Medical Management of Obesity: Options for Treatment in Clinical Practice

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American College of Physicians, Maryland Chapter
Annual Conference February 1, 2013
Objectives

• Define obesity and its role in chronic disease

• Examine rationale behind treating obesity

• Review lifestyle modification for treatment of obesity

• Review medical approaches to treating obesity
Weight Classification

BMI:   <18.5
       18.5 - 24.9
       25.0 - 29.9
       30.0 - 34.9
       35.0 - 39.9
       >40

Underweight    Normal     Overweight    Obesity I    Obesity II    Obesity III

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

Formula: Weight (lb) x 703 ÷ Height (in)^2

www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/
Overweight and Obesity Trends Among U.S. Adults aged 20-74 years (1960-2008)

Overweight

Obese

Extremely Obese

Years


Percent

**OBESITY**

- 72 million adults, 2007-08
  - 34.4% Overweight  
    - BMI 25-29.9
  - 33.9% Obese  
    - BMI >30
  - 5.7% Extremely obese  
    - BMI >40

- 1.68 million Maryland residents (28.8%), 2011

**DIABETES**

- 79 million adults with pre-diabetes (36%)
- 25.8 million adults and children with diabetes (8.3%)

Over 85% of diabetics are overweight, over 50% obese

**HEART DISEASE**

**LEADING CAUSE OF DEATH**

- 631,636 people died of heart disease, 2006
- 26% of all U.S. deaths - more than one in four

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2. Healthyamericans.org
Relationship Between BMI and Risk of Type 2 Diabetes Mellitus

Disease Prevalence Attributable to Obesity

- Type 2 Diabetes: 61%
- Endometrial Cancer: 34%
- Gallbladder Disease: 30%
- Osteoarthritis: 24%
- Hypertension: 17%
- CHD: 17%
- Breast Cancer: 11%
- Colon Cancer: 11%

* Obesity defined as BMI \( \geq 29.9 \text{ kg/m}^2 \)

Overweight and Obesity Increase the Risk of Total and Cardiovascular Disease Mortality

Data are from 1 million men and women followed for 16 years with an average age of 57 who never smoked and had no history of disease at enrollment.

Healthcare Costs

Obesity
• $147 billion (2008)\(^1\)
• 1.5x higher for obese person

Heart Disease
• $316.4 billion (2010)\(^2\)

Diabetes
• $218 billion (2007)\(^3\)
• 2-3x higher for diabetic person

## Adult Obesity Prevalence in Maryland (2010)

<table>
<thead>
<tr>
<th>County</th>
<th>Adults (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montgomery</td>
<td>17.5</td>
</tr>
<tr>
<td>Howard</td>
<td>22.4</td>
</tr>
<tr>
<td>Queen Anne's</td>
<td>23.7</td>
</tr>
<tr>
<td>Carroll</td>
<td>25.6</td>
</tr>
<tr>
<td>Frederick</td>
<td>26.2</td>
</tr>
<tr>
<td>Talbot</td>
<td>26.6</td>
</tr>
<tr>
<td>Baltimore County</td>
<td>27.1</td>
</tr>
<tr>
<td>Anne Arundel</td>
<td>27.4</td>
</tr>
<tr>
<td>Harford</td>
<td>27.4</td>
</tr>
<tr>
<td>St. Mary’s</td>
<td>28.1</td>
</tr>
<tr>
<td>Worcester</td>
<td>28.5</td>
</tr>
<tr>
<td>Kent</td>
<td>28.8</td>
</tr>
<tr>
<td>Washington</td>
<td>28.9</td>
</tr>
<tr>
<td>Garrett</td>
<td>29.2</td>
</tr>
<tr>
<td>Caroline</td>
<td>29.7</td>
</tr>
<tr>
<td>Calvert</td>
<td>31.1</td>
</tr>
<tr>
<td>Allegeny</td>
<td>31.6</td>
</tr>
<tr>
<td>Baltimore City</td>
<td>32.0</td>
</tr>
<tr>
<td>Charles</td>
<td>32.1</td>
</tr>
<tr>
<td>Wicomico</td>
<td>32.5</td>
</tr>
<tr>
<td>Cecil</td>
<td>33.1</td>
</tr>
<tr>
<td>Prince George’s</td>
<td>33.3</td>
</tr>
<tr>
<td>Dorchester</td>
<td>36.7</td>
</tr>
<tr>
<td>Somerset</td>
<td>41.6</td>
</tr>
</tbody>
</table>

