Objectives

• Updated definition of obesity using guidelines from AACE/ACE consensus statement 2014
• Anthropometric measures (waist circumference) used in the definition of metabolic syndrome and the association with central obesity
• Waist circumference also used in the diagnosis of obesity in the updated guidelines
• Primary, secondary, and tertiary intervention using the AACE/ACE algorithm
• Medications used for weight loss and when to incorporate into patient care
OBESITY ICEBERG:
US Population = 300 Million

Morbidly Obese: 15 mil
Obese: 85 mil
Over Weight: 100 mil
Normal Weight: 100 mil

Approximately 111 Million US Adults Are Overweight or Obese and Have a Weight-Related Comorbidity

- 88% (~97 million) have at least 1 weight-related comorbidity*
- 19.6% (~21.9 million) have 3 comorbidities*

* Adults with a body mass index (BMI) ≥ 30 kg/m², 18 years of age and older. Data from National Health and Nutrition Examination Survey (NHANES).
Obesity in the U.S. is a Major Public Health Challenge

- Approximately 66% of adults in the United States are overweight or obese
- Substantially raises risk for many chronic diseases
- As of 2001, obesity is now the number one cause of preventable death in the United States today

Smoking is currently the #2 leading cause of preventable death.

BMI-Associated Disease Risk

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>Increased</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 – 24.9</td>
<td>Normal</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 – 29.9</td>
<td>Increased</td>
</tr>
<tr>
<td>Obese I</td>
<td>30.0 – 34.9</td>
<td>High</td>
</tr>
<tr>
<td>Obese II</td>
<td>35.0 – 39.9</td>
<td>Very high</td>
</tr>
<tr>
<td>Obese III</td>
<td>≥ 40</td>
<td>Extremely high</td>
</tr>
</tbody>
</table>

Additional risks:
- Large waist circumference (men > 40 in; women > 35 in)
- Poor aerobic fitness
- Specific races and ethnic groups
Obesity rate in study population- based on WHO, NIH, and race ethnicity specific BMI cutoff values

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>Actual obesity rate based on WHO criterion standard (95% CI)</th>
<th>Obesity rate based on NIH’s BMI cut off value (95% CI)</th>
<th>Obesity rate based on race/ethnicity specific BMI cut off value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>58.7 (51.4 – 65.8)</td>
<td>28.0 (21.8 – 35.0)</td>
<td>52.9 (45.5 – 60.2)</td>
</tr>
<tr>
<td>Black</td>
<td>60.4 (52.3 – 68.0)</td>
<td>46.5 (38.6 – 54.6)</td>
<td>52.8 (44.8 – 60.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>69.1 (62.3 – 75.3)</td>
<td>37.7 (31.1 – 44.7)</td>
<td>61.4 (54.4 – 68.0)</td>
</tr>
<tr>
<td>Overall</td>
<td>63.1 (58.9 – 67.1)</td>
<td>36.9 (32.9 – 41.1)</td>
<td>56.0 (51.8 – 60.2)</td>
</tr>
</tbody>
</table>

WHO=World Health Organization; NIH=National Institute of Health; BMI = Body mass index.

*Based on percent body fat>35%

**BMI ≥30 kg/m²

*Cutoff value to define obesity according to the current study:

White: BMI≥25.5 kg/m²

Black: BMI≥28.7 kg/m²

Hispanic: BMI≥26.2 kg/m²

Ethnic Differences in BMI and Disease Risk

- Nurses Health Study tracked weight gain and development of diabetes in 78,000 U.S. women over 20 years, to determine if there were differences by ethnic group (1).
- Asians had more than double the risk of developing T2DM than whites at the same BMI (1).
- Hispanic and blacks also had higher risks of T2DM, but to a lesser degree (1).
- Other studies have found that at the same BMI, Asians have higher risks of hypertension and cardiovascular disease (CVD) and mortality from CVD or any cause compared to white European counterparts (2-4).
**Association between the incidence rate of diabetes and BMI by ethnic group.**

**Appropriate BMI cutoffs for Asian populations**

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>WHO</th>
<th>Asian</th>
<th>Weight Categories</th>
<th>Health Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 &amp; above</td>
<td>27.5 &amp; above</td>
<td>Chinese</td>
<td>High risk of developing heart disease, high blood pressure, stroke and diabetes</td>
<td></td>
</tr>
<tr>
<td>25 to 29.9</td>
<td>23 to 27.4</td>
<td>Overweight</td>
<td>Moderate risk of developing the above diseases</td>
<td></td>
</tr>
<tr>
<td>18.5 to 24.9</td>
<td>18.5 to 22.9</td>
<td>Healthy Range</td>
<td>Low risk of developing the above diseases</td>
<td></td>
</tr>
<tr>
<td>Below 18.5</td>
<td>Below 18.5</td>
<td>Underweight</td>
<td>At risk of developing nutritional deficiency diseases and osteoporosis</td>
<td></td>
</tr>
</tbody>
</table>

