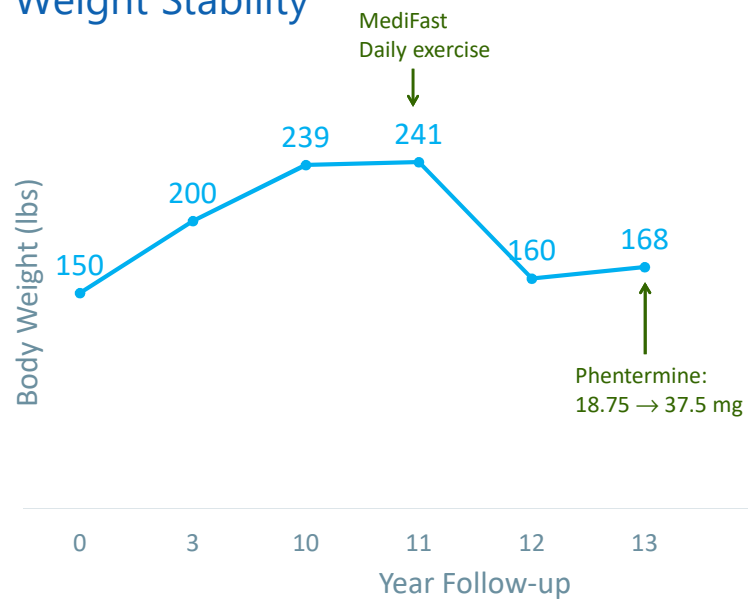
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### Weight Curve: Example of Using Rx for Weight Stability

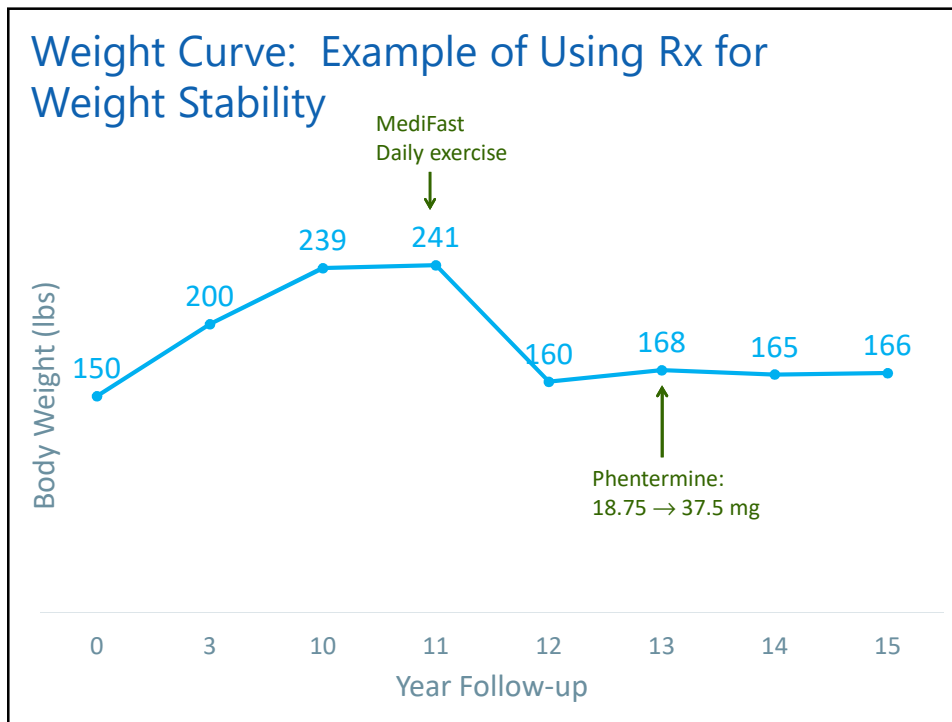


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### Weight Curve: Example of Using Rx for Weight Stability



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## Pharmacological Weight Management: The Skinny

- **Obtain a lifetime weight history**
- **Lifestyle** is always attempted **first** and continued during treatment.
- Once weight Rx started, weight loss is **variable and modest (4-10%)**.  
*Think management of hypercholesterolemia before statins and hypertension before ACEI*
- Continue treatment long-term (**do not stop**) unless:
  - Patient is a non-responder (a “responder” may maintain weight)
  - Side effect(s) emerge
- **Refer to bariatric surgery** when appropriate
  - BMI  $\geq 35 \text{ kg/m}^2$  + comorbidity
  - BMI  $\geq 40 \text{ kg/m}^2$



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## Reasons for Underutilization of Weight Management Medications

- Previous weight loss drugs had poor safety record (fenfluramine, sibutramine, rimonabant)
- Perceived need for frequent follow-ups needed for AE monitoring
- Some are controlled substances:
  - Phentermine and lorcaserin are DEA schedule IV (low potential for abuse and low risk of dependence)
- Need for long term use
  - Goal  $\geq 3\%$  weight loss at 3 months;  $\geq 5\%$  at 1 year
- Variable response among patients, including many “non-responders”
- Poor and inconsistent insurance coverage
  - Often cost to patient

 Slide credit: [clinicaloptions.com](http://clinicaloptions.com)

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## Thank You

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