

# Treating Obesity to manage NAFLD

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# OBJECTIVES



Discuss factors contributing to the epidemics of obesity and NAFLD



Review lifestyle modification and anti-obesity medications for treating obesity and NAFLD



Describe the use of bariatric surgery for improving health outcomes in obesity and NAFLD

# Opening Thoughts

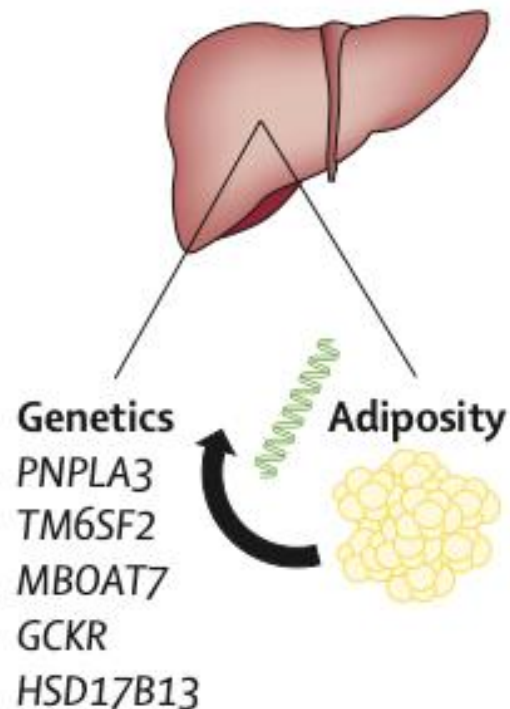
NAFLD was first described in 1980 and is now the most common liver disease worldwide

Prevalence is rising with increases in obesity and type 2 diabetes

Consider prevention in addition to treatment

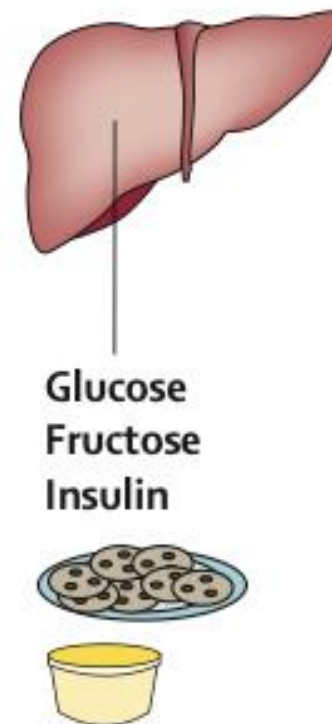
# Major pathways inducing NAFLD

## Genetic Component



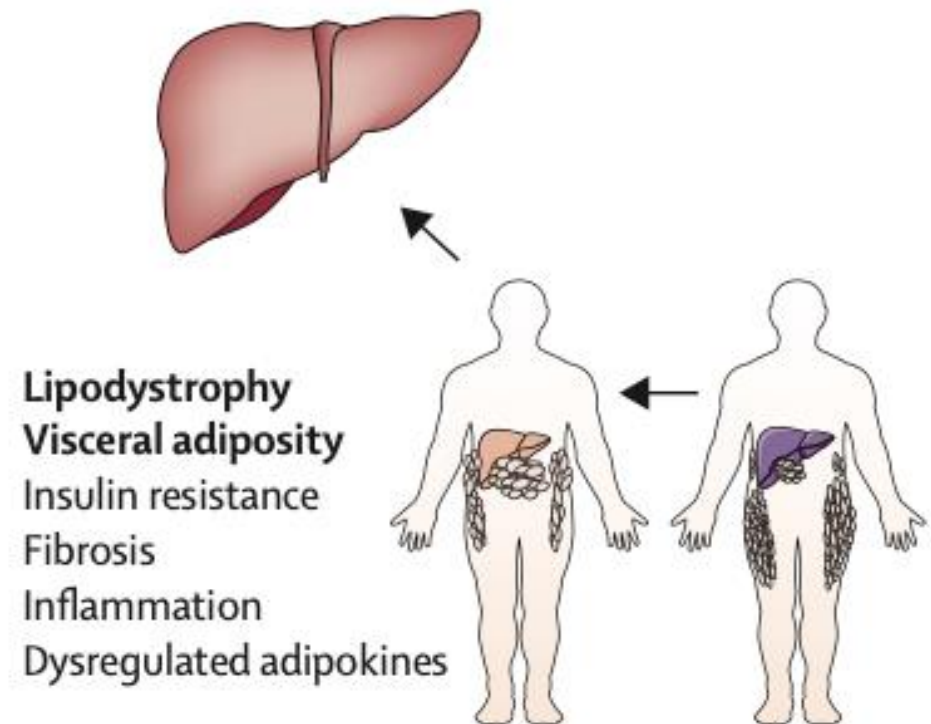
## Lifestyle Component

Predominantly driven by de-novo lipogenesis

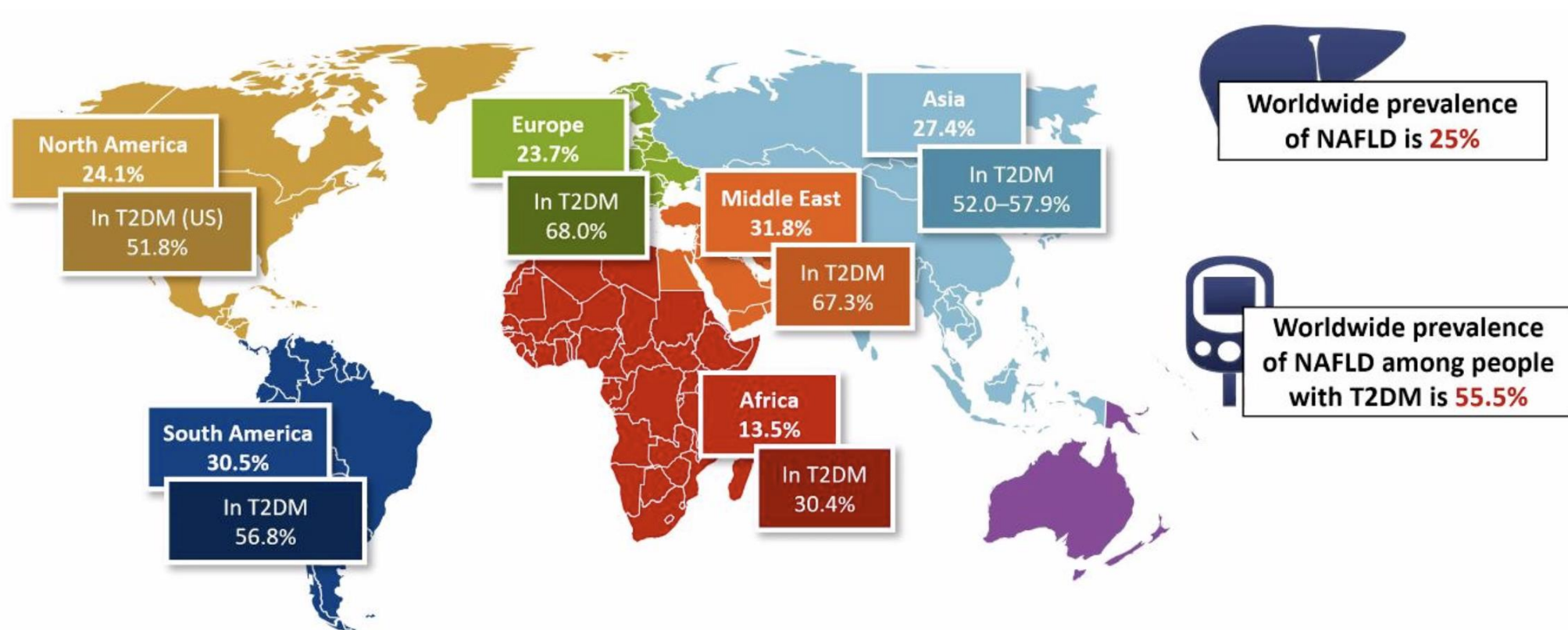


## Adipose Component

Predominantly driven by adipose tissue dysfunction



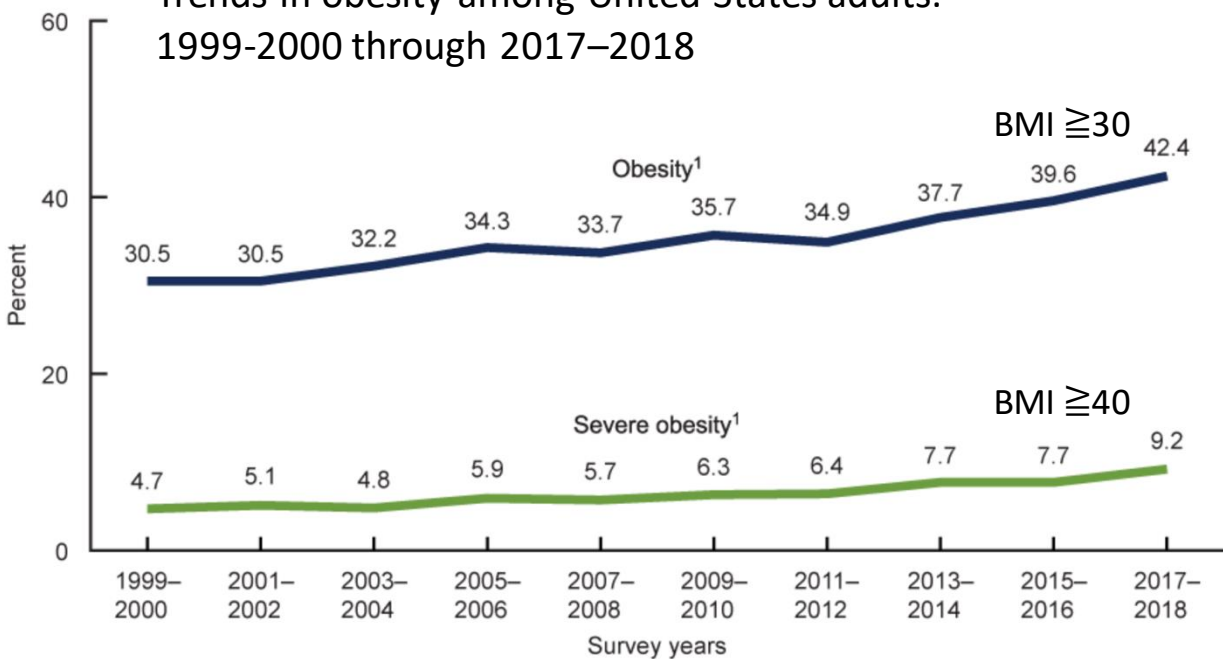
# Worldwide Prevalence of NAFLD



# US Obesity Epidemic Grows

African Americans and Hispanic Groups are most affected

Trends in obesity among United States adults:  
1999-2000 through 2017-2018

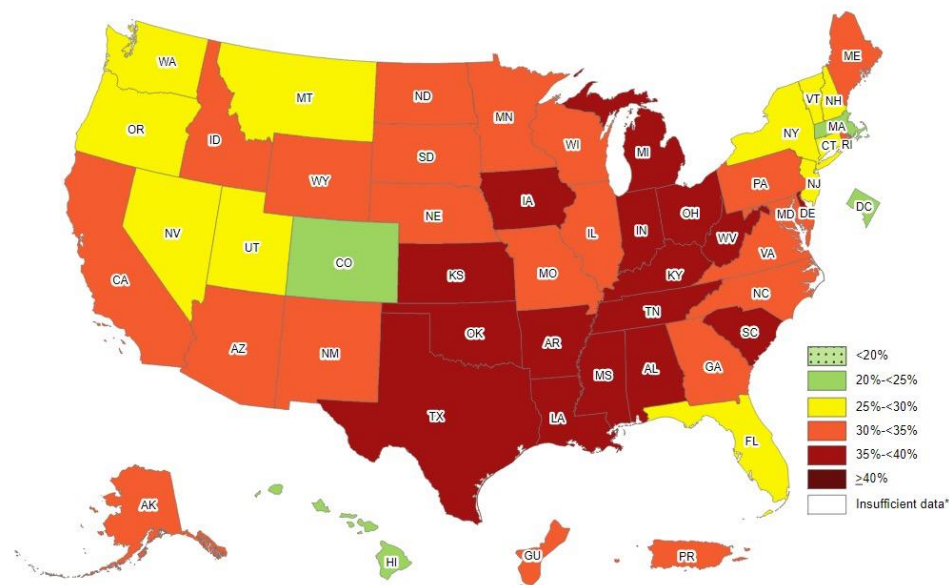


Obesity Prevalence 1999-2000 to 2017-2018:

- 1) Obesity increased 30.5% to 42.4%
- 2) Severe obesity increased 4.7% to 9.2%

## Prevalence<sup>1</sup> of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2020

<sup>1</sup> Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.



