The Skinny On Obesity Meds

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THE MEAL IS NOT OVER WHEN I'M FULL

THE MEAL IS OVER WHEN I HATE MYSELF
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 jolt people into losing weight."
<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>ANTHROPOMETRIC COMPONENT</th>
<th>CLINICAL COMPONENT</th>
<th>Prevention/Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>BMI &lt; 25</td>
<td></td>
<td>Primary</td>
</tr>
<tr>
<td>Overweight Stage 0</td>
<td>BMI 25-29.9</td>
<td>No obesity-related complications</td>
<td>Secondary</td>
</tr>
<tr>
<td>Obesity Stage 0</td>
<td>BMI ≥ 30</td>
<td>No obesity-related complications</td>
<td></td>
</tr>
<tr>
<td>Obesity Stage 1</td>
<td>BMI ≥ 25</td>
<td>Presence of 1 or more mild-to-moderate obesity-related complications</td>
<td>Tertiary</td>
</tr>
<tr>
<td>Obesity Stage 2</td>
<td>BMI ≥ 25</td>
<td>Presence of 1 or more severe obesity-related complications</td>
<td></td>
</tr>
</tbody>
</table>
AMA, June 2013

“…..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
  - Race (ancestral admixture)
  - Gene-Gene interactions

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

- **Biological factors**
  - In utero environment
  - Birth Weight
  - Gender
  - Age
  - Concurrent diseases

- **Behavior**
  - Dietary preferences
  - Physical activity
  - Psychological factors
  - Cultural factors
  - Diurnal life patterns
BMI increases as the number of alleles increases.
IT'S NATIONAL "GET YOUR $HIT TOGETHER DAY"

Unfortunately, it's the least celebrated holiday
## Old Treatment Paradigm

**Treat Weight LAST**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dyslipidemia</th>
<th>HTN</th>
<th>IGT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monitor</strong></td>
<td>Lipid panels</td>
<td>Blood Pressure</td>
<td>Blood sugar</td>
</tr>
<tr>
<td></td>
<td>Lipoproteins</td>
<td>Ambulatory Blood</td>
<td>Glycosylated</td>
</tr>
<tr>
<td></td>
<td>subsets</td>
<td>Pressure</td>
<td>hemoglobin</td>
</tr>
<tr>
<td><strong>Diet</strong></td>
<td>↓ Total fat</td>
<td>↓ Sodium</td>
<td>↓ Sugar</td>
</tr>
<tr>
<td></td>
<td>↓ Chol.</td>
<td>↑ K ++</td>
<td>Distribute CHO,</td>
</tr>
<tr>
<td></td>
<td>↑ Fiber</td>
<td></td>
<td>PRO, Fat</td>
</tr>
<tr>
<td><strong>Meds</strong></td>
<td>Statins</td>
<td>Central acting</td>
<td>Insulin</td>
</tr>
<tr>
<td></td>
<td>Fibrates</td>
<td>Renal effective</td>
<td>Sulfonylureas</td>
</tr>
<tr>
<td></td>
<td>Resins</td>
<td>Peripherally acting</td>
<td>Glidizones</td>
</tr>
<tr>
<td></td>
<td>Niacin</td>
<td>diuretics</td>
<td>Absorption agents</td>
</tr>
</tbody>
</table>

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**Overweight/Obesity**

<table>
<thead>
<tr>
<th>Monitor</th>
<th>Weight and BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet</strong></td>
<td>Any diet patient will adhere to</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td>150 minutes of moderate-intensity aerobic activity/wk and muscle-strengthening activities on &gt; 2 days/wk</td>
</tr>
<tr>
<td><strong>Meds</strong></td>
<td>Orlistat, phentermine, phentermine/topiramate, lorcaserin</td>
</tr>
</tbody>
</table>
### New Treatment Paradigm
Treat Weight FIRST

#### Overweight/Obesity

<table>
<thead>
<tr>
<th>Monitor</th>
<th>Weight and BMI</th>
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</table>

#### Dyslipidemia

<table>
<thead>
<tr>
<th>Monitor</th>
<th>Lipid panels Lipoproteins subsets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>↓ Sat + trans fat ↑ Omega-3s ↑ MUFA ↓ Simple CHO↓ ETOH</td>
</tr>
<tr>
<td>Meds</td>
<td>Statins Fibrates</td>
</tr>
</tbody>
</table>

