Objectives

• Discuss the rationale for using weight loss medications alone and or in combination with surgery

• Discuss the risks and benefits and describe the best candidates for newly prescribed weight loss medications

• Describe the physiological basis and lifestyle habits for weight regain
What is ‘Obesity’?

<table>
<thead>
<tr>
<th>BMI Classifications</th>
<th>Disease Risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI (kg/m²)</td>
</tr>
<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</td>
<td>30.0–34.9</td>
</tr>
<tr>
<td>Obesity</td>
<td>35.0–39.9</td>
</tr>
<tr>
<td>Extreme Obesity</td>
<td>40.0 +</td>
</tr>
</tbody>
</table>

* Disease risk for type 2 diabetes, hypertension, and CVD Relative to normal weight and waist circumference
+ Increased waist circumference also can be a marker for increased risk, even in persons of normal weight

Contribution of Obesity to Chronic Disease


Obesity defined as BMI >29 kg/m²

U.S. Obesity Prevalence, 2009-2010

CDC/NCHS, National Health and Nutrition Examination Survey, 2009-2010
http://www.cdc.gov/nchs/data/databriefs/db82.htm
50% of American MEN will be obese by 2030

45-52% of American WOMEN will be obese by 2030
Weight Classification

Body Mass Index (BMI)
Measure of weight in relation to height

Formula: \[ \frac{\text{Weight (lb)} \times 703}{\text{Height (in)}^2} \]

Overweight and Obesity Associated with Increased All-cause Mortality: MEN

Berrington de Gonzalez et al. NEJM. 2010;363: 2211-9
Overweight and Obesity Associated with Increased All-cause Mortality: **WOMEN**


**Obesity Treatment Guidelines**
How is Adult Diabetes Treated?

New Dogma – Treat the Obesity

- Surgery
  - Improves insulin sensitivity and may cause weight loss or at least are weight neutral
  - For select patients; most effective treatment
- Can add 3-8% placebo-subtracted weight loss
- Foundation of all weight management approaches
- Diet
- Physical Activity
- Pharmacotherapy
  - Diabetes Medication: Metformin, Januvia, Byetta
  - Weight Loss Medication: Orlistat, Phentermine, others

Guide for Selecting Obesity Treatment

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>25-26.9</th>
<th>27-29.9</th>
<th>30-34.9</th>
<th>35-39.9</th>
<th>&gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet, Exercise, Behavior Tx</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Pharmacotherapy</strong></td>
<td>+ With co-morbidities</td>
<td>+</td>
<td>+</td>
<td>+ With co-morbidities</td>
<td>+</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

Aim for Modest (5-10%) Weight Loss

- Increases life expectancy\(^1\)
- Improves glycemic control\(^2\)
- Lowers blood pressure\(^3\)
- Improves serum lipid profile\(^4\)
- May decrease cancer risk\(^5\)
- Improves lower back pain, reflux, lower extremity arthralgias, sleep apnea\(^6\)
- Can decrease drugs for obesity-related conditions\(^6\)

---

6. NHLBI Guidelines, June 1998

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Encourage 5-10% weight loss\(^6\)
Rate: 1-2 lbs/week

---

Obesity Treatment: What Works?
Dieting: Which is Best?

- Two recent studies
- Compared popular diets: Atkins, Zone, Weight Watchers, Ornish, Mediterranean, low-fat
- Same results

Adherence is more important than the diet itself


Diet and Physical Activity For Best Results

**CDC Recommendations for Physical Activity**

**Adults 18 to 64 Years of Age**

- **Moderate Intensity**
  - 150 mins/week
  - OR
  - 30 mins/day for 5 days

- **Vigorous Intensity**
  - 75 mins/week
  - OR
  - 15 mins/day for 5 days

- **Strength Training**
  - 2 or more days/week
  - Work all major muscles

Make gradual, incremental changes

**Ultimate goal is 420 minutes/week of moderate intensity activity**

www.cdc.gov/physicalactivity/everyone/guidelines/adults.html

---

**Diets and Long-term Weight Loss**

Preponderance of published literature and scientific research have found that diet and exercise is unsuccessful in 80-85% of patients at one year

Bariatric Surgery: currently best solution for obesity

Outcomes: Obesity Surgery

- **Weight Loss**
  - Meta-analysis 147 Studies 2005
  - Surgery is more effective than non-surgical treatment for weight loss in patients with a BMI of 40 kg/m² or greater

- **Diabetes**
  - Meta-analysis 621 Studies 1990-2006
  - 78.1% Complete resolution of diabetes (Band surgery)
  - 86.6% Diabetes - improved or resolved

- **Mortality**
  - 7-Year Follow-up 7925 Surgery Patients 1984-2002
  - 92% Decrease in cause-specific mortality from diabetes

Outcomes depend on race and genes

68.2 % initial complete diabetes remission 5 years post-op 1995-2008; n= 4,434
Published online: November 15, 2012
How Gut Hormones May Contribute to Regression of Diabetes After Roux-en-Y Surgery

Kashyap SR. Cleveland Clinic Journal of Medicine 2010;77:468-476.