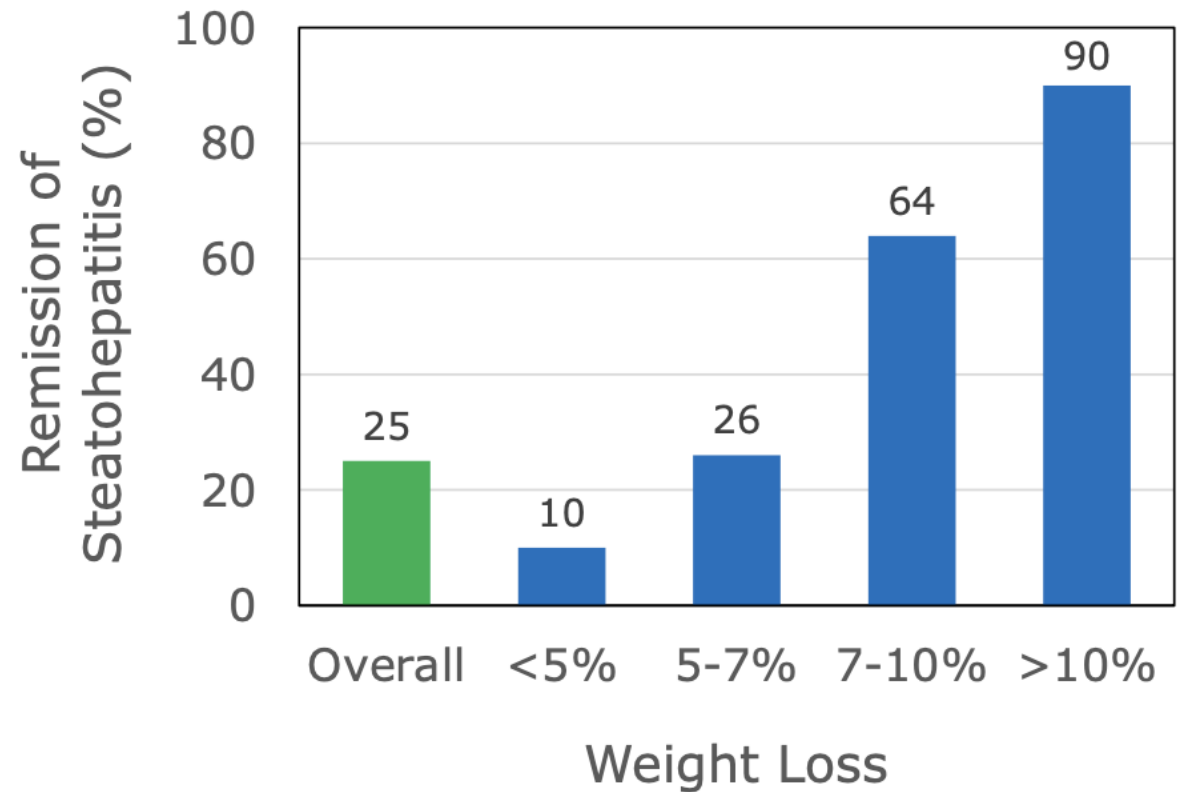
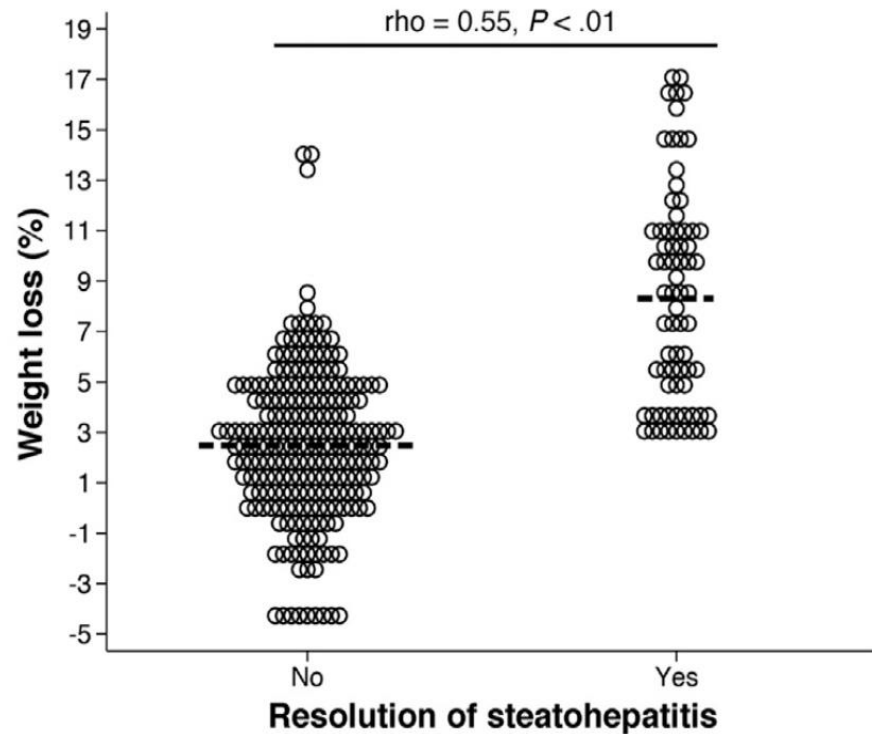
\*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.



# AGA Clinical Care Pathway for Management of Patients with NAFLD

	<b>LOW RISK</b> FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	<b>INDETERMINATE RISK</b> FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	<b>HIGH RISK<sup>1</sup></b> FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention <sup>2</sup>	Yes	Yes	Yes
Weight loss recommended if overweight or obese <sup>3</sup>	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes <sup>4, 5, 6</sup>	Yes <sup>4, 5, 6, 7</sup>
CVD risk reduction <sup>8</sup>	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

# Impact of Weight Loss on NAFLD is Dose Dependent



Average weight loss 3.8%  
30% lost  $\geq 5\%$  body weight



# Approach to treating NAFLD

There is currently **no** FDA-approved medication for NAFLD

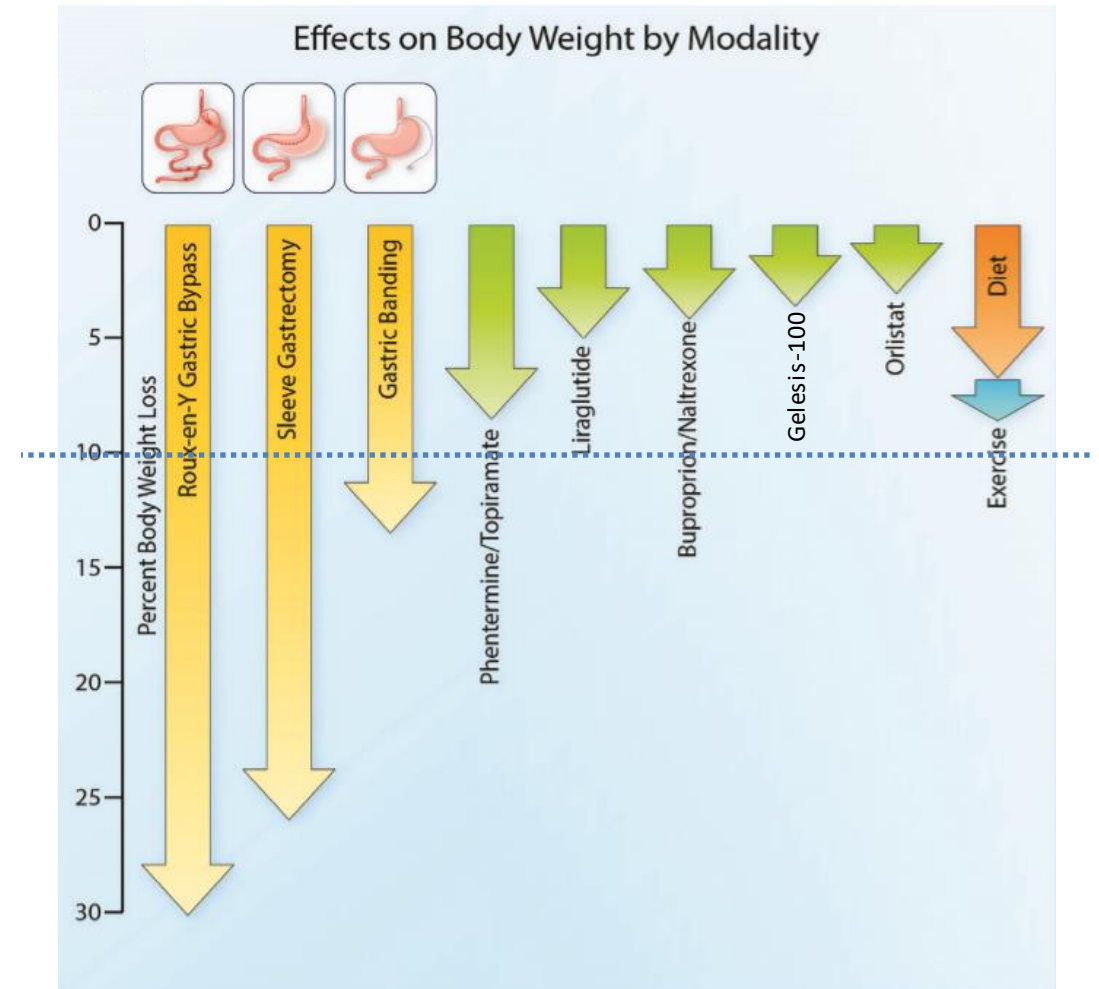
## Two strategies

**Treat the liver disease** –limited options

- Vitamin E\* - histological benefit in NASH **without** type 2 diabetes
- Pioglitazone\* - histological benefit in NASH

**Treat the underlying obesity** – mainstay

- At least 7-10% **durable** weight loss is needed to improve liver tests and histology



# Diets for treating NAFLD

**Efficacy of different diets for NASH has not been adequately assessed**

Calorie restriction of 30% or >750 kcal/day improves liver fat and IR

Hepatology 2011;53:1504-1514

Mediterranean diet decreases steatosis more but not body weight compared with low-fat diet

J Hepatol 2013;59:138-43

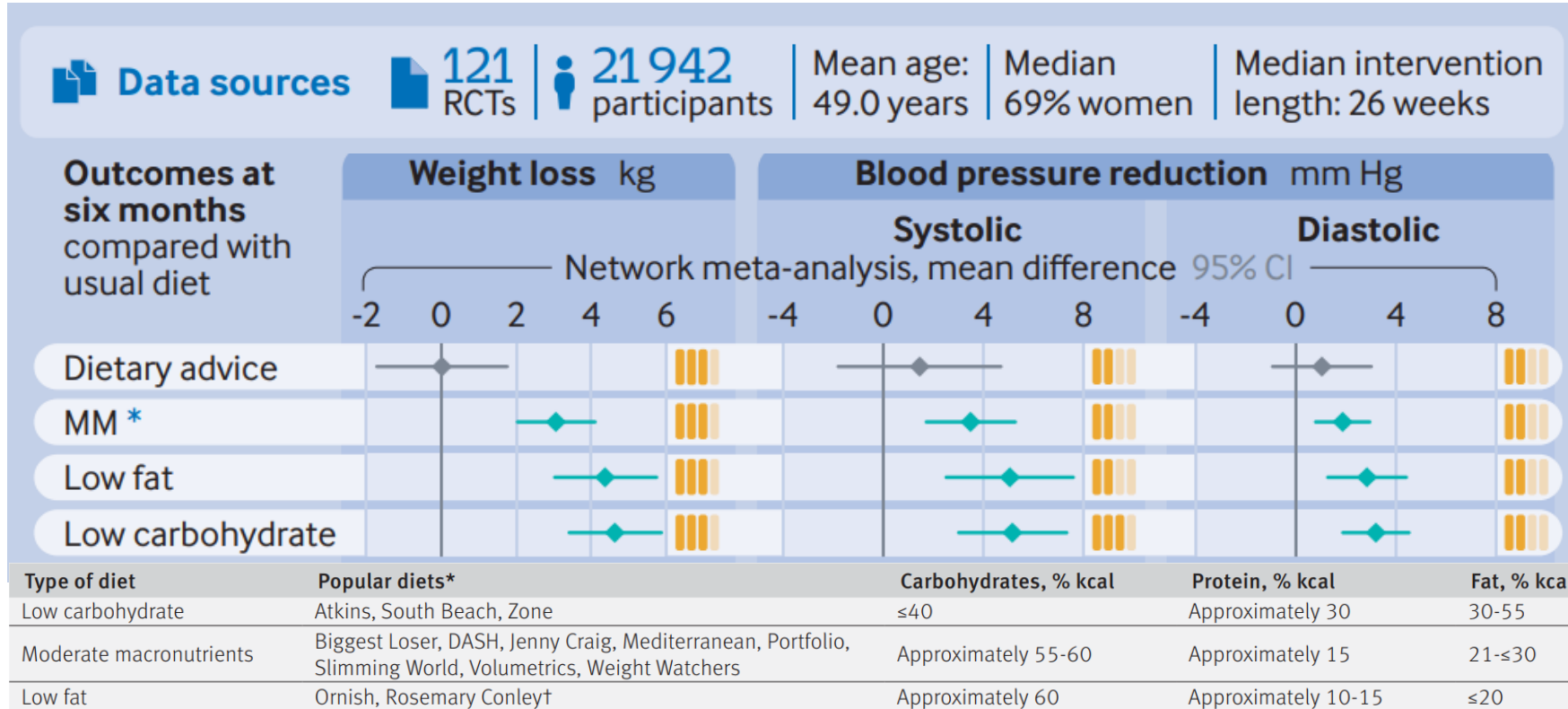
Short term interventions with <20 g/d of carb as part of low-calorie diet decreased IHTG significantly more than just calorie restriction

Am J Clin Nutr 2011;93:1048-52

Genetic and host-specific microbiome differences play a role in responses to dietary interventions – more research is needed



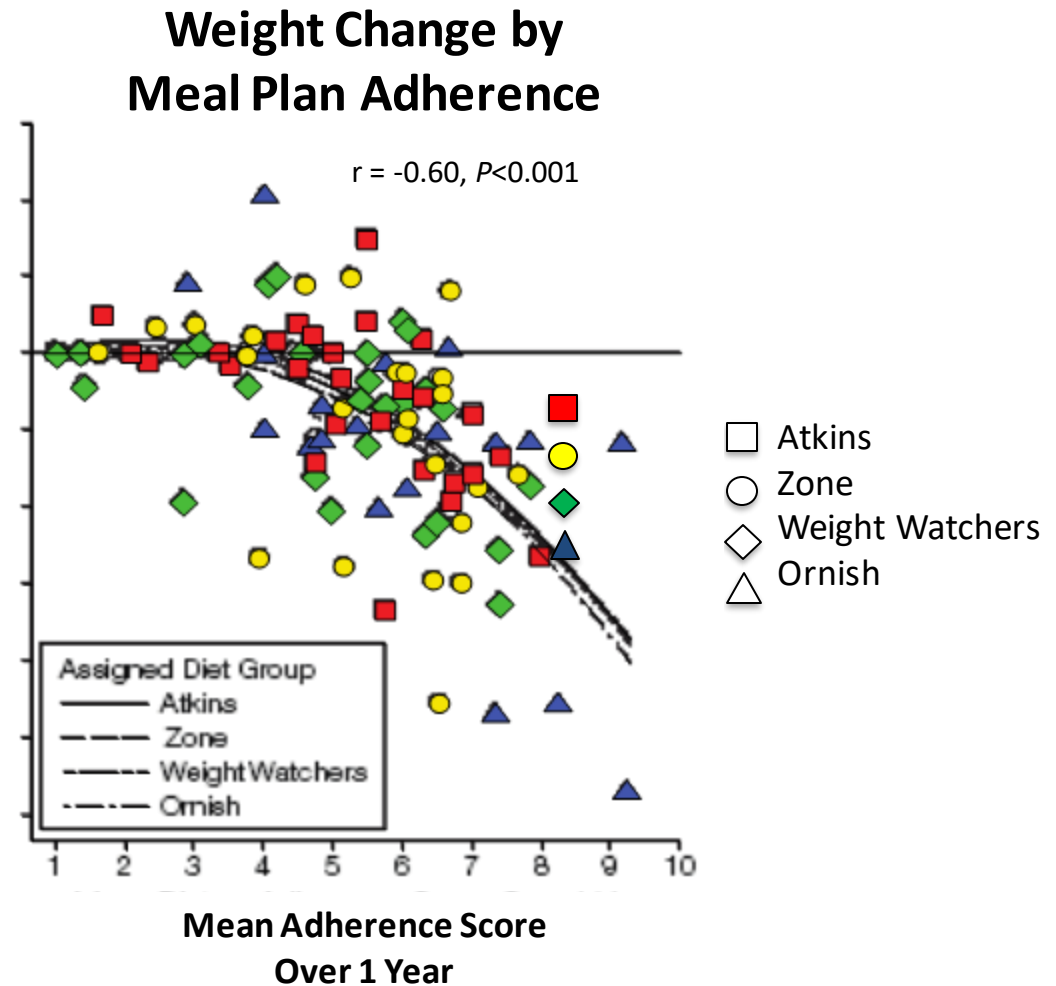
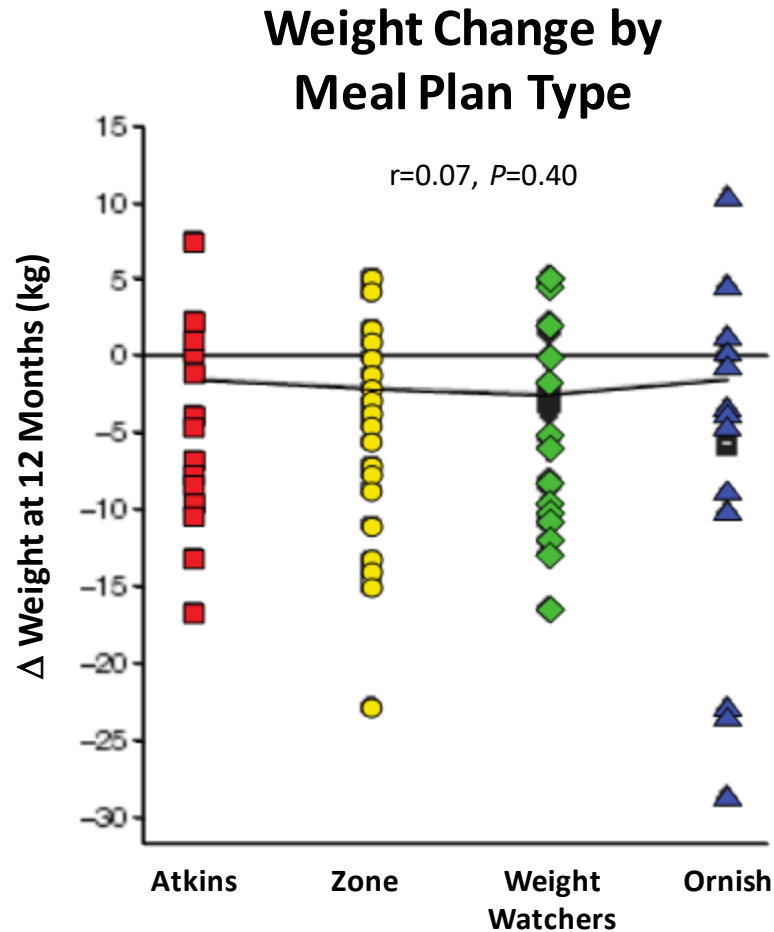
# Consistent calorie restriction is more important than macronutrients