Adapted from: Maryland DHMH, BRFSS-2008-2010 Cumulative Results
[www.marylandbrfss.org](http://www.marylandbrfss.org)
<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Gender</th>
<th>Obesity Rate</th>
<th>Diabetes Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic Whites</td>
<td>Males</td>
<td>31.9%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Hispanics</td>
<td></td>
<td>34.3%</td>
<td>11.8%</td>
</tr>
<tr>
<td>African Americans</td>
<td></td>
<td>37.3%</td>
<td>12.6%</td>
</tr>
<tr>
<td>Obese (Females)</td>
<td></td>
<td>33.0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Hispanics</td>
<td></td>
<td>43.0%</td>
<td>11.8%</td>
</tr>
<tr>
<td>African Americans</td>
<td></td>
<td>49.7%</td>
<td>12.6%</td>
</tr>
</tbody>
</table>

Rationale for Treating Obesity
Weight Loss Reduces Risk of Type 2 DM in Subjects with IGT

<table>
<thead>
<tr>
<th>Study</th>
<th>Type 2 DM Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Da Qing IGT and Diabetes Study(^1) (Diet and exercise)</td>
<td>42%</td>
</tr>
<tr>
<td>Finnish Diabetes Prevention Study(^2) (Diet and exercise)</td>
<td>58%</td>
</tr>
<tr>
<td>US Diabetes Prevention Program(^3) (Diet and exercise)</td>
<td>58%</td>
</tr>
<tr>
<td>XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study(^4) (orlistat)</td>
<td>37%</td>
</tr>
</tbody>
</table>


DPP: lifestyle interventions are more effective than medications

Slide courtesy of Dr. Caroline Apovian
DPP: “Dose Response”
of Diabetes Risk Reduction

At 15 kg of weight loss, the risk
of diabetes is approximately 2%

For every 2.2 lbs (1 kg) of weight loss there is
a 16% reduction in the risk of developing diabetes

N= 1079 overweight/obese subjects (BMI > 24 kg/m²) with IGT (25 – 84 years of age)
Slide courtesy of Dr. Caroline Apovian
DPP: Intensive Lifestyle Intervention (ILI) and Weight Loss

**GOAL:** 7% loss initial weight

**DIET**
- Low fat (< 30% energy)
- Reduced energy (1200-1800 kcal/d)
- Conventional Foods, Ad libitum

**ACTIVITY**
- 150 min/week or more of moderate intensity exercise

**COUNSELING**
- Weight Loss Phase (6 month):
  - 16 individual visits every 1-2 weeks
- Maintenance Phase:
  - Individual visits every 2 months
  - Group classes (3 sessions/year)
  - Online resources

**ILI PROGRAM**

3234 subjects in total; N = 1079 overweight/obese subjects with IGT (95-125 mg/dl), ages 25 - 84 yr

Hamman RF. *Diabetes Care*. 2006;29:2102-2107.
Look AHEAD – Four Year Results

- Multicenter randomized clinical trial – can loss > 7% initial weight along with increased activity reduce incidence of major CVD events?
- Overweight or obese subjects with type 2 DM (59.5% female, mean age 58.7)
- Diet = 1200-1800 kcal/day, less than 30% fat (10% saturated), used meal replacements
- 2 Arms = Usual care (DM support + education) versus usual care + ILI
- Study stopped October 2012 due to failure to show benefit (6.5 yrs)

<table>
<thead>
<tr>
<th></th>
<th>Lifestyle Intervention Group (n=2,496)</th>
<th>Diabetes Support and Education Group (n=2,649)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Loss</td>
<td>-6.15%</td>
<td>-0.88%</td>
<td>(P &lt; .001)</td>
</tr>
<tr>
<td>Treadmill Fitness</td>
<td>12.74%</td>
<td>1.96%</td>
<td>(P &lt; .001)</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>-0.36%</td>
<td>-0.09%</td>
<td>(P &lt; .001)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-5.33 mm Hg</td>
<td>-2.97 mm Hg</td>
<td>(P &lt; .001)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-2.92 mm Hg</td>
<td>-2.48 mm Hg</td>
<td>(P = .01)</td>
</tr>
<tr>
<td>HDL</td>
<td>3.67</td>
<td>1.97 mg/dL</td>
<td>(P &lt; .001)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-25.56 mg/dL</td>
<td>-19.75 mg/dL</td>
<td>(P &lt; .001)</td>
</tr>
<tr>
<td>LDL*</td>
<td>-11.27 mg/dL</td>
<td>-12.84 mg/dL</td>
<td>(P = .009)</td>
</tr>
</tbody>
</table>

* Reductions in LDL cholesterol levels were greater in DSE than ILI participants owing to greater use of medications to lower lipid levels in the DSE group.

Weight loss needed to achieve normoglycemia in untreated Type 2 DM is massive and influenced by initial BG control.
Obesity Treatment
What Works?

