Treatment of Obesity

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Rationale For Treating Obesity

- Many OSA patients are obese
- Reductions in weight are associated with improvements in SDB
- Reductions in weight improve many comorbid conditions that obesity and OSA share

Guide for Selecting Obesity Treatment

<table>
<thead>
<tr>
<th>BMI Category (kg/m²)</th>
<th>Treatment</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>Diet, Exercise, Behavior Tx</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>With co-morbidities</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>With co-morbidities</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Self-Monitoring Food Intake**

- Types of foods
- Portion sizes
- Calories (reduce by 500 kcal/d)
- Times, places, and activities
- Thoughts and moods

Brownell: *Learn Program for Weight Control*, 1998

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**Changes in Body Weight**

![Graph showing changes in body weight over years.]


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**Diabetes Prevention Program**

![Graph showing cumulative incidence of diabetes.]

The Dieter’s Dilemma

Calories or Carbs?

- N: 43
- Weeks: 6 (inpatient)
- Diets: Isocaloric (1000 kcal/d)
  (15% vs. 45% CHO)
- Weight Loss: 8.9 ± 0.6 kg  7.5 ± 0.5 kg

Golay. IJO, 1996.

Weight Loss – 6 Months

Weight Loss 1 Year
**Ongoing Study**

- NIH, 3-center study of 360 patients
- Comprehensive behavioral treatment
- Multiple outcomes (kidney, bone, exercise tolerance, endothelial function, insulin sensitivity)

**Antiobesity Agents: How They Work**

<table>
<thead>
<tr>
<th>Agents</th>
<th>Releasing Agent</th>
<th>Reuptake Inhibitor</th>
<th>Selective Lipase Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamphetamine</td>
<td>S-HT +++</td>
<td>S-HT NE ++</td>
<td></td>
</tr>
<tr>
<td>Phentermine</td>
<td>S-HT +++</td>
<td>S-HT NE ++</td>
<td></td>
</tr>
<tr>
<td>Sibutramine</td>
<td>S-HT +++</td>
<td>S-HT NE ++</td>
<td></td>
</tr>
<tr>
<td>Orlistat</td>
<td>S-HT +++</td>
<td>S-HT NE ++</td>
<td></td>
</tr>
</tbody>
</table>

5-HT = serotonin; NE = noradrenaline; DA = dopamine

Drugs Approved by FDA for Treating Obesity

<table>
<thead>
<tr>
<th>Status</th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx</td>
<td>Sibutramine</td>
<td>Meridia</td>
</tr>
<tr>
<td>Rx</td>
<td>Orlistat</td>
<td>Xenical</td>
</tr>
<tr>
<td>OTC (Approved 2/07)</td>
<td>Orlistat 60mg</td>
<td>alli</td>
</tr>
<tr>
<td>Approved in Europe but not U.S.</td>
<td>Rimonabant</td>
<td>Acomplia/Zimulti</td>
</tr>
</tbody>
</table>

STORM Trial

STORM: Change in Vital Signs—Baseline to 24 Months in Sibutramine Treatment Group

<table>
<thead>
<tr>
<th>Mean Change</th>
<th>Sibutramine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>0.1</td>
<td>-4.7</td>
</tr>
<tr>
<td>Diastolic</td>
<td>2.3</td>
<td>-1.6</td>
</tr>
<tr>
<td>Pulse rate (bpm)</td>
<td>4.1</td>
<td>-1.9</td>
</tr>
</tbody>
</table>

STORM: Safety and Tolerability—% of Patients Reporting AEs*

<table>
<thead>
<tr>
<th>Weight Loss Phase (n=605)</th>
<th>Weight Maintenance Phase</th>
<th>Placebo (n=115)</th>
<th>Sibutramine (n=552)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td></td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td></td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Increased appetite</td>
<td></td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td></td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Dry mouth</td>
<td></td>
<td>39</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Asthenia</td>
<td></td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td>12</td>
<td>3</td>
</tr>
</tbody>
</table>

*Same diet, exercise for sibutramine, placebo; P≤0.001, sibutramine vs placebo for weight maintenance

Adapted with permission from James WPT et al. Lancet. 2000;356:2119.

*Frequency of ≥10% in any treatment group; reported as therapy-related

**Sibutramine**

**Usage:**
- For patients with BMI > 30, or > 27 in the presence of risk factors
- Dose: 5 to 15 mg once a day
- Not for patients on MAOs with uncontrolled or poorly controlled hypertension, history of coronary artery disease, congestive heart failure, arrhythmias or stroke
- Use with caution in patients with hypertension
  - Regular BP monitoring recommended

*Sibutramine Prescribing Information*

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**Orlistat: Weight Loss and Maintenance Over 2 Years**


**Orlistat: Safety—Adverse Events (AEs) at 1 Year**


*There is concern about fat-soluble vitamin absorption*
Orlistat

Treatment Guidelines

• Prescribe 120 mg tid, with meals containing fat
• Patients should be on a nutritionally balanced, reduced-calorie diet
• Diet should contain approximately 30% of calories from fat
• Distribute fat among three meals a day
• Use a multivitamin daily
• Encourage patients to enroll in XeniCare®, the orlistat patient support group

