Medications for Obesity: Why No Magic Bullets?

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Learning Objectives

1. Describe evidence-based pharmacotherapy recommendations for overweight or obese people
2. Identify physiologic/pharmacologic targets for anti-obesity agent development
3. Identify pharmacologic agents that are used on/off-label and/or undergoing clinical trials for the treatment of obesity.
4. Identify characteristics that differentiate anti-obesity agents from one another

OBESITY - Pathophysiology

- Satiety centers in hypothalamus are triggered by neurotransmitters or peptides → reduced desire to eat
- Neurotransmitters
  - 5HT, DA, NE, histamine antagonism → weight gain
  - Glutamine agonism → weight gain
- Endocannabinoid Receptor system
  - CB1 receptor antagonism → weight loss
- Neuropeptides
  - Cholecystokinin, leptin increased → weight loss
  - Neuropeptide Y, peptide YY → weight gain
  - Opioid agonism → weight gain
- Gut peptides
  - GLP-1, amylin → weight loss

<table>
<thead>
<tr>
<th>FDA Approved Obesity Drugs</th>
<th>Drug</th>
<th>Year Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-Term Use</td>
<td>Desoxynephrine</td>
<td>1947</td>
</tr>
<tr>
<td></td>
<td>Phenmetrazine</td>
<td>1956</td>
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<tr>
<td></td>
<td>Phentermine</td>
<td>1959</td>
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<tr>
<td></td>
<td>Diethylprozine</td>
<td>1959</td>
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<td></td>
<td>Phenidimetazine</td>
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<td></td>
<td>Benzphetamine</td>
<td>1960</td>
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<tr>
<td></td>
<td>Mazindol</td>
<td>1973</td>
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<tr>
<td></td>
<td>Fenfluramine</td>
<td>1996</td>
</tr>
<tr>
<td>Long-Term Use</td>
<td>Dexfenfluramine</td>
<td>1996</td>
</tr>
<tr>
<td></td>
<td>Sibutramine</td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>Orlistat</td>
<td>1999</td>
</tr>
</tbody>
</table>
OBESITY: Pharmacological Therapy

Centrally acting medications
- Anorexiant
  - Diethylpropion*
  - Phentermine*
  - Sibutramine*
  - Bupropion SR + naltrexone SR
  - Bupropion + zonisamide
  - Phentermine + topiramate
- 5-HT agonists
  - Lorcasertin
- Endocannabinoid system
  - Rimonabant (rejected by FDA)
  - Taranabant

Peripheral acting medications
- Lipase inhibitors
  - Orlistat*
  - Cetilistat (ALT-962)
- GI hormonal regulation
  - Exenatide
  - Pramlintide
  - Pramlintide + metreleptin
  - Davalintide

1996 FDA Draft Guidance for the Clinical Evaluation of Weight-Control Drugs

- Duration and size of phase 3 studies
  - One year of placebo-controlled exposure in 1500 patients
  - Second year of open-label exposure in 200 to 500 patients

- Efficacy criteria
  - Mean weight loss is 5% greater in drug- vs. placebo-treated patients OR
  - Proportion of patients losing 5% is greater in drug- vs. placebo-treated group

Medications for Obesity: Why No Magic Bullets?

February 26, 2010

Medications Used for Weight Loss and Approved by the U.S. Food and Drug Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibutramine†</td>
<td>Appetite suppressant: combined norepinephrine and serotonin reuptake inhibitor</td>
<td>Modest increases in heart rate and blood pressure, nervousness, insomnia</td>
</tr>
<tr>
<td>Phentermine†</td>
<td>Appetite suppressant: sympathomimetic amine</td>
<td>Cardiovascular, gastrointestinal</td>
</tr>
<tr>
<td>Diethylpropion†</td>
<td>Appetite suppressant: sympathomimetic amine</td>
<td>Palpitations, tachycardia, insomnia, gastrointestinal</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Lipase inhibitor: decreased absorption of fat</td>
<td>Diarrhea, flatulence, bloating, abdominal pain, dyspepsia</td>
</tr>
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</table>

† Drug Enforcement Administration schedule IV

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**Summary of Findings on Medications for Weight Loss and FDA Approved**

