Antiobesity Agents

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Goals

• Outline management of obesity
• Review pharmacology of antiobesity agents
• Compare antiobesity agents for long-term use
 Obesity 

• 34.9% of adults and 16.9% of youth are obese 
• Estimated annual medical costs =$147 billion related to obesity 
  – Medical costs = $1,429 more for obese patients than those of normal weight

Prevalence* of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2012

*Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

Prevalence* of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2013

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Behavioral Risk Factor Surveillance Systems, CDC
Obesity

Energy Out

Energy In

Sugar

Fat

Starches

Exercise

Managing Obesity

Pt needs to lose weight if BMI ≥ 30 or BMI ≥ 25 with additional risk factor

Assess readiness to make lifestyle changes [take into account competing priorities (i.e. uncontrolled DM or HTN)]

Initial weight loss goal of 5-10% of baseline weight within 6 months. Decrease by ≥ 500 kcal/day. Manage other risk factors

Managing Obesity

Start comprehensive lifestyle interventions alone or with adjunctive therapies

Consider addition of pharmacotherapy agents after initial lifestyle changes with BMI ≥ 30 or BMI ≥ 27 with additional co-morbidity

Continue medication if ≥ 5% weight loss within 12 weeks, d/c if not. Refer for more intensive behavioral treatment or bariatric surgery.

Case 1

- AH 22 yo WF presents with 5 month hx of ongoing HA. DX with IIH. No previous PMH.
  - BP: 118/62 mmHg
  - HR: 70 bpm
  - 244 lbs, 64 in
  - BMI: 41

- BMP: WNL
- FLP:
  - TC: 183, TG: 190
  - LDL: 145, HDL: 48
- A1C= 7.5%
Case 1: What are your first steps in managing AH’s obesity?

A. Implement lifestyle changes  
B. Start antiobesity agent  
C. Manage comorbidities  
D. All of the above  
E. Only A and C

**Obesity= chronic disease**

- Maximum weight loss achieved at 6 months  
- **Maintenance** treatment  
  - Continue long-term (≥2 years) comprehensive weight loss programs  
    - Monthly contact  
    - Reduced-calorie diet  
    - Physical activity (>200 min/week)  
    - Pharmacotherapy (studies up to 2 years)
**Antibesity Agents**

<table>
<thead>
<tr>
<th>Short term</th>
<th>Long term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>Orlistat</td>
</tr>
<tr>
<td>Benzphetamine</td>
<td>Lorcanerin</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>Phentermine/Topiramate ER</td>
</tr>
<tr>
<td>Phendimetrazine</td>
<td>Naltrexone/Bupropion</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
</tr>
</tbody>
</table>

Ashley Crowl, PharmD, BCAP

Family Medicine Spring Symposium
April 10, 2015
Orlistat

**Dose**
- 120 mg TID before meals (RX)
- Can be used ≥ 12 yo
- 60 mg TID before meals (OTC)

**MOA**
- Pancreatic lipase inhibitor: Selectively inhibits lipases from stomach and intestines to reduce digestion of fat

**Cost**
- $16/day (RX)
- $1.50/day (OTC)

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**Efficacy**
- 4 yr, double-blind, RCT, 3304 patients achieved >5kg wt loss of 11% vs. 6% of placebo
- Average weight loss: 3.45 kg (7.6 lbs) > placebo

**Safety**
- Gas, oily spotting, fecal incontinence, abdominal/rectal pain, nausea.
- 1 in 28 patients stop orlistat due to ADE

**CI**
- chronic malabsorption syndrome, cholestasis, pregnancy
- Liver injury*

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Torgerson J. Orlistat. 2004
PL Detail-document, Drugs for weight loss. November 2014
Orlistat

• Drug interactions
  – Separate from levothyroxine by 1 hr
  – Monitor INR with vitamin K antagonist
  – Reduced amiodarone efficacy
• Tips
  – Take with MVI containing A,D,E,K 2hrs prior or after

Lorcaserin

Dose
• 10 mg BID [BMI ≥ 30 or BMI ≥ 27 with additional co-morbidity*]

MOA
• 5-HT₂c receptor agonist
  • promote satiety by decreasing food intake through melanocortin system

Cost
• $7/day

*HTN, T2DM, Dyslipidemia, CVD, sleep apnea
Lorcaserin

**Efficacy**
- Average wt loss: 3.3-5.8 kg (7.24-12.7 lbs) > placebo
- NNT = 4

**Safety**
- Nausea, dizziness, fatigue, and headache
- 1 in 53 patients stop lorcaserin due to ADE
- Drop out rates ~50%

