The Skinny On Obesity Meds

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Disclosures

- No financial disclosures
- Generic and branded names may be interchanged during the lecture
- Off-label use of medications will be discussed
Objectives

- Define Obesity
- Understand which patient is a candidate for weight loss medications
- Understand the new management approach to overweight and obesity
- Learn the MOA, risks, side effects, and potential efficacy of weight loss medications
- Recognition of common weight gaining medications

LONDON | Thu Jul 29, 2010

(Reuters) - British Public Health Minister has urged doctors to call overweight patients 'fat' rather than 'obese.'

"Doctors and health workers are too worried about using the term 'fat'," said the health minister, "but doing so will motivate people to take personal responsibility for their lifestyles."

"Calling them 'obese' does not provide sufficient motivation.
Just call them fat: Plain-speaking doctors will help people into losing weight."
"...the view of obesity as a behavioral decision is debunked by biomedical evidence......obesity is a primary disease, and the full force of our medical knowledge should be brought to bear on its prevention and treatment......"

AMA: Essential Criteria of A Disease
1. Characteristic signs or symptoms
2. Impairment in the normal functioning of some aspect of the body
3. Results in harm or morbidity
Obesity Definition

Obesity is a chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences.

Determinants of Obesity

- **Genes**
  - Protective and at risk alleles for weight gain
  - Random penetrance
  - Gender
  - Genetic-Gene interactions

- **Environment**
  - Food availability
  - Food quality
  - Built environment
  - Socioeconomic status
  - Education

- **Behavior**
  - Dietary preferences
  - Physical activity
  - Psychosocial factors
  - Cultural factors
  - Genetic life patterns

BMI increases as the number of alleles increases
IT'S NATIONAL "GET YOUR SHIT TOGETHER DAY"

Unfortunately, it's the least celebrated holiday
Use of Anti-Obesity Medications

- BMI: >30 or >27+comorbidity
- Combine with behavioral modification, physical activity, and nutrition for optimal results
- Continue medications only in responders
- Use combinations if monotherapy does not give desired results
- Long-term continuation if indicated
Interacting Pathways of Energy Regulation

Central Mechanisms of Action

Food intake

GABA
Liraglutide
Topiramate

SHT
Lorcaserin

NE
Phentermine

Dopamine
Bupropion/
Naltrexone

POMC=ProOpioMelanoCortin
NPY=Neuropeptide Y
AgRP=Agouti-Related Peptide
Current Anti-Obesity Medications

**FDA approved**
- Phentermine
- Diethylpropion
- Phendimetrazine
- Orlistat
- Lorcaserin
- Phentermine/Topiramate
- Naltrexone/Bupropion
- Liraglutide

**Off Label Use**
- Metformin
- Exenatide (and other GLP-1s)
- Canagliflozin (and other SGLT-2s)
- Pramlintide
- Topiramate
- Zonisamide
- Bupropion

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**Average Weight Loss with Anti-Obesity Meds**

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**Med Continuation:** 
*High Responders lose >5% in 3 months*

- Start Low Dose RX
- **FU 1 month**
- **FU 3 months**
- **D/C or lower dose**
  - **<3-5%**
  - **<12 lbs at max dose**
  - **D/C—Use alternative RX**
  - **OR**
  - **>3-5%**
  - **>12 lbs at max dose**
  - **Continue same dose**
  - **FU 3 months**
Medications are needed for long durations

BLOOM Trial
Smith et al, NEJM 2010;363-245-56

Medications are needed for maintenance

The SCAFE Maintenance randomized study
International Journal of Obesity (2013) 37, 1443-1451

Anti-Obesity Medications

Table:

<table>
<thead>
<tr>
<th>Mechanism of Action:</th>
</tr>
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<tbody>
<tr>
<td>Dosing:</td>
</tr>
<tr>
<td>Advice/Precautions:</td>
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Chart: Change in body weight (%) over time (weeks) for Liraglutide 3.0 mg vs Placebo.
### Orlistat

<table>
<thead>
<tr>
<th>Mechanism of Action:</th>
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<tbody>
<tr>
<td>• Pancreatic lipase inhibitor—Blocks ~30% of fat intake</td>
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<table>
<thead>
<tr>
<th>Dosing:</th>
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<tbody>
<tr>
<td>• Start 120mg daily</td>
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<tr>
<td>• Range: 120mg–150mg TID</td>
</tr>
<tr>
<td>• Alli is an OTC available in 60mg</td>
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<table>
<thead>
<tr>
<th>Advice/Precautions:</th>
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<tbody>
<tr>
<td>• Advise daily multivitamin</td>
</tr>
<tr>
<td>• Monitor fat-soluble vitamins (A,D,E,K)</td>
</tr>
<tr>
<td>• Decrease levels of cyclosporin if co-administered</td>
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<tr>
<td>• No causal relationship with liver failure</td>
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### Phentermine

