Drugs to Treat Obesity: Do They Work?

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UCSF Diabetes Updates 4/12/18

Obesity in the U.S.

Figure 1. Trends in Overweight, Obesity, and Extreme Obesity Among Adults Aged 20 to 74 years:

Note: Age-adjusted by the direct method to the year 2000 U.S. Bureau of the Census using age groups 20–39, 40–59 and 60–74 years. Pregnant females were excluded. Overweight defined as a BMI of 25 or greater but less than 30; obesity is a BMI greater than or equal to 30; extreme obesity is a BMI greater than or equal to 40.

### Classification of Overweight and Obesity by BMI

<table>
<thead>
<tr>
<th>Weight Class</th>
<th>BMI kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
</tr>
<tr>
<td>Obesity I</td>
<td>30.0-34.9</td>
</tr>
<tr>
<td>Obesity II</td>
<td>35.0-39.9</td>
</tr>
<tr>
<td>Obesity III/Severe</td>
<td>≥ 40</td>
</tr>
</tbody>
</table>

**Clinical trials:**

BMI 27-45kg/m²

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### Mortality and Obesity

- 3 prospective cohort studies (Nurses Health Study I and II, Health Professionals Follow Up Study) N>225,000 and >32,000 deaths

<table>
<thead>
<tr>
<th>Max BMI in 16 yr span</th>
<th>HR Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>1.47</td>
</tr>
<tr>
<td>18.5-24.9 (normal)</td>
<td>---</td>
</tr>
<tr>
<td>25-29.9 (overweight)</td>
<td>1.06</td>
</tr>
<tr>
<td>30-34.9 (grade 1)</td>
<td>1.24</td>
</tr>
<tr>
<td>≥35 (grade 2/3)</td>
<td>1.73</td>
</tr>
</tbody>
</table>

Yu et al, Ann Intern Medicine 2017
Complications of Obesity

- **ENDOCRINE**
  - Diabetes mellitus (type 2), metabolic syndrome
  - PCOS, infertility, male hypogonadism

- **NEUROLOGIC/PSYCHOLOGIC**
  - Stroke, depression, idiopathic intracranial hypertension, disordered eating

- **HEMATOLOGIC**
  - Deep vein thrombosis, hypercoagulable state, chronic venous stasis

- **CANCERS**
  - Breast, uterus, cervix, colon, esophagus, pancreas, kidney, prostate

- **RESPIRATORY**
  - Hypoventilation (Pickwickian) syndrome, OSA, asthma, respiratory failure

- **CARDIOVASCULAR**
  - Congestive heart failure, hypertension, myocardial infarction, dyslipidemia

- **GASTROINTESTINAL**
  - GERD, NASH, NASH, gastroparesis, gallstones, biliary tract disease, pancreatitis, hernias

- **MUSCULOSKELETAL**
  - Degenerative joint disease, Chronic back pain

60% of the prevalence of type 2 diabetes in the US can be attributed to obesity

Medical Cost of Obesity in US

- ~$147 billion medical spending attributable to obesity in 2008
- Compared to non-obese, obese patients incur:
  - 46% increased inpatient costs
  - 27% more physician visits and outpatient costs
  - 80% percent increased spending on prescription drugs

Causes of Obesity? Seems simple...

"I get exercise. I mean I walk, I this, I that"

Potential Contributors to Obesity

Inside the Person
- Increased intake
- Decreased expenditure
- Fast and processed foods
- Stress
- Sedentary lifestyle
- Emotional eating

Outside the Person
- Increased food availability
- Marketing of unhealthy foods
- Fast food availability
- Lack of physical activity
- Lack of access to healthy foods
- Lack of physical education
- Lack of health care access
- Economic factors
- Environmental factors

Contributors/Barrier
- Constrained Temperature (e.g., diurnal heating
  or temperature regulations)
- Limited energy intake
- Limited energy expenditure
- Limited physical activity
- Limited access to healthy foods
- Limited access to health care
- Limited access to education
- Limited access to transportation
- Limited access to financial resources
- Limited access to social support
- Limited access to community support
- Limited access to political support