*Lancet 2004; 363: 157-63*
Classification of Overweight and Obesity by BMI, Waist Circumference and Associated Disease Risks

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Obesity Class</th>
<th>Disease Risk Relative to Normal Weight and Waist Circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>--</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 – 24.9</td>
<td>--</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 – 29.9</td>
<td>Increased, High</td>
</tr>
<tr>
<td>Obesity</td>
<td>30.0 – 34.9</td>
<td>I High, Very High</td>
</tr>
<tr>
<td>Extreme Obesity</td>
<td>&gt;40</td>
<td>III Extremely High, Extremely High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnic specific values for waist circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country/Ethnic group</strong></td>
</tr>
<tr>
<td>Europids</td>
</tr>
<tr>
<td>In USA, ATP III values 102 cm (40 inches) male; 88 cm (35 inches) females</td>
</tr>
<tr>
<td>South Asians (Based on a Chinese, Malay and Asian-Indian population)</td>
</tr>
<tr>
<td>Chinese</td>
</tr>
<tr>
<td>Japanese</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>


Visceral Adiposity: The Critical Adipose Depot

Subcutaneous Fat
Abdominal Muscle Layer
Intra-Abdominal Fat

Intra-abdominal adiposity is closely correlated with abdominal obesity

To assess IAA, the simplest measure of abdominal obesity is waist circumference, which is strongly correlated with direct measurement of IAA by CT scan or MRI, considered to be the gold standard.

IAA: intra-abdominal adiposity

Despres JP et al., 2001; Pouliot MC et al., 2004
Central Obesity

- **IDF:**
  - Central obesity - waist circumference >94 cm for Europid men, >80 Europid women with ethnicity specific values for other groups
- **WHO:**
  - Waist-hip ratio >0.9 - men or >0.85 - women
- **ATP III:**
  - Waist circumference >40 in. - men,
    > 35 in. - women

Use of Waist Circumference

- Independent predictor of disease risk over and above BMI for individuals with a BMI < 35
- Central obesity is a prerequisite risk factor for metabolic syndrome which can be easily assessed using waist circumference.
Metabolic Syndrome: IDF Consensus Definition (2005)

Central Obesity

<table>
<thead>
<tr>
<th>Waist circumference</th>
<th>Ethnicity specific*</th>
<th>Male ≥ 94 cm</th>
<th>Female ≥ 80</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>for Europids</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Plus any two of the following:

- **Raised Triglycerides**: ≥150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
- **Low HDL Cholesterol**: <40 mg/dL (1.03 mmol/L) in males <50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
- **Raised blood pressure**: Systolic: ≥130 or Diastolic: ≥85 mmHg or Treatment of previously diagnosed hypertension
- **Impaired fasting glycaemia**: Fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

Global cardiometabolic risk*

* working definition

*Gland EV et al, 2006; Vasudevan AR et al, 2005*
Abdominal obesity and increased risk of cardiovascular events

The HOPE study

- Adjusted relative risk
- Men: 1.17, 1.16, 1.14
- Women: 1.29, 1.27, 1.35

CVD death, MI, All-cause deaths

- Tertile 1: <95
- Tertile 2: 95–103
- Tertile 3: >103

Waist circumference (cm)

INTERHEART: Waist-to-Hip Ratio Is a Better Predictor for MI Than BMI

- Adjusted for age, sex, smoking, and other INTERHEART risk factors
- Adjusted for all other INTERHEART risk factors

MI = myocardial infarction
WHR = waist-to-hip ratio
BMI = body mass index
Vertical bars = 95% CIs

Body Fat Percentage Recommendations

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Healthy Range of Body Fat for Females</th>
<th>Healthy Range of Body Fat for Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-40</td>
<td>21-33%</td>
<td>8-19%</td>
</tr>
<tr>
<td>41-60</td>
<td>23.35%</td>
<td>11-22%</td>
</tr>
<tr>
<td>61-79</td>
<td>24-36%</td>
<td>13-25%</td>
</tr>
</tbody>
</table>

New Guidelines for Obesity

- **Obesity 2- Guidelines (2013)**
  - Based on systematic evidence review
  - Promoted by AHA/ACC/TOS
- **AACE Algorithm-2013**
  - *Complications centric approach*
- ASBP Algorithm-2014
  - Holistic approach; practical
- ENDO Guideline Pharmacological Management of Obesity
  - Due in 2014
The AACE Advanced Framework for a New Diagnosis of Obesity