<table>
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<tr>
<th>Mechanism of Action:</th>
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<tr>
<td>• Inhibits Na-dependent NE transporter to reduce NE uptake</td>
</tr>
<tr>
<td>• Inhibits serotonin and dopamine reuptake</td>
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</tbody>
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<thead>
<tr>
<th>Dosing:</th>
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<tbody>
<tr>
<td>• 15-30mg capsule, 37.5mg tablet QD-BID</td>
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<tr>
<td>• 4mg TID</td>
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<tr>
<td>• 1/2 of 37.5mg tablet</td>
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<tr>
<th>Advice/Precautions:</th>
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</thead>
<tbody>
<tr>
<td>• Schedule IV controlled substance</td>
</tr>
<tr>
<td>• Monitor BP, awareness of caffeine intake</td>
</tr>
<tr>
<td>• NO evidence of addiction, withdrawal</td>
</tr>
<tr>
<td>• NO established relationship related to cardiac valvulopathy or pulmonary hypertension</td>
</tr>
</tbody>
</table>
Why you shouldn’t be afraid of phentermine

- Phentermine is the most widely used anti-obesity drug in the U.S.
- Warnings of adverse CV and psychiatric effects are included in FDA labeling. However, the few clinical reports of such adverse effects are anecdotal.
- When phentermine was approved (1959) the expectations were that it would prove to be addictive. Due to the structural similarities between phentermine and amphetamine and on evidence in rats that phentermine stimulated spontaneous activity. No evidence suggesting the drug had human addiction potential appeared in clinical trials conducted prior to approval.
- After 60 years, there is no evidence in peer-reviewed medical literature to support the hypothesis that phentermine has significant human addiction potential.
- One retrospective study investigated symptoms occurring when patients treated with long-term phentermine ceased taking it. The study found that patients on long-term phentermine who ceased phentermine abruptly by their choice did not have an amphetamine-like withdrawal symptom complex. Significantly, there was no evidence of phentermine cravings.

Topiramate (Topamax®)

- Migraines, seizures, binge eating, excessive cravings (carbs), on mood stabilizers (sub/add), on phentermine
- Severe depression
- Pregnancy
- Kidney Stones

**WARNING:** Acute angle glaucoma, SI, pregnancy

**Mechanism of Action:** Unclear
- AMPA, Glutamate receptor
- Carbonic anhydrase
- GABA-A (isozymes II, IV)
- Voltage-dependent sodium channels

**Dosing:**
- Start 25mg daily
- Range: 25-200mg/daily

**Advice/Precautions:**
- Take at night if trouble with drowsiness
- Interaction with OCPs
- Use BIRTH CONTROL d/t increased risk of cleft lip and palate
- Hyperchloremic NAGMA

Try zonisamide if cognitive impairment or dysgeusia in intolerable
### Phentermine/Topiramate CR (Qysmia®)

**Mechanism of Action:**
- Sympathomimetic (NE) release in hypothalamus decreases hunger
- AMPA, GABA receptor—decreases cravings

**Dosing:**
- Start 3.75/23mg x 14 days then 7.5/46mg
- Range 3.75/23mg—15/92mg/day

**Advice/Precautions:**
- Schedule IV controlled substance
- Counsel on use of BIRTH CONTROL due to increased risk of cleft lip and palate
- Pregnancy test prior to start then MONTHLY
- Increase hydration
- 1/4 cup lemon/lime juice for paresthesias

### Responders to Phentermine/Topiramate (Qsymia)

**Study 1 (EQUIP)**
- **Time (Week):** 1, 6, 16, 37
- **Weight Change (%):** -6, -2.2, -0.8, 0.6

**Study 2 (CONQuISiTER)**
- **Time (Week):** 1, 6, 24, 56
- **Weight Change (%):** -6, -2.2, -0.8, 0.6

### Lorcaserin (Belviq®)

**Mechanism of Action:**
- Selective serotonin 5HT2c receptor agonist
- Increases satiety via alpha-MSH and POMC neuron activation

**Dosing:**
- 10mg BID or 20mg XR daily
- Can use QD daily in evening as combination

**Advice/Precautions:**
- Schedule IV controlled substance
- Watch co-administration with SSRIs, bupropion or concern about serotonin syndrome
- Caution with congestive heart failure
- No concern about combo with phentermine
Weight Loss Over 2 Years

