Medical Management of Obesity

Ben O’Donnell, MD

Objectives

- Background
  - Impact and scope of Obesity
  - Control of Energy Homeostasis
- Methods of treatment
- Medications
Impact of Obesity

According to CDC data:

- 2009-2010 estimated prevalence of adults who are obese is 35.7%
- The estimated annual medical cost of obesity in the U.S. was $147 billion in 2008 U.S. dollars
- The per capita medical costs for people who are obese were $1,273 higher than those of normal weight.
- Obesity leads to heart disease, diabetes, stroke, and increases risk for certain types of cancer.

http://www.cdc.gov/obesity/data/adult.html#Groups

Background

http://www.cdc.gov/obesity/data/adult.html#Groups
Most Recent Data

Prevalence of Self-Reported Obesity Among U.S. Adults
BRFSS, 2012

Gallup Survey (March 4th, 2014) self-reported height and weight survey conducted from Jan 2nd to Dec 29th, 2013 by random phone calls to over 178,000 participants in all 50 states.

- Ohio is 8th nationally for highest rate of obesity; West Virginia is 2nd, Kentucky 9th, Indiana 12th
- Rates of hypertension, high cholesterol, depression, diabetes, and heart attack were all higher in the 10 most obese states as compared to the 10 least obese states.


http://www.cdc.gov/obesity/data/adult.html#Groups
Figure 1. Prevalence of obesity among adults aged 20 years and over, by poverty income ratio, sex, and race and ethnicity: United States 2005–2008

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>32.9</td>
<td>29.0</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>32.2</td>
<td>27.5</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>35.5</td>
<td>47.6</td>
</tr>
<tr>
<td>Mexican American</td>
<td>30.5</td>
<td>45.5</td>
</tr>
</tbody>
</table>

*Significant trend.
NOTES: PIR is poverty income ratio. Persons of other race and ethnicity included in total.

Figure 2. Obese adults aged 20 years and over, by poverty income ratio and race and ethnicity: United States 2005–2008

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>15.3</td>
<td>14.2</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>12.6</td>
<td>11.0</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>8.3</td>
<td>9.8</td>
</tr>
<tr>
<td>Mexican American</td>
<td>5.1</td>
<td>4.7</td>
</tr>
</tbody>
</table>

NOTES: PIR is poverty income ratio. Persons of other race and ethnicity included in total.
Population data

![Figure 3. Prevalence of obesity among adults aged 20 years and over, by education, sex, and race and ethnicity: United States 2005–2006.](image)

Pathophysiology

- “Obesity, by definition, results from ingesting calories in excess of ongoing requirements.”
- Food is necessary for life.
- Caloric restriction leads to decreased metabolic rate, the body’s defense against starvation.
- In obesity the body defends the higher set point – patients often refer to this as yo-yo dieting.
- Resistance to satiety hormones also exists in the obese state (e.g. leptin resistance).

Within the CNS and hypothalamus, energy homeostasis is controlled via the melanocortin system. Melanocortin peptides derive from pro-opiomelanocortin (POMC) which is also responsible for endorphin & ACTH production. The melanocortin peptides α, β, and γ-melanocyte-stimulating hormones (MSH) act through 5 G-protein coupled receptors, MCR 1-5. Melanocortin receptors 3 and 4 exist within the CNS. POMC derived peptides act as agonists on MC3R and MC4R. Neuropeptide Y(NPY) and Agouti related protein (AgrP) serve as high-affinity antagonists to these receptors and exist in the same neuronal beds within the CNS as POMC.
Treatment

- Multiple modes of therapy
  - Diet – Medical Nutrition Therapy
  - Exercise/Activity
  - Behavioral therapy
  - Combination Therapy
  - Pharmacotherapy

Nutrition

- Low calorie diet
  - Men 1500-1800 kcal/day
  - Women 1200-1500 kcal/day
- 500 kcal/day deficit should produce roughly 1 lbs per week of weight loss
- Decrease portion size
- Maintain appropriate balance of nutrients
- Diet should not be lower than 800 calories per day
- Initial goal of 10% decrease in body weight

Activity

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Activity</th>
<th>Approximate duration in minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>Volleyball, noncompetitive</td>
<td>43</td>
</tr>
<tr>
<td>Moderate</td>
<td>Walking, moderate pace (3mph, 20 min/mile)</td>
<td>37</td>
</tr>
<tr>
<td>Moderate</td>
<td>Walking, brisk pace (4mph, 15 min/mile)</td>
<td>32</td>
</tr>
<tr>
<td>Moderate</td>
<td>Table tennis</td>
<td>32</td>
</tr>
<tr>
<td>Moderate</td>
<td>Raking leaves</td>
<td>32</td>
</tr>
<tr>
<td>Moderate</td>
<td>Social dancing</td>
<td>29</td>
</tr>
<tr>
<td>Moderate</td>
<td>Lawn mowing (powered push mower)</td>
<td>29</td>
</tr>
<tr>
<td>Hard</td>
<td>Jogging (5 mph, 12 min/mile)</td>
<td>18</td>
</tr>
<tr>
<td>Hard</td>
<td>Field hockey</td>
<td>16</td>
</tr>
<tr>
<td>Very Hard</td>
<td>Running (6 mph, 10 min/mile)</td>
<td>13</td>
</tr>
</tbody>
</table>