Please see complete Product Information.

alli vs. Xenical

<table>
<thead>
<tr>
<th>Use</th>
<th>OTC</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>60 mg</td>
<td>120 mg</td>
</tr>
<tr>
<td>Target Pop</td>
<td>Overweight</td>
<td>BMI ≥ 27 kg/m² or ≥ 30 kg/m² (w/ co-morbidities) or (without)</td>
</tr>
<tr>
<td>Indication</td>
<td>Weight Loss</td>
<td>Weight Loss &amp; Maintenance</td>
</tr>
<tr>
<td>Age Range</td>
<td>18+</td>
<td>12+</td>
</tr>
<tr>
<td>GI AEs (withdrawal rates)</td>
<td>3.2</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Behavioral Support Program
myalliplan.com | Xenicare

Rimonabant

• Investigational agent that inhibits the cannabinoid-1 receptor (CB1)
• The endocannabinoid system is postulated to regulate energy balance, food intake, and lipid and glucose metabolism
• Rimonabant has been shown to reduce body weight and improve cardiovascular risk factors in obese patients
• Tested in RIO-Europe, RIO-North America and the Canada-based Rio-Lipids large, prospective, randomized, placebo controlled trials

Pi-Sunyer et al. JAMA, 2006: 761-775.

Changes in Body Weight-1 Year

[Graph showing changes in body weight over 1 year with lines for Placebo, 5 mg of Rimonabant, and 20 mg of Rimonabant.]
Changes in Body Weight-2 Years

Weeks

Changes from Baseline (kg)

-10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0

Placebo 20 mg of Rimonabant/Placebo 20 mg of Rimonabant 20 mg of Rimonabant

Pi-Sunyer et al. JAMA, 2006: 761-775.

Change from Baseline in Body Weight and Waist Circumference: RIO-Europe

Weeks

Weight Change from Baseline (kg)

Change from Baseline in Waist Circumference (cm)

Placebo Rimonabant 5 mg Rimonabant 20 mg


Change from Baseline in Body Weight and Waist Circumference: RIO-Lipids

Weeks

Change from Baseline in Body Weight (kg)

-10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0

Placebo Rimonabant at 5 mg Rimonabant at 20 mg

P=0.001 P=0.001


Change from Baseline in HDL and Triglycerides: RIO-Lipids

Weeks

Change from Baseline in HDL (mL/dL)

Change from Baseline in Triglycerides (mL/dL)

Placebo Rimonabant at 5 mg Rimonabant at 20 mg

P=0.001 P<0.001

**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.”

NHLBI, 1998

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**Subject Characteristics**

<table>
<thead>
<tr>
<th>60 obese women¹</th>
<th>397 obese individuals²</th>
</tr>
</thead>
<tbody>
<tr>
<td>40.0 ± 8.7 years</td>
<td>43.1 ± 10.9 years</td>
</tr>
<tr>
<td>99.1 ± 12.3 kg</td>
<td>109.0 ± 28.9 kg</td>
</tr>
<tr>
<td>BMI = 36.3 ± 4.3 kg/m²</td>
<td>BMI = 39.3 ± 9.5 kg/m²</td>
</tr>
</tbody>
</table>

¹Foster et al. JCCP 65(1):79-85 1997
²Foster et al Arch Int Med. 161:2133-2139 2001

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**Goal Weights**

- Averaged 32% reduction in body weight
- Three times greater than the goals recommended by the National Academy of Science and Department of Agriculture
- Greatly exceeds weight losses of nonsurgical treatments

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**Defined Weights**

**Dream Weight**

A weight you would choose if you could weigh whatever you wanted.

**Happy Weight**

This weight is not as ideal as the first one. It is a weight, however, that you would be happy to achieve.

**Acceptable Weight**

A weight that you would not be particularly happy with, but one that you could accept, since it is less than your current weight.

**Disappointed Weight**

A weight that is less than your current weight, but one that you could not view as successful in any way. You would be disappointed if this were your final weight after the program.

Foster et al, J Consult Clin Psychol, 1997
**Defined Weights**

<table>
<thead>
<tr>
<th></th>
<th>1997 % Reduction</th>
<th>2001 % Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dream</td>
<td>38%</td>
<td>38.4%</td>
</tr>
<tr>
<td>Happy</td>
<td>31%</td>
<td>30.9%</td>
</tr>
<tr>
<td>Acceptable</td>
<td>25%</td>
<td>24.9%</td>
</tr>
<tr>
<td>Disappointed</td>
<td>17%</td>
<td>15.7%</td>
</tr>
</tbody>
</table>

1Foster et al. JCCP 65(1) 79-85 1997
2Foster et al Arch Int Med. 161 2133-2139 2001

**% Achieving Defined Weights at Week 48 (N=45)**

- Weight loss: $16.3 \pm 7.2$ kg
- Acceptable: 24%
- Happy: 9%
- Dream: 0%
- Disappointed: 20%
- Did not reach Disappointed Weight: 47%

Helping Patients Accept More Modest Weight Losses

- Be clear about what treatment can do and what it cannot do
- Discuss biological limits
- Focus on nonweight outcomes
- Be empathic about dissatisfaction with weight/shape.