Overcoming Challenges in the Management of Obesity:
A Closer Look at Emerging Therapeutic Options

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• Disclosures: NONE

• I will not be discussing off-label medication use
Objectives

• Review definition of obesity and prevalence
• Review guidelines for obesity treatment
• Review specific therapies for obesity
  – Lifestyle
  – Pharmacotherapy
    • Focus on emerging pharmacologic options
      – Mechanism of action
      – Efficacy
      – Safety
      – Managing Adverse Effects
    • Considerations for patients with multiple co-morbidities
  – Surgery

What is the definition of obesity?

<table>
<thead>
<tr>
<th></th>
<th>BMI (kg/m²)</th>
<th>Obesity Class</th>
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<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td></td>
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<tr>
<td>Normal</td>
<td>18.5 - 24.9</td>
<td></td>
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<tr>
<td>Overweight</td>
<td>25.0 - 29.9</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>30.0 - 34.9</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>35.0 - 39.9</td>
<td>II</td>
</tr>
<tr>
<td>Morbid Obesity</td>
<td>≥ 40</td>
<td>III</td>
</tr>
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</table>
Medical Complications of Obesity

- Pulmonary disease
  - abnormal function
  - obstructive sleep apnea
  - hypoventilation syndrome

- Nonalcoholic fatty liver disease
  - steatosis
  - steatohepatitis
  - cirrhosis

- Gall bladder disease

- Gynecologic abnormalities
  - abnormal menses
  - infertility
  - polycystic ovarian syndrome

- Osteoarthritis

- Skin

- Gout

- Idiopathic intracranial hypertension

- Stroke

- Cataracts

- Coronary heart disease

- Diabetes

- Dyslipidemia

- Hypertension

- GERD

- Severe pancreatitis

- Cancer
  - breast, uterus, cervix
  - colon, esophagus, pancreas
  - kidney, prostate

- Phlebitis

- venous stasis
A Guide to Selecting Treatment: National Institutes of Health (NIH) Guidelines*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>25–26.9</th>
<th>27–29.9</th>
<th>30–34.9</th>
<th>35–39.9</th>
<th>≥40</th>
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</thead>
<tbody>
<tr>
<td>Diet, physical activity, behavior</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>therapy</td>
<td>*comorbidities</td>
<td>*comorbidities</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Pharmacotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Weight-loss surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>***</td>
<td>*comorbidities</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

*Yes alone indicates that the treatment is indicated regardless of the presence or absence of comorbidities. The solid arrow signifies the point at which therapy is initiated.

*** The FDA has approved use of LAGB for patients with BMI ≥ 30 who also have at least one condition linked to obesity, such as heart disease or diabetes.


Weight Loss Treatments

- Lifestyle Changes
- Pharmacotherapy
- Bariatric Surgery
Non-Pharmacologic Therapy for Obesity

Lifestyle changes

Lifestyle Changes

- Behavior Therapy
- Diet
- Exercise
Behavior Therapy

- **Self-monitoring:** includes recording dietary intake (food choices, amounts, times), exercise and changes in body weight.

- **Stimulus control:** identify and change cues that are associated with eating too much and exercising too little. For example, limiting exposure to food or separating eating from other activities such as reading or watching television.

Behavior Therapy (cont.)

- **Reinforcement:** encourages attainment of difficult to achieve goals. Reinforcement may come from a social support network or getting non-food rewards for reaching goals or maintaining healthy lifestyle changes.

- **Stress management:** helps coping with stressful events by developing outlets besides eating for reducing stress. Evaluating setbacks and determining how to do better next time can break the chain of negative thinking and self-punishment when lapses occur.
Dietary Therapy

- Main component for weight loss is to create a calorie deficit.
- Recommend a plan based on your patient’s food preferences. Many eating plans work.
- Present them a few meal plan options:
  - Meal replacements, pre-packaged food (most structure)
  - Calorie counting
  - Specific meal plan
- Have handouts/resources to help them with dietary changes or write down options for them.
- Food diary
- Referral to Nutritionist

