"Why Can't My Patients Lose Weight?"
Treating Obesity as a Chronic Disease State

Regional Conference
New York, New York
May 28, 2014

Content Collaborator
Session 1: "Why Can't My Patients Lose Weight?" Treating Obesity as a Chronic Disease State

Learning Objectives

1. Discuss the basics of neuroendocrine regulation of body weight and why it is difficult for obese patients to lose weight.
2. Describe the basics of the clinical evaluation and management of patients with obesity.
3. Assess the basics of pharmacologic management of obesity including the currently available medical treatments for obesity.
4. Discuss the management of the bariatric surgery patient.

Faculty

Louis J. Aronne, MD, FACP
Clinical Associate Professor of Medicine
Weill Medical College of Cornell University
New York Presbyterian Hospital
New York, New York

Dr Louis Aronne is an internationally recognized weight management specialist and the CEO of BMIQ.com. He is a professor of clinical medicine at Weill Cornell Medical College and has an adjunct appointment at Columbia University College of Physicians and Surgeons. He is director of the comprehensive weight control program at New York Presbyterian/Weill Cornell Medical Center: a state of the art, multidisciplinary obesity research and treatment program.

Dr Aronne is a past president of The Obesity Society and a fellow of the American College of Physicians. He edited the National Institutes of Health Practical Guide to the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults and has authored more than 60 papers and book chapters on obesity.

Dr Aronne helped develop the VA MOVE Program, currently the largest weight program in the country. Since 2001, he has been ranked annually in Castle-Connolly’s Top Doctors in NY directory as a specialist in obesity and internal medicine. He is a graduate of Johns Hopkins University School of Medicine and graduated Phi Beta Kappa from Trinity College, Hartford, Connecticut. He is a member of the Alpha Omega Alpha medical honor society.

Dr Aronne's program, BMIQ (BMIQ.com), is a unique online weight control program delivered by doctors, nurses and dietitians. This web and phone based program provides evidence based programs that integrate medical care with healthy lifestyle in an efficient, inexpensive, and accessible manner; and provides a network of superior support resources for both patients and health care providers.

Dr Aronne is widely quoted in news media as an expert in the areas of diet, nutrition, obesity, and weight management. He was one of the founding hosts of the TV Food Network, cohosting Getting Healthy: a nightly call in show from 1993 to 1996. He has made dozens of appearances on Late Night with David Letterman since 1984 and is perhaps best known for diagnosing Letterman’s heart problem in 2000. His book, The Skinny: On Losing Weight without Being Hungry (Random House/Broadway, 2009), was a New York Times best seller.

Faculty Financial Disclosure Statement
The presenting faculty reports the following:

Dr Louis Aronne is a consultant, speaker, or advisor for and/or receives research support from Aspire Bariatrics, Amylin Pharmaceuticals Inc., Arena Pharmaceuticals, Eisai Inc., Ethicon Endo-Surgery Inc., GlaxoSmithKline Consumer Healthcare LP, GI Dynamics; High Point Pharmaceuticals LLC, Medical University of South Carolina, Novo Nordisk, Pfizer, Takeda Pharmaceuticals, USGI, VIVUS Inc., and Zafgen Inc.; is on the board of directors for Myos Corporation and Jameson Laboratories; and has ownership interest in BMIQ, Cardiometabolic Support Network, Myos Corporation, and Zafgen, Inc.
SESSION 1
7:45–9am

"Why Can't My Patients Lose Weight?" Treating Obesity as a Chronic Disease State

SPEAKER
Louis J. Aronne, MD, FACP

Presenter Disclosure Information

Off-Label/Investigational Discussion

► In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Learning Objectives

• Discuss the basics of neuroendocrine regulation of body weight, and why it is difficult for obese patients to lose weight
• Describe the basics of the clinical evaluation and management of patients with obesity
• Assess the basics of pharmacologic management of obesity including the currently available medical treatments for obesity
• Discuss the management of the bariatric surgery patient

Why don't people just lose weight?