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<tr>
<th>Medication</th>
<th>Source of Data</th>
<th>Characteristics of Study Patients</th>
<th>Period at Which Weight Loss was Assessed, wk</th>
<th>Mean Weight Change in Treated Patients Compared with Placebo (95% CI)</th>
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<tr>
<td>Sibutramine</td>
<td>Existing meta-analysis of 29 RCTs</td>
<td>Mean age, 42 yr; 53% women; average BMI, 45 kg</td>
<td>52</td>
<td>-4.64 kg (-5.59 to -3.69 kg)</td>
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<tr>
<td>Phentermine</td>
<td>Existing meta-analysis of 9 RCTs</td>
<td>Average age, 43 yr; 71% women; average BMI, 35.3 kg</td>
<td>24 to 52</td>
<td>-3.45 kg (-4.19 to -2.71 kg)</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Meta-analysis of 14 RCTs</td>
<td>Average age, 46 yr; 73% women; average BMI, 36.7 kg</td>
<td>52</td>
<td>-2.75 kg (-3.31 to -2.20 kg)</td>
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**Medications Used for Weight Loss and Not Approved by the U.S. Food and Drug Administration**

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<td>Bupropion</td>
<td>Appetite suppressant: mechanism unknown</td>
<td>Paresthesia, insomnia, central nervous system effects</td>
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<tr>
<td>Fluoxetine</td>
<td>Appetite suppressant: selective serotonin reuptake inhibitor</td>
<td>Agitation, nervousness, gastrointestinal</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Appetite suppressant: selective serotonin reuptake inhibitor</td>
<td>Agitation, nervousness, gastrointestinal</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Mechanism unknown</td>
<td>Paresthesia, changes in taste</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Mechanism unknown</td>
<td>Somnolence, dizziness, nausea</td>
</tr>
</tbody>
</table>

**Investigational Products**

- **Bupropion/zonisamide (Empatic)**
  - Increased metabolism; Suppresses appetite
- **Bupropion/naltrexone (Contrave)**
  - Increase metabolism; counteract body ‘starvation effect’
- **Phentermine/topiramate (Qnexa)**
  - Increases metabolism; increases satiety
- **Lorcaserin (No brand yet)**
  - Selective serotonin 2C receptor agonists.
  - More specific than fen-phen
  - Binds to receptor that regulates appetite, but not causes valvulopathy

**Summary of Findings on Medications for Weight Loss and Not FDA Approved**

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<tr>
<td>Bupropion</td>
<td>The authors' meta-analysis of 3 RCTs</td>
<td>Average age, 43 yr; 61% women; average weight, 84.5 kg</td>
<td>24 to 52</td>
<td>-2.77 kg (-4.9 to -1.6 kg)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Narrative synthesis of 9 RCTs</td>
<td>Average age, 46 yr; 66% women; average BMI, 35.5 kg</td>
<td>35.5 kg</td>
<td>Range in weight loss varied among studies from 14.0 kg lost to 0.4 kg gained</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1 RCT</td>
<td>Average age, 42 yr; 100% women; average BMI, 30 kg</td>
<td>26</td>
<td>In maintenance trial, no significant difference between drug and placebo</td>
</tr>
<tr>
<td>Topiramate</td>
<td>The authors’ meta-analysis of 6 RCTs</td>
<td>Average age, 44 yr; 68% women; average weight, 102 kg</td>
<td>24</td>
<td>Additional 8.5% (4.8% to 8.3%) of pretreatment weight loss</td>
</tr>
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</table>
OBESITY - FDA Withdrawn

- Phenylpropranolamine
  - Synthetic catecholamine
  - OTC weight-loss products (Dexatrim®, Acutrim®); OTC decongestants (Contac®)
  - Hemorrhagic Stroke Project - \( \uparrow \) risk of hemorrhagic stroke w/appetite suppressants containing PPA
  - Voluntary withdrawal in October 2000

OBESITY – FDA Withdrawn

- Fenfluramine
  - “FenPhen” ingredient
- Dextfenfluramine
  - Isomer of fenfluramine
  - Used for long-term treatment
  - Increase satiety by increasing serotonin in neuronal synapse
- Both agents withdrawn in 1997 - associated with valvular heart disease and pulmonary HTN

OBESITY - Treatment

- Phentermine (Adipex-P®) (C-IV)
  - Indicated for short-term treatment
  - MOA: Increase NE, DA in hypothalamic feeding center
  - 5-15% weight loss in 60% of patients
  - Side effects: dry mouth, insomnia, constipation, HTN, tolerance, addiction
  - Dose: 8mg TID (30” before food) or 15-37.5 mg QD (before breakfast)
  - Structurally related to dextroamphetamine but has lower incidence and severity of CNS side effects