**Comparison of the Atkins, Ornish, Weight Watchers, and Zone Diets for Weight Loss and Heart Disease Risk Reduction**

A Randomized Trial

• RCT of 160 overweight/obese adults (mean BMI 35, range 27-42) w/HTN, HL, or fasting hyperglycemia, randomized to 1 of 4 diets:
  - Atkins (carbohydrate restriction/high fat)
  - Zone (high protein)
  - Weight Watchers (caloric restriction)
  - Ornish (fat restriction/high carb)

• After 2 months, pts chose own level of dietary adherence

RESULTS at 1 yr:
  - adherence- low for all diets (50-65%)
  - wt loss- modest in all groups (4-7 lbs)
  - cardiac risk markers- improvement in all groups: decr LDL/HDL by 10%, decr CRP, decr insulin

CONCLUSION: macronutrient composition did NOT determine degree of improvement in wt or cardiac risk markers; dietary adherence did.

Exercise

• Counters tendency to regain weight due to:
  – More efficient muscles (burn less calories for same amount of activity)
  – Baseline calorie expenditure is lower (carrying around less weight burns less calories than prev)
  – For every 1 lb. lost, pts burn 8kcal/day less.
• Start where patient is and slowly build


Physical Activity Recommendations

• 1st recommendation to reduce chronic disease risk: 30 minutes of moderate-intensity aerobic activity x 5d (150 min/week).

• 2nd recommendation to help manage body weight and prevent weight gain in adulthood: 60 minutes of moderate PA most days of the week (300 min/week).

• 3rd recommendation to prevent weight regain: 60-90 minutes of moderate PA most days of the week (350 min/week).

• Strength training on 2 or more days a week for ≥20 minutes each time.

2010 Dietary Guidelines; Look AHEAD
Lifestyle Modification For Obesity Tom Wadden 2012
Pharmacotherapy for Obesity

• Short-term

• Long-term

Weight effects of common chronic medications

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>WT GAIN</th>
<th>WT LOSS/NEUTRAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants/Anti-psychotics</td>
<td>TCA’s, SSRI’s/Seroquel</td>
<td>Wellbutrin</td>
</tr>
<tr>
<td>BP meds</td>
<td>Beta-blockers</td>
<td>CCBs, ACE-I, ARBs</td>
</tr>
<tr>
<td>Anti-epileptics</td>
<td>Gabapentin</td>
<td>topiramate, zonisamide</td>
</tr>
</tbody>
</table>
Impact of Anti-Diabetic Therapies on Weight

<table>
<thead>
<tr>
<th>GAIN</th>
<th>NEUTRAL</th>
<th>LOSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Non-sulfonylurea secretagogues (Prandin)</td>
<td>Metformin</td>
</tr>
<tr>
<td>TZDs</td>
<td>α-Glucosidase Inhibitor (Acarbose)</td>
<td>GLP-1 agonist (Byetta/Victoza)</td>
</tr>
<tr>
<td>Insulin</td>
<td>DPP4-Inhibitor (Januvia)</td>
<td>Pramlintide (Symlin)</td>
</tr>
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</table>


Short-term Pharmacotherapy

Noradrenergic Medications
Noradrenergic Agents

- Schedule IV drugs have a low potential for abuse

- **Phentermine** (Adipex-P, Fastin): 18.75-37.5 mg/day

- **Phentermine resin** (Ionamin): 15-30 mg/day

- **Diethylpropion** (Tenuate, Tenuate Dospan): 25 mg 3x/day or sustained release 75 mg/day

- **Phenylpropanolamine** (Dexatrim, Acutrim): withdrawn from market due to association with hemorrhagic stroke

Yanovski NEJM 346:591 2002

Noradrenergic Agents (cont’d)

- Approved by the FDA for short-term use: ~ 3 months
- Studies show between 2-10 kg weight loss over placebo
- Adverse effects: insomnia, dry mouth, constipation, palpitations, hypertension
Long-term Pharmacotherapy

- Orlistat
- Lorcaserin
- Qsymia

Orlistat (Alli/Xenical)
Mechanism of Action

30% of fat not absorbed
Subjects (%) who Lost $\geq 5\%$ and $\geq 10\%$ of Initial Weight after 1 Y Orlistat or Placebo. 
Data are from Trials in Europe, the U.S., and in Subjects With Diabetes*


Orlistat Adverse Effects

- Adverse effects: 
  - abdominal discomfort
  - oily spotting
  - flatulence with discharge
  - fecal urgency and incontinence

- Absorption of fat-soluble vitamins and some medications (e.g. Cyclosporine, levothyroxine, warfarin) may be affected.