Preventable Factors
- Economic development
- Political will
- Social support
- Community support
- Personal choice

Endnotes:
1. Obesity is a chronic disease that affects an estimated 1.9 billion adults worldwide.
2. Overweight and obesity are the second leading cause of preventable death worldwide.
3. Central to the obesity epidemic is the rapid rise of overweight children.
Obesity Drug Failures

- 1800’s- use of sheep thyroid extract $\rightarrow$ cardiac arrhythmias & death
- 1930’s- DNP, an uncoupling agent $\rightarrow$ fatal hyperthermia
- 1940-1960’s- widespread use of amphetamines $\rightarrow$ cardiac death, pulmonary hypertension w/50% mortality
- 1970-1980’s- PPA, a sympathomimetic amine $\rightarrow$ stroke
- 2008-rimonabant, cannabinoid receptor antagonist $\rightarrow$ depression and suicidality

*Clin Pharmacol Ther. 2010 June; 87(6):652-662*

Orlistat

- *Xenical* 120mg TID, *Alli* 60 mg TID
- FDA approved 1999
- Pancreatic lipase inhibitor with GI side effects in >90%
- Placebo subtracted weight loss of ~2-3% with long term use, diabetes prevention
- 13 cases of severe hepatotoxicity, including 2 deaths (in a background of millions of users worldwide).
- Approved in children ≥12 yo
Orlistat

2.8kg more weight loss at 4 years with Orlistat

Figure 2—Weight loss (mean ± SEM) during 4 years of treatment with orlistat plus lifestyle changes or placebo plus lifestyle changes in obese patients (LOCF data).

4 year RCT, n=3305
BMI 30+, nondiabetic or IGT
51% dropout in treatment arm:
14% refused treatment
8% cited ineffective therapy

Diabetes Onset

Diabetes Care 27:155–161, 2004

Regulation of Hunger and Satiety

Nature Reviews Neuroscience 2011 12, 638-651
Regulation of Hunger and Satiety

Hormonal Influences
Leptin
Insulin
GLP-1
Peptide YY
Ghrelin

Other CNS influences:
Dopaminergic, adrenergic, serotonergic, endocannabinoid, opioid pathways

Nature Reviews Drug Discovery 2012, 11, 675-691

POMC Mutations Cause Human Obesity

• Obesity: due to lack of alpha-MSH in the hypothalamus
• Adrenal insufficiency: due to lack of ACTH in the anterior pituitary
• Red Hair Pigmentation: due to lack of α-MSH activating MC1-R signaling

MC4R Deficiency is the Commonest Monogenic Form of Obesity

9-year-old boy homozygous for a mutation in MC4R

16-year-old brother with normal genotype


Leptin Deficiency in Humans

Child B before leptin
(wt = 42 kg at 3 yrs)

Child B after leptin
(wt = 32 kg at 7 yrs)

Endocrinology 2003. 144:3757-3764
Plasma Leptin Levels are Elevated in Obesity

Majority of obese individuals are leptin resistant

Molecular Targets of Anti-Obesity Drugs

Lorcaserin

- *Belviq*
- FDA approved for weight loss June 2012 in obese (BMI ≥30) or overweight (BMI ≥27) + comorbidities
- Activates serotonin receptors in the hypothalamus

Serotonin and Energy Balance

- Since 1970s, it's been recognized that serotonin (5-HT) action serves as a satiety signal leading to reduced food intake
- Role in energy expenditure via thermogenesis?
- More recent research links serotonin signaling to the modification of impulse and reward signaling in the brain

Neuron 2006, 51; 239-249
J Psychopharmacology 2017, 31(11)1403-1418
Fenfluramine/Phentermine

• Fenfluramine is a potent 5HT2c receptor agonist
  – Metabolite norfenfluramine is a non-selective 5HT receptor agonist\(^1\)
    • 5HT2b receptors are found on mitral & aortic valves → mitotic activity → valve thickening
• Fen/Phen withdrawn from market in 1997 due to severe valvulopathy