Bariatric Surgery Trends
Expands need for peri-op care expertise

200+ medications to treat hypertension

10 classes of medications and 100 medication choices to treat diabetes

Few choices for obesity

Anti-obesity Drugs and their Pathways
Complex System – needs expert understanding

Endogenous Signaling of Appetite-regulating Hormones, Neuropeptides, and Neurotransmitters, and The Drugs That Target These Pathways
Anti-obesity Medications
Rationale and Criteria

- 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)


The Problem
Effectiveness of current three prescription diet drugs:

- Sibutramine (Meridia) 3-4% ave. weight loss in 6 mos – 1 year of use (withdrawn from market Oct 2010)

- Phentermine 4-5% ave. weight loss in 3 months (longest it is approved for)

- Orlistat (Xenical) 3-4% ave. in 1 year

www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM218821.pdf
## Expected Weight Loss with Currently Approved and Investigational Drugs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Drug</th>
<th>Placebo</th>
<th>Net weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>6.8 kg</td>
<td>2.8 kg</td>
<td>4.0 kg</td>
</tr>
<tr>
<td>Orlistat</td>
<td>7.3 kg</td>
<td>3.5 kg</td>
<td>3.0 kg</td>
</tr>
<tr>
<td>Topiramate</td>
<td>4.5 kg</td>
<td>1.7 kg</td>
<td>2.8 kg</td>
</tr>
<tr>
<td>Bupropion</td>
<td>6.0 kg</td>
<td>2.8 kg</td>
<td>3.2 kg</td>
</tr>
<tr>
<td>Qnexa</td>
<td>Topiramate/Phentermine 14.7 kg</td>
<td>2.5 kg</td>
<td>12.2 kg</td>
</tr>
<tr>
<td>Contrave</td>
<td>Bupropion/naltrexone 8.2 kg</td>
<td>1.9 kg</td>
<td>6.2 kg</td>
</tr>
<tr>
<td></td>
<td>Bupropion/zonisamide 7.2 kg</td>
<td>2.9 kg</td>
<td>4.3 kg</td>
</tr>
<tr>
<td></td>
<td>Pramlintide/metreleptin 12.7 kg</td>
<td>No placebo</td>
<td>12.7 kg (vs. No placebo)</td>
</tr>
<tr>
<td>Lorqess</td>
<td>Lorcaserin 8.2 kg</td>
<td>3.4 kg</td>
<td>4.8 kg</td>
</tr>
<tr>
<td></td>
<td>Liraglutide 7.2 kg</td>
<td>2.8 kg</td>
<td>4.4 kg</td>
</tr>
<tr>
<td></td>
<td>Cetilistat 4.3 kg</td>
<td>2.8 kg</td>
<td>1.5 kg</td>
</tr>
<tr>
<td></td>
<td>Tesofenside 11.2 kg</td>
<td>2.8 kg</td>
<td>9.2 kg</td>
</tr>
<tr>
<td></td>
<td>Velneperit 7.1 kg</td>
<td>4.3 kg</td>
<td>2.8 kg</td>
</tr>
</tbody>
</table>


## CONQUER Trial: Weight Loss Over Time

### Phentermine/Topiramate

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Mid</th>
<th>Full</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean % Weight Loss</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Placebo**
-2.4%, 6 lbs

**Mid-dose**
-10.5%, 24 lbs

**Full-dose**
-13.2%, 30 lbs

Full-dose
15 mg Phentermine/92 mg Topiramate

**Patients**

| Completers (%) of randomized | 564 | 344 | 634 |

1. Statistically greater number of patients completing study on Qnexa vs. placebo, p<0.0001
2. Data from patients that completed 56 weeks on treatment
CONQUER Trial: Significant Weight Loss
Phentermine/Topiramate

Completers

<table>
<thead>
<tr>
<th>% of Patients</th>
<th>Placebo</th>
<th>P/T Mid</th>
<th>P/T Full</th>
</tr>
</thead>
<tbody>
<tr>
<td>15%</td>
<td>4%</td>
<td>26%</td>
<td>39%</td>
</tr>
<tr>
<td>10%</td>
<td>10%</td>
<td>49%</td>
<td>64%</td>
</tr>
<tr>
<td>5%</td>
<td>26%</td>
<td>75%</td>
<td>85%</td>
</tr>
</tbody>
</table>