Atkins, DASH, and Zone had the highest certainty evidence and the most consistent effects for reduction in weight and BP at 6 months

Estimated effects at 12 months for weight loss and CV risk factor improvements diminished for all popular diets, except for the Mediterranean diet

# Adherence is more Important than Diet for Weight Loss



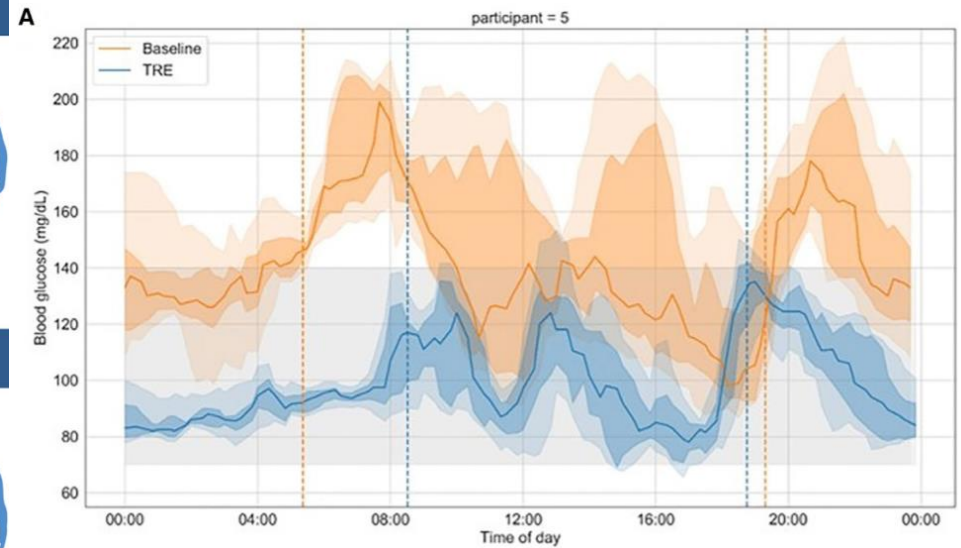
# Intermittent Fasting

## 10-hour Time Restricted Eating (TRE)

### BASELINE



### 10-HR TIME-RESTRICTED EATING (TRE)

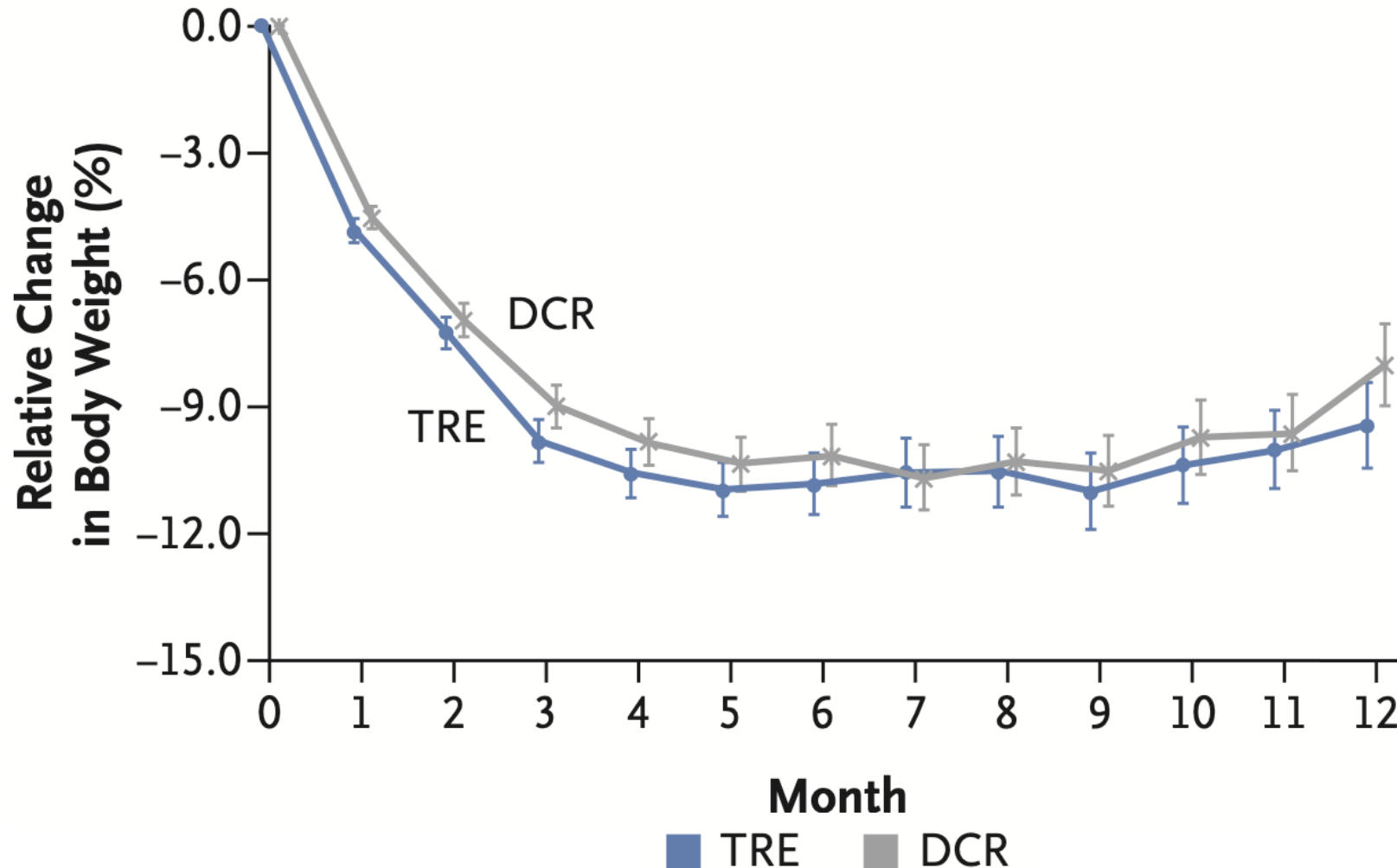


CGM at Baseline and after 12 weeks TRE

	Baseline (mean (SD))	TRE (mean (SD))	Change in TRE Baseline (mean (SD))	Percent Change	p Value
<b>Weight, BMI, Body Fat, and Blood Pressure</b>					
Daily eating interval <sup>a</sup>	15.13 (1.13)	10.78 (1.18)	-4.35 (1.32)	-29%	8.847E-11
Weight (kg)	97.84 (19.73)	94.54 (18.38)	-3.30 (3.20)	-3%	0.00028
BMI (kg/m <sup>2</sup> )	33.06 (4.76)	31.97 (4.44)	-1.09 (0.97)	-3%	0.00011
Percent body fat (%)	36.62 (4.18)	35.61 (4.02)	-1.01 (0.91)	-3%	0.00013
Waist circumference (cm)	109.14 (11.21)	104.68 (14.79)	-4.46 (6.72)	-4%	0.0097
Visceral fat rating	16.68 (5.97)	16.11 (5.89)	-0.58 (0.77)	-3%	0.004
Systolic BP (mmHg) <sup>b</sup>	127.88 (8.89)	122.76 (13.35)	-5.12 (9.51)	-4%	0.041
Diastolic BP (mmHg) <sup>b</sup>	78.47 (8.74)	72.00 (10.75)	-6.47 (7.94)	-8%	0.004

# Daily Calorie Restriction +/- TRE

F:1200-1500 or M:1500-1800 kcal/day. TRE: 0800-1600h

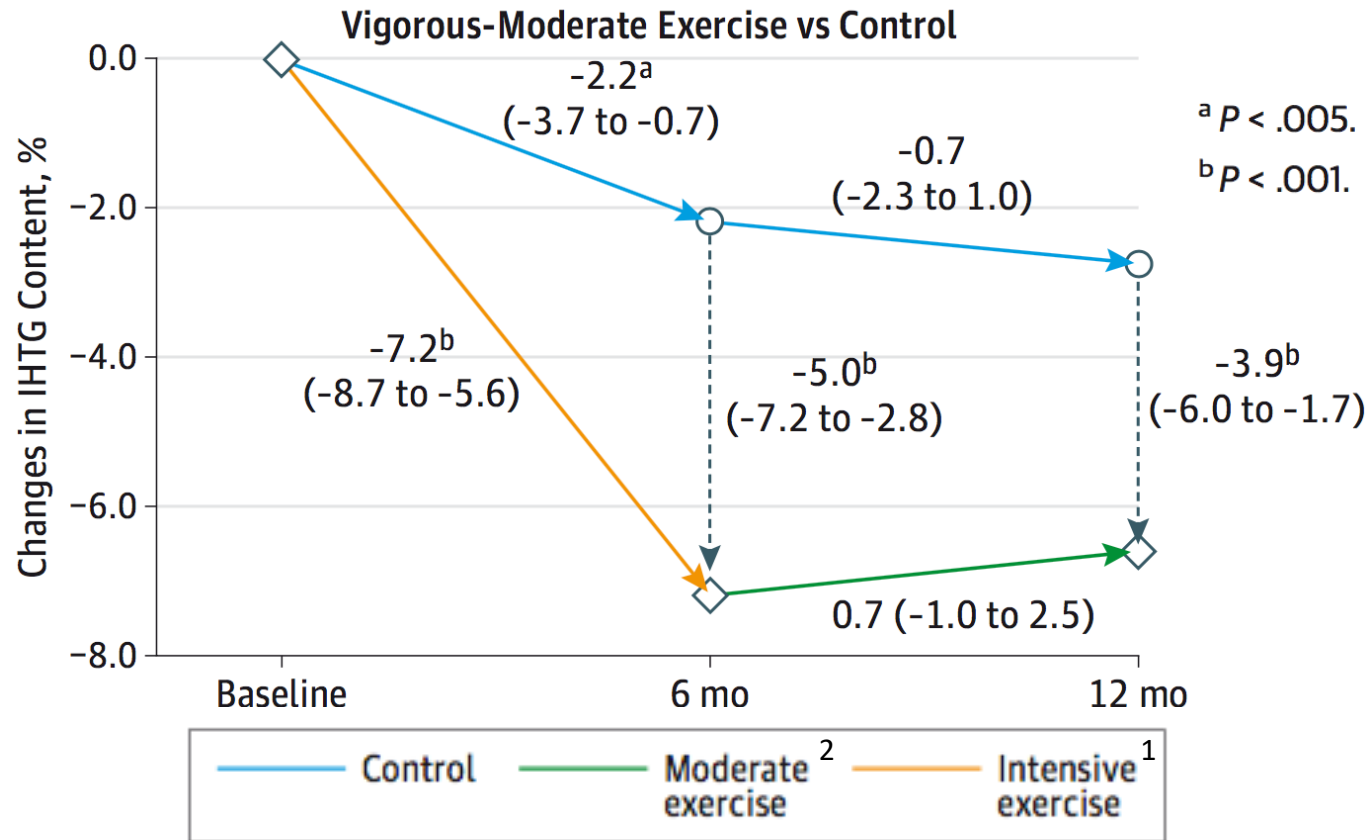


**No differences between groups**

- Body weight
- Waist circumference
- Body fat mass
- Body fat %
- Area of abdo visceral fat
- Area of abdo subcut fat

# Exercise improves NAFLD

Effects on IHTG are mediated by weight reduction (-4.3 kg) and weight loss-independent effects of exercise  
Effects on histology and fibrosis are unknown



1) 65-80% Max HR for 30 mins x 5 session/week

2) 45-55% Max HR for 30 mins x 5 session/week

# Physical Activity Recommendations

## Aerobic physical activity (>150 minutes/week)

- Modest weight loss of 1 to 3 kg with exercise alone
- Additional 1-3% weight loss when combined with calorie deficit
- Improved outcomes with longer duration and higher intensity