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Anthropometric Component</th>
<th>Clinical Component</th>
<th>Prevention/Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Weight</td>
<td>BMI &lt; 25kg/m²</td>
<td>No obesity-related complications</td>
<td>Primary</td>
</tr>
<tr>
<td>Overweight</td>
<td>BMI ≥ 25-29.9kg/m²</td>
<td>No obesity-related complications</td>
<td>Secondary</td>
</tr>
<tr>
<td>Obesity</td>
<td>BMI ≥ 30kg/m²</td>
<td>No obesity-related complications</td>
<td>Secondary</td>
</tr>
<tr>
<td>Obesity stage 1</td>
<td>BMI ≥ 25kg/m²</td>
<td>Presence of one or more mild-to-moderate obesity-related complications</td>
<td>Tertiary</td>
</tr>
<tr>
<td>Obesity stage 2</td>
<td>BMI ≥ 25kg/m²</td>
<td>Presence of one or more severe obesity-related complications</td>
<td>Tertiary</td>
</tr>
</tbody>
</table>
### Checklist of Obesity Related Complications

<table>
<thead>
<tr>
<th>Obesity Related Complication</th>
<th>Identification based on information available in initial evaluation</th>
<th>Possible secondary tested needed to confirm presence of complication, stage complication, or guide therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic Syndrome</td>
<td>waist circumference, blood pressure, triglycerides, HDL cholesterol, fasting glucose (ATPIII criteria)</td>
<td>initial evaluation completes diagnosis; screen for cardiovascular disease</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>fasting glucose</td>
<td>repeat fasting glucose completes diagnosis of impaired fasting glucose, but patient should be further evaluated with 2-hour oral glucose tolerance test to identify Prediabetes due to impaired glucose tolerance or Diabetes based on raised 2-hour glucose value and/or with HbA1C; screen for cardiovascular disease</td>
</tr>
<tr>
<td>Type 2 Diabetes Mellitus</td>
<td>fasting glucose</td>
<td>overly elevated or repeat fasting glucose completes diagnosis, but patients with moderate elevations in glycemia may require further evaluation with 2-hour oral glucose tolerance glucose value or HbA1C or both; screen for cardiovascular disease and microvascular complications</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>fasting triglycerides and HDL-c with lipid panel</td>
<td>initial evaluation completes diagnosis; lipoprotein subclasses may further define risk</td>
</tr>
</tbody>
</table>

---

### Checklist of Obesity Related Complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Identification</th>
<th>Possible secondary testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>systolic and diastolic sitting blood pressures</td>
<td>repeat blood pressure completes diagnosis; further testing may include ambulatory blood pressure monitoring; screen for complications of hypertension</td>
</tr>
<tr>
<td>Non-Alcoholic Fatty Liver Disease</td>
<td>liver examination, liver function tests</td>
<td>additional studies are needed for diagnosis: imaging, liver biopsy as indicated</td>
</tr>
<tr>
<td>Polycystic Ovary Syndrome</td>
<td>physical exam, review of systems</td>
<td>additional studies are needed for diagnosis: hormonal testing</td>
</tr>
<tr>
<td>Obstructive Sleep Apnea</td>
<td>physical exam, review of systems</td>
<td>additional studies are needed for diagnosis: naso-circumference, sleep study</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>physical exam, review of systems</td>
<td>additional studies are needed for diagnosis: radiographic imaging</td>
</tr>
<tr>
<td>Urinary Stress Incontinence</td>
<td>physical exam, review of systems</td>
<td>additional studies may be indicated: urology, urodynamics testing</td>
</tr>
<tr>
<td>Gastroesophageal Reflux Disease</td>
<td>physical exam, review of systems</td>
<td>additional studies may be indicated: endoscopy, esophageal motility</td>
</tr>
<tr>
<td>Disability/Immobility</td>
<td>physical exam, review of systems</td>
<td>initial evaluation may complete diagnosis, functional testing may be needed</td>
</tr>
<tr>
<td>Psychological Disorder and/or Stigmatisation</td>
<td>physical exam, review of systems</td>
<td>additional studies may be needed: psychological testing</td>
</tr>
<tr>
<td>Obesity secondary to genetic syndromes, hormonal disease, immunogenic medications</td>
<td>physical exam, review of systems</td>
<td>additional studies may be needed: genetic testing, hormonal testing</td>
</tr>
</tbody>
</table>
Staging of Obesity-Related Complications That Can Be Improved by Weight Loss

### A) Prerequisites, Metabolic Syndrome, and Type 2 Diabetes

<table>
<thead>
<tr>
<th>Stage 0 (none)</th>
<th>Stage 1 (mild/moderate)</th>
<th>Stage 2 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factors related to insulin-resistance (BMI, BP, HDL, TG, fasting glucose)</td>
<td>2 risk factors (BMI, BP, HDL, TG, CMDS stage 1)</td>
<td>3 or more risk factors (BMI, BP, HDL, TG, CMDS stage 2)</td>
</tr>
</tbody>
</table>

