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

FDA Approved Obesity Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-Term Use</strong></td>
<td></td>
</tr>
<tr>
<td>Desoxynephrine</td>
<td>1947</td>
</tr>
<tr>
<td>Phenmetrazine</td>
<td>1956</td>
</tr>
<tr>
<td>Phentermine</td>
<td>1959</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>1959</td>
</tr>
<tr>
<td>Phendimetrazine</td>
<td>1959</td>
</tr>
<tr>
<td>Benzphetamine</td>
<td>1960</td>
</tr>
<tr>
<td>Mazindol</td>
<td>1973</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>1973</td>
</tr>
<tr>
<td><strong>Long-Term Use</strong></td>
<td></td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>1996</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>1997</td>
</tr>
<tr>
<td>Orlistat</td>
<td>1999</td>
</tr>
</tbody>
</table>
FDA Guidelines for Prescription Drug Treatment of Obesity - 1

- BMI ≥ 30 or ≥ 27 with comorbidities
  - American Obesity Association (2005)
  - NAASO, The Obesity Society (ref NIH)
  - American Gastroenterology Association (2002)
- BMI ≥ 30
  - American College of Physicians (2005)

1996 FDA Draft Guidance for the Clinical Evaluation of Weight-Control Drugs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
  - Proportion of patients losing 5% is greater in drug-vs. placebo-treated group

OBESITY: Pharmacological Therapy

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

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

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>
</tbody>
</table>

† Drug Enforcement Administration schedule IV

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

<table>
<thead>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Sibutramine</td>
<td>Existing meta-analysis of 29 RCTs</td>
<td>Mean age, 34–54 y; 53–100% women; average BMI NA</td>
<td>52</td>
<td>-4.45 kg (-5.29 to -3.62 kg)</td>
</tr>
<tr>
<td>Phentermine</td>
<td>Existing meta-analysis of 9 RCTs</td>
<td>Average age, 54 y; 78% women; average BMI, NA</td>
<td>2 to 24</td>
<td>-3.6 kg (-6.0 to -0.6 kg)</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>Existing meta-analysis of 2 RCTs</td>
<td>Average age, 48 y; 73% women; average BMI, 30.7 kg/m²</td>
<td>6 to 52</td>
<td>-3.0 kg (-11.5 to -1.6)</td>
</tr>
<tr>
<td>Orlistat</td>
<td>The authors’ meta-analysis of 22 RCTs</td>
<td>Average age, 48 y; 77% women; average BMI, 30.7 kg/m²</td>
<td>52</td>
<td>-2.75 kg (-3.31 to -2.20 kg)</td>
</tr>
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BMI = body mass index; NA = not available; RCT = randomized controlled trial; FDA = Food and Drug Administration

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

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</thead>
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<tr>
<td>Bupropion</td>
<td>The authors’ meta-analysis of 3 RCTs</td>
<td>Average age, 43 y; 81% women; average weight, 94.3 kg</td>
<td>24 to 52</td>
<td>-2.77 kg (-4.10 to -1.0 kg)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Narrative synthesis of 9 RCTs</td>
<td>Average age, 48 y; 69% women; average BMI, 35.5 kg/m²</td>
<td>52</td>
<td>Range in weight loss varied among studies from 14.5 kg lost to 0.4 kg/m²</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1 RCT</td>
<td>Average age, 42 y; 100% women; average BMI, 30 kg/m²</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, 47 y; 68% women; average weight, 102 kg</td>
<td>24</td>
<td>Additional 8.5% (4.3% to 8.3%) of pretreatment weight loss</td>
</tr>
</tbody>
</table>

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## Medications Used for Weight Loss and Not Approved by the U.S. Food and Drug Administration

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<th>Side Effects</th>
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<td>Bupropion</td>
<td>Appetite suppressant: mechanism unknown</td>
<td>Paresthesia, insomnia, central nervous system effects</td>
</tr>
<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>

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## 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

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OBESITY - FDA Withdrawn

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

OBESITY – FDA Withdrawn

- Fenfluramine
  - “FenPhen” ingredient
- Dexfenfluramine
  - 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 ≥ 16 years of age
  - Pregnancy Category C
  - **MOA:** Inhibit reuptake of NE, 5HT, DA → satiety
  - 5% weight loss in 40% of patients
  - **Side effects:** ↑ BP, ↑ HR, dry mouth, anorexia, insomnia, constipation
  - **Dose:** 10mg QAM, may ↑ 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
- Neurotransmitter
- CB1 Presynaptic Neuron: Inhibits activity of post-synaptic neuron
- ECs
- Prolongs eating during a meal
- Continued eating

**OBESITY - Treatment**

- **Sibutramine (Meridia®) (C-IV)**
  - 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

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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

*Marketed by Sanofi-Aventis

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OBESITY - Treatment

- **Orlistat (Xenical®; Alli™)**
  - **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)

*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

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**Why No Magic Bullet?**

Complex physiologic system with multiple mechanisms for maintaining body weight

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**Traditional Treatment Approach**

<table>
<thead>
<tr>
<th>Dyslipidemia</th>
<th>Hypertension</th>
<th>Type 2 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monitor</strong></td>
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<td><strong>Monitor</strong></td>
</tr>
<tr>
<td>Lipid panels</td>
<td>BP Ambulatory</td>
<td>Blood sugar</td>
</tr>
<tr>
<td>Lipoprotein subsets</td>
<td>BP</td>
<td>Glycosylated</td>
</tr>
<tr>
<td>↓ Total fat</td>
<td>Sodium</td>
<td>hemoglobin</td>
</tr>
<tr>
<td>↓ Cholesterol</td>
<td>↑ K**</td>
<td></td>
</tr>
<tr>
<td>↑ Fiber</td>
<td>ACEI</td>
<td>Sugar</td>
</tr>
<tr>
<td>Statins</td>
<td>DIABETIC</td>
<td>Distribute CHO, Pro,</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Ca-channel</td>
<td>Fat</td>
</tr>
<tr>
<td>Niacin</td>
<td>blockers</td>
<td>Insulin</td>
</tr>
<tr>
<td>Resins</td>
<td></td>
<td>Sulfonylureas</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td>TZDs</td>
</tr>
</tbody>
</table>

**Diet**

- Statins
- Fibrates
- Niacin
- Resins

**Meds**

- ACEI
- ARB
- Diuretic
- Ca-channel blockers
- Weight

- Diabetic
- Hypertension
- Type 2 DM

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**Emerging Treatment Approach**

↑ Adipose Tissue

Reduce BMI and waist circumference

- ↓ Calories, glycemia
- ↑ Daily activity/exercise
- Behavior/therapy
- Medication—Current: 5-HT₃ agonists, CB₁ antagonists, others in development, combinations

**Dyslipidemia**

- ↑ Omega-3s
- ↑ MUFA
- ↓ Fat
- ↓ Trans fat
- ↓ Glycemia + ETOH

**Hypertension**

- DASH
- ↓ Na
- ↓ ETOH

**IGT**

- Fiber
- ↓ Glycemic diet

**Meds**

- Statins
- Fibrates
- ACEI
- ARB
- Metformin
- Exenatide