1) Surgery
2) Medications
3) Diet

In that order!
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>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet, Exercise, Behavior Modification</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Medication</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td>With co-morbidity</td>
<td></td>
<td></td>
<td>With co-morbidity</td>
</tr>
<tr>
<td>Comorbidities include diabetes, HTN, OSA, dyslipidemia or high-risk feature such as waist circumference (F&gt;35in, M&gt;40in)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dieting: Which is Best?

• Two recent studies, same results

• Compared popular diets: Atkins, Zone, Weight Watchers, Ornish, Mediterranean, low-fat

ADHERENCE is more important than the diet itself

USPTF: Evidence-based Diet Modification

• Consume meals and snacks at regular intervals

• Reduce intake of sugar-sweetened beverages (soda, juice)

• Reduce energy intake by 500-1000 calories/day
  Women:  1200-1500 kcal/day
  Men: 1500-1800 kcal/day

• Limit calories from fat to < 30%

• Limit alcohol intake

• Consider meal replacements

DPP Research Group, NEJM 2002.
Behavioral Interventions

• Modify current eating and activity habits
• Learn new habits via individual or group-based education
• Record food intake, activity and weight for the purpose of review and feedback
• Set realistic goals for WL and behavior change
• Session frequency directly impacts success

DPP Research Group, NEJM 2002.
Monitor Adherence

Keeping a Food/Activity Record

- Self-monitoring is a strategy to increase a person's awareness of targeted behaviors and the circumstances that surround those behaviors\(^1\)

- Patients who self-monitor lose more weight on average than those who don’t\(^1,2\)

- Record food intake and physical activity *regularly* during weight loss, *periodically* during maintenance\(^2\)

- Review records during visits and provide feedback

- Encourage use of online software or apps
  - My PAL, My FitnessPal
  - Calorie King, Calorie Counter

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Encourage Regular Exercise

- **Goal > 150 minutes of moderate exercise or equivalent per week**
  1, 2
- Helps to prevent weight re-gain
- Pre-exercise safety counseling, EKG, stress-testing where appropriate
- Set goals based on baseline level of fitness

2. USPTF Executive Summary, 2011.
Set realistic goals for your patients

• Most individuals can expect to lose 5–10% of their starting weight over the course of 6-12 months.

• Rates of weight loss vary among individuals, but on average:
  - Calorie-deficit diet: 0.2-1% weight/week (0.5-2lbs/week)
  - VLC Ketogenic Diet: >2% weight/week (3-8 lbs/week)

• Improves attrition and trust. Remember, no one will be disappointed if they exceed their WL goals!

Encourage 5-10% weight loss
Rate: 1-2 lbs/week
Average weight loss of subjects completing a minimum 1-year weight loss intervention

Meta-analysis of 80 studies (n=26,455; 18,199 completers)

Combination Therapy is Most Effective

- **Individualize** diet for best adherence

- Monthly visits with PCP, combined with weight loss medication and the patient’s use of food records, can lead to a clinically significant weight loss

- **Accountability** is key

Consider Pharmacotherapy

- Does patient have BMI ≥ 30 or BMI ≥ 27 with comorbid conditions?

- Are there any contraindications to medications?

- Will medication enhance the likelihood of success? **YES!**
  - Enhances success of diet + exercise
  - Improves attrition and adherence rates

- **Limited Insurance Coverage of Obesity Drugs**
  - Medicare Part D: excluded
  - Medicaid: only 10 states, Maryland is not one of them
  - Private Payers: about 30% of plans reimburse
# 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>Adipex</td>
<td>Phentermine</td>
<td>6.8 kg</td>
<td>4.0 kg</td>
</tr>
<tr>
<td></td>
<td>Orlistat</td>
<td>7.3 kg</td>
<td>3.0 kg</td>
</tr>
<tr>
<td></td>
<td>Topiramate</td>
<td>4.5 kg</td>
<td>2.8 kg</td>
</tr>
<tr>
<td></td>
<td>Bupropion</td>
<td>6.0 kg</td>
<td>3.2 kg</td>
</tr>
<tr>
<td></td>
<td>Topiramate/phentermine</td>
<td>14.7 kg</td>
<td>12.2 kg</td>
</tr>
<tr>
<td>Qsymia</td>
<td>Bupropion/naltrexone</td>
<td>8.2 kg</td>
<td>6.2 kg</td>
</tr>
<tr>
<td></td>
<td>Bupropion/zonisamide</td>
<td>7.2 kg</td>
<td>4.3 kg</td>
</tr>
<tr>
<td></td>
<td>Pramlintide/metreleptin</td>
<td>12.7 kg</td>
<td>12.7 kg (vs. No placebo)</td>
</tr>
<tr>
<td>Contrave</td>
<td>Lorcaserin</td>
<td>8.2 kg</td>
<td>4.8 kg</td>
</tr>
<tr>
<td>Empatic</td>
<td>Liraglutide</td>
<td>7.2 kg</td>
<td>4.4 kg</td>
</tr>
<tr>
<td></td>
<td>Cetilistat</td>
<td>4.3 kg</td>
<td>1.5 kg</td>
</tr>
<tr>
<td></td>
<td>Tesofensine</td>
<td>11.2 kg</td>
<td>9.2 kg</td>
</tr>
<tr>
<td></td>
<td>Velneperit</td>
<td>7.1 kg</td>
<td>2.8 kg</td>
</tr>
</tbody>
</table>