Sibutramine

• *Meridia*- FDA approved in 1997 for weight loss
• Suppressed appetite and increased energy expenditure by central regulation of serotonin and norepinephrine
• 2003-2009 multi-national MACE trial of 10K high risk subjects: 16% increased risk of major CV event or death (mean exposure 3.5 years)
• In 2010, FDA requested the voluntary withdrawal of the drug

https://www.fda.gov/Drugs/DrugSafety/ucm228746.htm
Lorcaserin

• 5HT2c receptor agonist
  – Binds 5HT2c receptor in hypothalamus with 105x’s more affinity than 5HT2b on cardiac valves
• No effect on metabolic rate

Appetite Reduction with Lorcaserin

Blinded RCT of 57 obese adults taking Lorcaserin 10mg BID vs placebo

PFC=Prospective Food Consumption using visual analog scale of hunger before and after meals

Lorcaserin

- 2 year RCT designed to assess weight loss efficacy and valvulopathy risk
- 3182 subjects with BMI 30-45 kg/m\(^2\) or 27-45 kg/m\(^2\) with comorbidity (HTN, dyslipidemia, OSA, glucose intolerance, CVD)
- Lorcaserin 10mg BID vs. placebo
- All arms instructed to exercise 30 minutes per day and reduce food intake by 600 kcal
- ECHO at baseline and q6 months

Mean BMI 36 kg/m\(^2\)
Mean weight 100kg

Drop Out:
55% Placebo
45% Lorcaserin

Placebo subtracted wt loss
3.6%
Responders vs. Non-responders

Lorcaserin did not increase valvulopathy at 2 years

- Rate of valvulopathy in year 1:
  - 2.3% placebo
  - 2.6% lorcaserin
- Rate of valvulopathy in year 2:
  - 2.7% placebo
  - 2.6% lorcaserin
- No difference in BP reduction or lipids vs. placebo

*P<0.01

Postgraduate Medicine, 126:6, 7-18
Lorcaserin

- Prescribing considerations
  - Most common AE: headaches, dizziness, nausea
  - Risk for serotonin syndrome (do not use with other serotonergic agents)
  - Valvular heart disease, heart block
  - Pregnancy class X

Clinical pharmacology & Therapeutics 2014;95(1) 53-66

Lorcaserin Phase III Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>Placebo subtracted weight loss</th>
<th>≥5% Weight Loss @ 1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLOOM</td>
<td>10mg BID Placebo</td>
<td>-3.65%</td>
<td>47.5%</td>
</tr>
<tr>
<td>104 weeks</td>
<td>N=3182</td>
<td></td>
<td>20.3%</td>
</tr>
<tr>
<td>BLOOM-DM</td>
<td>10mg Daily 10mg BID Placebo</td>
<td>-3.5% -3% --</td>
<td>37.5% 44.7% 16.1%</td>
</tr>
<tr>
<td>52 weeks</td>
<td>N=604</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLOSSOM</td>
<td>10mg Daily 10mg BID Placebo</td>
<td>-1.9% -3% --</td>
<td>40.2% 47.2% 25%</td>
</tr>
<tr>
<td>52 weeks</td>
<td>N=4008</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Placebo subtracted A1c drop = 0.6%

Ann Pharmacother 2013;47:1007-16
Phentermine/Topiramate ER

- Qsymia
- FDA approved July 2012 for obesity or overweight (BMI ≥27 kg/m²) with comorbidities

Phentermine

- Sympathomimetic amine similar to amphetamine
- Causes a release of norepinephrine and dopamine in the hypothalamus → satiety

**Phentermine**

- FDA approved for short-term monotherapy for weight loss since 1959 (#1 prescribed drug)
- 15mg, 30mg, 37.5mg dosed daily
- Concern for dependency, abuse potential though no good data to support this

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**Topiramate**

- Observed to have anorectic effect
- ~3% weight loss at 6-months when used alone
- Topiramate has many effects in the CNS but weight loss mechanism unclear

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Obesity Res 2003; 11(6):722-33
Phentermine/Topiramate ER