THE PROBLEM
Regain of weight lost through diet and exercise
• Body weight is controlled by complex interactions between hormones and neurons in the hypothalamus, influencing appetite and food intake and, in most obese people, conspiring to prevent permanent weight loss
• Obese individuals are biologically defending their elevated body weight / 'set-point'

POSSIBLE EXPLANATION
Structural change in the hypothalamus
• Results of a high-fat diet in the brains of mice and rats bred to become obese revealed evidence of very early and lasting injury to neurocircuits that control energy balance in specific part of the hypothalamus
• Similar damage in the same area of the brain in obese humans

NEEDED NEXT
Prove cause and effect between hypothalamic neuron injury and defense of elevated body weight

15% Weight Loss: Reduced
• Leptin – 65%
• Peptide YY
• Cholecystokinin
• Insulin
• Amylin

Increased
• Ghrelin
• Gastric inhibitory polypeptide
• Pancreatic polypeptide

Net result of these hormonal changes: WEIGHT GAIN!
The Fat Trap

- 2009, 50 obese men and women
- Men 233 lbs/average
- Women 200 lbs/average
- Extreme low-calorie diet
  - Optimax shakes + 2 cups of low-starch vegetables
- Total 500 to 550 calories a day for eight weeks
- At 10 weeks: 30-lb ave. weight loss
  At year one: 11-lb ave. weight regain
- Reported feeling more hungry and preoccupied with food than before the weight loss

Thus, the front lines of the obesity epidemic often lie in a primary care doctor’s office. But most primary care providers are overworked, and their attention is focused on pharmacologically treatable conditions, such as hypertension and diabetes. Obesity is often relegated to the bottom of the problem list: there are no wonder drugs, no useful biomarkers that define or predict prognosis, and no standard protocol that works for every patient."

BMIQ Professionals Program Description

- System to deliver a comprehensive weight management program in the office setting.
- Provides everything you and your staff need to deliver an evidence-based weight loss intervention.
- Combines in-office or phone-based counseling as well as web-based support between visits to most effectively impact positive lifestyle change.
- Weight loss goal of 1-2 lbs. per week, personalized calorie goals, stepwise guidance to increase physical activity to 3 hours (180 minutes) per week, and interactive tools for monitor food intake, physical activity, weight and personal goals.
- Mean Weight loss - 15.9 lbs - 6.5% at 6 months

Assessment and Management - 1

- Measure height and weight
  - Estimate Body Mass Index
- Measure waist circumference
- Review the patient’s medical condition
  - Assess comorbidities:
    - How many are present, and how severe are they?
    - Do they need to be treated in addition to the effort at weight loss?
- Look for causes of obesity including the use of medications known to cause weight gain
- Assess the risk of this patient’s obesity

Assessment and Management - 2

- Assess patients readiness and motivation to lose weight?
  - If patient is not ready to lose weight, urge weight maintenance and manage the complications
- If patient is ready, agree with patient on reasonable weight and activity goals and write them down
- Use the information you have gathered to develop a treatment plan
- Involve other professionals if necessary
- Don’t forget that a supportive, empathetic approach is necessary throughout treatment

Exam

- Blood Pressure - use the right cuff
- Acanthosis nigricans, skin tags
  - Causes skin lesions that are darker than the skin around them, velvety feel, form in the folds along neck, armpits, groin, knuckles, between legs, at elbow, under breasts, around belly button
- Thyroid - but treatment won’t help weight
- Polycystic Ovary Syndrome (PCOS)
  - Not in this age group

Labs

- Glucose
  - Look for impaired fasting glucose
- Lipids (TG, HDL, TC, LDL)
- Liver Function Test
  - Abnormalities may suggest Non-Alcoholic Steatohepatitis (NASH)
- Microalbumin
- Hba1c
- TSH
- Ultrasensitive or “cardio” C-reactive protein
  - Often quite elevated

Obstructive Sleep Apnea (OSA)

- Often overlooked in obese patients
- May lead to further weight gain if not treated

<table>
<thead>
<tr>
<th>History Loud Snoring</th>
<th>Exam</th>
<th>Laboratory Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cessation of breathing during sleep which is often followed by a loud clearing breath, then brief awakening</td>
<td>Hypertension narrowing of the upper airway</td>
<td>May show polycythemia</td>
</tr>
<tr>
<td>Restless sleeper; some persons find that they can only sleep comfortably in the sitting position</td>
<td>Sternal injection</td>
<td></td>
</tr>
<tr>
<td>Partner may best describe these symptoms</td>
<td>Leg edema, secondary to pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>Daytime fatigue, with episodes of sleepiness at inappropriate times</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Referral to a pulmonologist, or sleep specialist, is appropriate

Determine Treatment Option

<table>
<thead>
<tr>
<th>NLHBI Guide for Selecting Obesity Treatment</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BMI Category (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25-26.9</td>
</tr>
<tr>
<td>Diet, Exercise, Behavior Therapy</td>
<td>+</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
</tbody>
</table>
What Diet is Best?