- Liver failure?

- Managing adverse effects

Lorcaserin (Belviq)- Mechanism of Action

- Selective serotonin R agonist
- Doesn’t bind to 5HT-2b R’s on heart, as non-specific fenfluramine did
- Binds to 5HT-2c R’s in hypothalamus
- Activates POMC neurons and ultimately induces a feeling of satiety with a decr in food intake -> wt loss.

Lorcaserin Adverse Effects

- **Headaches** (16.8% lorcaserin vs 10.1% placebo)
- Dry Mouth
- Fatigue
- Nausea
- Vomiting
- Dizziness

Hoy SM. Drugs March 2013, epub.

Qsymia- Mechanism of Action

- **Phentermine**
  - Increase in NE -> incr metabolism
    -> incr locomotor activity
  - Increase in DA -> decr appetite

- **Topiramate**
  - Decr appetite via unknown mechanism

**Qsymia**
*(phentermine/topiramate)*

Randomized, placebo-controlled extension study of controlled release phentermine/topiramate (Qsymia)

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**Qsymia and Progression to DM2**

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Garvey et al, AJCN 2012,95:297-308
Qsymia Adverse Effects

- Dry mouth
- Dizziness
- Constipation
- Insomnia
- Dysgeusia
- Paresthesia
- Headache
- Nephrolithiasis
- Depression
- Anxiety
- Irritability
- Disturbance to attention
- CLEFT PALATE

Garvey et al, AJCN 2012;95:297-308

Qsymia Adverse Effects

- Preventing Adverse Effects
  - Do not use in patients w/glaucoma or recent MI/CVA
  - Cleft palate: Effective contraception
  - Renal Stones: Increase H2O intake, drink crystal light

- Managing Adverse Effects
  - Insomnia: dosing schedule
  - Fatigue/difficulty concentrating: slow titration
  - Constipation: increase fiber & H2O intake
  - Paresthesias: take 1 alka-seltzer daily
Pharmacologic management of obesity in patients with multiple co-morbidities

Hyperlipidemia

- Xenical: leads to sig decr in total cholesterol, LDL-C and TGs over wt loss alone


Pharmacologic management of obesity in patients with multiple co-morbidities

Diabetes

- Qsymia (?)
Weight Reduction: Pharmacotherapy

- Initiate when weight goals are difficult to achieve or maintain through diet and physical activity
- Set realistic goals
- Administer for the long term
- Always use in conjunction with diet, physical activity, and behavior therapy
- Future therapies may involve a “cocktail” of different medications targeting different pathways
  - Contrave- bupropion/naltrexone
  - Empatie- bupropion/zonisamide

Non-Pharmacologic Therapy for Weight Loss

Bariatric Surgery
ADJUSTABLE GASTRIC BAND  
ROUX-EN-Y GASTRIC BYPASS  
SLEEVE GASTRECTOMY

SLEEVE GASTRECTOMY
ROUX-EN-Y GASTRIC BYPASS

Remission of Weight-Related Co-Morbidities after RYGB

- HTN- 50% w/complete resolution; remainder w/decr in meds
- Sleep apnea- 40% w/resolution; 70% of remainder of pts have apneic episodes reduced to minimal amounts
- Improved QoL
- Decr disability
- DM2 - resolution in 70-84% (1-2 yrs)
  - sustained resolution in 36% (10 yrs)

Sjöström et al, NEJM 2004; 351:2683-93
Weight Recidivism after Bariatric Surgery

- Successful RYGB: $\geq 50\%$ EBW remains off at 5 yrs
- Success rate w/RGyb = 70%
- Success rate w/LAGB = 50%

SUMMARY - Obesity Therapy

• Use a stepwise approach
• Remember that lifestyle changes are framework for success w/meds & surgery
• Prior to adding anti-obesity meds, review pt medication list for chronic meds which cause wt gain and change to therapeutic alternatives which are wt neutral or cause wt loss
• Plan to use medication therapy long-term, as obesity is a chronic disease
• Surgery may provide durable wt loss for some, others may benefit from adjunctive medication therapy if they experience wt regain

Thank you!
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