#### HTN

<table>
<thead>
<tr>
<th>Blood Pressure Ambulatory Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>DASH Diet ↓ Sodium ↓ ETOH</td>
</tr>
<tr>
<td>Glycemic index diet ↑ Fiber Diabetic diet</td>
</tr>
</tbody>
</table>

#### IGT

<table>
<thead>
<tr>
<th>Blood sugar Glycosylated hemoglobin distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins Fibrates</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACE Inhibitors Thiazide diuretics Metformin Exenatide Liraglutide</th>
</tr>
</thead>
</table>
Treatment Pyramid

Continuum of Care

BMI ≥35 with co-morbidites
BMI ≥40 without co-morbidites

BMI ≥27 with co-morbidites
BMI ≥30 without co-morbidites

BMI ≥25

Lifestyle Modification
(diet, physical activity, behavior modification)

Pharmacotherapy

Surgery
Use of Anti-Obesity Medications

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


Central Mechanisms of Action

- GABA
- Liraglutide
- Topiramate
- POMC
- CART
- AgRP
- NPY

Food Intake

5HT
Lorcaserin
NE
Phentermine
Dopamine
Bupropion/ Naltrexone

POMC=ProOpioMelanoCortin
CART=Cocaine and Amphetamine Regulated Transcript
NPY=Neuropeptide Y
AgRP=Agouti-Related Peptide
# Current Anti-Obesity Medications

<table>
<thead>
<tr>
<th>FDA approved</th>
<th>Off Label Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>Metformin</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>Exenatide (and other GLP-1s)</td>
</tr>
<tr>
<td>Phendimetrazine</td>
<td>Canagliflozin (and other SGLT-2is)</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Pramlintide</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Phentermine/Topiramate</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Naltrexone/Bupropion</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Liraglutide</td>
<td></td>
</tr>
</tbody>
</table>
Average Weight Loss with Anti-Obesity Meds

Note: Diethylpropion not listed, 3.0kg, duration 6-52wks
* Most trials are ≥ 1 year (*except Phentermine, 2-24wks, meta-analysis of trials, weight range 0.6-6.0kg)
**Med Continuation**: *High Responders lose >5% in 3 months*

- **Start Low Dose RX**
  - **F/U 1 month**
  - **F/U 3 months**
    - <3-5% <12 lbs at max dose → **D/C—Use alternative RX**
    - OR
    - >3-5% >12 lbs at max dose → **Continue same dose**

**Adverse Effects**
- **D/C or lower dose**
Medications are needed for long durations

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

Completer population at Year 2

Baseline weight

-2.6 kg/-5.7 lb

-3.8 kg/-8.4 lb

-6.0 kg/-13.2 lb

LS Mean weight change (kg)

study week

Placebo Year 1 and 2 (N=507)

BELVIQ® Year 1/Placebo Year 2 (N=195)

BELVIQ® Year 1 and 2 (N=426)

All patients received lifestyle modification counseling.
Medications are needed for maintenance

The SCALE Maintenance randomized study

International Journal of Obesity (2013) 37, 1443-1451
# Anti-Obesity Medications

<table>
<thead>
<tr>
<th>Potential Targets</th>
<th>Contraindications*</th>
<th>Common Adverse Effects</th>
</tr>
</thead>
</table>

### Contraindications*

*Not a complete list

<table>
<thead>
<tr>
<th>Mechanism of Action:</th>
<th>Dosing:</th>
<th>Advice/Precautions:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Orlistat**

**Mechanism of Action:**
- Pancreatic lipase inhibitor—Blocks ~30% of fat intake

**Dosing:**
- Start 120mg daily
- Range: 120mg/d—120mg TID
- Alli is an OTC available in 60mg

**Advice/Precautions:**
- Advise daily multivitamin
- Monitor fat-soluble vitamins (A,D,E,K)
- Decrease levels of cyclosporin if co-administered
- No causal relationship with liver failure

**Hypercholesterolemia**
- Low risk medication

**Cholestasis**
- Chronic malabsorption syndrome

**Flatulence, diarrhea, bloating, cramping, abd pain**
- Increase urinary oxalate
- Fat soluble vitamin deficiency
Please Excuse Me From Being Late.
I HAVE Explosive Diarrhea.
-K
Phentermine