**CI**
- Pregnancy, valvular heart disease, ESRD
- Caution: CHF, neuroleptic malignant syndrome, pulmonary hypertension, hyperprolactinemia

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Lorcaserin

- Drug interactions
  - Caution/avoid use with other serotonergic agents
  - Increases levels of drugs metabolized by CYP2D6 drugs
- Tips
  - Check CBC periodically
  - Monitor for suicidal thoughts/behavior
  - Seek medical attention for erection lasting over 4 hrs
  - D/C if <5% weight-loss from baseline after 12 weeks
  - Schedule CIV prescription

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PL Detail-document, Drugs for weight loss. November 2014
Phentermine/topiramate-ER

Dose

- **Initial**: P:3.75 mg/T:23 mg daily x 14 days then P:7.5mg/T:46 mg daily.
- May ↑ P:11.25mg/T:69 mg daily x 14 days, P:15mg/T:92 mg daily

MOA

- Phentermine: sympathomimetic, increases release of NE to reduce appetite.
- Topiramate: Works on GABA receptors and reduces appetite

Cost

- $7/day

Efficacy

- Average wt loss: 9 kg (20 lbs) > placebo [w/ 15 mg]
- NNT =2

Safety

- 1 in 12 patients stop phentermine/topiramate-ER due to ADE
- ~50% drop-out rates in trials

CI

- Pregnancy, glaucoma, hyperthyroidism, MAOIs, suicidal ideation, moderate-high CVD
- Caution: Renal or hepatic impairment
Phentermine/topiramate-ER

- Drug interactions
  - Avoid with carbonic anhydrase inhibitors
  - Avoid with alcohol
  - Decreased efficacy of OCPs
- Tips
  - Check CMP (baseline & periodically); BP & HR; UPT
  - Monitor for suicidal thoughts/behavior, depression
  - D/C if <5% weight-loss from baseline after 12 weeks
    - Taper slowly to prevent withdrawal seizures
  - Schedule CIV prescription

Bupropion/naltrexone

- Bupropion 90 mg/naltrexone 8 mg
  - Week 1: 1 tab daily in AM
  - Week 2: 1 tab BID
  - Week 3: 2 tabs AM & 1 tab PM
  - Week 4: 2 tabs BID
- MOA
  - Bupropion: stimulates melanocortin neurons
  - Naltrexone: blocks opioid-mediated auto-inhibition of melanocortin system
- Cost
  - $7/day
Bupropion/naltrexone

**Efficacy**
- Average wt loss: 4.1 kg (9 lbs) > placebo
- NNT= 3

**Safety**
- 1 in 9 patients stop bupropion/naltrexone due to ADE
- ~50% drop-out rates in trials

**CI**
- uncontrolled HTN, seizures, bulimia, anorexia, or pregnancy
- Caution: Renal or hepatic impairment

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Bupropion/naltrexone

- Drug interactions
  - Avoid with opioids or acute alcohol/benzodiazepines/barbiturates withdrawal
  - Caution with inhibitors/inducers of CYP2D6
- Tips
  - Monitor depression/suicidal behavioral
  - D/C if <5% weight-loss from baseline after 12 weeks
    - Taper slowly to prevent withdrawal seizures
Liraglutide

**Dose**
- Start 0.6 mg SQ daily and increase by 0.6 mg weekly to dose of 3 mg daily

**MOA**
- Glucagon-like peptide-1 receptor agonist, reduce appetite and energy intake

**Cost**
- $40/day

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PL Detail document, Drugs for weight loss. November 2014
Liraglutide

• Drug interactions
  – Hypoglycemia with insulin/sulfonylureas

• Tips
  – A1c not further reduced
  – Can not use Victoza at this dose
  – Monitor HR (increases)
### Co-morbidities

<table>
<thead>
<tr>
<th></th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>LDL</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorcaserin</td>
<td>-1.9</td>
<td>-1.9</td>
<td>-0.7</td>
<td>-27.4</td>
</tr>
<tr>
<td>Phen/Top</td>
<td>-2.9</td>
<td>-1.5</td>
<td>-8.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>-4.9</td>
<td>-2.8</td>
<td>-0.43</td>
<td>-26</td>
</tr>
</tbody>
</table>
Lorcaserin Efficacy

**Blossom: RCT**
47.2% achieved 5% wt-loss vs. 25% (p<0.001)

**Bloom: RCT; Year 1:** 47.5% achieved 5% wt-loss vs. 20.3% (p<0.001).
Maintained wt-loss in year 2.
Lorcaserin Safety

Figure 2. Findings on Echocardiography, According to Study Group.
Phentermine/Topiramate Efficacy

RCT, 66.7% pts w/ 5% wt-loss vs. 17.3% (p<0.0001)

RCT, 84% completed 2 yrs & 79% maintained 5% wt-loss
# Phentermine/Topiramate Safety

## Table 3

All adverse events with frequency of ≥5% in any PHEN/TPM CR group.

