A Weight-Centric Approach: Strategies to Individualize Weight Loss Treatment

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Faculty Disclosure

Weight Loss Medications

<table>
<thead>
<tr>
<th>FDA-Approved for Obesity Management</th>
<th>In Review for Obesity Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Phentermine (short-term use)</td>
<td>• Bupropion/naltrexone&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Orlistat</td>
<td>• Liraglutide&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>• Lorcaserin</td>
<td></td>
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<tr>
<td>• Phentermine/topiramate ER</td>
<td></td>
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</tbody>
</table>

<sup>a</sup>Bupropion approved for depression; naltrexone for alcohol, opioid dependence.

<sup>b</sup>Approved for T2DM.

ER = extended release; FDA = Food and Drug Administration.
Phentermine

- Phentermine HCl developed in 1970s with doses of 8-37.5 mg (generally equivalent to 6.4-30 mg of phentermine resin)
- Mechanism: noradrenergic, sympathomimetic amine—decreases appetite
- Most common AEs: tachycardia, increase in BP, tremor, overstimulation of central nervous system, dry mouth, constipation
- Generic; most commonly prescribed/least expensive option

AE = adverse event; HCl = hydrochloride.
Orlistat

- Prescription orlistat 120 mg 3 times daily approved for long-term weight management in 1999; OTC orlistat (60 mg 3 times daily) approved in 2007
- Mechanism: GI lipase inhibitor; decreases intestinal energy absorption
- Most common AEs: oily rectal discharge, fecal urgency, fatty/oily stool
- Rare postmarketing reports of severe liver injury

OTC = over-the-counter.
Xenical [prescribing information]. South San Francisco, CA: Genentech USA, Inc; 2012.
Lorcaserin

- Approved in 2012 (10 mg twice daily) for long-term weight management
- Selective 5-HT2C receptor agonist—increases satiety
- Most common AEs: headache, nausea, dizziness, fatigue, dry mouth, constipation
- No increase in rate of valvulopathy in pivotal trials

Lorcaserin (cont’d)

• Notes
  – Discontinue if 5% weight loss is not achieved by week 12
  – Extreme care when using with drugs that affect the serotonin system
  – DEA Schedule IV
  – Pregnancy category X

DEA = Drug Enforcement Administration.
BLOOM Study:
Body Weight Over Years 1 and 2

BLOOM = Behavioral Modification and Lorcaserin for Obesity.

## BLOOM Study:  
Key Secondary End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Lorcaserin</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>-6.8</td>
<td>-3.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>-1.4</td>
<td>-0.8</td>
<td>.04</td>
</tr>
<tr>
<td>DBP</td>
<td>-1.1</td>
<td>-0.6</td>
<td>.01</td>
</tr>
<tr>
<td>TC (% Δ)</td>
<td>-0.90</td>
<td>0.57</td>
<td>.001</td>
</tr>
<tr>
<td>TGs (% Δ)</td>
<td>-6.15</td>
<td>-0.14</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>-2.0</td>
<td>-1.6</td>
<td>.0499</td>
</tr>
<tr>
<td>PASP (mm Hg)</td>
<td>-0.92</td>
<td>-0.23</td>
<td>.14</td>
</tr>
<tr>
<td>Beck depression II score</td>
<td>-1.1</td>
<td>-0.9</td>
<td>.26</td>
</tr>
</tbody>
</table>

PASP = pulmonary artery systolic pressure.

BLOOM-DM: Change in Glycemic Parameters

Change From Baseline (%)

<table>
<thead>
<tr>
<th>Study Week</th>
<th>Placebo</th>
<th>Lorcaserin 10 mg twice a day</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>-1.5</td>
<td>-1.0</td>
</tr>
<tr>
<td>24</td>
<td>-1.0</td>
<td>-0.5</td>
</tr>
<tr>
<td>36</td>
<td>-0.5</td>
<td>*</td>
</tr>
<tr>
<td>52</td>
<td>0.0</td>
<td>*</td>
</tr>
</tbody>
</table>

A1C

Change From Baseline (mg/dL)

<table>
<thead>
<tr>
<th>Study Week</th>
<th>Placebo</th>
<th>Lorcaserin 10 mg twice a day</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-20</td>
<td>*</td>
</tr>
<tr>
<td>24</td>
<td>-10</td>
<td>*</td>
</tr>
<tr>
<td>52</td>
<td>0</td>
<td>†</td>
</tr>
</tbody>
</table>

FPG

*P < .001; †P < .05; least square mean change ± SEM.

Phentermine/Topiramate

- IR phentermine HCl/ER topiramate approved for weight management in 2012 (titrated in AM up to 7.5/46 mg/d; max 15/92 mg/d)
- Phentermine: decreases short-term appetite
- Topiramate: decreases longer-term appetite and may have glycemic effects
- Most common AEs: paresthesia, dizziness, cognitive dysfunction, dysgeusia, insomnia, constipation, dry mouth, metabolic acidosis, elevated creatinine

IR = immediate release.

CONQUER: Change in Weight, A1C, and SBP From Baseline to Week 56 (T2DM Sample; ITT-LOCF)

Weight Loss

A1C

SBP

*P < .0001 vs placebo; †P = .0288 vs placebo; ‡P = .0043 vs placebo; §1 subject in the 15/92 group was missing an SBP measurement at week 56 and is not included in SBP analysis.