Mechanism of Action:
- Inhibits Na-dependent NE transporter to reduce NE uptake
- Inhibits serotonin and dopamine reuptake

Dosing:
- 15-30mg capsule, 37.5mg tablet QD-BID
- 8mg TID
- 1/2 of 37.5mg tablet

Advice/Precautions:
- Schedule IV controlled substance
- Monitor BP, awareness of caffeine intake
- NO evidence of addiction, withdrawal
- NO established relationship related to cardiac valvulopathy or pulmonary hypertension

Increased hunger
Low metabolic rate

Active CV disease
Poorly controlled HTN
Cardiac arrhythmias
Hyperthyroidism
Glaucoma

Dry mouth
Constipation
Insomnia
Palpitations, HA, Irritability

CI

AE
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.
Safety and Effectiveness of Longer-Term Phentermine Use: Clinical Outcomes from an Electronic Health Record Cohort


Conclusions: Greater weight loss without increased risk of incident CVD or death was observed in patients using phentermine monotherapy for longer than 3 months. Despite the limitations of the observational design, this study supports the effectiveness and safety of longer-term phentermine use for low-risk individuals.

Topiramate (Topamax®)

**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/day

**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 dyspepsia is intolerable

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

**Warnings:**
- Acute angle glaucoma, SI, pregnancy
- Parasthesias, somnolence, kidney stones, cognitive impairment, taste aversion
**Phentermine/Topiramate CR (Qysmia®)**

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

**Dosing:**
- Start 3.75/23mg x14d 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

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**Non-child bearing pt**
- Excessive hunger
- Mild SE with phentermine

**Active CV Disease**
- Uncontrolled HTN
- Hyperthyroidism
- Glaucoma
- Kidney Stones
- During or within one day of MAOI

**Dry mouth, restlessness, insomnia, palpitations, HA, constipation**
- Parasthesias, dysgeusia, somnolence, cognitive impairment
Responders to Phentermine/Topiramate (Qsymia)

**Study 1 (EQUIP)**
- Time (Week): 8, 16, 24, 32, 40, 48, 56
- Weight Change, %
- Placebo
- Qsymia Low
- Qsymia Mid
- Qsymia Top
- Week 56 Data in lbs.

3.75/23mg/d
- 6 responders
- 18 responders
- 37 responders

7.5/46mg/d
- 6 responders
- 24 responders
- 30 responders

15/92mg/d


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

**Unable to tolerate phentermine**
- Older pt on multiple meds
- Diabetes
- Night eating

**Pregnancy**

**Headache, nausea, dizziness, dry mouth, fatigue, nasopharyngitis, priapism**
Weight Loss Over 2 Years

Completer population at Year 2

Baseline weight

-2.6 kg/5.7 lb
-3.8 kg/8.4 lb
-6.0 kg/13.2 lb

Study week

Placebo Year 1 and 2 (N=507)
BELVIQ® Year 1/Placebo Year 2 (N=195)
BELVIQ® Year 1 and 2 (N=426)

All patients received lifestyle modification counseling.
Secondary End-Points of Lorcaserin

Blood Pressure

Resting Heart Rate

HbA1c%

Fasting Glucose
Naltrexone/Bupropion (Contrave ®)

**Mechanism of Action:**
- Reuptake inhibitor DA and NE activity increases POMC activity
- Naltrexone blocks β-endorphin, POMC auto inhibitor

<table>
<thead>
<tr>
<th></th>
<th>Morning dose</th>
<th>Evening dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>🌅</td>
<td>🌅</td>
</tr>
<tr>
<td>Week 2</td>
<td>🌅</td>
<td>🌅</td>
</tr>
<tr>
<td>Week 3</td>
<td>🌅 🌅</td>
<td>🌅</td>
</tr>
<tr>
<td>Week 4-onward</td>
<td>🌅 🌅 🌅</td>
<td>🌅 🌅 🌅</td>
</tr>
</tbody>
</table>

**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**
- Bulimia
- Chronic Opioid Use
- Upcoming surgery

**WARNING:** Neuropsychiatric rxns, SI, behavior changes
- Nausea, headache, insomnia, dizziness, dry mouth
Reduces the probability that compensatory pathways mitigate drug benefits over time!
**Liraglutide (Saxenda ®)**