**Phentermine**

**Mechanism**
- Increases norepinephrine (via CART)

**Contraindications**
- Pregnancy or breastfeeding
- Hyperthyroidism or mania
- Cardiovascular disease, CHF, HTN
- Glaucoma or equivalent
- Renal or liver disease

**Side Effects**
- Dry mouth, headache
- Nervousness, insomnia
- Tachycardia, hypertension
- Increased intraocular pressure
- Changes in libido, bowel habits
- Hypoglycemia

**Dosing**
- Available 15, 30, and 37.5 mg
- Tablet, capsule, and rapid-acting lozenge
- Dosing 1-2x/day, typically before breakfast
- Start at 15 or 18.75 mg/day x 1 week
- Can increase to 30 or 37.5 mg as needed
- FDA Approved for use up to 3 months
Long-term weight and cardiovascular effects of phentermine therapy

Qsymia (topirimate/phentermine)

**Mechanism**
- Increases norepinephrine (via CART)
- Potentiates GABA, antagonizes AMPA

**Contraindications**
- Pregnancy or breastfeeding
- Hyperthyroidism
- Severe renal or liver disease
- Glaucoma or equivalent

**Side Effects**
- Dry mouth
- Nervousness, insomnia
- Increased intraocular pressure
- Metabolic acidosis*
- Suicidal ideation, mood changes*
- URI or nasal symptoms*

**Dosing**
- Start 3.75/23 mg dose x 2 weeks
- Titrate dose up every 8-12 weeks
- FDA Approved for use up to 1 year

**Contraindications**
- Pregnancy or breastfeeding
- Hyperthyroidism
- Severe renal or liver disease
- Glaucoma or equivalent
Pivotal 1-Year Studies:
Weight Loss Over Time (Observed Data)

**EQUIP**
Time (Week)

**CONQUER**
Time (Week)

![Graphs showing weight change over time for Placebo, Qsymia Low, Qsymia Mid, and Qsymia Top groups.](image)

All observed data: *p<0.0001 vs placebo; *p<0.0001 vs. Qsymia Mid or Low
Orlistat

Mechanism
• Lipase inhibitor

Contraindications
• Cholestasis
• Hepatobiliary disease
• Chronic malabsorption

Side Effects
• Headache
• Steatorrhea, GI disturbance
• Flatulence, oily spotting
• Fat-soluble vitamin malabsorption

Dosing
• Available in 60 mg (OTC) and 120 mg tablets
• Dosing 3x/day, with first bite of food
• FDA Approved for long-term use
Belviq (lorcaserin)

**Mechanism**
- Serotonin 5HT$_{2c}$ (activates POMC in hypothalamus)

**Contraindications**
- Pregnancy or breastfeeding
- Renal disease (GFR <50)

**Side Effects**
- Headache, URI symptoms
- Suppressed WBC, RBC
- Hypoglycemia
- Hyperprolactinemia (5x ULN)

**Dosing**
- 10 mg twice daily
- Discontinue if WL >5% not achieved in 12 weeks
Successful Long-term Weight Loss
National Weight Control Registry

NWCR Cohort includes over 10,000 registrants who have maintained weight loss of 30 lbs (13.6 kg) for at least 1 year

DIETARY FACTORS
• Eat 1800 kcal/day with 27% fat
• Limit diet variety
• 78% eat breakfast
• Eat fast food no more than 1x per week
• Use more artificially sweetened beverages
• They are VIGILANT

BEHAVIOR
• 40% weigh themselves daily, 20% weekly
• Reduced TV watching
• Perform 2700 kcal/week of physical activity
• If exercise decreased by 500 kcal/wk they regain 9 kg
• If exercise is maintained they regain only 4.5% or 4.5 kg

National Weight Control Registry http://www.nwcr.ws/
Establish a plan for long-term success

• Formulate a plan for weight maintenance or continued loss

• Maintenance of healthy eating behaviors and regular exercise habits

• Continued self-monitoring

• Long-term monitoring and follow-up

• Visits every 2-6 months with healthcare provider