- Two recent studies
- Compared popular diets: Atkins, Zone, Weight Watchers, Ornish, Mediterranean, low-fat
- Results:
  - All diets worked equally well in the long run
  - Reduced-calorie diets result in clinically meaningful weight loss regardless of which macronutrients they emphasize

**Adherence to a diet is more important than the diet itself**

I prefer using a lower carb Mediterranean-style diet:
- Evidence of health benefit even without weight loss
- Easier to comply, less hunger

**Diet and Physical Activity For Best Results**

<table>
<thead>
<tr>
<th>Treatment (wk)</th>
<th>Follow-up (mo)</th>
<th>Weight Loss/Gain (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>-2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>-4</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>-6</td>
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<tr>
<td>7</td>
<td>8</td>
<td>-8</td>
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<tr>
<td>9</td>
<td>10</td>
<td>-10</td>
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<td>11</td>
<td>12</td>
<td>-12</td>
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<tr>
<td>13</td>
<td>14</td>
<td>-14</td>
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<tr>
<td>15</td>
<td>16</td>
<td>-16</td>
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<tr>
<td>17</td>
<td>18</td>
<td>-18</td>
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<td>19</td>
<td>20</td>
<td>-20</td>
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<td>21</td>
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<td>-22</td>
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<td>23</td>
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<td>25</td>
<td>26</td>
<td>-26</td>
</tr>
<tr>
<td>27</td>
<td>28</td>
<td>-28</td>
</tr>
<tr>
<td>29</td>
<td>30</td>
<td>-30</td>
</tr>
</tbody>
</table>

**Obesity Pharmacotherapy**

An adjunct to lifestyle modification — not a substitute
Can increase chances of meaningful weight loss

**Obesity Pharmacotherapy**

- Non-drug interventions should be attempted for at least 6 months before considering pharmacotherapy
- For patients with BMI ≥ 30
- For patients with BMI ≥ 27 or above with concomitant risk factors or diseases (hypertension, dyslipidemia, CHD, type 2 diabetes, sleep apnea)

Hypertension Treatment

Let’s think about for a minute:

- >120 drugs in 10 categories
- Up to triple drug combinations available
  - Diuretics
  - Beta-blockers
  - ACE inhibitors
  - Angiotensin II receptor blockers
  - Calcium channel blockers
  - Alpha blockers
  - Alpha-2 Receptor Agonist
  - Combined alpha and beta-blockers
  - Central agonists
  - Peripheral adrenergic inhibitors

Source: L. Aronne

Anti-obesity Drugs Presently on the Market and Pending Approval

<table>
<thead>
<tr>
<th>Drug Approved Drug</th>
<th>Company</th>
<th>Mechanism of Action</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Phenetermine Topiramate 46 mg ER | Qnexa | - Prolongs satiety
- Increases GABA activity
- Antagonizes AMPA/kainate glutamate receptor,
carbonic anhydrase inhibitor
- Prolongs satiety | Approved by FDA, July 2012, schedule IV |
| Bupropion/Naltrexone | Contrave Orexigen | - Approved by FDA, schedule IV
- Weight los in pts
with BMI ≥30 kg/m2
with weight-related co-morbid condition(s)
- Treatment Dose Daily phentermine 7.5 mg,
topiramate ER 46 mg
- Max Dose Daily phentermine 15 mg,
topiramate ER 92 mg | Approved July 2013 |
| Phentermine/Topiramate ER | Qysmia | - Prolongs satiety
- Increases GABA activity
- Antagonizes AMPA/kainate glutamate receptor,
carbonic anhydrase inhibitor
- Prolongs satiety | Approved June 2013 |

Modified from Powell AG, Apovian CM, Aronne LJ.