## Weight training (2-3 times per week)

- Enhances fat loss, preserves fat-free mass
- Improved weight maintenance

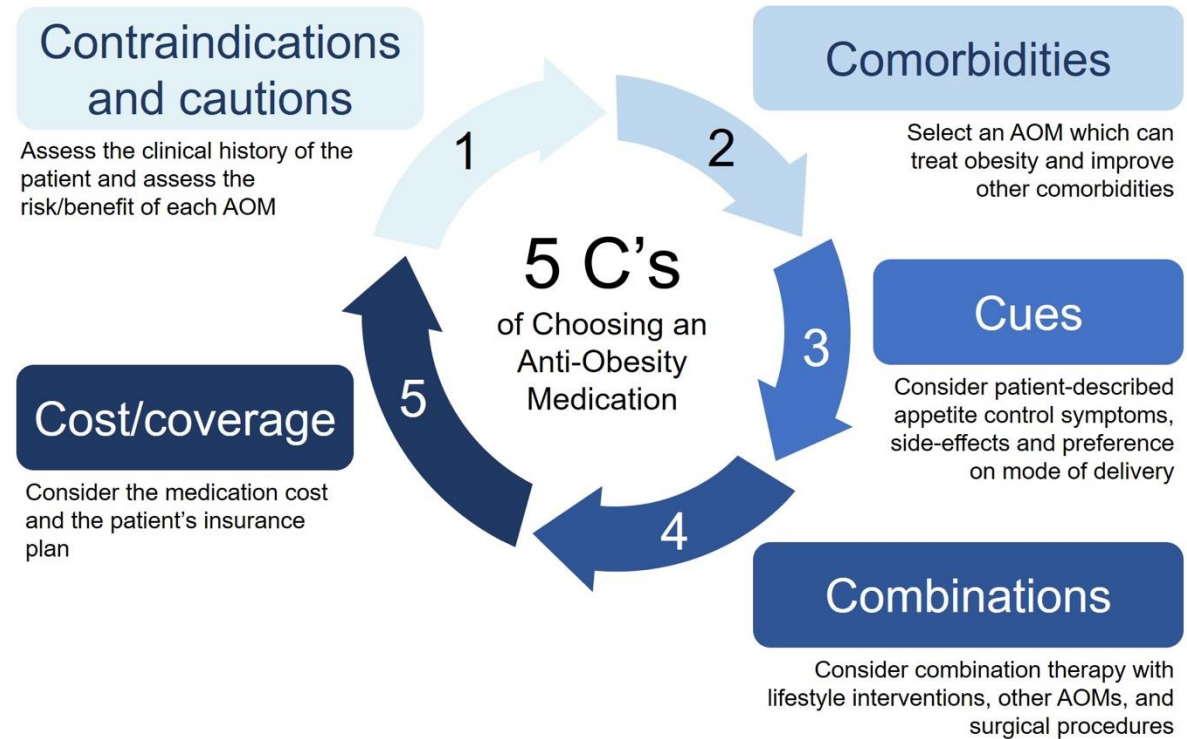


# Anti-Obesity Medications

BMI  $\geq 30$  or  $\geq 27$  kg/m<sup>2</sup> +  $\geq 1$  comorbidity

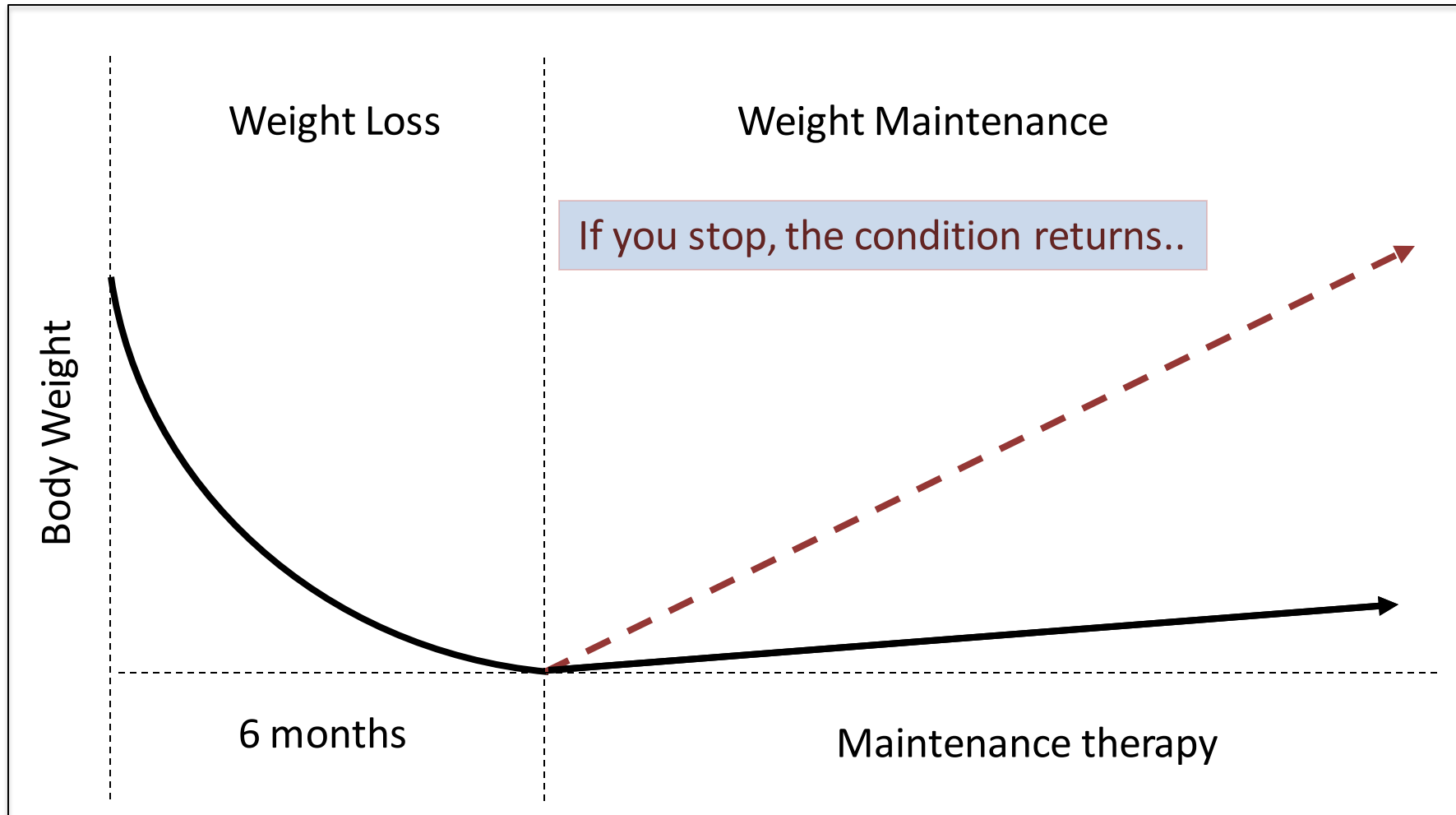
## Obesity Treatment Guidelines AHA - ACC -TOS

*Medications work to reinforce lifestyle change and should be prescribed as an adjunct to lifestyle interventions...*

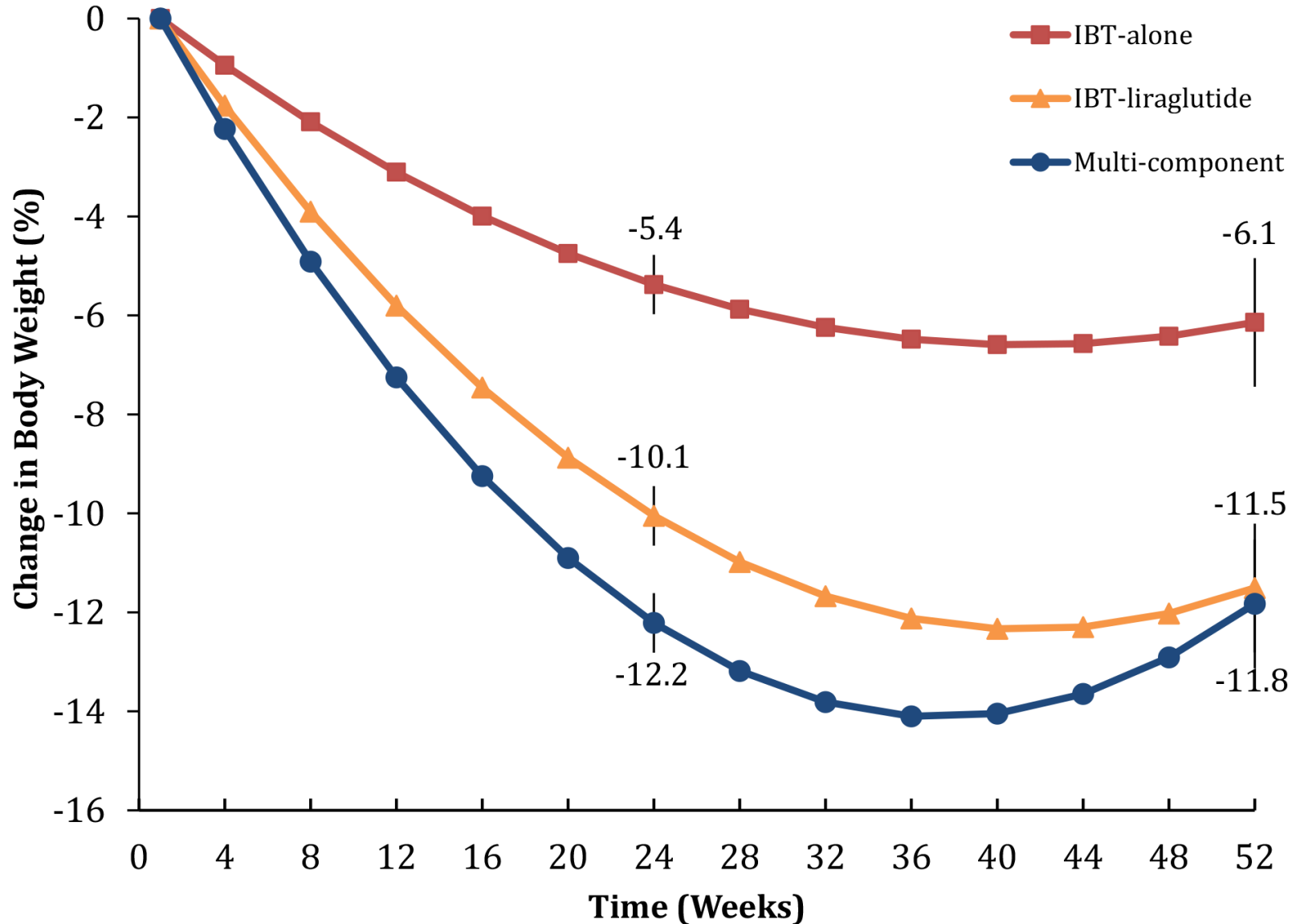


Anti-obesity medications are prescribed to <2% of eligible people

# Think of Treating Obesity like Hypertension



# AOM Augment Lifestyle Modification



# Cellulose-Citric Acid Hydrogel

## Dosing

Gelesis100 - 2.25 g: 3 caps before meals

## Side Effects & Considerations

GI related

## Features

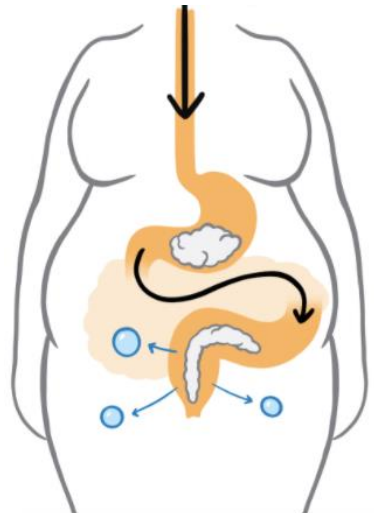
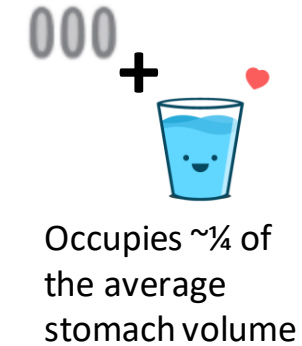
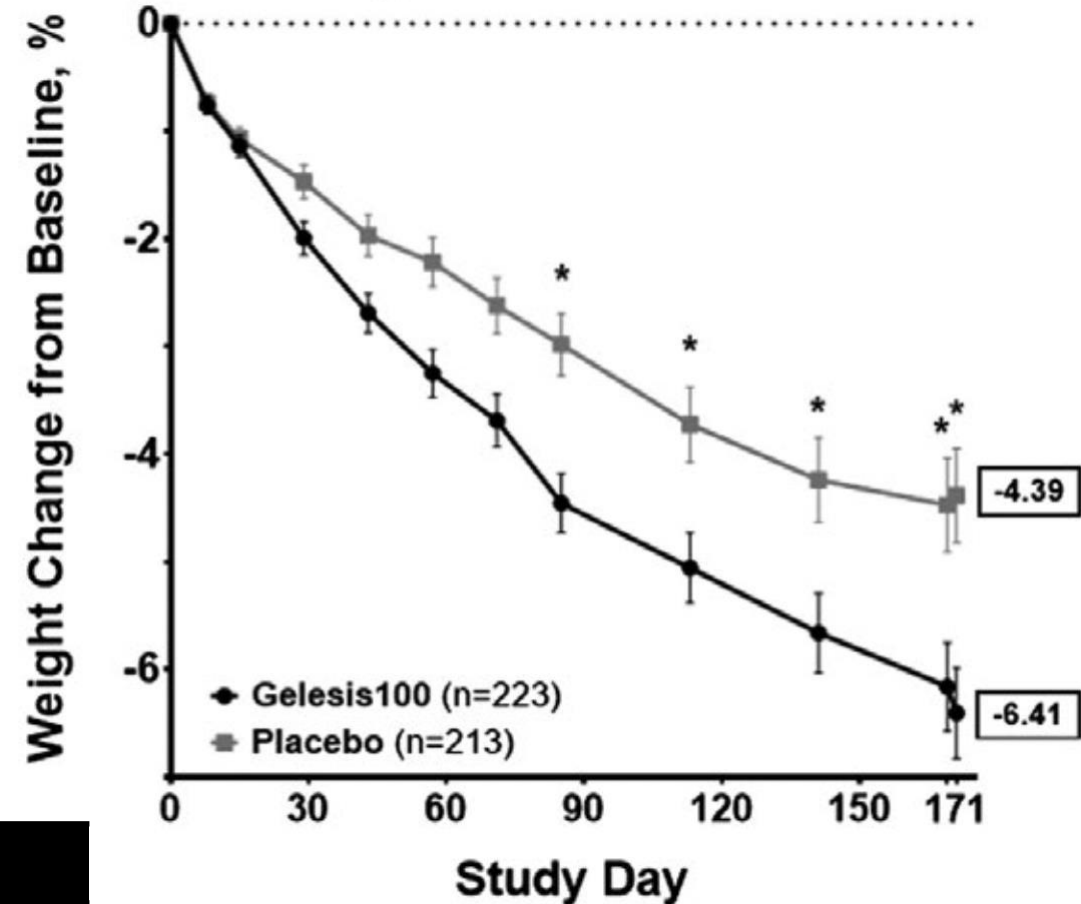
BMI criteria 25-40 kg/m<sup>2</sup>

Greater weight loss with hyperglycemia

## Average cost per month

\$98

	Gelesis-100	Placebo
Weight loss	6.4%	4.4%
>5% weight loss	58.6%	42.2%
>10% weight loss	27.2%	15%