<table>
<thead>
<tr>
<th>Standardized lifestyle intervention across all treatment groups</th>
<th>Weeks 0–56</th>
<th>Weeks 56–108</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PHEN/TPM CR</td>
<td>PHEN/TPM CR</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 227)</td>
<td>7.5/46 (n = 153)</td>
</tr>
<tr>
<td>Constipation</td>
<td>16 (7.1)</td>
<td>25 (16.3)</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>6 (2.6)</td>
<td>21 (13.7)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5 (2.2)</td>
<td>21 (13.7)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>47 (29.7)</td>
<td>22 (15.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>25 (15.1)</td>
<td>20 (13.1)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>4 (1.8)</td>
<td>18 (11.8)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>19 (8.4)</td>
<td>17 (11.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>21 (9.3)</td>
<td>8 (5.2)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>15 (6.6)</td>
<td>12 (7.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (5.3)</td>
<td>14 (9.2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>19 (8.4)</td>
<td>11 (7.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (2.6)</td>
<td>9 (5.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (5.7)</td>
<td>5 (3.3)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>8 (3.5)</td>
<td>9 (5.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (4.9)</td>
<td>7 (4.6)</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>6 (2.6)</td>
<td>7 (4.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>20 (8.8)</td>
<td>13 (8.5)</td>
</tr>
<tr>
<td>Influenza</td>
<td>11 (4.9)</td>
<td>11 (7.2)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11 (4.9)</td>
<td>8 (5.2)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>12 (5.3)</td>
<td>3 (2.0)</td>
</tr>
</tbody>
</table>

Fig. 3 Garvey et al. SEQUEL. AJCN. 2012
Bupropion/Naltrexone Efficacy

Figure 3: Proportion of participants who lost at least 5%, 10%, and 15% of baseline weight at week 56

# Bupropion/Naltrexone Safety

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Placebo (n=569)</th>
<th>Naltrexone 16 mg plus bupropion (n=569)</th>
<th>Naltrexone 32 mg plus bupropion (n=573)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants reporting any adverse event</td>
<td>390 (68.5%)</td>
<td>455 (80.0%)†</td>
<td>476 (83.1%)†</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>30 (5.3%)</td>
<td>155 (27.2%)†</td>
<td>171 (29.8%)†</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>32 (5.6%)</td>
<td>90 (15.8%)†</td>
<td>90 (15.7%)†</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>64 (11.2%)</td>
<td>49 (8.6%)</td>
<td>57 (9.9%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (2.6%)</td>
<td>44 (7.7%)†</td>
<td>54 (9.4%)†</td>
</tr>
<tr>
<td>Insomnia</td>
<td>29 (5.1%)</td>
<td>36 (6.3%)</td>
<td>43 (7.5%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (2.5%)</td>
<td>36 (6.3%)†</td>
<td>56 (9.8%)†</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>34 (6.0%)</td>
<td>34 (6.0%)</td>
<td>30 (5.2%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>11 (1.9%)</td>
<td>42 (7.4%)†</td>
<td>43 (7.5%)†</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>31 (5.4%)</td>
<td>32 (5.6%)</td>
<td>29 (5.1%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>28 (4.9%)</td>
<td>31 (5.4%)</td>
<td>26 (4.5%)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>7 (1.2%)</td>
<td>13 (2.3%)</td>
<td>30 (5.2%)†</td>
</tr>
</tbody>
</table>