#### Hypertension

<table>
<thead>
<tr>
<th>Stage 0 (none)</th>
<th>Stage 1 (mild/moderate)</th>
<th>Stage 2 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP &lt; 120/80 mmHg</td>
<td>BP = 120/80 mmHg (in absence of other risk factors)</td>
<td>BP = &gt;120/80 mmHg (in high risk individual)</td>
</tr>
</tbody>
</table>

#### Hypoglycemic/Hyperglycemic Imbalance

<table>
<thead>
<tr>
<th>Stage 0 (none)</th>
<th>Stage 1 (mild/moderate)</th>
<th>Stage 2 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose &lt; 100 mg/dL</td>
<td>Fasting glucose = 100 mg/dL (in absence of other risk factors)</td>
<td>Fasting glucose &gt; 100 mg/dL (in high risk individual)</td>
</tr>
</tbody>
</table>

### B) Insulin Resistance and Type 2 Diabetes

<table>
<thead>
<tr>
<th>Stage 0 (none)</th>
<th>Stage 1 (mild/moderate)</th>
<th>Stage 2 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>Non-insulin-resistant</td>
<td>Insulin-resistant</td>
</tr>
</tbody>
</table>

### C) Metabolic Syndrome

<table>
<thead>
<tr>
<th>Stage 0 (none)</th>
<th>Stage 1 (mild/moderate)</th>
<th>Stage 2 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>Insulin resistance</td>
<td>Severe insulin resistance</td>
</tr>
</tbody>
</table>

### D) Non-Obstructive Pregnancy Obesity

<table>
<thead>
<tr>
<th>Stage 0 (none)</th>
<th>Stage 1 (mild/moderate)</th>
<th>Stage 2 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No obesity</td>
<td>Presence of obesity but no inflammation or fibrosis</td>
<td>Severe obesity (NODP)</td>
</tr>
</tbody>
</table>

### E) Polycystic Ovary Disease

<table>
<thead>
<tr>
<th>Stage 0 (none)</th>
<th>Stage 1 (mild/moderate)</th>
<th>Stage 2 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does not meet criteria: absence of PCOS</td>
<td>1 or 2 risk factors (BMI, BP, HDL, TG, CMDS stage 1)</td>
<td>3 or more risk factors (BMI, BP, HDL, TG, CMDS stage 2)</td>
</tr>
</tbody>
</table>

### G) Osteoarthritis

<table>
<thead>
<tr>
<th>Stage 0 (none)</th>
<th>Stage 1 (mild/moderate)</th>
<th>Stage 2 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms and no radiographic joint changes</td>
<td>Mild/moderate symptoms and functional impairment (e.g., validated questionnaires)</td>
<td>Moderate-severe symptoms and functional impairment (e.g., validated questionnaires)</td>
</tr>
</tbody>
</table>

### H) Stress and Urge Urinary Incontinence

<table>
<thead>
<tr>
<th>Stage 0 (none)</th>
<th>Stage 1 (mild/moderate)</th>
<th>Stage 2 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms and/or normal urodynamics</td>
<td>Mild/moderate symptom severity score</td>
<td>Severe symptom severity score</td>
</tr>
</tbody>
</table>

### I) Gastroesophageal Reflux Disease

<table>
<thead>
<tr>
<th>Stage 0 (none)</th>
<th>Stage 1 (mild/moderate)</th>
<th>Stage 2 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms or findings</td>
<td>Mild/moderate symptoms</td>
<td>Severe symptoms</td>
</tr>
</tbody>
</table>

B) Barrett's Esophagus (if not accompanied by progressive weight loss)
Figure 1.

AACE/ACE Diagnostic Algorithm for the Disease of Obesity

Screen with BMI and waist circumference

1. **Step 1**
   - Anthropometric Component
   - BMI 26
     - BMIs 25-29 and waist circumference above
     - Risk threshold for certain conditions
   - Overweight or Obesity
   - Physical examination, Review of Systems, Clinical Laboratory
   - BMI < 25
     - BMIs 23-25 and waist circumference below
     - Risk threshold for certain conditions
   - Normal Weight — No Obesity

2. **Step 2**
   - Clinical Component
   - Overweight or Obesity
     - Stage 0
   - No obesity related complications
   - One or more obesity related complications