- CONQUER- 56 week RCT, n=2487, BMI 27-45 kg/m² with 2+ comorbidities. No BMI limit if DM.
  - 52% hypertension
  - 36% hypertriglyceridemia
  - 60% glucose intolerance
  - 16% DM2
  - 98% abdominal obesity
- Randomized to PHEN 7.5mg/TOP 46mg, PHEN 15mg/TOP 92mg, or placebo
- All arms received monthly lifestyle counseling and asked to reduce intake by 500 kcal

Placebo subtracted weight loss:

- 6.6%
- 8.6%

86% White
70% Female
Mean BMI 36
Mean Weight 103 kg

Lancet 2011;377:1341-52
Phentermine/Topiramate ER

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>7.5/46mg</th>
<th>15/92 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>d/c BP meds</td>
<td>5%</td>
<td>11%</td>
<td>15%</td>
</tr>
<tr>
<td>ΔA1c</td>
<td>-0.1%</td>
<td>-0.4%</td>
<td>-0.4%</td>
</tr>
<tr>
<td>pre-DM → DM</td>
<td>--</td>
<td>0.78</td>
<td>(0.4-1.5)</td>
</tr>
</tbody>
</table>

Lancet 2011;377:1341-52

1-Year Extension

Am J Clin Nutr 2012;95:297-308
Phentermine/Topiramate ER

- Adverse events: 15-20% constipation, paresthesias, dry mouth, 2-8% worsening depression or anxiety
- Transient reduction in serum bicarbonate in ~15% treatment arm
- Pregnancy class X (oral clefts)
- Avoid in those with substance abuse, uncontrolled hypertension, CVD, tachyarrhythmia, glaucoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Arms</th>
<th>Placebo Subtracted Weight Loss</th>
<th>≥5% Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQUIP¹</td>
<td>PHEN 3.75/TOP 23mg</td>
<td>3.5% 9.3%</td>
<td>44.9% 66.7%</td>
</tr>
<tr>
<td>56 weeks</td>
<td>PHEN 15/TOP 92mg</td>
<td>--</td>
<td>17.3%</td>
</tr>
<tr>
<td>N=1267</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONQUER²</td>
<td>PHEN 7.5/TOP 46mg</td>
<td>6.6% 8.6%</td>
<td>62.1% 70.0%</td>
</tr>
<tr>
<td>56 weeks</td>
<td>PHEN 15/TOP 92mg</td>
<td>--</td>
<td>21.0%</td>
</tr>
<tr>
<td>N=2487</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEQUEL³</td>
<td>PHEN 7.5/TOP 46mg</td>
<td>7.5% 8.7%</td>
<td>75.2% 79.3%</td>
</tr>
<tr>
<td>108 weeks</td>
<td>PHEN 15/TOP 92mg</td>
<td>--</td>
<td>30.0%</td>
</tr>
<tr>
<td>N=676</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Obesity. 2012 Feb;20(2):330-42
2 Lancet 2011;377:1341-52
3 Am J Clin Nutr 2012;95:297-308
Naltrexone/Bupropion ER

• *Contrave*
• FDA approved in 9/2014 for weight loss in obese or overweight with co-morbidities

Naltrexone

• Opioid receptor antagonist
  – Naltrexone + 6β-naltrexol competitively antagonize opioid receptors in CNS
• Noted since 1979 to reduce food intake in rats\(^1\)
  – Opioid antagonists decrease appetite for palatable food
• Clinical trials in 1980’s showed no/minimal weight loss with monotherapy\(^2\)

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1 Life Sci. 1979; 24(3):219-226
2 Expert Opin Pharmacother. 2009; 94(12):4898-4906
Bupropion ER

• Dopamine + norepinephrine reuptake inhibitor
• Modest placebo subtracted weight loss w/monotherapy (-2 to -5%)¹
• Mouse studies show enhanced effect of bupropion with naltrexone²

Naltrexone/Bupropion ER

• COR-I, n=1742, BMI 30-45 kg/m² or 27-45 kg/m² + HTN or dyslipidemia
• Randomized to:
  – Naltrexone 16mg+Bupropion 360mg
  – Naltrexone 32mg+Bupropion 360mg or
  – Placebo
• All subjects asked to reduce food intake by 500 kcal/day and exercise more