Source: Surgeon General's Report on Physical Activity and Health
Pharmacotherapy

Medications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Year approved</th>
<th>Year approval withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathomimetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Phenetermine</td>
<td>Short term</td>
<td>1959</td>
</tr>
<tr>
<td>• Diethylpropion</td>
<td>Short term</td>
<td>1959</td>
</tr>
<tr>
<td>• Phendimetrazine</td>
<td>Short term</td>
<td>1961</td>
</tr>
<tr>
<td>• Benzphetamine</td>
<td>Short term</td>
<td>1960</td>
</tr>
<tr>
<td>Lipase inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Orlistat</td>
<td>Long term</td>
<td>1997</td>
</tr>
<tr>
<td>Approval Withdrawn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fenfluramine</td>
<td>1973</td>
<td>1997</td>
</tr>
<tr>
<td>• Dexfenfluramine</td>
<td>1997</td>
<td>1997</td>
</tr>
<tr>
<td>• Sibutramine</td>
<td>1997</td>
<td>2010</td>
</tr>
<tr>
<td>• Rimonabant</td>
<td>2006</td>
<td>2008</td>
</tr>
</tbody>
</table>

FDA approval information. *Approved in Europe only.

Phentermine

Comparison of Continuous and Intermittent Anorectic Therapy in Obesity


- 108 women aged 21 to 60
- All were counseled on a 1000 kcal diet
- Placed into groups of 36; placebo, 30mg daily of Phentermine, and alternating placebo or phentermine every 4 weeks
- Treatment period was 36 weeks
- 44 women withdrew, the highest proportion from the continuously treated group

Phentermine

- Currently indicated for short term use only (accepted to mean 12 weeks)
- Dose of 15mg or 37.5mg daily; should use lowest effective dose
- Classified as a schedule IV controlled substance
- Contraindicated in pregnancy and for nursing mothers, patients with glaucoma, hyperthyroidism or a history of drug abuse; also should not be used in combination with monoamine oxidase inhibitors (MAOIs)

¶ The histopathologic features were similar to those observed in carcinoid-induced valvular disease, a serotonin-related syndrome.

**Pathophysiology of Valvular Disease**

Possible Role of Valvular Serotonin 5-HT\textsubscript{2B} Receptors in the Cardiopathy Associated with Fenfluramine


Evidence for Possible Involvement of 5-HT\textsubscript{2B} Receptors in the Cardiac Valvulopathy Associated With Fenfluramine and Other Serotonergic Medications

Richard B. Rothman, MD, PhD; Michael H. Baumann, PhD; Jason E. Savage, BS; Laura Rauzer, BS; Ace McBride, BS; Sandra J. Hufelsen, BS; Bryan L. Roth, MD, PhD

*Circulation*, 2000;102:2836-2841.\hfill
Lorcaserin

Multicenter, Placebo-Controlled Trial of Lorcaserin for Weight Management


- Study included over 3000 patients, over 80% female, avg age 44
- Avg weight similar between the two groups (about 100 kg); BMI for inclusion 30-45 without comorbidity, or 27-45 with one comorbidity (hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea).
- Divided between Lorcaserin 10mg or placebo twice daily
- Lorcaserin works through serotonin 5HT-2C receptor

- Significant reductions in total and LDL cholesterol, triglycerides, fasting glucose, and insulin resistance.
- Decrease in systolic and diastolic blood pressure, but not significantly different from placebo group.
Lorcaserin

- Patients on lorcaserin for year 2 had significant difference in sustained weight loss compared to those who switched to placebo.


Lorcaserin

- Adverse effects:
  - Upper respiratory infections, headache, dizziness, nasopharyngitis, and nausea.

- Cautions:
  - Labeled for valvular heart disease since it works through serotonin pathways
  - Also caution use in combination with other serotonergic or antidopaminergic medications
  - Contraindicated in pregnancy

Phentermine-Topiramate

Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial

Katherine M. Goldstone, David B. Allison, Donna H. Ryan, Craig A. Peterson, Barbara Traupman, Michael L. Schweim, Wesley W. Day

- Included around 2500 patients, avg age 51, 70% women, with BMI of 27-45 with two of the following:
  - Hypertension
  - Hyperlipidemia
  - Diabetes
  - Waist circumference of at least 102 cm for men or at least 88 cm for women

Lancet 2011; 377: 1341–52

CONQUER Study

- Significant decreases in total cholesterol, triglycerides, systolic blood pressure, fasting glucose, and Hgb A1C.

