What Will be Discussed

• Obesity is a chronic physiologic disease
• When to treat obesity with medication
• Approved obesity medication options
• Off-label combination use of two approved medications.
• Using obesity medications in the context of obesity surgery
Weight Loss Curve

Sumithran et al. NEJM 2011; 365:1597-1604.

Gut Hormone Changes Persistently Oppose Diet-induced Weight Loss

Sumithran et al. NEJM 2011; 365:1597-1604.
Diet, Activity, and Other Interventions with Drugs

- Diet and Activity
- Types of nutrients
- Eating schedules
- Physical activity
- Sleep health
- Drugs and medications
- Local stressors

Amenable to individual action

Fenfluramine
1-Year Rx & 1-Year Follow-up
No Behavior Modification


With Behavior Modification

Edmonton Obesity Staging System

- Stage 0: No obesity related risk factors
- Stage 1: Subclinical risk factors – borderline HTN or DM, minor aches or psychopathology
- **Stage 2**: Established obesity-related disease – HTN, DM, PCO, moderate limitations ADL
- **Stage 3**: Established organ damage – MI, CHF, DM comp, significant limitations of ADL
- **Stage 4**: Severe disabilities – end stage and limitations like wheelchair use

Sharma AM and Kushner RF. Int J Obes. 2009;33:289-95
Phentermine

• Approved in 1959 when obesity was thought to be bad habits at doses from 15 to 30 mg/d.
• Tested and approved for up to 12 weeks.
• Extensive experience with longer use and apparently well tolerated.
• Blood pressure does not drop as much as placebo, and can give adrenergic symptoms
• In DEA class IV with diethylpropion, but abuse has been low.
Phentermine: A Noradrenergic Drug Reduces Body Weight

Munro JF et al BMJ 1968;1:352-4

Orlistat

- Approved for long-term use to treat obesity at 120 mg tid and causes 33% of dietary fat to be lost into the stool.
- Safety is good, but side effects of anal leakage, passage of oil with flatus and incontinence have dampened enthusiasm by patients.
- Sold now without a prescription at half the dose which gives about 80% of the weight loss seen with the higher dose.
Orlistat 120 mg tid Induces Weight Loss

Orlistat 60 mg tid Compared to Prescription Orlistat

Percent Change from Initial Body Weight Over Two Years
Integrated Database

Torgerson et al., Diabetes Care. 2004;27(1):155-61
Lorcaserin

- Phentermine and fenfluramine gave additive weight loss, but fenfluramine was withdrawn due to cardiac valvulopathy.
- Lorcaserin is a selective serotonin (5HT) 2c agonist (suppresses hunger centrally) without valve problems related to 5HT2b.
- Well tolerated with few adverse events (headache, dizziness), DEA IV but low addictive potential and drops HgbA1c 0.5%.

Phase III Study (BLOOM)
Body Weight Over Years 1 and 2

**BLOOM-DM**

**Change in Glycemic Parameters**

HbA1C, -0.5%

Fasting Plasma Glucose


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**Phentermine/Topiramate**

- Approved at 3.75/23 mg/am for 2 weeks then 7.5/46 mg, but at 12 weeks if weight loss <3%, stop or 15/92 mg. Stop (taper) if <5% loss after 12 weeks.

- Safety: fetal cleft palate - pregnancy test q mo. Elevated heart rate, suicidal ideation, glaucoma, sleep disorders, impaired cognition, metabolic acidosis. DEA Class IV and REMS program

- Adverse events >5% and 1.5 times greater than placebo: paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth.
Topiramate-Phentermine Phase III Trial
Placebo, 48mg/7mg & 96mg/15mg

N = 1,267


Naltrexone/Bupropion

- A 3-week dose escalation to 16/180 mg SR bid
- HgbA1c dropped 0.5% in diabetics
- Adverse events >5% and >1.5 times control: Nausea, headache, constipation, dizziness, vomiting, insomnia, dry mouth & hot flashes
- Not scheduled by DEA, reduces cravings and cardiovascular safety trial stopped and will be reinitiated (to evaluate BP & pulse rate)
Bupropion 360 & Naltrexone 32 mg

Placebo-subtracted weight loss

Week 56
- NB16: -3.7%
- NB32: -4.8%

Placebo-subtracted weight loss

Completers
- NB16: -4.9%
- NB32: -6.2%

P<0.001 for NB16 and NB32 vs. Placebo at all time points


Liraglutide 3 mg

- Same parenteral drug used to treat diabetes, but at a higher dose. The dose is escalated 0.6 mg/wk to 3mg.
- Common side effects were nausea, vomiting, diarrhea, and constipation usually mild to moderate and transient.
- Incidence of pancreatitis, gall stones and breast neoplasms were low but greater in the liraglutide group.
Completers on Liraglutide 3 mg

![Graph showing % weight loss over weeks for Placebo and Liraglutide 3mg treatments.]

Greenway FL et al. Presentation Obesity Week, Boston, Nov, 2014

Zonisamide 360 mg & Bupropion 360 mg)
Weight Loss at 1 Year of Treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight Loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (a) (N=72)</td>
<td>-1.2%</td>
</tr>
<tr>
<td>Z120/B280 (N=27)</td>
<td>-11.6%</td>
</tr>
<tr>
<td>Z120/B360 (N=36)</td>
<td>-12.1%</td>
</tr>
<tr>
<td>Z240/B280 (N=28)</td>
<td>-12.9%</td>
</tr>
<tr>
<td>Z240/B360 (N=32)</td>
<td>-13%</td>
</tr>
<tr>
<td>Z360/B280 (N=32)</td>
<td>-12.9%</td>
</tr>
<tr>
<td>Z360/B360 (N=39)</td>
<td>-14.9%</td>
</tr>
</tbody>
</table>

(a) Placebo weight loss through 24 weeks
Phentermine Adds to Lorcaserin Weight Loss

A. LOCF Lorcaserin 10mg/Phentermine 15mg BID  B. Completer analysis projects to weight loss projects to 10.8% 13%


Efficacy of Obesity Drugs

- Drug
  - Phentermine
  - Orlistat
  - Lorcaserin
  - Topiramate-Phentermine
  - Bupropion-Naltrexone
  - Liraglutide
  - Lorcaserin-Phentermine
  - Bupropion-Zonisamide  
  (Off-label Use)

Average Weight Loss LOCF
- 3.6% > placebo
- 2.75% > placebo
- 3.3% > placebo
- 9% > placebo
- 4.8% > placebo
- 5% > placebo
- 5.9% > placebo
- 9% > placebo  
  (Off-label Use)
**Gastric Bypass Weight Loss Requires the Melanocortin-4 Receptor**

A. Wild-type mice with Roux-en-Y Gastric Bypass or Sham surgery

B. MC-4 receptor knockout mice with Roux-en-Y Gastric Bypass or Sham surgery


**Serotonin Agonists Add to Gastric Bypass Weight Loss – Not Topiramate**

Carmody JS et al. Endocrinology. 2015;156(9):3183-91
Conclusions

• Obesity is a chronic disease, and long-term weight loss usually requires changing physiology, but lifestyle programs help, are safe, and should be part of treatment
• Obesity trials evaluate the drug & lifestyle Rx
• Treatment requires weighing risks & benefits
• Many more obesity medication options now exist and treating obesity after obesity surgery requires more research.