Evaluation using complications-specific criteria
<table>
<thead>
<tr>
<th>Step 3</th>
<th>Complications Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity Stage 1</td>
<td>One or more complications mild to moderate in severity and/or may be treated effectively with a moderate degree of weight loss</td>
</tr>
<tr>
<td>Obesity Stage 2</td>
<td>At least one complication that is severe and/or requires more aggressive weight loss therapy for effective treatment</td>
</tr>
</tbody>
</table>

Step 4
Treatment based on clinical judgment

- Overweight/Obesity Stage 0
  - Intensive Lifestyle/Behavioral Therapy
  - Medications
  - Healthy meal pattern, Calorie reduction, Physical activity

- Obesity Stage 1
  - Intensive Lifestyle/Behavioral Therapy
  - Medications
  - Consider Bariatric Surgery

- Obesity Stage 2
  - Intensive Lifestyle/Behavioral Therapy
  - Medications
  - Consider Bariatric Surgery
Goals for Weight Loss

“The initial goal of weight loss therapy for overweight patients is a reduction in body weight of about 10%…moderate weight loss of this magnitude can significantly decrease the severity of obesity-associated risk factors.”

NIH recommends 10% weight loss over the course of 6 months as a goal for clinically meaningful differences in patients health.
Recommended Methods for Weight Loss

- Create an energy deficit through caloric restriction, physical activity, or both.
- Energy deficit of $\geq 500$ kcal/day typically may achieved with dietary intake of 1,200-1,500 kcal/day for women and 1,500-1,800 kcal/day for men.
- Choice of calorie restricted diet can be individualized based on the patient’s preference and health status.
- VLCD ($< 800$ kcal/day) should be used only in limited circumstances with medical supervision and a high-intensity lifestyle intervention can be provided.
- Monitor patient’s requirements for medication change as weight loss progresses.
## Weight Loss Drugs (FDA Approved)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Drug</th>
<th>Placebo</th>
<th>Net Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>6.8</td>
<td>2.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>6.5</td>
<td>3.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Phendimetrazine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzphetamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orlistat</td>
<td>7.3</td>
<td>5.0</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Off Label</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>4.8</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Topiramate</td>
<td>4.5</td>
<td>1.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Bupropion</td>
<td>6.0</td>
<td>2.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Metformin</td>
<td>2.5</td>
<td>0.5</td>
<td>2.0</td>
</tr>
</tbody>
</table>

George a. Bray, MD; Bariatric Challenge, January 9, 2010

## Combination Drugs and New Single Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Drug</th>
<th>Placebo</th>
<th>Net</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tesofensine (not approved)</td>
<td>11.2</td>
<td>2</td>
<td>9.2</td>
</tr>
<tr>
<td>Lorcaserin (FDA approved 7/12/12)</td>
<td>8.2</td>
<td>3.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Liraglutide (FDA committee 14/1 approved 9/10/14)</td>
<td>7.2</td>
<td>2.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Phentermine/fenfluramine (fenfluramine off market)</td>
<td>15</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Ephedrine/caffeine (ephedrine off market)</td>
<td>18</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Bupropion/naltrexone (FDA approved 9/10/14)</td>
<td>8.2</td>
<td>1.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Phentermine/topiramate (FDA approved 7/17/12)</td>
<td>14.7</td>
<td>2.5</td>
<td>12.2</td>
</tr>
<tr>
<td>Amylin/leptin (not approved)</td>
<td>12.7</td>
<td>8.4</td>
<td>4.3</td>
</tr>
</tbody>
</table>
Lorcaserin (Belviq)

- Serotonergic weight loss drug
- Selective 5-HT$_{2c}$ receptor agonist
- Appetite suppression occurs by activation of receptors on the POMC/CART neurons located in arcuate nucleus
- Activates 5-HT$_{2c}$ not 5-HT$_{2a}$, 5-HT$_{2b}$, or other 5-HT receptor subtypes
- Fenfluramine withdrawn by FDA 1997 (valvular heart disease and pulmonary hypertension); active metabolites activates 5-HT$_{2b}$ receptors (which are plentiful on heart valves)

BLOOM$^1$, BLOSSOM$^2$, BLOOM-DM$^3$ Trials

- Involved 7648 overweight and obese individuals
- 3 trials revealed that the combination of lorcaserin with lifestyle intervention resulted in significantly greater reductions in weight, BMI, and waist circumference than the combination of placebo with lifestyle intervention
- Mean reductions in weight ranged from 4.7kg to 5.8kg over 1 year for lorcaserin 10mg bid (FDA approved dose)
- > 5% weight loss with lorcaserin vs placebo (37.5% to 47.5% vs 16.1% to 25%, respectively)
- BLOOM-DM trial included diabetics only, lorcaserin 10mg once or twice daily led to significant improvement in A-1-C levels compared with placebo (-1.0% vs -0.9% vs -0.4%, respectively; $P < .001$ for both doses of lorcaserin vs placebo)