Expected Weight Loss with Newly Approved and Investigational Anti-obesity Medications

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Agent</th>
<th>Brand Name</th>
<th>Drug (mg)</th>
<th>Placebo (mg)</th>
<th>Max Weight Loss (mg)</th>
<th>Duration</th>
<th>FDA Approved</th>
</tr>
</thead>
</table>
| Dopaminergic 
Inhibitors | Lorcaserin | Belviq | 8.2 | 7.3 | 11 | 2012 | June |
| Sympathetic/ 
Noradrenergic 
Agonists | Phendimetrazine | Adderall XR | 37.5 | 37.5 | 52 | 2012 | July |
| Sympatholytic 
Drugs | Phentermine/Topiramate 15/92 | Topiramate ER | 92 mg | 10.3 | 7.1 | 104 weeks | Pending for FDA Approval |
| Glucoagon-like peptide 1 (GLP1) | Liraglutide | Victoza | 10.3±7.1 | 10.4 | 4.7 | 2012 | July |
| Sympathomimetic 
Drugs | Phentermine | 3.75 | 3.75 | 2.4 | 0.79 | 0.0001 |
| Targeted 
Enzymes | Orlistat | Xenical | 120 | 120 | 2.4 | 0.0001 |
| Acetylcholinesterase 
Inhibitors | Donepezil | Namenda | 5 | 5 | 2.4 | 0.0001 |
| β-Adrenergic 
Blockers | Metoprolol | Toprol XL | 25 | 25 | 1.2 | 0.0001 |
| H2 Receptor 
Blockers | Ranitidine | Zantac | 150 | 150 | 1.2 | 0.0001 |
| Corticosteroids | Prednisone | Deltasone | 5 | 5 | 1.2 | 0.0001 |


Phentermine/Topiramate ER Improves Risk Factors and Manifestations of Cardiometabolic Disease CONQUER Study

Changes from baseline to week 56 in secondary endpoints

<table>
<thead>
<tr>
<th>Variable</th>
<th>Phentermine</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>↓</td>
<td>-2.6</td>
<td>-2.4</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>↓</td>
<td>-4.7</td>
<td>-2.4</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>↓</td>
<td>-3.4</td>
<td>-2.7</td>
</tr>
<tr>
<td>Triglycerides (%)</td>
<td>↓</td>
<td>-8.6</td>
<td>4.7</td>
</tr>
<tr>
<td>LDL-C (%)</td>
<td>↑</td>
<td>-3.7</td>
<td>-4.1</td>
</tr>
<tr>
<td>HDL-C (%)</td>
<td>↑</td>
<td>5.2</td>
<td>1.2</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>↓</td>
<td>-2.4</td>
<td>-0.79</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>↑</td>
<td>1.4</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Modified from Zhi-yun Zhang Z-y and Wang M-w.

Phentermine/Topiramate ER

- Once-a-day, oral, extended release topranamate
- Low doses of previously approved medications to minimize side effects

<table>
<thead>
<tr>
<th>Phentermine/Topiramate ER</th>
<th>Max Dose Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5 mg</td>
<td>46 mg ER</td>
</tr>
<tr>
<td>15 mg</td>
<td>92 mg ER</td>
</tr>
</tbody>
</table>

Dosing:
- Begin with low dose for 2 wks phentermine 3.75/ topiramate ER 15/92 mg
- Reduce to treatment dose phentermine 7.5 mg/topiramate ER 46 mg
- If <5% weight loss after 12 wks, either discontinue or advance to full dose phentermine 15 mg/topiramate ER 92 mg for 2 wks
- If <5% weight loss after 12 wks on full dose, discontinue (take every other day for one wk)