BLOOM Trial
Smith et al, NEJM 2010;363-245

Secondary End-Points of Lorcaserin

- Blood Pressure
- Resting Heart Rate
- HbA1c%
- Fasting Glucose

Naltrexone/Bupropion (Contrave®)

Mechanism of Action:
- Reuptake inhibitor decreases DA and NE activity
- Increases POMC activity
- Naltrexone blocks B-endorphin, POMC auto inhibitor

Advice/Precautions:
- Avoid opioid use, ask about surgery!
- Results of LIGHT trial (2016) do NOT show reduction in CV events
- Avoid high-fat diet (increases bioavailability)

EXCESSIVE HUNGER AND CRAVINGS
- Patients who smoke
- On bupropion already

SEIZURES, UNCONTROLLED HTN
- Butina
- Chronic opioid use
- Upcoming surgery

WARNING: Neuropsychiatric reactions, SI, behavior changes
- Nausea, headache, insomnia, dizziness, dry mouth
Reduces the probability that compensatory pathways mitigate drug benefits over time!

Liraglutide (Saxenda ®)

Mechanism of Action:
• GLP-1 receptor agonist
• Increase satiety, decreases gastric emptying
• 97% homologous to human GLP-1
• Central acting by inhibition of NPY/AgRP

Dosing: Daily SC injections

Advice/Precautions:
• Nausea may improve with time
• No data to support reports on increased risk of pancreatic ductal neoplasia and pancreatic cancer

Average Weight Loss With Liraglutide 3mg

Improvements in Secondary End-Points with Liraglutide 3mg

Comparison of Anti-Obesity Medications

Before Adding A Med…

Determine if a med is the cause!
### Weight Gain Promoting Medications and Alternate Agents

<table>
<thead>
<tr>
<th>Diabetes Treatments:</th>
<th>Alternative Agents:</th>
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<tbody>
<tr>
<td>Insulin</td>
<td>Amylin analog—pramlintide</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>GLP-1 agonists</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Metformin</td>
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<tr>
<td>Glucocorticoids</td>
<td>DPP4 inhibitors</td>
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<tr>
<td>Prednisone, Methylprednisolone, etc.</td>
<td>Immunosuppressive agents</td>
</tr>
<tr>
<td>Contraceptives:</td>
<td>Non-hormonal contraception</td>
</tr>
<tr>
<td>Depressives:</td>
<td>OCPs</td>
</tr>
<tr>
<td>Beta-Blockers:</td>
<td>Other anti-hypertensives such as ACEI (Third generation) BBs have less weight gain (candesartan, nebivolol)</td>
</tr>
<tr>
<td>Proprietary, Blockers, Aleterol</td>
<td></td>
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<tr>
<td>Anti-Histamines:</td>
<td>Levaldine</td>
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<tr>
<td>Diphenhydramine, Cetirizine, Fexofenadine</td>
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<thead>
<tr>
<th>Antipsychotics:</th>
<th>Alternate Agents:</th>
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<tbody>
<tr>
<td>Clozapine, olanzapine, quetiapine, risperidone, aripiprazole</td>
<td>Ziprasidone</td>
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<tr>
<td>Atypical Antipsychotics:</td>
<td></td>
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<tr>
<td>Medroxyprogesterone acetate, risperidone, aripiprazole, olanzapine</td>
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<table>
<thead>
<tr>
<th>Antidepressants:</th>
<th>Alternate Agents:</th>
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<tbody>
<tr>
<td>Serotonin reuptake inhibitors:</td>
<td>Sertraline</td>
</tr>
<tr>
<td>Amoxapine, nortriptyline, amitriptyline</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Mirtazapine, trazodone, tricyclics</td>
<td>CBT</td>
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<tr>
<td>Memantine or ketamine</td>
<td></td>
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<tr>
<td>Other:</td>
<td></td>
</tr>
<tr>
<td>Gabapentin, valproic acid, topiramate, lamotrigine</td>
<td>L-methylfolate (Deplin®)</td>
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<table>
<thead>
<tr>
<th>Mood Stabilizers:</th>
<th>Alternate Agents:</th>
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<tbody>
<tr>
<td>Lithium</td>
<td>Cariprazine (Vraylar®)</td>
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**Questions?**

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Want to know more?

Sign up for a roundtable event

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Learn about available clinical obesity treatment tools at our Fundamentals of Obesity Treatment Course!

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Feb. 16 | Dallas, TX
March 2 | Chicago, IL
May 4 | Cleveland, OH
Oct. 19 | San Francisco, CA

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