| Safety endpoints:                     |                |                                        |                                        |
|---------------------------------------|                |                                        |                                        |
| Systolic blood pressure (LOCF; mm Hg) |                |                                        |                                        |
| Baseline                              | 119.0 (9.8)   | 119.3 (9.9)                            | 119.0 (9.8)                            |
| Change                                | -2.1 (0.4)     | 0.2 (0.4)†                             | -0.4 (0.4)†                            |
| Systolic blood pressure (observed; mm Hg) |            |                                        |                                        |
| Baseline                              | 119.7 (9.7)   | 119.5 (9.9)                            | 118.9 (9.5)                            |
| Change                                | -2.8 (0.5)     | -0.4 (0.5)†                            | -1.6 (0.5)                             |
| Diastolic blood pressure (LOCF; mm Hg) |                |                                        |                                        |
| Baseline                              | 77.3 (6.7)    | 76.6 (7.2)                             | 77.1 (7.2)                             |
| Change                                | -1.0 (0.3)     | -0.0 (0.3)†                            | -0.1 (0.3)†                            |
| Diastolic blood pressure (observed; mm Hg) |            |                                        |                                        |
| Baseline                              | 77.5 (6.7)    | 76.2 (7.4)                             | 77.1 (7.2)                             |
| Change                                | -1.4 (0.4)     | -0.5 (0.4)‡                            | -0.8 (0.4)‡                            |
| Pulse rate (LOCF; beats per min)      |                |                                        |                                        |
| Baseline                              | 71.8 (8.0)    | 71.4 (8.7)                             | 72.0 (8.7)                             |
| Change                                | -0.1 (0.3)     | 1.5 (0.3)†                             | 1.0 (0.3)†                             |
| Pulse rate (observed; beats per min)  |                |                                        |                                        |
| Baseline                              | 71.6 (7.9)    | 71.1 (8.6)                             | 72.4 (8.6)                             |
| Change                                | -1.0 (0.4)     | 1.1 (0.4)†                             | 0.4 (0.4)†                             |

Liraglutide Efficacy

Figure 3: Percentage of individuals who lost more than 5% and more than 10% of baseline weight at week 20 (intention-to-treat population)
*p=0.002 vs placebo. †p=0.0001 vs placebo. ‡p=0.0001 vs placebo or orlistat.

Figure 2: Change in bodyweight
Data are mean (95% CI) (ANCOVA estimate) for the intention-to-treat population with the last observation carried forward.

Case 2

- MG 48 yo AAF “I’m in too much pain to exercise”
- PMH: depression, chronic pain, hyperlipidemia
  - No CVD hx
- BP: 128/78 mmHg
- HR: 84 bpm
- 285 lbs, 66 in.
- BMI: 32.9

- Meds:
  - bupropion 300 mg XL qday
  - Fluoxetine 40 mg qday
  - tramadol 50 mg 2 tabs q12H
  - atorvastatin 20 mg HS
- FLP: WNL
- BMP: WNL
- Has failed lifestyle changes, but willing to enroll in intense behavioral program

You are going to initiate tx for MG, which agent would you select?

A. Bupropion/Naltrexone
B. Phentermine/Topiramate
C. Lorcaserin
D. Liraglutide
Case 3

- CG 41 yo WM “I just can’t get rid of this tire around my waist”
- PMH: DMT2, hyperlipidemia, tobacco abuse, GERD
- BP: 116/70 mmHg
- HR: 80 bpm
- BMI: 30.5
- BMP: WNL
- LDL: 173

- A1C= 11.3%
- Medications:
  - Atorvastatin 40 HS
  - Lantus 20 u HS
  - Lisinopril 2.5 mg Qday
  - Metformin 1000 mg BID
- Attempted 3 months of lifestyle changes, achieved 5% weight loss

What would be the best agent to help further reduce CG’s weight?

A. Bupropion/Naltrexone
B. Phentermine/
   Topiramate
C. Lorcaserin
D. Saxenda
Case 4

- KC 54 yo WF “I just want to lose those last few pounds and need some help”
- PMH: HTN, tobacco abuse, GERD, MI (2013)
- BP: 136/78 mmHg
- HR: 84 bpm
- 145 lbs, 53 in.
- BMI: 36.3
- BMP: WNL
- FLP: WNL

- Medications:
  - Atorvastatin 80 HS
  - Lisinopril 20 mg Qday
  - Metoprolol XL 50 mg Qday
  - Aspirin 81 mg Qday
- Attempted 3 months of lifestyle changes, achieved 10% weight loss

What medication will assist KC to help lose additional weight?

A. Bupropion/Naltrexone
B. Phentermine/Topiramate
C. Lorcaserin
D. Liraglutide
Summary

• Start with **lifestyle** changes
  – This needs to be ingrained!
• Add pharmacotherapy agents
  – Most studies only looked at 18-65 yo, BMI 27-45
  – Avoid bupropion/naltrexone with opioids
  – Avoid phentermine/topiramate in moderate-high CV risk
  – Avoid lorcaserin with other serotonin agents

**Individualize treatment!**

References

Resources for patients:

- [http://www.cdc.gov/healthyweight/](http://www.cdc.gov/healthyweight/)
- [https://www.supertracker.usda.gov/](https://www.supertracker.usda.gov/)