Phentermine/Topiramate

3 Trials

** Phentermine/Topiramate ER: EQUIP and CONQUER

** Most Commonly Reported Treatment Emergent Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Phentermine/Topiramate ER (N=3749)</th>
<th>Placebo (N=3185)</th>
<th>Placebo (N=3185)</th>
<th>Placebo (N=3185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paronychia</td>
<td>1.9/6.2</td>
<td>13.7/19.9</td>
<td>19.9/25.9</td>
<td>19.9/25.9</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2.8/6.7</td>
<td>13.5/19.1</td>
<td>19.1/25.9</td>
<td>19.1/25.9</td>
</tr>
<tr>
<td>Constipation</td>
<td>6.1/7.9</td>
<td>13.5/18.2</td>
<td>13.3/16.9</td>
<td>13.3/16.9</td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td>3.8/5.5</td>
<td>13.0/13.1</td>
<td>13.1/13.0</td>
<td>13.1/13.0</td>
</tr>
<tr>
<td>Headache</td>
<td>3.6/3.3</td>
<td>7.0/7.6</td>
<td>7.6/7.4</td>
<td>7.4/7.4</td>
</tr>
<tr>
<td>Dogmatic</td>
<td>1.1/1.3</td>
<td>7.4/9.4</td>
<td>9.4/11.1</td>
<td>11.1/11.1</td>
</tr>
<tr>
<td>Nervousness</td>
<td>1.8/2.8</td>
<td>5.0/6.2</td>
<td>6.2/7.5</td>
<td>7.5/7.5</td>
</tr>
<tr>
<td>Treatments</td>
<td>4.7/5.0</td>
<td>5.8/6.8</td>
<td>6.8/8.4</td>
<td>8.4/8.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.4/3.8</td>
<td>7.2/8.6</td>
<td>8.6/9.7</td>
<td>9.7/9.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.2/4.9</td>
<td>7.9/8.7</td>
<td>8.7/9.3</td>
<td>9.3/9.3</td>
</tr>
<tr>
<td>Headache</td>
<td>1.3/1.6</td>
<td>7.3/7.9</td>
<td>7.9/9.0</td>
<td>9.0/9.0</td>
</tr>
<tr>
<td>Back pain</td>
<td>1.5/1.7</td>
<td>7.6/8.0</td>
<td>8.0/9.0</td>
<td>9.0/9.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4.2/3.8</td>
<td>6.4/6.5</td>
<td>6.5/6.8</td>
<td>6.8/6.8</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>3.1/3.8</td>
<td>6.0/6.3</td>
<td>6.3/6.5</td>
<td>6.5/6.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.4/0.6</td>
<td>2.2/3.0</td>
<td>3.0/3.5</td>
<td>3.5/3.5</td>
</tr>
</tbody>
</table>

Contraindications and Warnings

- Pregnancy
- Drug interactions with other serotoninergic or anti-dopaminergic agents
- Valvular heart disease
- Cognitive impairment
- Psychiatric disorders (euphoria, suicidal thoughts, depression)
- Priapism
- Risk of hypoglycemia with diabetes meds

** Summary of Phentermine and Topiramate Neuropsychiatric Safety

- No serious AEs related to depression, anxiety or cognition
- No increase in the risk of suicidality (C-SSRS*, PHQ-9**, and AE reporting) in a population where 20% had a prior history of depression
- Can be prescribed in patients with stable depression and patients on SSRIs

* Columbia Suicide Severity Rating Scale  
** Patient Health Questionnaire 9-item depression scale


Hypoglycemia:

- Weight by Week 12: Week 52 Responders

- Studies 009 and 011, MITT

- Extension of CONQUER Trial

- Same treatment as CONQUER study in a blinded fashion: either once-a-day treatment with 15 mg QNEXA (n=295), 7.5 mg QNEXA (n=153), or placebo (n=227)

- 108-week treatment period, all patients were advised to follow a simple lifestyle modification program including reduction of food intake by 500 calories per day

www.qsymia.com/hcp/conquer-trial.aspx

** Phentermine and Topiramate ER

** Patient Health Questionnaire 9-item depression scale

** Columbia Suicide Severity Rating Scale


- Increases satiety
- Stimulates appetite suppression
- Selective 5-HT2C Action
- Mechanism of Action

- Selective 5-HT2C receptor agonist
- Stimulates α-MSH production from POMC neurons resulting in activation of MC4R
- Increases satiety

- Discontinue if 5% weight loss is not achieved in 12 wks
- Approved by FDA June 2012
- Indication: Weight loss in patients with BMI ≥35 kg/m2 or BMI ≥30 kg/m2 with weight-related co-morbid condition(s)
- 10 mg po bid
- Schedule IV
- Discontinue if 5% weight loss is not achieved in 12 wks

Contraindications:

- Pregnancy
- Drug interactions with other serotoninergic or anti-dopaminergic agents
- Valvular heart disease
- Cognitive impairment
- Psychiatric disorders (euphoria, suicidal thoughts, depression)
- Priapism
- Risk of hypoglycemia with diabetes meds

Lorcaserin: Those Who Lost ≥4.5% Total Body Weight by Week 12 Were Week 52 Responders