Baseline A1C 6.8%

ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; PHEN/TPM = phentermine/topiramate.

P < .0001 compared with placebo at all time points assessed.

CR = controlled release.

Beyond diet and exercise, what therapy would you recommend for George?

(Select all that apply)

1. Lorcaserin
2. Phentermine/topiramate
3. Glucagon-like peptide-1 (GLP-1) receptor agonist
4. Gastric bypass
Beyond diet and exercise, what therapy would you recommend for George?

**Audience Response**

1. Lorcaserin
2. Phentermine/ topiramate
3. GLP-1 receptor agonist
4. Gastric bypass
Words of Wisdom: There Is No Ideal Weight Loss Medication

- Evaluate the patient
  - His/her comorbidities
  - Obesity risk stratification
- Consider AE profile of the medication
- Monitor patients for AEs and weight loss
- Medications always augment diet and exercise; health benefits and improvements in risk factors begin with weight loss of ~5%
- Must be discontinued if nonresponse
- Must be taken long term; if stopped, weight regain is likely
Take Home Message

• Nonresponders
  – 20%-50% of patients with obesity do not respond to a particular weight loss medication

• Established cut points
  – Lorcaserin: 5% at 3 months
  – Phentermine/topiramate ER: 3% at 3 months and 5% at 6 months

• If one drug does not work, be prepared to try a different drug
Bariatric Surgery

- Bariatric surgery criteria: 2013 update from AACE, TOS, and American Society for Metabolic & Bariatric Surgery
  - BMI $\geq 40$ kg/m$^2$ without comorbid disease
  - BMI $\geq 35$ kg/m$^2$ with concurrent comorbid disease
  - Patients with diabetes or metabolic syndrome and a BMI of 30-34.9 kg/m$^2$ can "be offered a bariatric procedure, although current evidence is limited"

TOS = The Obesity Society.
Outcomes: Obesity Surgery

**Weight Loss**

Meta-analysis

147 studies

Surgery more effective than nonsurgical treatment for weight loss in patients with BMI $\geq 40$ kg/m$^2$

**Mortality**

7-year follow-up, 7925 surgery patients 1984-2002

92% decrease in cause-specific mortality from diabetes

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Outcomes: Obesity Surgery (cont’d)

Diabetes

SOS, multicenter nonrandomized, prospective, controlled intervention trial (N = 1658 surgery, 1771 control)

15-year follow-up: T2DM incidence rates,
6.8 cases/1000 person-yr with surgery, 28.4 cases/1000 person-yr with usual care, \( P < .001 \)

BMI↓ of 5 U, independent of initial degree of obesity, associated with ↓ diabetes risk compared with weight stability at any obese BMI level

SOS = Swedish Obese Subjects.
Naltrexone/Bupropion

- Investigational agent undergoing CV outcomes trial (Light Study)
- Mechanism: naltrexone—opioid antagonist for treatment of alcohol dependence and blockade of effects of exogenous opioids; may reduce appetite and addictive behavior
- Bupropion—antidepressant of the aminoketone class chemically unrelated to tricyclic, tetracyclic, selective serotonin reuptake inhibitor, or other antidepressant agents that may reduce appetite
- Most common AEs: nausea, constipation, dizziness, dry mouth, tremor, upper abdominal pain, tinnitus

Percent Change in Body Weight With Naltrexone/Bupropion: COR/BMOD Trial

*P < .001, for NB32 + BMOD vs placebo + BMOD.

COR/BMOD = Contrave Obesity Research/Behavioral Modification;
MITT = modified ITT analysis; NB32 = naltrexone 32 mg/bupropion 360 mg.

Liraglutide for Weight Loss in Obese Patients With T2DM

N = 564, 19 sites in Europe
Age 18-65 years, BMI 30-40 kg/m²

Mean Weight Loss (kg)

Weeks

Placebo
Orlistat
Liraglutide 1.2 mg
Liraglutide 1.8 mg
Liraglutide 2.4 mg
Liraglutide 3.0 mg

P < .003, liraglutide 1.2 mg vs placebo; P < .0001, liraglutide 1.8-3.0 mg vs placebo.

Liraglutide: Changes in Weight and Waist Circumference in Patients Without Diabetes

Liraglutide 3 mg/d resulted in loss of 35.6% excess body weight at 1 year

N = 564 (90-98 per group), 19 sites in Europe; age 18-65 y, BMI 30-40 kg/m²; FPG 7 mmol/L (126 mg/dL) at week 2

The weight loss in lorcaserin studies is about 5%. However, isn’t it much higher in responders?
In patients who are taking a diabetes medication such as a sulfonylurea or insulin, how do you decide how much to taper those medications when you start a weight loss drug?
If you have patients who have lost weight successfully with behavior and lifestyle change, would you put them on a drug for the rest of their lives to keep the weight off?
Why are the reductions in A1C twice as great in the lorcaserin studies as in the phentermine/topiramate studies, even though the weight loss is less?
Question

What are the key barriers to wider use of antiobesity medications?
Question

What type of patient would you put on lorcaserin and what type of patient would you put on phentermine/topiramate?
In the weight-centric management of diabetes, have you used a GLP-1 along with one of the new SGLT2 inhibitors? What happens when you do that?