# Orlistat

## Dosing

60 mg or 120 mg

Three times daily before meals

## Side Effects & Considerations

Diarrhea

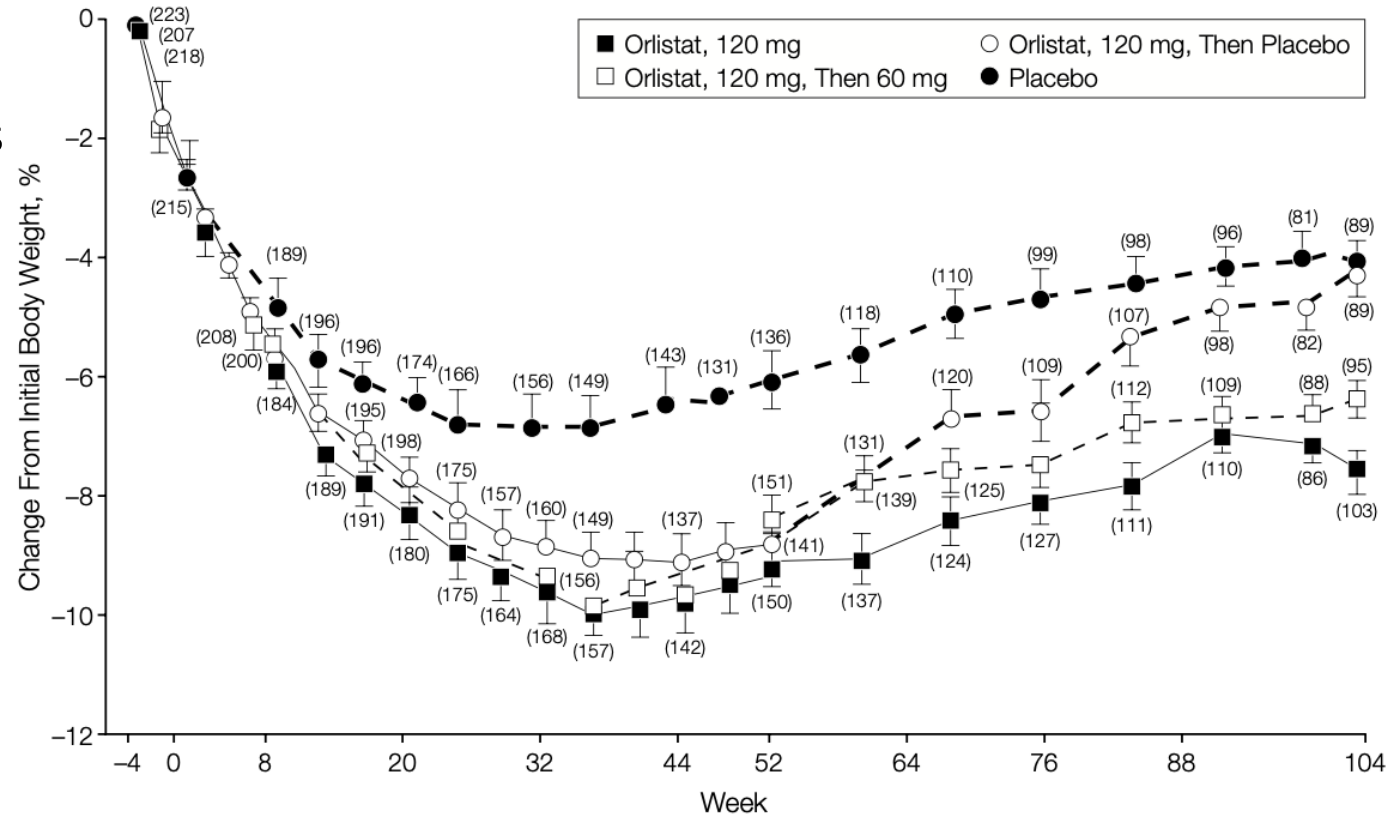
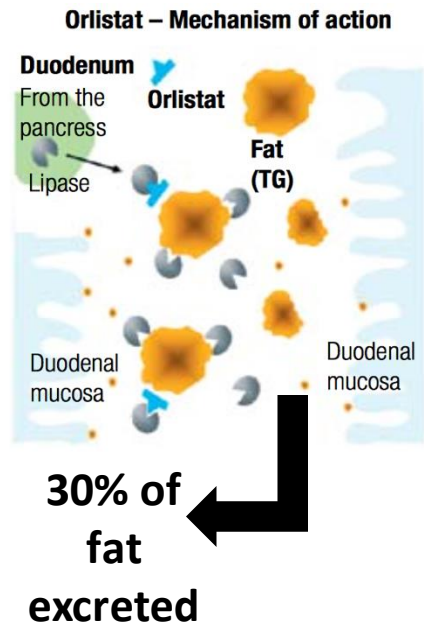
Malabsorption

Nephrolithiasis

Severe liver injury (rare)

## Cost per month

\$42 (60 mg), \$556 (120 mg)



	Orlistat	Placebo
Weight loss 1 year	8.8%	5.8%
>5% weight loss	65.7%	43.6%
>10% weight loss	38.9%	24.8%

# Naltrexone Bupropion ER

## Dosing

8/90 mg – two tabs twice daily

## Side Effects & Considerations

Gastrointestinal upset

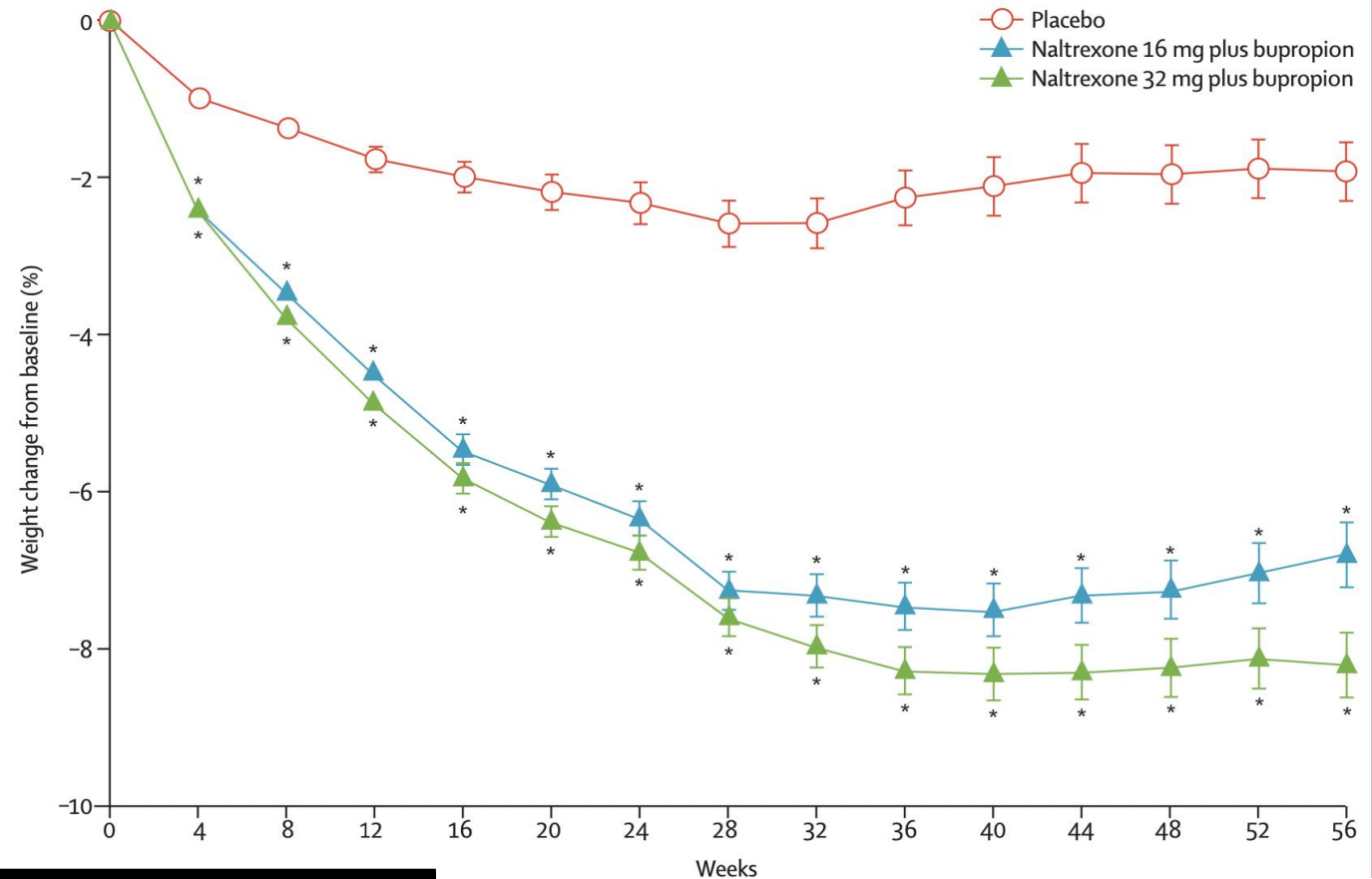
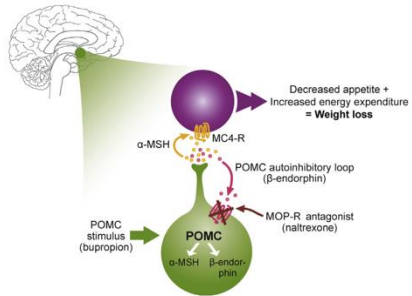
Opiates efficacy

Insomnia, mood changes

Lower seizure threshold

## Average cost per month

\$231-290



	NAL/BUP	Placebo
Weight Loss	6.1%	1.3%
>5% weight loss	48%	16%
>10% weight loss	21%	7%

# Phentermine

## Dosing

8 mg once/thrice daily

15 mg once/twice daily

37.5 mg once daily

## Side Effects & Considerations

Insomnia, dry mouth, palpitations

ASCVD, atrial fibrillation, hypertension

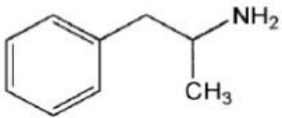
Antidepressants: MAOI, TCA

Abuse

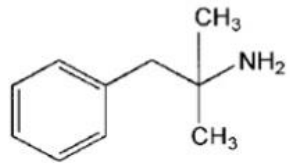
Hyperthyroidism

## Average cost per month

\$10-\$45 per month



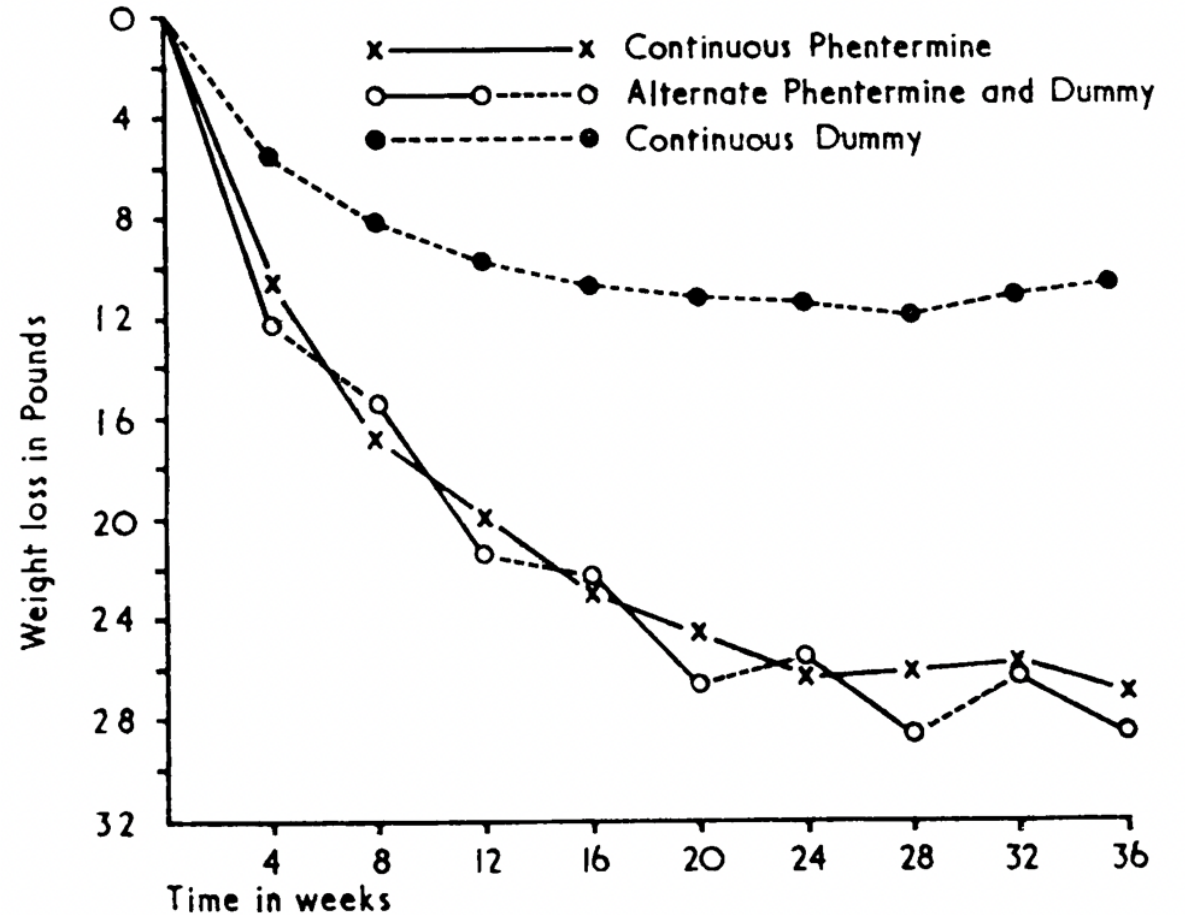
Amphetamine



Phentermine

## Mechanism of Action

Blocks uptake and increases release of norepinephrine



	Phentermine	Placebo
Weight loss 26 wks	6.1%	1.7%
>10% weight loss	20.8%	6.8%

# Phentermine Topiramate ER

## Dosing

7.5/46 mg once daily

15/92 mg once daily

## Side Effects & Considerations

Teratogenicity

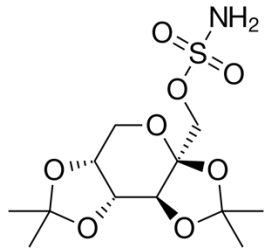
Paresthesias

Memory, Fatigue

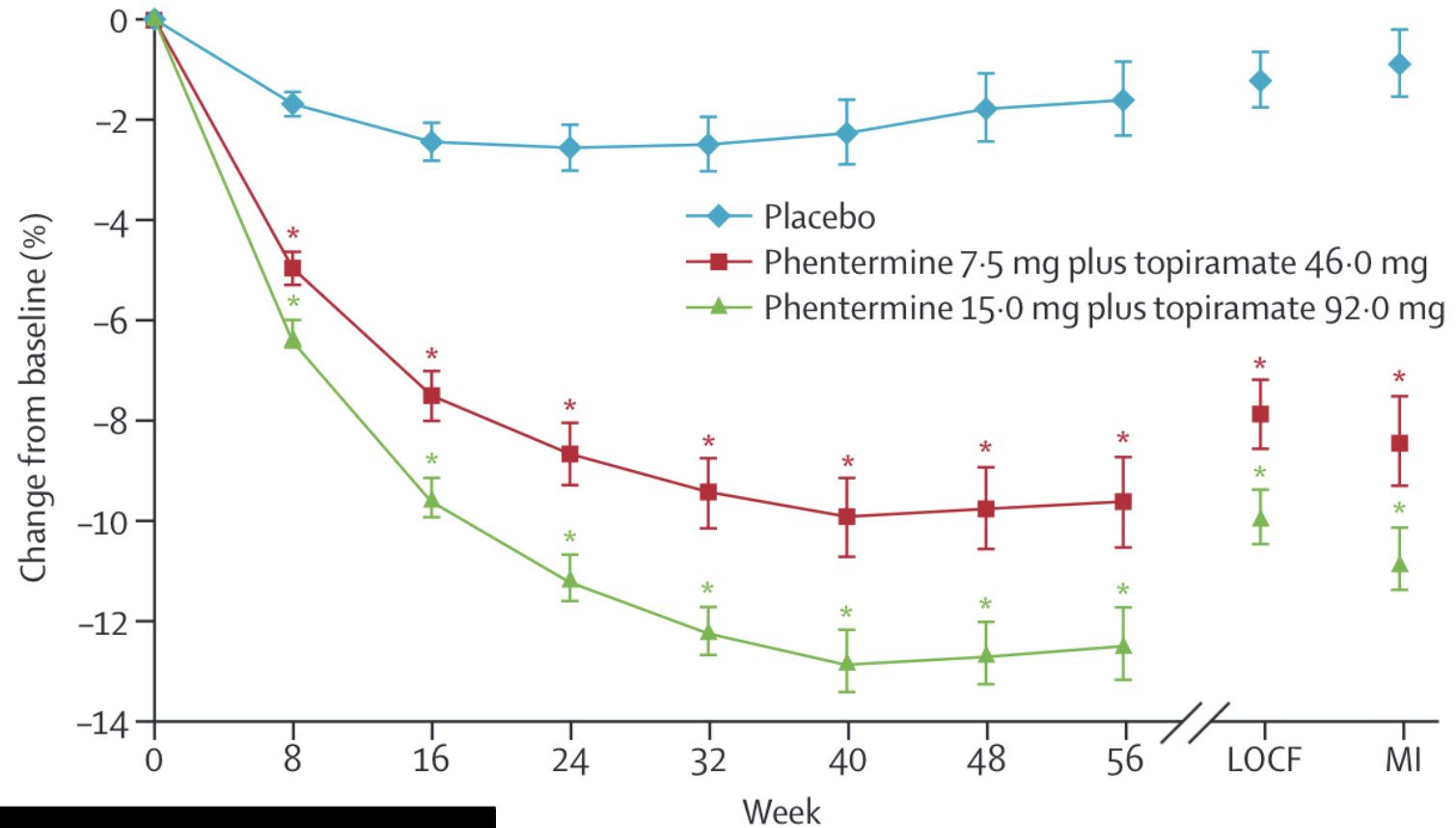
Kidney stones

## Average cost per month

\$192-239 for maximum dose



**Topiramate**  
GABA-A RA



	PHN/TOP	Placebo
Weight Loss	9.8%	1.2%
> 5% weight loss	70%	21%
>10% weight loss	48%	7%