Studies 009 and 011, MITT

<table>
<thead>
<tr>
<th>Event</th>
<th>Phentermine/Topiramate ER (N=3749) (%)</th>
<th>Placebo (N=3185) (%)</th>
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<th>Placebo (N=3185) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>537 (16.6)</td>
<td>321 (10.1)</td>
<td>10.1</td>
<td>10.1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>270 (8.5)</td>
<td>122 (3.8)</td>
<td>3.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>264 (8.3)</td>
<td>170 (5.3)</td>
<td>5.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>186 (5.8)</td>
<td>125 (3.9)</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>229 (7.2)</td>
<td>114 (3.6)</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>169 (5.3)</td>
<td>74 (2.3)</td>
<td>2.3</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Lorcaserin: Adverse Events Reported by ≥5% in Any Group

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N = 3185)</th>
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</tr>
<tr>
<td>Fatigue</td>
<td>229 (7.2)</td>
<td>114 (3.6)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>169 (5.3)</td>
<td>74 (2.3)</td>
</tr>
</tbody>
</table>

Interventional Trial Analysis with LOCF Imputation

Lorcaserin — BLOOM Study: Key Secondary Endpoints

<table>
<thead>
<tr>
<th>Endpoint</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;0.001</td>
</tr>
<tr>
<td>SBP/DBP (mm Hg)</td>
<td>↓ -1.4 / -1.1</td>
<td>-0.8 / -0.6</td>
<td>0.04/0.01</td>
</tr>
<tr>
<td>Cholesterol (% Δ)</td>
<td>↓ -0.90</td>
<td>0.57</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL</td>
<td>↓ 2.87</td>
<td>4.03</td>
<td>0.049</td>
</tr>
<tr>
<td>HDL</td>
<td>0.05</td>
<td>-0.21</td>
<td>0.72</td>
</tr>
<tr>
<td>Triglycerides (%)</td>
<td>↓ -6.15</td>
<td>-0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Safety</td>
<td>↓ -2.0</td>
<td>-1.6</td>
<td>0.049</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>↓ -1.1</td>
<td>-0.9</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Naltrexone/Bupropion

- Mechanism of Action
  - Naltrexone - Opioid receptor antagonist
  - Bupropion - Dopamine/noradrenaline reuptake inhibitor
- Approved by FDA committee but FDA did not approve until a CVD outcome study is performed due to concerns about blood pressure and pulse in some patients
- The Light Study (CVD outcomes) is under way; estimated completion: July 2017

Liraglutide

- Glucagon-Like Peptide 1 (GLP-1) receptor agonist approved in 2010 for treatment of type 2 diabetes (1.8 mg/day)
- Appetite effect mediated by both the activation of GLP-1 receptors expressed in the hypothalamus
- Affects appetite, food preference, and cardiovascular biomarkers in patients with type 2 diabetes
- Phase III trials assessing effects of doses as high as 3.0 mg/day submitted to FDA

Liraglutide: Adverse Events

- Generally well tolerated and improved quality of life
- Adverse events mostly mild or moderate
- Gastrointestinal events (particularly nausea and vomiting), consistent with the known physiological effects of GLP-1, were more frequent than with placebo
- At year 1, nausea and/or vomiting was associated with greater weight loss with liraglutide 3.0 mg, but even those who did not experience these events lost more weight than those on placebo or orlistat
- Injection regimen did not impair adherence or cause significant withdrawal during treatment or run-in

Naltrexone/Bupropion: Side Effects

- Most frequent events:
  - Nausea
    - N=171 (29.8%) N 32 mg plus bupropion
    - N=155 (27.2%) N 16 mg plus bupropion
    - N=30 (5.3%) placebo
  - Headache, constipation, dizziness, vomiting, and dry mouth were also more frequent in the naltrexone plus bupropion groups vs. placebo
  - Transient increase of ~1.5 mm Hg in mean systolic and diastolic blood pressure was followed by a reduction of around 1 mm Hg below baseline in the naltrexone plus bupropion groups
  - Combination treatment was not associated with increased depression or suicides vs. placebo
**Metabolic and Bariatric Surgery**

- An available weight loss option for well-informed and motivated patients with a BMI ≥40 kg/m² or with a BMI ≥35 kg/m², who have comorbid conditions and acceptable operative risk.
- FDA recently approved BMI ≥30 kg/m² + comorbidity for lap-band.
- Patients should have instituted but failed an adequate exercise and diet program.


