Update on Weight Loss Pharmacotherapy

Dan Bessesen, MD
Daniel.bessesen@ucdenver.edu

Learning Objectives

• List the medications that are currently available for the treatment of obesity, describe their mechanisms of action, and list their side effects.
• List the medications that are used for other health problems that contribute to weight gain and describe an approach to minimizing this problem.
• List the medications that are in the pipeline that likely will become available over the coming several years.

Currently Available Options

• Accept weight where it is
• Diet/Exercise, 4-8% weight loss
• Drugs, 5-8% weight loss
• Surgery 20-30% weight loss
Currently Available Options

- Accept weight where it is
- Diet/Exercise, 4-8% weight loss
- Drugs, 5-8% weight loss
- Surgery 20-30% weight loss

A Guide to Selecting Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BMI category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25-26.9</td>
</tr>
<tr>
<td>Diet, physical activity, and behavior therapy</td>
<td>+</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>With co-morbidity</td>
</tr>
<tr>
<td>Surgery</td>
<td>With co-morbidity</td>
</tr>
</tbody>
</table>

The Practical Guide. 2000

Obesity Treatment Pyramid
Drug Treatment of Obesity

- Current medications 5-8% wt loss
- Treatment probably needs to be lifelong.
- Drugs probably not paid for by insurance.
- Issues of FDA approval, long term safety, and efficacy.
- Choice of mechanisms, OTC versus prescription, combinations?

Clinical Practice Guideline
From the American College Of Physicians
Ann Intern Med
142:525-531, 2005

“For patients who choose to use Adjunctive drug therapy, options include sibutramine, orlistat, phentermine, diethylpropion, fluoxetine, and bupropion. The agent of choice will depend on the Side effects profile of each drug and the Patient’s tolerance of these side effects.”

Sibutramine

- Meridia (Abbott) 10-15mg/d, $90.00/mo
- combination NE/serotonin re-uptake inhibitor
- Inhibits appetite (increases satiety)
- 50-60% lose 5% of body weight or more
- 30% of subjects lose 10%
**Effect of 1-Year Sibutramine Therapy on Body Weight**

![Bar chart showing weight loss percentages with asterisks indicating significant differences.]

*P<0.001 vs placebo.


**Initial Responders to Sibutramine Can Maintain Long-term Weight Loss**

![Line graph showing body weight changes over months.]

Randomization at 6 months in those with ≥5% weight loss.


**Effects of Sibutramine on Triglyceride and HDL Cholesterol Levels**

![Graphs showing changes in triglycerides and HDL cholesterol levels.]

Effect of Continuous vs Intermittent Sibutramine Therapy on Body Weight

Sibutramine dose=15 mg/d.


Effects of Sibutramine on Waist Circumference in Obese Adolescents

Fujioka, Obesity Research Sept 2005

Combining Diet and Medications is Better Than Either Alone

Panel A: Intention to Treat
Panel B: Last observation carried Forward

Wadden, NEJM 363:2111-2120, 2005
Adherence correlates with weight loss when combining diet and medications

Adverse Effects of Sibutramine Therapy

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Placebo (%)</th>
<th>Sibutramine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>4.2</td>
<td>17.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>6.0</td>
<td>11.5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.5</td>
<td>10.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.4</td>
<td>7.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0.8</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Orlistat

- Xenical (Roche)
- Pancreatic Lipase inhibitor
- Inhibits fat absorption by 30%
- 120 mg tid, $100.00/mo
- GI side effects: oily stools, urgency
- MVI to prevent fat soluble vitamin deficiency
Orlistat

- Thousands of patients studied up to 4 years of exposure.
- Approved for long term use
- 5-8% weight loss on average
- May be useful in those with poorly controlled hypertension or psych problems
- Recently FDA panel supported OTC application

Effect of Orlistat on Body Weight

Clinical Trials Evaluating Effect of 1-Year Orlistat Therapy on Body Weight


Effects of Orlistat on Glucose and HbA1c in Overweight and Obese Patients with Type 2 Diabetes

Kelley Diabetes Care 25:1033-41, 2002

4 Years of Treatment With Orlistat Reduces the Risk of Developing Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Orlistat*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss at 1 y, kg</td>
<td>7.5</td>
<td>11.4</td>
</tr>
<tr>
<td>Weight loss at 4 y, kg</td>
<td>4.1</td>
<td>6.0**</td>
</tr>
<tr>
<td>&gt;10% weight loss at 4 y</td>
<td>16%</td>
<td>26%**</td>
</tr>
<tr>
<td>&gt;5% weight loss at 4 y</td>
<td>37%</td>
<td>53%**</td>
</tr>
<tr>
<td>4-year incidence of T2DM</td>
<td>9.0%</td>
<td>6.2%‡</td>
</tr>
</tbody>
</table>

*Represents a 37% reduction in the incidence of T2DM beyond the impact of diet and lifestyle intervention (P = 0.0032)

‡Using TID
**P < 0.001 vs placebo.