¹ Obes Res. 2002; 10(7):633-642
² Obesity 2009;17(1):30-39
Baseline Characteristics:
- BMI 36
- Wt 99 kg
- 85% Female
- 75% White
- 20% HTN
- 50% dyslipidemia

Placebo subtracted weight loss:
-3.7%
-4.8%

Lancet 2010;376:595-605

Naltrexone/Bupropion ER

- Compared to placebo, LDL unchanged and HDL up ~3.4 mg/dL
- In 505 subjects with T2DM, placebo subtracted A1c reduction of 0.5%

1. Lancet 2010;376:595-605
Naltrexone/Bupropion ER

• 40% drop out due to AE in treatment arms (vs. 23% placebo)
  • 30% of AE = nausea
• No increase in mood-related adverse events including suicidality
• No seizures

Naltrexone/Bupropion ER

• Effects on blood pressure across trials:
  – SBP change: -0.1 to +0.3 in treatment arm vs -1.9 in placebo
  – DBP change: 0 to +0.1 in treatment arm vs. -0.9 placebo
• And heart rate:
  – Increase of 1.5-2.5 BPM in treatment arms vs. no change in placebo
Naltrexone/Bupropion ER

• 3 cardiovascular events:
  – Placebo arm: pericardial effusion
  – High dose arm: fatal MI, non-fatal cardiac failure
• 2012 “Light Study” MACE study
  – 2013 interim analysis showed no increase in MACE¹
  – Manufacturer leaked these interim findings though only 25% of the study had been completed- study terminated
  – Results published at 50% completion did not show increased CV risk. Study had high dropout.
• New MACE trial required

JAMA. 2016;315:984-986

Naltrexone/Bupropion ER

• Other prescribing considerations
  – Black box warning for 1) suicidality especially in young patients with depression, 2) “neuropsychiatric events” (behavior change, hostility, etc)
  – Bupropion can lower seizure threshold
  – Naltrexone contraindicated in those on chronic opioid therapy
  – Not recommended with anti-retrovirals that induce CYP2B6
Phase III Clinical Trials

<table>
<thead>
<tr>
<th>Drug Dose</th>
<th>Placebo Subtracted Weight Loss</th>
<th>≥ 5% weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenway et al(^1) 56 weeks n=1742</td>
<td>N16+B360 N32+B360 Placebo</td>
<td>-3.7% -4.8% --</td>
</tr>
<tr>
<td>Apovian et al(^2) 56 weeks n=1496</td>
<td>N32+B360 Placebo</td>
<td>-5.2% --</td>
</tr>
<tr>
<td>Wadden et al(^3) 56 weeks n=793</td>
<td>N32+B360 Placebo</td>
<td>-4.2% --</td>
</tr>
</tbody>
</table>

1 Lancet 2010; 376:595  
2 Obesity 2013; 21:935  
3 Obesity 2011; 19:110

Liraglutide

- **Saxenda**
- GLP-1 agonist
- Endogenous GLP-1 is released by the L cells of the small intestine when exposed to glucose
- GLP-1 receptors in the hypothalamus → satiety effect

Liraglutide Obesity and Prediabetes Trial

Liraglutide 3.0 mg (N = 2487)  
Placebo (N = 1244)

-5.4% placebo subtracted weight loss  
36% drop out

Pi-Sunyer X et al. N Engl J Med  
2015;373:11-22

Liraglutide and Glucose Levels during Oral Glucose-Tolerance Test and Glycemic Status.