# Liraglutide 3 mg



Decreases  
Appetite

Decreases  
Gastric Emptying



## Dosing

0.6-3 mg subcutaneously once daily  
(Increase weekly in 0.6 mg increments)

## Side Effects & Considerations

Nausea

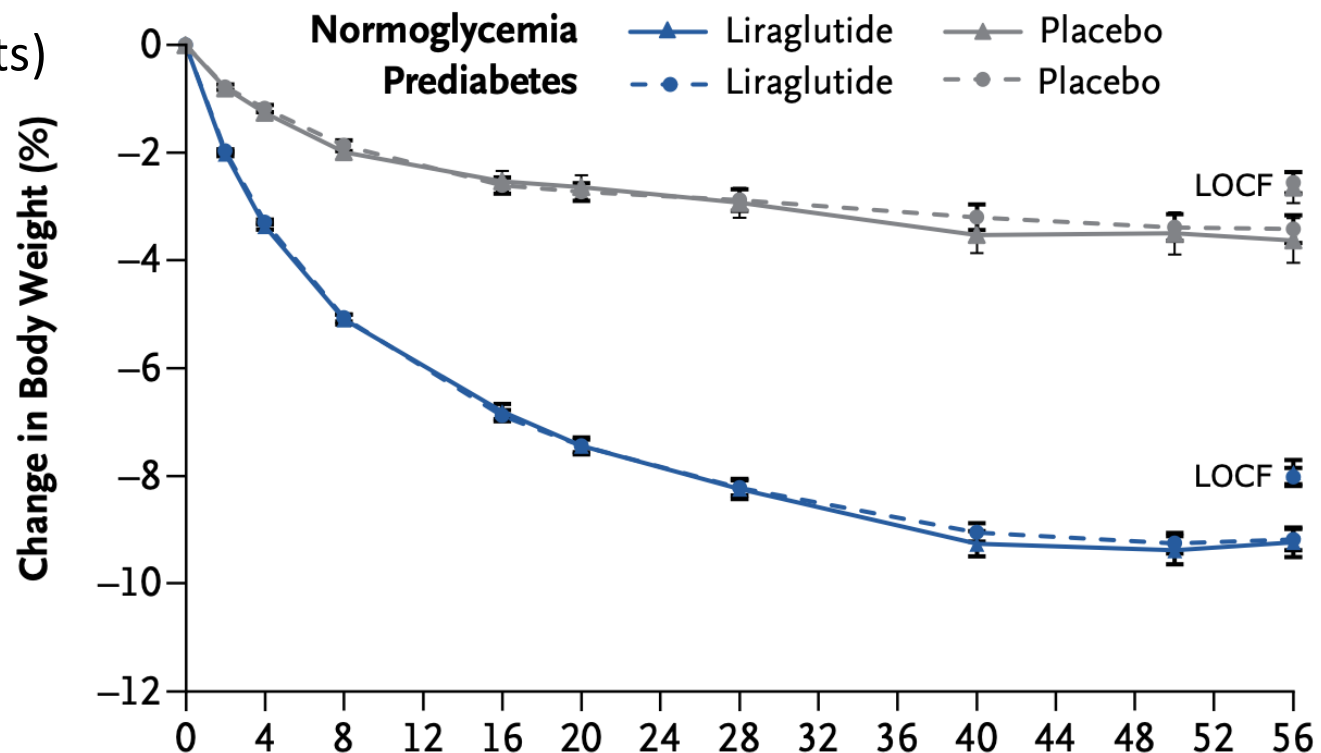
Pancreatitis

Thyroid C-cell tumors, MEN-2B

DPP-4 inhibitor use

## Average cost per month

\$1200



	Liraglutide	Placebo
Weight loss at 1 yr	8.0%	2.6%
>5% weight loss	63.2%	27.1%
>10% weight loss	33.1%	10.6%



# Semaglutide 2.4 mg

## STEP-1

### Dosing

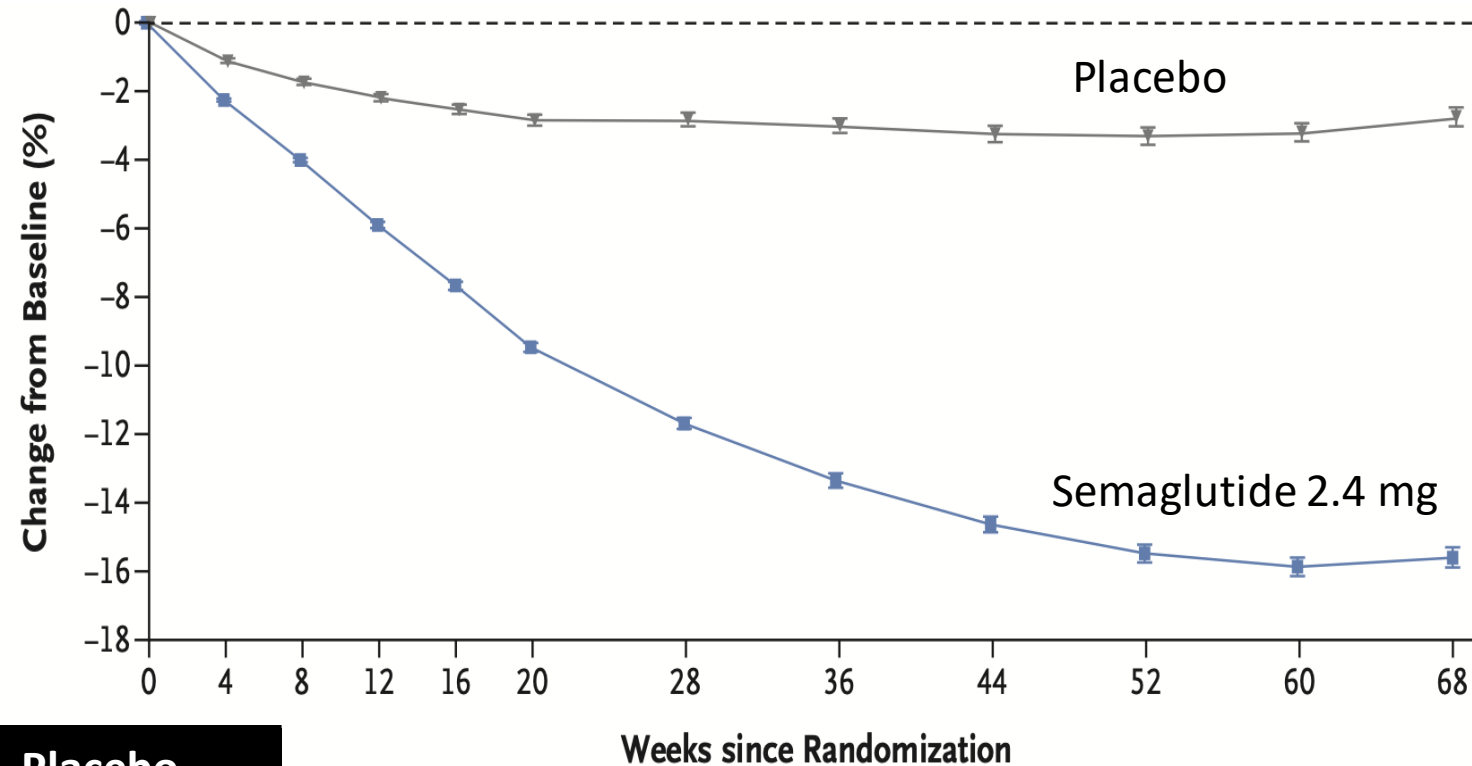
2.4 mg subcutaneously once WEEKLY  
0.25, 0.5, 1, 1.7, 2.4 mg single-use pens  
Dose increased every 4 weeks

### Side Effects & Considerations

Nausea (44%)  
Diarrhea (32%)  
Constipation (24%)

### Average cost per month

\$1,400



	Semaglutide	Placebo
Weight loss at 68 wk	14.9%	2.4%
>10% weight loss	69.1%	12.0%
>20% weight loss	32.0%	1.7%

**SELECT-COVT results awaited**  
**Event-driven trial 17,500 participants**

# Tirzepatide

SURMOUNT-1

## Dosing

5 mg, 10 mg, 15 mg weekly injection

## Side Effects & Considerations

Nausea (24.6%, 33.3%, 31.0%)

Vomiting (8.3%, 10.7%, 12.2%)

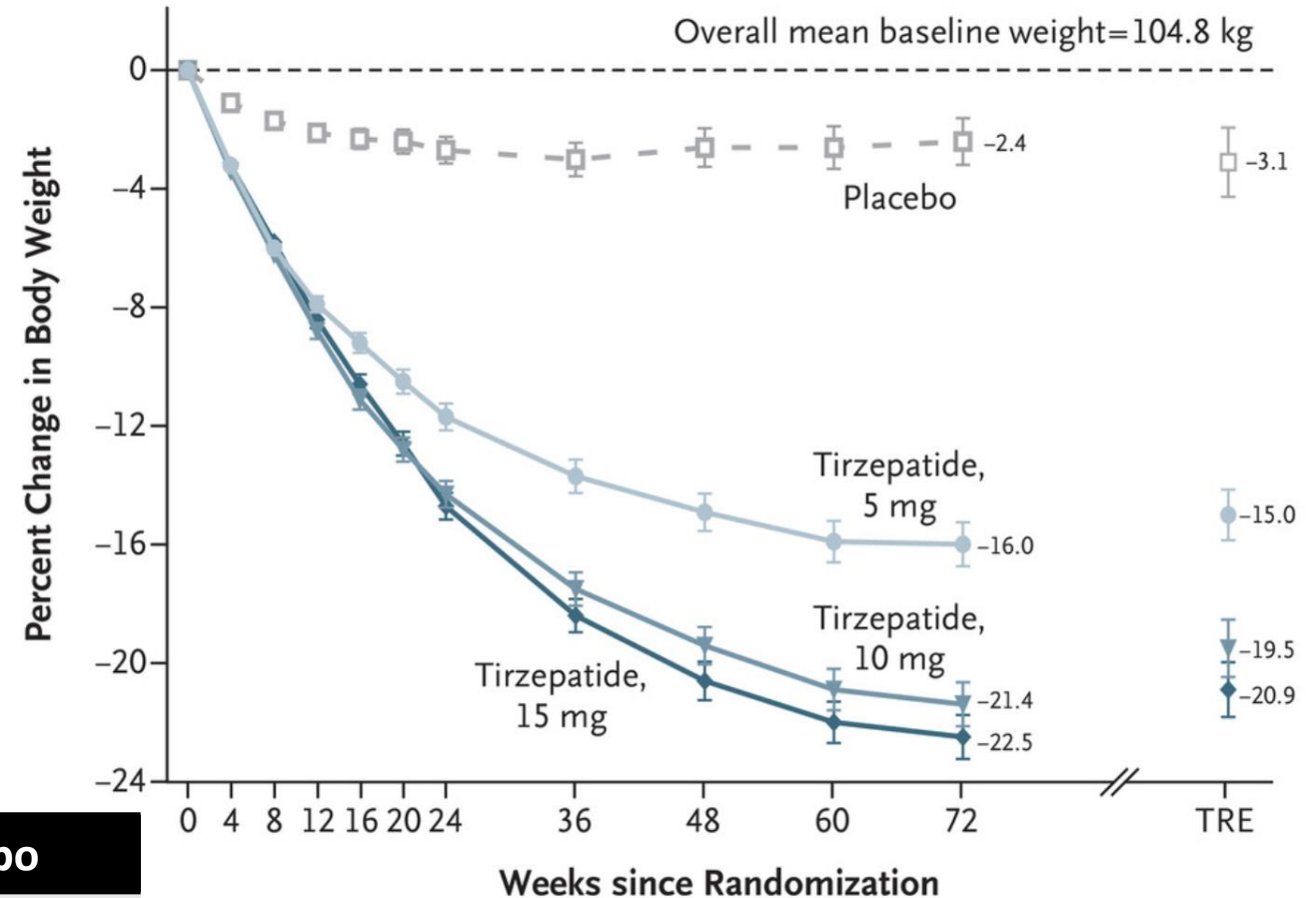
Diarrhea (18.7%, 21.2%, 23.0%)

Constipation (16.8%, 17.1%, 11.7%)