**BLOOM¹, BLOSSOM², BLOOM-DM³ Trials**

- Most common adverse reactions reported were headache, dizziness, fatigue, nausea, dry mouth, and constipation
- In patients in the BLOOM-DM trials; hypoglycemia, headache, back pain, cough, and fatigue was the most common adverse reactions
- Across the 3 trials, valvulopathy occurred in 2.73% on lorcaserin and 2.04% on placebo
- Concern is the use of lorcaserin with other serotenergic medications due to risk of serotonin syndrome
- Lorcaserin should be discontinued after 12 weeks if the patient has not lost > = 5% weight


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**Phentermine/topiramate (Qsymia)**

- Once daily combination of phentermine and extended-release (ER) topiramate
- Most effective medication available, 10-12% weight loss
- Phentermine; sympathomimetic amine, reduced hunger from release of catecholamines in the hypothalamus
- Topiramate ER, delayed release suppresses appetite and enhance satiety by augmenting GABA activity, modulation of voltage-gated ion channels, and inhibition of carbonic anhydrase
- Most commonly observed side effects; dry mouth, constipation, parasthesias, and dysgeusia.
- Monthly pregnancy test at baseline and monthly while on the drug.
CONQUER, SEQUEL, EQUIP Trials

- 4426 overweight or obese individuals
- Results of the 3 trials revealed the combination of diet/lifestyle with phentermine/topiramate ER, (doses of 3.75mg/23mg, 7.5mg/46mg, or 15mg/92mg once a day) yielded significantly greater reductions in body weight and waist circumference than the combination of diet/lifestyle intervention with placebo
- Mean weight loss ranged from 5.1% with 3.75mg/23mg dose to 10.9% with 15mg/92mg dose, and 1.6% with placebo
- > 5% weight loss occurred at all 3 doses of phentermine/topiramate ER compared to placebo (ranging from 44.9% to 79.3% phentermine/topiramate ER and 17.3% to 30% for placebo)

Clinical Approval Trials for Qsymia

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Number of patients</th>
<th>Study population</th>
<th>Medication treatment arms</th>
<th>Study duration</th>
<th>Mean % weight loss from baseline in maximum dose group</th>
<th>% of subjects with at least 5% weight loss in maximum dose group</th>
<th>% of subjects with at least 10% weight loss in maximum dose group</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQUIP**</td>
<td>1287</td>
<td>SMI ≥ 35</td>
<td>3.75mg/23 mg and 7.5mg/5mg</td>
<td>56 weeks</td>
<td>14.4</td>
<td>67</td>
<td>47</td>
</tr>
<tr>
<td>EQUIPELL10</td>
<td>756</td>
<td>Non-diabetic, BMI ≥ 35</td>
<td>7.5mg/46 mg and 15mg/92mg</td>
<td>28 weeks</td>
<td>9.2</td>
<td>46.8</td>
<td>40</td>
</tr>
<tr>
<td>CONQUIER**</td>
<td>2487</td>
<td>SMI ≥ 37 and BMI ≥ 40</td>
<td>7.5mg/46 mg and 15mg/92mg</td>
<td>56 weeks</td>
<td>12.4</td>
<td>70</td>
<td>40</td>
</tr>
<tr>
<td>SEQUEL*</td>
<td>676</td>
<td>Same as CONQUIER</td>
<td>Same as CONQUIER</td>
<td>3 yrs</td>
<td>10.5</td>
<td>79.1</td>
<td>52.9</td>
</tr>
</tbody>
</table>

Qnexa®: 24 Week Weight Loss
Topiramate and Phentermine (ITT)

![Graph showing weight loss over time for different treatments.]

Conquer Trial (56 week phase 3 trial)

- 2487 overweight and obese adults (18-70 y/o), BMI 27-45 c/\( \geq \) (2) comorbidities assigned to placebo, once daily (phentermine/topiramate) 7.5/46 mg (mid-dose) or 15/92 mg (high-dose).
- 994 assigned to placebo, 498 to mid-dose, and 995 to high-dose.
- At 56 weeks, change in body weight: -1.4 kg, placebo; -8.1 kg, mid-dose; -10.2 kg, high-dose.
- Patients achieving at least 5% weight loss were: 21%, placebo; 62%, mid-dose; 70%, high-dose
- Patients achieving at least 10% weight loss were: 7%, placebo; 37%, mid-dose; 48%, high-dose.
- Annualized incidence rates for progression to T2DM among patients without T2DM at baseline were: 3.7%, placebo; 1.7%, mid-dose; 0.9%, high-dose.