Effects of Orlistat on BMI and Weight in Obese Adolescents

JAMA 293:2873-2883, 2005
Gastrointestinal Side Effects of Orlistat Therapy

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Orlistat</td>
</tr>
<tr>
<td>Fatty/oily stool</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>Increased defecation</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Liquid stools</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Fecal urgency</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Flatus with discharge</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Oily evacuation</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>


OTC Orlistat (Alli)

- On the market since spring 2007. 100 million in sales so far
- 60 mg dose, about 60 cents/tablet
- Data suggests less weight loss in “overweight” category
- Drug interactions with coumadin (vit K) and cyclosporin (reduced drug levels)

Phentermine

Zhaoping L et al. *Ann Int Med. 2005*

- Increases NE content in the brain
- Chemically related to amphetamine, not addictive
- 15-37.5 mg/d, $40.00/month
- FDA approved for only 3 months use
- 5-8% weight loss
- Side effects: hypertension, headache, nervousness
**Phentermine**

- Most widely prescribed anti-obesity drug
- No evidence of serious side effects when used as a single drug
- Is it ethical to prescribe long term?
  - Legally?
  - Beneficence
  - Non-Maleficience
  - Autonomy

---

**Sales of Rx Obesity Medications (US)**

Average length of therapy per patient per year is 90-93 days

---

**Other Medications: That may Increase Weight**

- Anti-diabetic medications
  - Sulfonylureas
  - Insulin
  - TZDs
- Mood Stabilizers, antipsychotics
- Birth Control Pills: Depo Provera
- Glucocorticoids: Prednisone
What to do About These Medications

- Monitor weight and encourage lifestyle changes
- Choose a different medication that does not cause weight gain
- Choose a lower dose
- Weigh risks and benefits of this medication

Bupropion (Wellbutrin)

- Antidepressant
- Not FDA approved for weight loss
- However, there is some evidence of this drug inducing a slow gradual weight loss
- I don’t prescribe for weight loss, but suggest that the individual speak with their psychiatrist about this.

Topiramate (Topimax)

- Developed and FDA approved as an anti-seizure medication
- “Side effect” of weight loss noted
- A number of weight loss trials begun with thousands of patients planned for 2 years duration.
- Studies halted due to side effects: cognitive problems, memory loss, paresthesias.
Summary of Medications

- Xenical and Sibutramine are options but are not ideal because of limited weight loss, cost and lack of insurance coverage.
- Phentermine is less expensive but is not FDA approved for long term use.
- Make sure that other medications are not contributing to weight gain.

Pharmacotherapy: New Drugs

- Only 4% of obese people get a prescription medication to treat this condition.
- 66% of hypertensive people get Rx medication.
- If 66% of obese patients were treated this would equal 43 million people.
- In 2001 the antihypertensive market in the US was $8.3 billion.
- New Drugs: Pentermine/topiramate, Bupropion/naltrexone, lorcaserin, Tesofensine and liraglutide.
Exenatide for Weight Reduction
Open-Label Extension – Combined

Liraglutide (Victoza)

• Novo Nordisk once daily GLP-1 analog.
• Seeking approval for use in diabetes
• Approved for marketing in Europe in July 2009
• FDA has expressed some concern over risk for inducing thyroid tumors.
• Company is conducting studies to support a weight loss indication.

Astrup A, Lancet. 2009 Nov 7;374(9701):1606-16
Garber A, Lancet. 2009 Feb 7;373(9662):473-81
Percent of Patients Taking Liraglutide who Experienced Nausea

Astrup A, Lancet. 2009 Nov 7;374(9701):1606-16

Qnexa (Vivus)

- Combination of phentermine and topiramate
  - Full dose 15 mg phentermine, 92 mg topiramate
- EQIP randomized placebo controlled trial
  1,267 morbidly obese patients followed for 1 year
  - 10.4% placebo subtracted weight loss, 14.7% total weight loss among completers
- CONQUER Trial: 2,487 obese patients with co-morbidities
  - Full dose 13.2% weight loss, improved CVD risk markers

Qnexa

- Side effects
  - Dry mouth: 21%
  - Tingling: 20%
  - Insomnia: 10%
  - Nausea: 7%
- Neurocognitive effects resulted in discontinuation in 2.6%, 18% stopped medication for some AE
- No evidence of increased levels of depression or suicidal ideation.
Bupropion plus Naltrexone (Contrave, Orexigen) in the Treatment of Obesity

Randomization included: BUP (300 mg) + NAL (50 mg), BUP (300 mg) + placebo (P), NAL (50 mg) + P or P+P for up to 24 weeks

Greenway FL, Obesity (2008) 17 1, 30–39

Side Effects of Bupropion plus Naltrexone in the Treatment of Obesity

Greenway FL, Obesity (2008) 17 1, 30–39

Lorcaserin in the Treatment of Obesity

Lorcaserin (APD356) is a potent, selective 5-HT2C agonist with ~15-fold and 100-fold selectivity vs. 5-HT2A and 5-HT2B receptors, respectively

Smith S, Obesity (Silver Spring). 2009 Mar;17(3):494-503
Summary of Medications

• A large number of new medications in the pipeline
• Qnexa looks the best for weight loss
• Lorcaserin may be fenfluramine in sheep’s clothing
• Liraglutide may have the best acceptance
• A fair amount of side effects but they don’t look severe