## Average cost per month

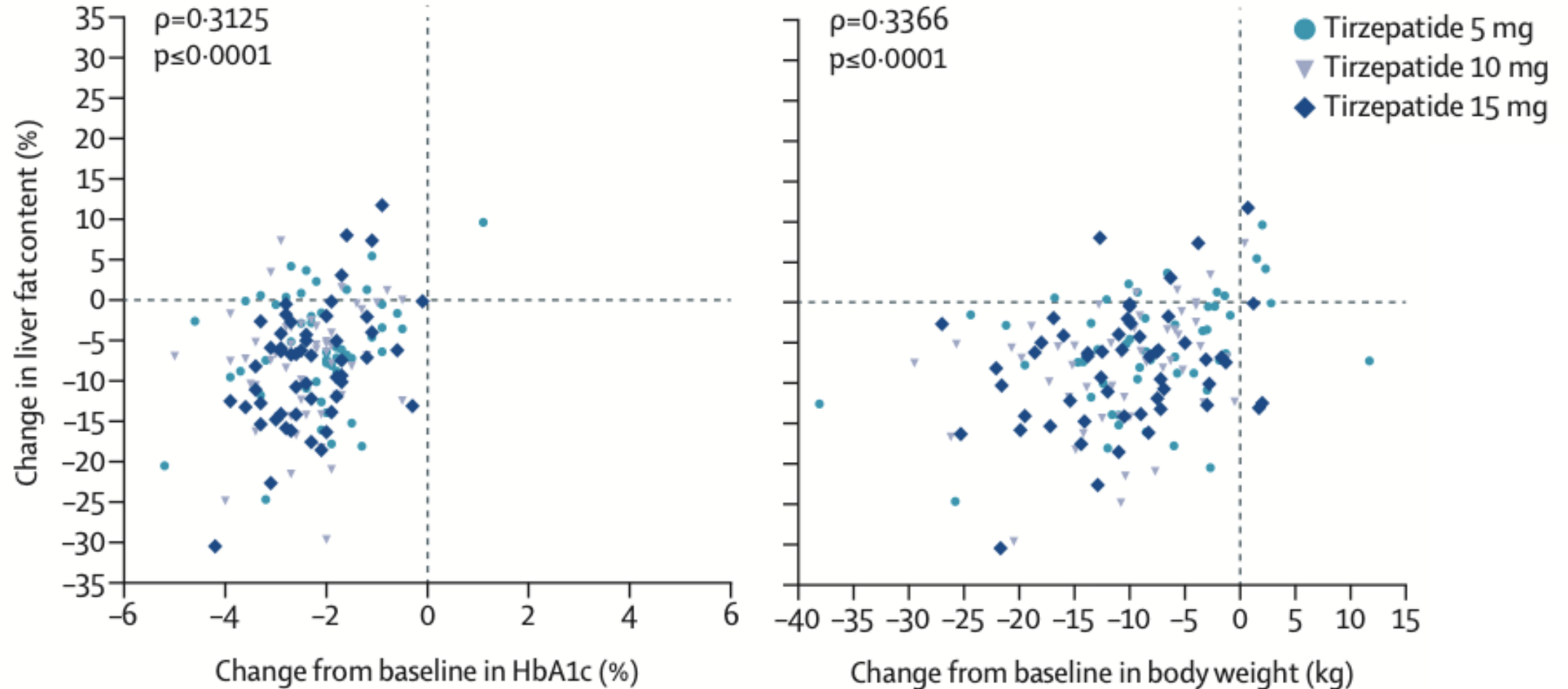
\$1000

Treatment Estimand	Tirzepatide	Placebo
Weight loss at 72 wk	20.9%	3.1%
>5% weight loss	90.9%	34.5%
>20% weight loss	56.7%	3.1%



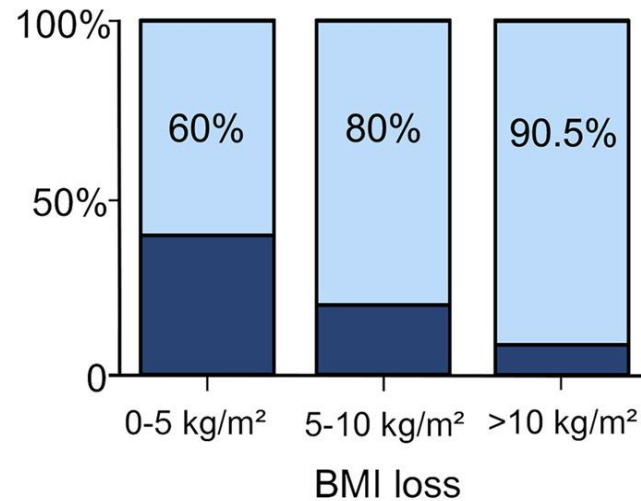
# Changes in Liver Fat Correlate with A1c & Weight Reduction

Tirzepatide vs. insulin degludec on liver fat content in people with T2DM: SURPASS-3 MRI



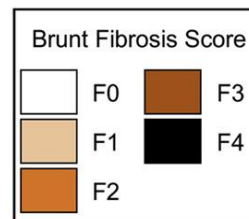
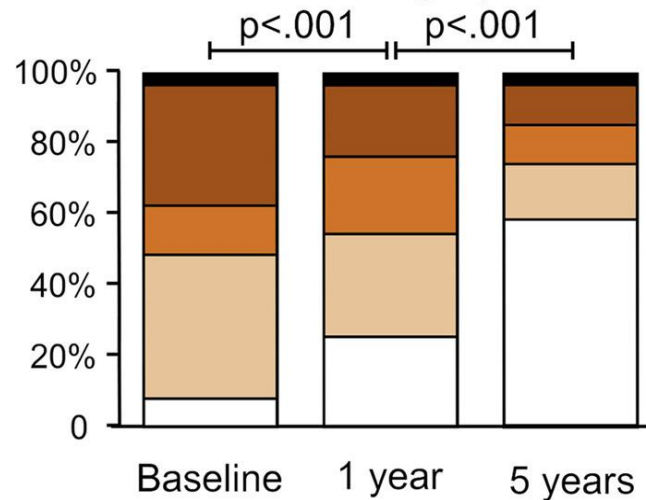
# MBS Provides Long-term Resolution of NASH and Regression of Fibrosis

Resolution of NASH according to weight loss

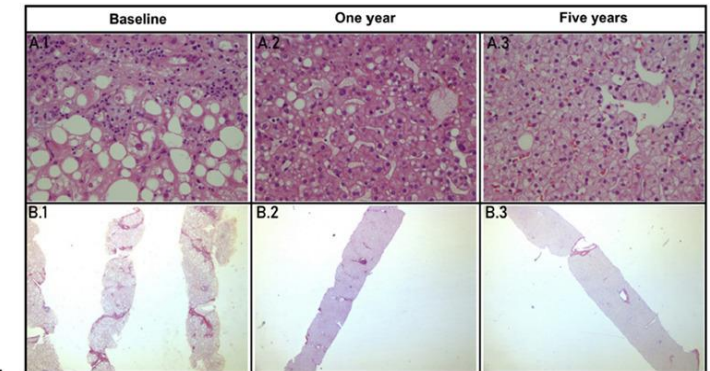


180 patients with NASH  
 BMI 48.1 -> 36.1 kg/m<sup>2</sup>  
 T2DM 71%,

Evolution of Fibrosis after Bariatric Surgery



Histological Evolution of NASH and Fibrosis after Bariatric Surgery

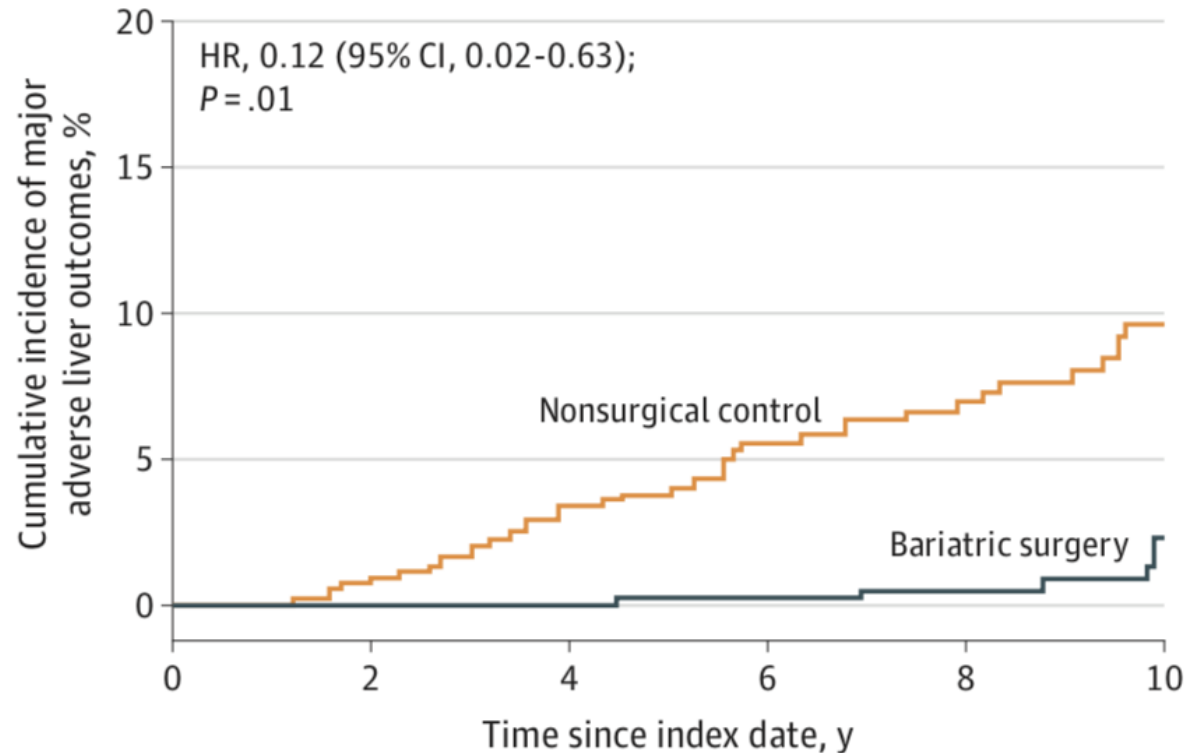


**A:** Upper panel  
 H&E staining,  
 (X400)  
**B:** Lower panel  
 Sirius Red  
 staining, (X25)

In a long-term follow-up of patients with NASH who underwent MBS, we observed resolution of NASH in 84% of patients 5 years later. The reduction of fibrosis is progressive, beginning during the first year and continuing through 5 years.

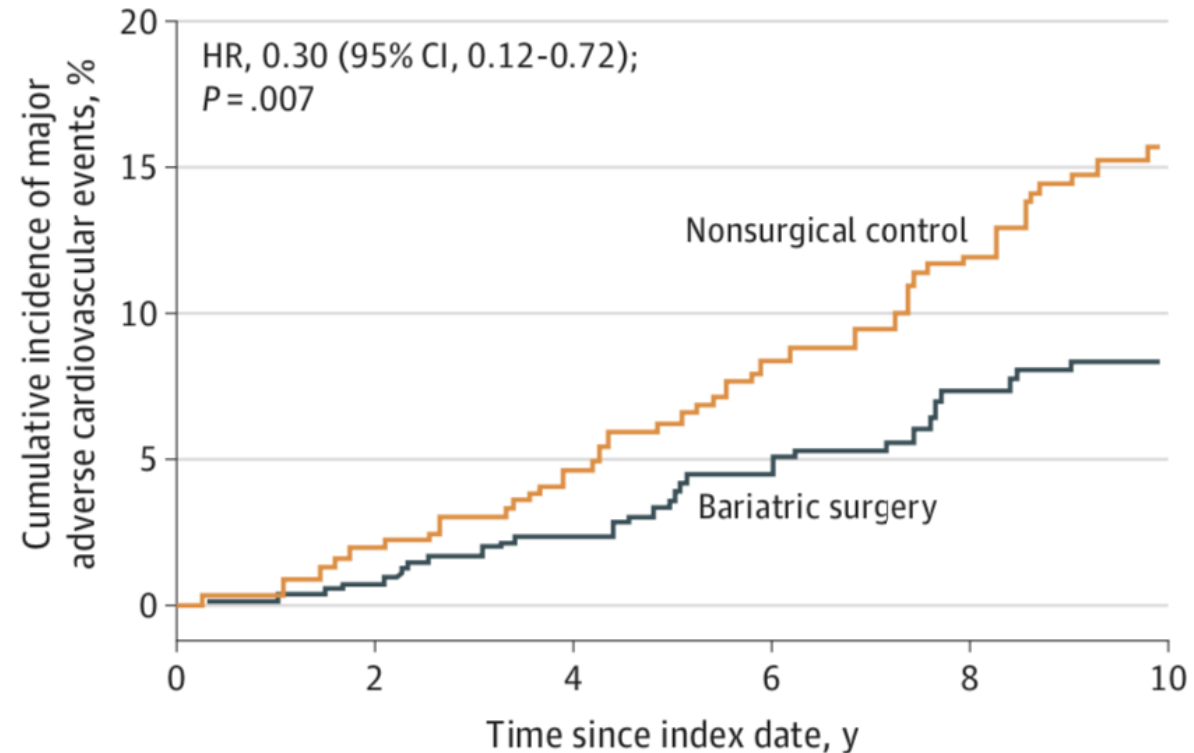
# MBS Reduces Adverse Liver Outcomes and CV Events in People with NASH

## Major Adverse Liver Outcomes



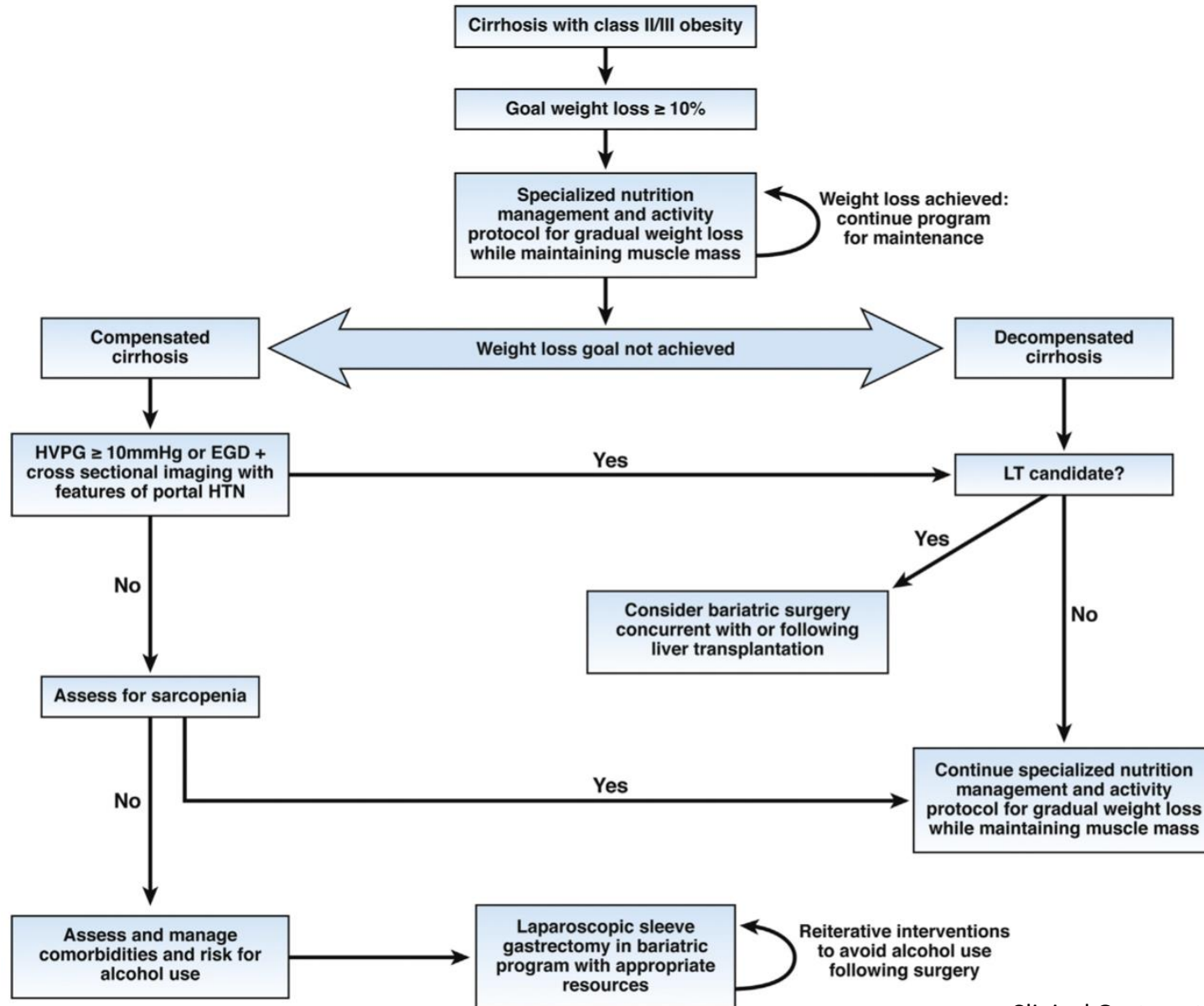
Occurrence of progression to clinical or histological cirrhosis, development of hepatocellular carcinoma, liver transplantation, or liver-related mortality