Naltrexone/bupropion (Contrave)

- Reduces food intake by acting on adrenergic and dopaminergic receptors in the hypothalamus.
- Naltrexone is an opioid receptor antagonist with minimal effect of weight loss when used alone.
- Rationale for using naltrexone with bupropion; naltrexone blocks the inhibitory influences of opioid receptors activated by the β-endorphins released by the hypothalamus.
- Blocking of β-endorphins amplifies the effects of bupropion which stimulates the activity of α-melanocyte stimulating hormone to inhibit food intake.
Naltrexone/bupropion (Contrave)

- All four trials in the COR Phase 3 program (COR-I, COR-II, COR-BMOD and COR-Diabetes) were randomized, double-blind, placebo-controlled trials.
- The co-primary endpoints were the proportion of patients achieving at least 5% weight loss and percent change in body weight compared to placebo.
- Secondary endpoints included multiple measures of cardiometabolic risk, quality of life, control of eating, and glycemic control.

COR-I Phase 3 Study

- 56-week placebo-controlled, double-blind randomized trial enrolling patients whose BMI was 30-45 with uncomplicated obesity, or BMI 27-45 with controlled hypertension or dyslipidemia, or both.
- 1742 patients were randomized to receive either Contrave32, Contrave16 (16mg naltrexone SR/360mg bupropion SR), or placebo in a 1:1:1 ratio.
- 62% of the patients completing study (Contrave32) lost at least 5% of body weight compared to 23% of patients on placebo.
- 34% of patients completing the study(Contrave32) lost at least 10% of body weight as compared to 11% on placebo.
**Contrave™ COR-I Phase 3 Mean Weight Loss**

*56 Weeks – Completer Population*

- Naltrexone SR/Bupropion SR

**COR-I Phase 3 Study**

- Significant improvements over placebo in waist circumference, insulin resistance, HDL cholesterol, triglycerides, and hsCRP.
- Significant improvements in patient-reported control of eating, including reduced food cravings and reduced difficulty resisting food cravings.
- The most frequently observed treatment-emergent adverse events in COR-I included nausea, headache, constipation and upper respiratory tract infection.
Liraglutide (Saxenda) phase 3a obesity trial

- 3,731 overweight or obese individuals randomized 2:1 to treatment with liraglutide 3mg or placebo, both in combination with diet and exercise
- Patients without signs of prediabetes treated x 56 weeks, followed by a 12 week follow-up period
- Average mean baseline weight 106 kg and BMI of 38
- Average weight loss for those treated with liraglutide 3mg, 8% compared to 2.6% for placebo
- Proportion achieving 5% weight loss, 64%, liraglutide, and 27% for placebo
- Proportion achieving 10% weight loss, 33%, liraglutide, and 10% for placebo

Empatic™ Phase Llb Mean Weight Loss
24 Weeks – Completer Population
Zonisamide sustained release (SR) and Bupropion SR
# Weight Loss Medications Recently Evaluated or Approved by the FDA

<table>
<thead>
<tr>
<th>Obesity Drug</th>
<th>Trade Name</th>
<th>Mechanism</th>
<th>Proposed Dosage</th>
<th>Phase 3 Clinical Trials</th>
<th>Average Expected Weight Loss</th>
<th>Most Common Adverse Events</th>
<th>Safety Concern Raised by the FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorcaserin</td>
<td>Belviq</td>
<td>Selective serotonin 2C receptor agonist</td>
<td>10 mg BID</td>
<td>BLOSSOM, BLOOM, BLOOM-DM</td>
<td>Drug, 5-6%; placebo, 2-3%</td>
<td>Headache, nausea, dizziness, fatigue</td>
<td>Carcinogenicity, valvulopathy, cardiovascular risk</td>
</tr>
<tr>
<td>PHEN/TPM</td>
<td>Qsymia</td>
<td>Sympathomimetic amine and anticonvulsant agent</td>
<td>Low, 3.75/23 mg, mid, 7.5/46 mg; high, 15/92 mg QD</td>
<td>EQUATE, EQUIP, CONQUER, SEQUEL</td>
<td>Drug, 5-11%; placebo, 1-2%</td>
<td>Headache, paraesthesia, dry mouth, altered taste, dizziness</td>
<td>Depression, cognitive issues, CV risk from increased heart rate, birth defects</td>
</tr>
<tr>
<td>Bupropion SR/ naltrexone SR</td>
<td>Contrave</td>
<td>Dopamine &amp; norepinephrine reuptake inhibitor &amp; opioid receptor antagonist</td>
<td>Sustained release 160/32 mg QD</td>
<td>COR-I, COR-II, COR-BMOD, COR-Diabetes</td>
<td>Drug, 5-6%; placebo, 1-2%</td>
<td>Nausea, headache, insomnia, constipation, tremor</td>
<td>Cardiovascular risk from increased blood pressure and heart rate</td>
</tr>
</tbody>
</table>