Lancet 2011; 377: 1341–52
Phentermine-Topiramate

Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study

W Timothy Garvey, Donna H Ryan, Michelle Lock, Kishore M Gaddis, David B Allison, Craig A Peterson, Michael Schoeters, Wesley W Day, and Charles H Bowden

Am J Clin Nutr 2012;95:297–308

SEQUEL Study

- Decreases in total cholesterol, triglycerides, systolic blood pressure maintained through the second year of therapy.

Am J Clin Nutr 2012;95:297–308
Phentermine-Topiramate

- Adverse effects:
  - dry mouth, constipation, dysgeusia, paraesthesia, insomnia, dizziness, anxiety, irritability, and disturbance in attention
- Caution/Contraindications:
  - Pregnancy
  - Hyperthyroidism
  - Glaucoma
  - Concomitant use of MOAIs

Orlistat

- Pancreatic lipase inhibitor, reduces absorption of dietary fats.
- Available in prescription dose (120mg three times a day) and OTC 60mg dose.
- Mean weight loss after 1 year on full dose compared with placebo was 3%.
- Approved for long term use.
- Significant GI side effects.
Orlistat

**XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study**

A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients

JAN S. TORGENSEN, MD, MPH

JONATHAN HAFTHMAN, MD

MARK N. BOYDEN, MD

LARS SIMONSSON, MD, PHD

- 4 year study of 3,305 patients randomized to either a diabetes prevention program (DPP)-type intensive intervention plus placebo or DPP plus orlistat.
- Both groups achieved and maintained significant weight loss over the 4-year period.
- Patients on DPP plus placebo maintained an average weight reduction of 3kg, while those treated with DPP plus orlistat lost 5.8 kg by the end of the trial.

*Diabetes Care* 27:155–161, 2004

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**Orlistat**

![Graph showing change in body weight over weeks for patients on placebo plus lifestyle, orlistat plus lifestyle, or placebo plus orlistat.](image)

**Table 2**—The effect of baseline strata on the relative risk of developing type 2 diabetes over 4 years in patients, irrespective of treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group: orlistat versus placebo</td>
<td>0.63</td>
<td>(0.46–0.87)</td>
<td>0.0052</td>
</tr>
<tr>
<td>Glucose tolerance: impaired versus normal</td>
<td>10.60</td>
<td>(7.30–15.40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex: male versus female</td>
<td>1.41</td>
<td>(1.02–1.96)</td>
<td>0.0300</td>
</tr>
<tr>
<td>Age (years): &gt;44 vs. ≤44</td>
<td>1.44</td>
<td>(1.02–2.04)</td>
<td>0.0383</td>
</tr>
<tr>
<td>BMI (kg/m²): ≥37 vs. &lt;37*</td>
<td>1.36</td>
<td>(0.97–1.91)</td>
<td>0.0720</td>
</tr>
</tbody>
</table>

*Median.*

*Diabetes Care* 27:155–161, 2004
**DPP Weight Loss for Reference**


**Potential Medications**

- **Liraglutide** – GLP-1 agonist
  - augments insulin secretion, suppresses appetite, delays gastric emptying, and is known to affect visceral fat adiposity, appetite, and food preference in patients with DM II

- **Bupropion/Naltrexone**
  - Bupropion, a dopamine/noradrenaline reuptake inhibitor & Naltrexone, an opioid receptor antagonist

Liraglutide

Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study

Anne Axton, Stephan Kirsten, Lui Van Gestel, Ailí Rismanen, Laoi Nichols, Marie-Alice Haken, Jasper Mudde, Mark F. Ranner, Michael E. Lean

on behalf of the NN022-1852 Study Group

Figure 2: Change in bodyweight
Data are mean (95% CI) (ANOVA estimate) for the intention-to-treat population with the last observation carried forward.

Lancet 2009; 374: 1606-16

Bupropion/Naltrexone

Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Frank L. Greenway, Kim Fuglægård, Raymond J. McAllister, Sumbul Modeller, Maria Gottschedtz, Janelle Crichton, Dennis O'Keen, Eduardo Dempsch, for the COR-I Study Group

Figure 2: Change in bodyweight
Gedmedalised linear regression: (1) percentage change in body weight and number of participants at each 12-week interval compared with placebo.

Lancet 2010; 376: 595-605
A note on schedule IV

- Drugs, substances, and certain chemicals used to make drugs are classified into five (5) distinct categories or schedules depending upon the drug’s acceptable medical use and the drug’s abuse or dependency potential.
- Phentermine, lorcaserin, and the combination phentermine/topiramate fall under schedule IV


State of Ohio Laws

- “…determine that the patient has a BMI of at least thirty, or at least twenty-seven with comorbid factors, and rule out the existence of any recognized contraindications to the use of the controlled substance to be utilized…”
- “The physician shall personally meet face-to-face with the patient, at a minimum, every thirty days when controlled substances are being utilized for weight reduction…”

http://codes.ohio.gov/oac/4731-11-04