$P < .0001$ vs placebo for both doses


Side Effects
Phentermine/Topiramate

- FDA saw increases in heart rate among patients taking the drug, but the clinical significance was not conclusive
- Other side effects included:
  - Increased anxiety
  - Sleep disturbances
  - Dry mouth
  - Tingling
  - Constipation
  - Altered taste
  - Depression
  - Infections in the sinus and respiratory tracts

http://ir.vivus.com/releasesdetail.cfm?ReleaseID=407933
Lorcaserin Phase 3 Trials

• n=3,182
• 2 years tx
• Dosage 10 mg QD


Arena Pharmaceuticals

Lorcaserin

Side Effects

• The most frequent adverse events were headache, nausea, dizziness, fatigue and dry mouth
• Headache the only adverse event increased over placebo by > 5%

Arena Pharmaceuticals
Mean Weight Loss
Naltrexone SR/Bupropion SR
COR-I Phase 3
56 Weeks – Completer Population

Percent Change in Body Weight
Naltrexone/Bupropion
COR/BMOD Trial
BMI 36.5 ± 4.2 kg/m²

*P < .001, for NB32 + BMOD vs placebo + BMOD
COR/BMOD = Contrave Obesity Research/Behavioral Modification
ITT = intent to treat
NB32 = naltrexone 32 mg/bupropion 360
Side Effects

Naltrexone/Bupropion

Most frequent events:

- Nausea
  - N=171 (29.8%) naltrexone 32 mg plus bupropion
  - N=155 (27.2%) naltrexone 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

The Plateau Phenomenon
Why can't people lose weight?

![Graph showing weight change over time for different diets.](image)

P<0.001 for both comparisons with the low-fat diet

**Obstacle to Successful Weight Loss**

**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

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


---

**Hypothetical “Feed-forward”**
Positive Feedback Mechanism to Drive Weight Up

- **High Fat/High Carb Food**
  - Increased endocannabinoids and resistance to leptin and insulin
  - CNS insulin and leptin resistance

- **1. Increased food intake**
- **2. Weight gain**

- **“Brain can’t tell how much fat is stored”**

- **1. Reduced sense of satiety**
- **2. Craving**

© 2007 Louis J. Aronne, MD
Wang J. Diabetes, 2001; DiMarzo V pers comm
Ozcan L et al Cell Metabolism; 2009

© 2007 Louis J. Aronne, MD
The Fat Trap
Body continues to fight against weight loss long after dieting has stopped

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


Long-Term Persistence of Hormonal Adaptations to Weight Loss
Changes in Weight from Baseline to Week 62

ITT = intention to treat
Fasting/Postprandial Hormone Levels
Mean (+SE) Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and CCK at Baseline, 10 weeks, 62 Weeks

Short Sleep Duration Associated with Reduced Leptin, Elevated Ghrelin, and Increased BMI
Summary

- Obesity epidemic expected to increase
- Surgery is the best solution for severe obesity
- Medications can enhance weight loss for select candidates despite adverse effects
- Weight regain may be related to structural changes in the brain
- Sleep deprivation contributes to overweight
Medical Weight Management at BMC
Nutrition and Weight Management Center
(617) 638-7470 for Adults

- Longest-running program in Boston
- Treat ~450 patients/week
- Comprehensive programs: diet to surgery
- Modest weight loss to severe obesity
- Individual or group settings
- Current 12 week wait for appointment

Medical Weight Management at BMC
Nutrition and Weight Management Center
Additional Services

- Food Pantry
  Stocked with fresh fruits and vegetables in addition to canned foods
- Demo Kitchen
  Classes for patients with diseases (type II diabetes, cardiovascular disease, hypertension, obesity)
- Pediatric Program
  – Family-focused, pediatric weight management
  – Individual, group or community settings
  – Nutrition, behavior, physical activity
Medical Weight Management at BMC
Nutrition and Weight Management Center

**Operations**

- Staff: 2 MDs, 4 RDs, psychologist, 4 admin, registration
- Facility expanded in 2002, 3150 sq ft
- Size-friendly equipment
- Wheelchair accessible
- State-of-the-art medical equipment and computer tracking system
- Free, weekly patient orientation led by RD
  - Strongly encouraged to make their first appt at orientation

---

Medical Weight Management at BMC
Nutrition and Weight Management Center

**Weight Loss Options**

- **5 Diet Plans:**
  - Balanced Calorie Deficit
  - Food and Liquid Formula
  - Full Liquid Formula
  - Medication and Balanced Calorie Deficit
  - Protein-Sparing Modified Fast

- **Weight Loss Medications**

- **Obesity Surgery**
Weight Management Resources

**The Evidence Report, June 1998**
www.nhlbi.nih.gov

**The Practical Guide, October 2000**
www.nhlbi.nih.gov

**Assessment and Management of Adult Obesity: A Primer for Physicians**
www.ama-assn.org/ama/pub/category/10931.html