**Bariatric Surgery: Common Procedures**

- Roux-en-Y Gastric Bypass
- Vertical Sleeve Gastrectomy
- Gastric Band
- Biliopancreatic Diversion/ Duodenal Switch

**Types of Surgeries Performed in the US**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Approx. Percentage of Procedures</th>
<th>Estimated Body Weight Loss</th>
<th>Major Complications</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roux-en-Y Gastric Bypass</td>
<td>50%</td>
<td>33%</td>
<td>6%-10%</td>
<td>1%-2%</td>
</tr>
<tr>
<td>Laparoscopic Adjustable Band</td>
<td>35%</td>
<td>20%</td>
<td>2%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Vertical Sleeve Gastroplasty</td>
<td>10%</td>
<td>25%</td>
<td>2%</td>
<td>&lt;0.1%</td>
</tr>
</tbody>
</table>

**Bariatric Surgery: Long-Term Weight Loss and Decreased Mortality**

Swedish Obese Subjects Study

- Up to 16 years follow-up
- Overall mortality: Hazard ratio =0.76 (95% CI: 0.59–0.99), P=0.04

**Bariatric Surgery Reduces Overall Mortality, Diabetes Mortality by 88%**

<table>
<thead>
<tr>
<th>Matched Subjects</th>
<th>Surgery Group (n=7925)</th>
<th>Control Group (n=7925)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes of death</td>
<td>213/10,000 person-yr</td>
<td>37.8/10,000 person-yr</td>
</tr>
<tr>
<td>Death rate</td>
<td>26.8</td>
<td>57.1</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>55/10,000 person-yr</td>
<td>104/10,000 person-yr</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8/10,000 person-yr</td>
<td>19/10,000 person-yr</td>
</tr>
<tr>
<td>Cancer</td>
<td>31/10,000 person-yr</td>
<td>73/10,000 person-yr</td>
</tr>
<tr>
<td>Other diseases</td>
<td>62/10,000 person-yr</td>
<td>155/10,000 person-yr</td>
</tr>
<tr>
<td>Accidental death</td>
<td>61/10,000 person-yr</td>
<td>116/10,000 person-yr</td>
</tr>
<tr>
<td>Poisoning</td>
<td>17/10,000 person-yr</td>
<td>34/10,000 person-yr</td>
</tr>
<tr>
<td>Suicide</td>
<td>15/10,000 person-yr</td>
<td>26/10,000 person-yr</td>
</tr>
<tr>
<td>Other non-disease causes</td>
<td>18/10,000 person-yr</td>
<td>32/10,000 person-yr</td>
</tr>
</tbody>
</table>


**Long-Term Nutritional Complications Can Occur: Follow-up is MANDATORY**

Sites of Nutrient Absorption in the GI Tract

- Calcium
- Iron
- Phosphorus
- Copper
- Magnesium
- Iodine
- Molybdenum
- Intrinsic Factor

**Slide courtesy of Scott Gilmore MD**
Follow Up

Watch out for:

- Nausea, vomiting
- B12 deficiency
- Iron deficiency
- GI irritation/marginal ulcers from NSAIDs
- Secondary Hyperparathyroidism

Recommended follow-up of the bariatric surgery patient by the nonsurgeon*

<table>
<thead>
<tr>
<th>Month</th>
<th>2</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>Annually</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
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<td>Chemistry panel</td>
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<tr>
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<td></td>
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<td>Magnesium</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Complete blood count</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Iron studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vitamin D</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bone density</td>
</tr>
</tbody>
</table>

*This table is made up of recommendations based on clinical practice.
† If the patient is found to have an abnormally low bone density, or decreasing bone density, then measure bone density annually.

Summary

- Obesity is a disease of hypothalamic signaling pathways
- Persistent hormonal changes affect hunger, appetite, and metabolism, contribute to weight regain
- Diet and exercise are the foundation of all weight loss approaches
- Adherence is the important factor in dieting
- Few choices of anti-obesity medications, but growing
  - Two new medications approved in 2012
  - Two more are pending approval
- Medications are a reasonable option and can enhance weight loss for select candidates and improve cardiometabolic outcomes
- Obesity surgery is the most effective weight loss option for the severely obese

Questions

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