## Major Adverse Cardiovascular Outcomes






Occurrence of coronary artery events, cerebrovascular events, heart failure, or cardiovascular mortality

# AGA guideline for MBS in People with Cirrhosis



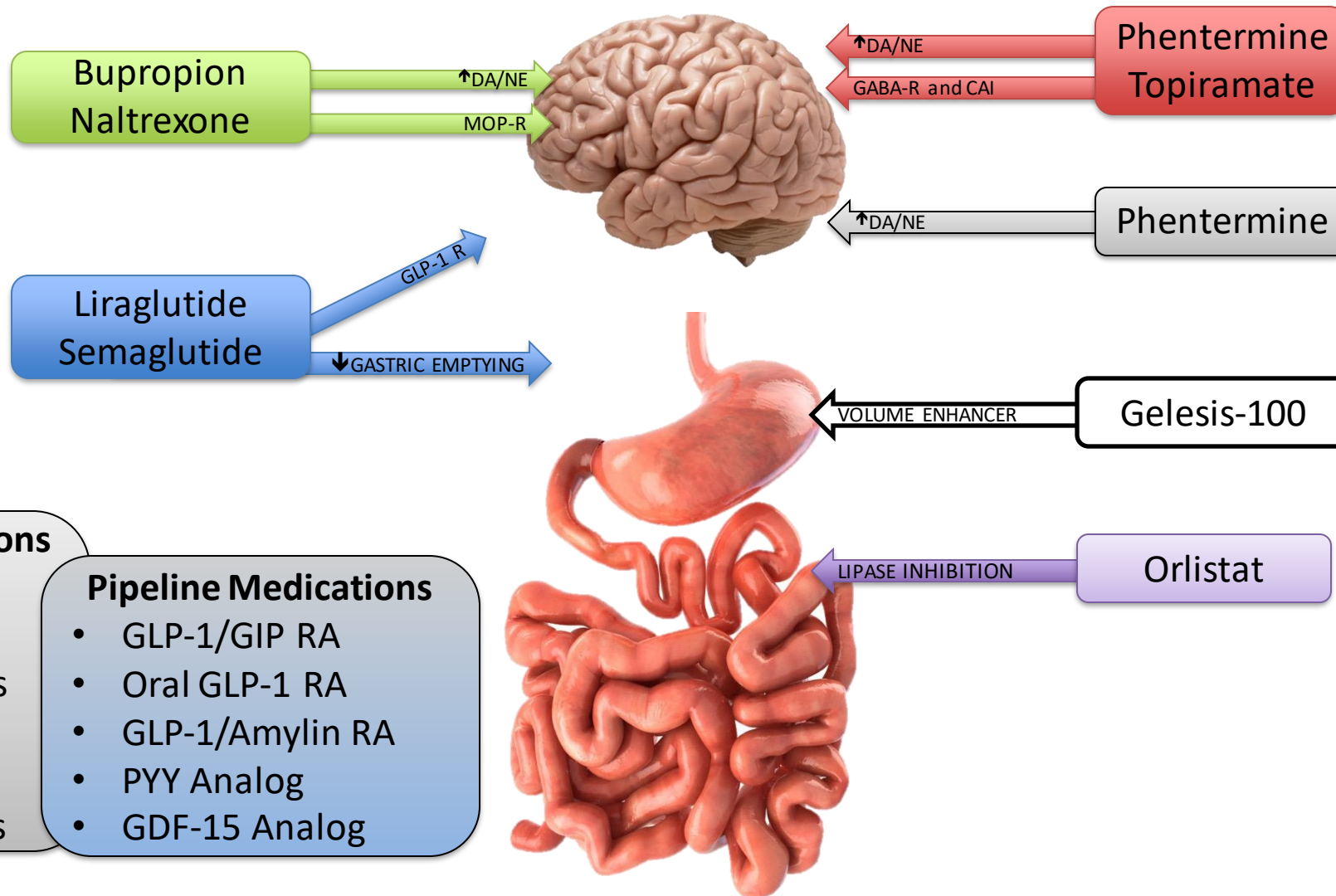
# Weight Management in NAFLD

## Fibrosis Risk Stratification

	 <p><b>Low Risk</b></p> <p>FIB-4: &lt;1.3 LSM &lt;8 kPa ELF &lt;7.7</p>	 <p><b>Indeterminate Risk</b></p> <p>FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8</p>	 <p><b>High Risk</b></p> <p>FIB-4: &gt;2.67 LSM &gt;12 kPa ELF &gt;9.8</p>
General lifestyle changes	Decrease sedentary time and increase daily movement. Stress reduction through exercise and other methods.		
Dietary recommendations	Creating an energy deficit is the priority with reduction of saturated fat, starch, & added sugars. Persons with cirrhosis need an individualized nutritional assessment and treatment plan.		
Exercise	To improve cardiometabolic health, support weight loss and mitigate sarcopenia. Aerobic exercise for 30-60 min (3-5 days/week) + resistance training 20-30 min (2-3 times/week).		
Alcohol intake	Minimize	Minimize	Avoid if F3 or cirrhosis (F4) <sup>1</sup>
Weight loss goal to treat NAFLD (if overweight or obesity) <sup>2</sup>	Greater weight loss associated with greater liver and cardiometabolic benefit.		
Weight loss tools	Behavioral modification counseling. In person or remote programs.	Greater intensity of weight loss to reverse steatohepatitis and fibrosis.	Specialized obesity management, with a structured program, anti-obesity medications, bariatric surgery.
Medical therapy to treat obesity	Phentermine, phentermine/topiramate ER, naltrexone/bupropion, orlistat, liraglutide 3 mg/d, semaglutide 2.4 mg/wk	GLP-1 RA preferred for NASH. <sup>3,4</sup>	GLP-1 RA preferred for NASH. <sup>3,4</sup>
Bariatric surgery	Consider to treat obesity and comorbidities.	Strong consideration to treat steatohepatitis and fibrosis.	Stronger consideration to treat steatohepatitis and fibrosis. Avoid in decompensated cirrhosis.



# FDA Approved Anti-Obesity Medications



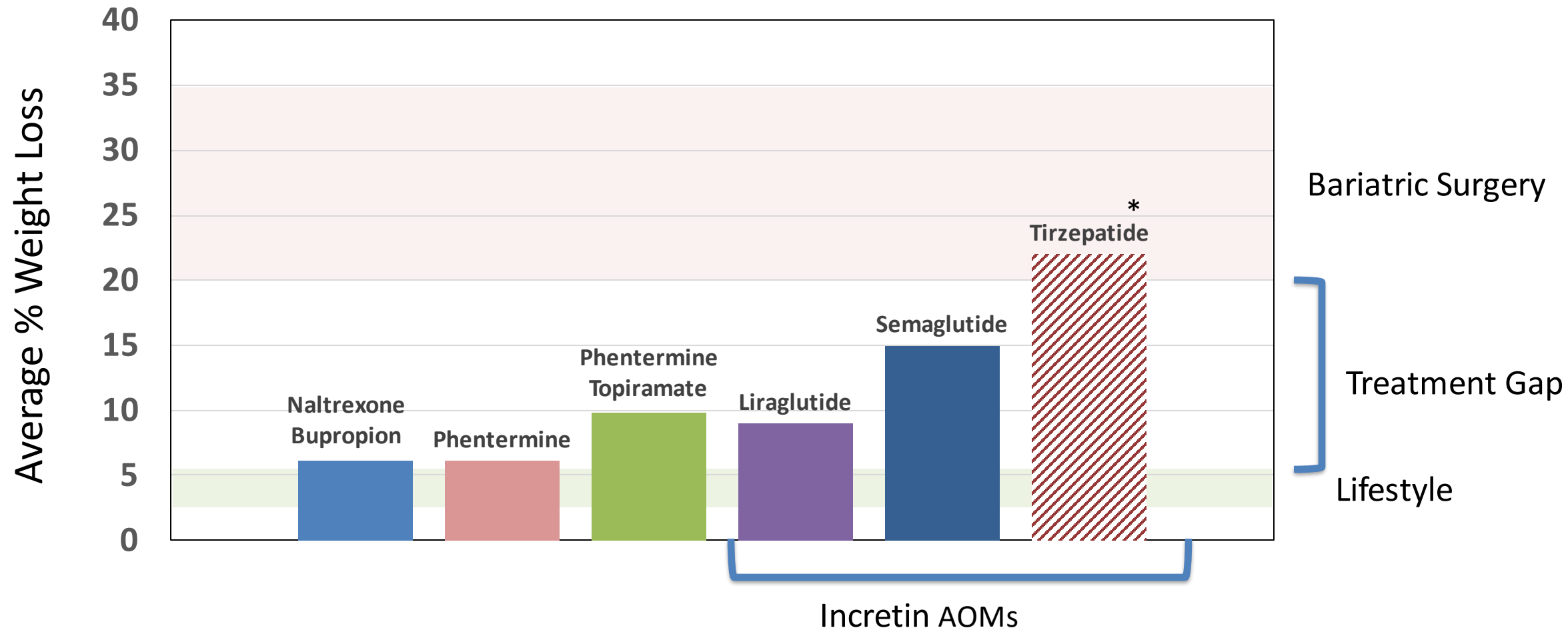
## Off-Label Medications

- Metformin
- GLP-1R agonists
- SGLT-2 inhibitors
- Topiramate
- Bupropion
- Other stimulants

## Pipeline Medications

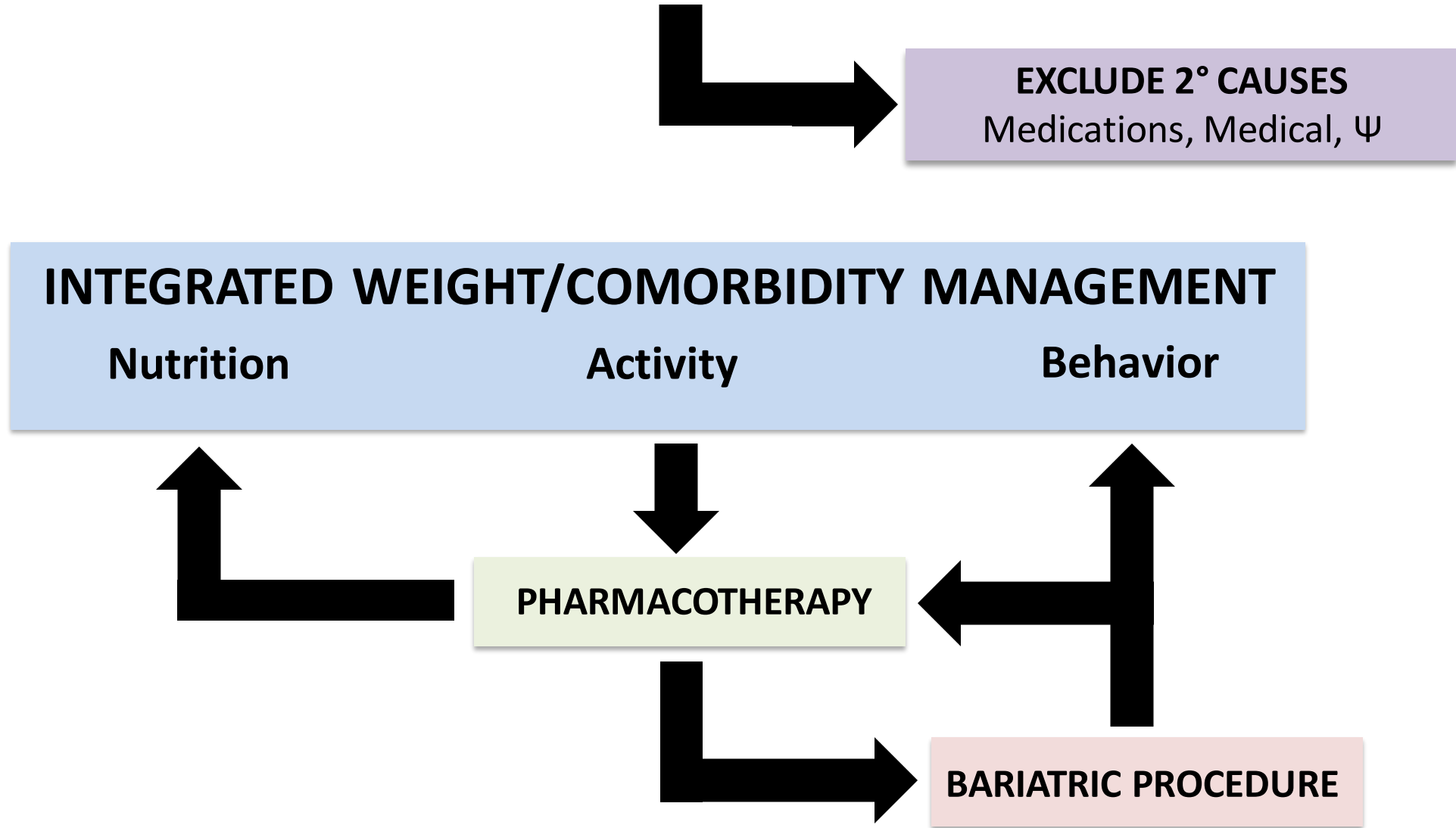
- GLP-1/GIP RA
- Oral GLP-1 RA
- GLP-1/Amylin RA
- PYY Analog
- GDF-15 Analog

# Closing the Bariatric Treatment Gap with AOM



\*Not approved for obesity treatment

# Chronic Obesity Management for NAFLD



# Treating Obesity to Manage NAFLD



Typically, lifestyle modification alone is insufficient for durable weight loss >10%. AOM and Surgery are underutilized.



Newer incretin therapies appear superior to older AOM for treating obesity in those with and without T2DM



Bariatric surgery is safe, effective for treating obesity, NAFLD, and decreasing cardiometabolic disease and cancer risks



Treat NAFLD and obesity as complex chronic diseases to improve the magnitude and durability of clinical outcomes

# Thank you

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Weight Wellness