**Diabetes or Prediabetes**
(Not indicated for diabetes tx)
**Pts with insurance coverage**

**Medullary thyroid CA**
(including FHx)
**MEN type II**
**Hx of pancreatitis**

**Nausea, HA, Angioedema**
**Gastroparesis**
**Cannot be combined with DPP4i**

**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

<table>
<thead>
<tr>
<th>WEEK 1</th>
<th>WEEK 2</th>
<th>WEEK 3</th>
<th>WEEK 4</th>
<th>WEEK 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6 mg</td>
<td>1.2 mg</td>
<td>1.8 mg</td>
<td>2.4 mg</td>
<td>3.0 mg</td>
</tr>
</tbody>
</table>

**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

**Blood Pressure**

- Baseline SBP: 123 mm Hg
- Baseline DBP: 78.7 mm Hg
- Change in SBP: -1.5 mm Hg
- Change in DBP: -1.8 mm Hg

**Lipids**

- Baseline Total Cholesterol: 193.8 mg/dL
- Baseline LDL Cholesterol: 111.8 mg/dL
- Baseline HDL Cholesterol: 51.4 mg/dL
- Baseline Triglycerides: 125.7 mg/dL
- Change in Total Cholesterol: -3.2 mg/dL
- Change in LDL Cholesterol: -3.1 mg/dL
- Change in HDL Cholesterol: 2.3 mg/dL
- Change in Triglycerides: -4.1 mg/dL
Comparison of Anti-Obesity Medications
Before Adding A Med…

Determine if a med is the cause!
<table>
<thead>
<tr>
<th>Weight Gain Promoting Medications</th>
<th>Alternate Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes Treatments:</strong></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td></td>
<td>SGLT-2 inhibitors</td>
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<td></td>
<td>DPP4 inhibitors</td>
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<tr>
<td><strong>Glucocorticoids</strong></td>
<td></td>
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<tr>
<td>Prednisone, Methyl-prednisolone,</td>
<td>Immunosuppressive</td>
</tr>
<tr>
<td>etc</td>
<td>agents DMARDs</td>
</tr>
<tr>
<td><strong>Contraceptives</strong></td>
<td></td>
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<tr>
<td>Depo-provera</td>
<td>Non-hormonal</td>
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<td></td>
<td>contraception OCPs</td>
</tr>
<tr>
<td><strong>Beta-Blockers</strong></td>
<td></td>
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<tr>
<td>Propranolol, Metoprolol, Atenolol</td>
<td>Other anti-hypertensives such as ACEi</td>
</tr>
<tr>
<td></td>
<td>Third generation BBs have less weight gain (carvediolol, nebulol)</td>
</tr>
<tr>
<td><strong>Anti-Histamines</strong></td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine, Hydroxyzine,</td>
<td>Loratadine</td>
</tr>
<tr>
<td>Cetirizine, Fexofenadine</td>
<td></td>
</tr>
<tr>
<td>Weight Gain Promoting Medications</td>
<td>Alternate Agents</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Atypical Antipsychotics:</strong> clozapine, olanzapine, quetiapine, risperidone, aripiprazole</td>
<td>ziprasidone</td>
</tr>
<tr>
<td><strong>Anti-Depressants:</strong> Tricyclics: nortriptyline, amitriptyline</td>
<td>bupropion, sertraline, CBT, memantine or ketamine, L-methylfolate (Deplin®)</td>
</tr>
<tr>
<td>SSRIs: paroxetine, citalopram, escitalopram</td>
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</tr>
<tr>
<td>Others: trazodone, mirtazapine, venlafaxine</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-Epileptics</strong> gabapentin, valproic acid</td>
<td>topiramate, zonisamide, lamotrigine</td>
</tr>
<tr>
<td><strong>Mood Stabilizers</strong> lithium</td>
<td>topiramate, zonisamide, lamotrigine, cariprazine (Vraylar®)</td>
</tr>
</tbody>
</table>
Want to know more?
Sign up for a roundtable event

Questions?

stacy.chronister@okstate.edu
Learn about available clinical obesity treatment tools at our Fundamentals of Obesity Treatment Course!

View Course Dates and Cities