### Large Phase III Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Dose</th>
<th>Placebo Subtracted Weight Loss</th>
<th>≥ 5% weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pi-Sunyer et al(^1)</td>
<td>3.0mg daily</td>
<td>-5.4%</td>
<td>63.2%</td>
</tr>
<tr>
<td>56 weeks</td>
<td>Placebo</td>
<td>--</td>
<td>27.1%</td>
</tr>
<tr>
<td>N=3731</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davies et al (^2)</td>
<td>3.0mg daily</td>
<td>-4.0%</td>
<td>54.3%</td>
</tr>
<tr>
<td>SCALE Diabetes</td>
<td>1.8mg Daily</td>
<td>Placebo</td>
<td>21.4%</td>
</tr>
<tr>
<td>56 wks N=846</td>
<td></td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Wadden et al (^2)</td>
<td>3.0mg daily</td>
<td>-6.1%</td>
<td>50.5%</td>
</tr>
<tr>
<td>SCALE Maintenance</td>
<td>Placebo</td>
<td>--</td>
<td>21.8%</td>
</tr>
<tr>
<td>56 wks N=422</td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

2. JAMA 2015; 314: 687–699

### Cost

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose</th>
<th>Placebo subtracted weight loss @ 1 yr</th>
<th>Monthly out of pocket on GoodRx (coupon site)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat: Xenical Alli</td>
<td>120mg TID 60mg TID</td>
<td>2-3%</td>
<td>$200 $60</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>10 mg BID</td>
<td>1.9-3.6%</td>
<td>$280</td>
</tr>
<tr>
<td>Phentermine/Topiramate ER</td>
<td>7.5/46 to 15/92mg Daily</td>
<td>6.6-9.3%</td>
<td>$200 (for high dose)</td>
</tr>
<tr>
<td>Naltrexone/Bupropion ER</td>
<td>16/180mg BID</td>
<td>3.7-5.2%</td>
<td>$240</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>3.0mg Daily</td>
<td>6%</td>
<td>$1200</td>
</tr>
</tbody>
</table>

www.Goodrx.com
Do these new drugs work?

• Compare to:
  – Popular diets (Zone, Atkins, Ornish, Weight Watchers): 2.1-3.3 kg loss in 1 yr, 35-50% drop out¹
  – DPP and Look AHEAD: 5-7% weight loss (intensive lifestyle programs with high retention)
  – Bariatric 14 to 37% placebo subtracted weight loss at 2-3 years depending on procedure²

¹ JAMA 2005;293:43-53
² MANAGING OVERWEIGHT AND OBESITY IN ADULTS: SYSTEMATIC EVIDENCE REVIEW FROM THE OBESITY EXPERT PANEL, 2013

Do these new drugs work?

• Unlike bariatric surgery, no evidence that medication induced weight loss reduces CV events or mortality
• There is short term data to show that these medications reduce onset of diabetes and have small reductions in CV risk factors like blood pressure and lipids
Diabetes Prevention Program


NNT Lifestyle: 6.9 people x 3 yrs
NNT Metformin 13.9 people x 3 yrs

Lost 7% body weight with diet and moderate exercise

Follow up: 10 yrs post randomization

Lancet 374:1677-86, 2009

Initial BMI 34, Wt 94 kg

68% completion rate
10 years post randomization

Look AHEAD

• RTC of intensive lifestyle intervention vs. diabetes support and education for the prevention of major cardiovascular events in overweight/obese T2DM

• Intervention: 7% weight loss with a reduced calorie, low fat diet and 175 min of mod-strenuous exercise per week

• >90% retention in both arms

Lancet 374:1677-86, 2009

Look AHEAD Results

Improvement in CV risk factors:
- ↓ 3 kg → ↓ TG by 15 mg/dL
- ↓ 5-8 kg → ↓ LDL by 5 mg/dL
  ↑ HDL by 2-3 mg/dL
- ↓ 5% → ↓ SBP by 3 mmHg
  ↓ DBP by 3 mmHg

Diabetes Remission in Look AHEAD

Higher rates of remission in those with:
- Less than 2 yr diabetes duration
- Baseline lower A1c
- Baseline not on insulin
- More weight loss in year 1
- Highest fitness change during study


Gregg et al. JAMA 2012;308:2489-2496
Take Home Points

• Medication induced weight loss is on the range of 3-10% and variable between individuals
• Modest weight loss improves CV risk factors and may prevent future diabetes
• Unknown yet if they can prevent CV outcomes or mortality
• Side effects and cost can limit use
• No long term data on safety and efficacy

Thank You