OBESITY - Treatment

- Phentermine (PRECAUTIONS)
  - Avoid use in mod-severe HTN, CV disease, substance abuse, anxiety d/o
  - Caution use with TCAs
  - DO NOT use with or within 2 wks of MAOIs
  - Avoid use with SSRIs
  - Drug-interactions with clonidine, guanethidine, methyldopa, thyroid supplements
OBESITY - Treatment

- Sibutramine (Meridia®) (C-IV)
  - Approved for patients \( \geq 16 \) years of age
  - Pregnancy Category C
  - MOA: Inhibit reuptake of NE, 5HT, DA \( \rightarrow \) satiety
  - 5\% weight loss in 40\% of patients
  - Side effects: \( \uparrow \) BP, \( \uparrow \) HR, dry mouth, anorexia, insomnia, constipation
  - Dose: 10mg QAM, may \( \uparrow \) to 15mg QD if no weight loss > 4 lbs within 4 weeks

Endocannabinoid System

- Satiety signals activate the presynaptic neuron
- Neuron stimulated by palatable food or a positive hedonic situation
- Postsynaptic Neuron: Prolongs eating during a meal
- Presynaptic Neuron: Inhibits activity of post-synaptic neuron

Pharmacokinetics

- Hepatic metabolism via CYP3A4
- Ketoconazole and erythromycin may inhibit metabolism (CYP3A4)
- Avoid use in uncontrolled HTN, CAD, CHF, arrhythmias, stroke
- Avoid use with or within 2 wks of MAOIs
- Avoid use with SSRIs, decongestants or other meds that increase BP
OBESITY - Treatment

- Rimonabant (Acomplia®/Zimulti) Not approved by FDA*
  - MOA: Blocks endogenous cannabinoid from binding to neuronal CB1 receptors.
    - Dosage: 20mg pill; taken daily
  - ADE: Most common: nausea, depressive disorders, suicidal ideation, anxiety and dizziness
  - Depressive disorders in 3.2% of obese patients or overweight patients treated with rimonabant 20 mg.
    - Mild or moderate in severity
  - Resulted in recovery in all cases after corrective treatment or D/C of rimonabant
  - *FDA withheld approval in Feb 2006 and June 2007 due to concerns of psychiatric ADE

- Orlistat
  - Approved for use in patients >/=12 years
  - Pregnancy Category B
  - MOA: Inhibit gastric and pancreatic lipase resulting in ↓ fat absorption
    - Little systemic absorption of drug
  - Dose: 120mg TID with or up to 1 hour after fatty meal (may skip if non-fatty meal)
  - Side effects: GI SYMPTOMS, malabsorption of fat soluble vitamins (ADEK)

GI Hormonal Regulation

Published by AAAS

Exenatide (Byetta): Study in Progress...

- Title: The Effect of Exenatide on Body Weight, Energy Expenditure and Hunger in Obese Women Without Diabetes Mellitus
- Purpose: This study will evaluate the effect of exenatide on body weight, appetite, and energy expenditure among moderately obese women without DM.
- Duration: Study is 35 weeks long. Participants will receive exenatide for 16 weeks and placebo for 16 weeks with a 3 week rest period in between.
- Study start: Apr 2007; Expected completion: Sept 2009

Why No Magic Bullet?

Complex physiologic system with multiple mechanisms for maintaining body weight

Traditional Treatment Approach

Dyslipidemia
- Lipid panels
- Lipoprotein subsets
- Total fat
- Cholesterol
- Fiber

Hypertension
- BP
- Ambulatory BP
- Sodium
- K^+

Type 2 DM
- Blood sugar
- Glycosylated hemoglobin
- Sugar
- Distribution CHO, Pro, Fat
- Insulin
- Sulfonylureas
- TZDs

Emerging Treatment Approach

- Adipose Tissue
  - Reduce BMI and waist circumference
  - Calories, glycemia
  - Daily activity/exercise
  - Behavior therapy
  - Medication-Current, S-HT2 agonists, CB1 antagonists, others in development, combinations

Dyslipidemia
- Statins
- Fibrate
- Niacin
- Resins

Hypertension
- ACEI
- ARB
- Diuretic
- Ca-channel blocker

Type 2 DM
- Monitor
- Diet
- Meds
- Monitoring?
  - Diet/Exercise?
  - Medications?