*J Clin Endocrinol Metab, April 2013*
Bariatric/Metabolic Surgery 2013

55% 28% 15% 2%

Comparative Mortality

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniotomy</td>
<td>10.7%</td>
</tr>
<tr>
<td>Esophagectomy</td>
<td>9.1%</td>
</tr>
<tr>
<td>Pancreatectomy</td>
<td>8.3%</td>
</tr>
<tr>
<td>Peds Heart</td>
<td>5.4%</td>
</tr>
<tr>
<td>Aortic Aneurysm</td>
<td>3.9%</td>
</tr>
<tr>
<td>CABG</td>
<td>3.5%</td>
</tr>
<tr>
<td>Hip Replacment</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

BARIATRIC SURGERY
0.28%

Conclusion

• Obesity is currently under-recognized and under-treated.

• Physicians need to identify and evaluate the overweight and obese patient at an earlier stage of development.

• Screening begins by measuring the BMI, a good predictor of underlying body fat and future morbidity and mortality.

• Anthropometric measurements such as waist circumference, WHR, and percent body fat may help identify those with normal weight, overweight, and obese at risk for metabolic syndrome and the development of diabetes.

• Treatment always includes lifestyle modification. Consideration for pharmacotherapy and surgery is based upon the individual patient.
References


TOPIC: New obesity algorithm

Question 1 of 6

You're right!

A. Theory
   (chosen by 1% of respondents)
B. Eating disorder
   (chosen by 13% of respondents)
C. Disease
   (chosen by 93% of respondents)
D. None of the above
   (chosen by 3% of respondents)

Explaination

Obesity was declared a disease by the AMA in 2013. A new algorithm for the diagnosis and treatment of obesity emerged from the American Association of Clinical Endocrinologists and the American College of Endocrinology (ACE/ACE) 2014 Consensus Conference on Obesity.

To read the full article, click here: "New obesity algorithm reduces complications in addition to BMI."

Next Question

TOPIC: New obesity algorithm

Question 2 of 6

You're right!

A. True
   (chosen by 84% of respondents)
B. False
   (chosen by 16% of respondents)

Explaination

According to the American Association of Clinical Endocrinologists and the American College of Endocrinology (ACE/ACE) leaders, BMI alone isn't enough to characterize obesity and the impact of obesity-related complications into the screening and treatment plans.

To read the full article, click here: "New obesity algorithm reduces complications in addition to BMI."

Next Question
TOPIC: New obesity algorithm

Question 3 of 5

You're right!

A. BMI of at least 30, with no obesity-related complications
done by 46% of respondents

B. BMI of at least 35 with one more complications that are mild to moderate in severity
done by 40% of respondents

C. BMI of greater than or equal to 25 and one or more severe complications
done by 14% of respondents

Next Question

Explanation

Under the new framework put forth by the AASCE, the diagnostic categories of obesity would be defined as:

- Obesity Stage 1: BMI of at least 30, with no obesity-related complications
- Obesity Stage 2: BMI of at least 35 and one or more complications mild to moderate in severity
- Obesity Stage 3: BMI of greater than or equal to 25 and one or more severe complications

To read the full article, click here: [New obesity algorithm moves complications in addition to BMI.]}

Next Question

TOPIC: New obesity algorithm

Question 4 of 5

You're right!

A. BMI screening and adjusting for ethnic differences
done by 5% of respondents

B. Clinical evaluation for the presence of obesity-related complications, using a checklist
done by 11% of respondents

C. Staging for the severity of complications using complication-specific criteria
done by 9% of respondents

D. Selection of prevention and/or intervention strategies targeting specific complications
done by 15% of respondents

E. All of the above
done by 94% of respondents

Next Question

Explanation

The AASCE is proposing new algorithms on diagnosing, staging and treating overweight and obese patients. The four-step diagnostic and treatment approach includes:

- BMI screening and adjusting for ethnic differences
- Clinical evaluation for the presence of obesity-related complications
- Staging for the severity of complications using complication-specific criteria
- Selection of prevention and/or intervention strategies targeting specific complications

To read the full article, click here: [New obesity algorithm moves complications in addition to BMI.]
TOPIC: New obesity algorithm

Question 5 of 5

You're right!

A. Bariatric surgery
   (chosen by 9% of respondents)

B. Lifestyle intervention
   (chosen by 0% of respondents)

C. Medications
   (chosen by 0% of respondents)

D. All of the above
   (chosen by 100% of respondents)

Explaination

The American Association for bariatric surgery has released a new algorithm to diagnose and treat obesity. The algorithm helps healthcare providers identify patients who are candidates for bariatric surgery.

To read the full article, click here: http://www.bariatrictimes.com/algorithm/

Cleveland Clinic