OBESITY TREATMENT UPDATE

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DISCLOSURES

Juliana Simonetti, MD – NOTHING TO DISCLOSE
Outline:

- Epidemiology of obesity in UT
- Pathophysiology of obesity
- Current treatments: Medical, surgical, non-surgical
Teaching Points:

- Excess fat causes chronic inflammation which leads to metabolic dysfunction
- Obesity’s leads to early mortality
- Causes of obesity beyond diet and exercise: genetics, environment, biology
- Treatment:
  - Medical treatment is more effective than diet and exercise alone
  - Devices, important to have options
  - Surgical options for those with severe obesity
Obesity: Rationale For Treatment

111 Million US Adults Are Obese or Overweight

In the USA, 40.4% of women and 35% of men are obese (BMI ≥ 30)

Adipose tissue is an endocrine organ

Significant physiological functions of white adipose tissue:
Appetite regulation, Immunity, glucose and lipid metabolism

Adiposopathy, sick fat

Fat hypertrophy causes direct and indirect adverse health consequences

Pathogenic Adipose Tissue

Deranged endocrine and immune response

Sick Fat Disease (Adiposopathy)
  - Elevated glucose
  - Elevated BP
  - Dyslipidemia
  - Other metabolic disease

Abnormal physical forces

Fat Mass Disease (FMD)
  - Stress on weight bearing Joints
    - Immobility
  - Tissue compression (sleep apnea, gastric reflux, high BP)
  - Tissue Friction (intertrigo)

Excess fat leads to chronic inflammation

1. **Overnutrition**
2. **Increase demand for lipid storage**
3. **Adipocyte hyperplasia and hypertrophy**

   - Hypoxia
   - Cytokines
   - Acute phase proteins
   - Recruitment of leukocytes
   - Reparative tissue response

**Chronic Inflammation**
Medical Complications of Obesity

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

- Nonalcoholic fatty liver disease
  - steatosis
  - steatohepatitis
  - cirrhosis

- Gallbladder disease

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

- Osteoarthritis

- Skin

- Gout

- Idiopathic intracranial hypertension

- Stroke

- Cataracts

- Coronary heart disease

- Diabetes

- Dyslipidemia

- Hypertension

- Severe pancreatitis

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

- Phlebitis
  - venous stasis
Significantly increases mortality

- A BMI of 30-35 reduces life expectancy by 2-4 years
- Severe obesity (BMI > 40) reduces life expectancy by 10 years

Solution= Weight Loss

Small amount of weight loss 5-10% will lead to significant health improvements

IMPROVING

- HTN: both systolic and diastolic, decrease by 5 mmHg on average
  - DM TYPE II: decrease in A1C 0.5-1%
  - HLD: can result in a 5 point increase in HDL and decrease triglycerides by an average of 40 mg/dl

Even a small weight loss (2%) in anovulatory obese infertile women resulted in improvements in ovulation, pregnancy rate, and pregnancy outcome

Why is it so hard to lose weight?

Humans have evolved an energy regulation system that at its core is to protect against energy deprivation.

**ENERGY EXPENDITURE**
- cortisol
- fat oxidation
- thyroid hormones

**FOOD INTAKE**
- GIP
- Ghrelin
- Leptin
- PYY
- Amylin
- Insulin
Obesity is a highly heritable disease

- Heritability of obesity ranges between 65% to 70%

Parks, B et al, Cell Metabolism, Volume 17, Issue 1, 141 - 152
http://www.cdc.gov/features/obesity/

• "thrifty genotype" hypothesis
Is Sugar Toxic?

By GARY TAUBES

APRIL 13, 2011

Environmental causes

http://dietdatabase.com/causes-of-obesity/

Per Capita Energy Intake in U.S. 1970-2009

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The image contains various food items and beverages, including sugar cubes and Dunkin' Donuts, suggesting a discussion on the consumption of sugary products and their potential health impacts.
Stress/Sleep Deprivation -> Weight Gain

CHRONIC STRESSOR

Hypothalamic-pituitary-adrenocortical (HPA) axis

↑ Insulin + ↑ Cortisol

↑ WEIGHT GAIN

↑ Appetite
↑ Anxiety, depression, apathy
↑ Activation of Lipoprotein Lipase
↑ Deposition of Visceral fat
↑ Cravings for fat and sugar
↓ Fat break down

↑ Overweight and Obesity
Microbiome

Prepregnancy

Normal gut microbiota

Pregnancy

Maternal gut microbiota

Fetal gut microbiota

Offspring

Healthy metabolic outcome

b

Disrupted gut microbiota

Maternal gut microbiota

Fetal gut microbiota

Adverse metabolic outcome

Weight promoting medications:

<table>
<thead>
<tr>
<th>CLASS</th>
<th>DRUGS</th>
<th>Affect on appetite and satiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensives</td>
<td><strong>Beta blockers</strong></td>
<td>-reduce metabolic rate&lt;br&gt;- slow utilization of nutrients</td>
</tr>
<tr>
<td>corticosteroids</td>
<td><strong>Prednisone</strong> (usually if taken for prolonged duration)</td>
<td>Multiple mechanisms:&lt;br&gt;-fluid retention&lt;br&gt;-stimulate appetite&lt;br&gt;- Increase fat deposition</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td><strong>Sodium valproate</strong>&lt;br&gt;Carbamazepine&lt;br&gt;gabapentin</td>
<td>Increasing appetite</td>
</tr>
<tr>
<td>Psych meds</td>
<td><strong>TCA antidepressant</strong>&lt;br&gt;-Atypical antipsychotics&lt;br&gt;-SSRIs</td>
<td>-antihistaminic activity and increase in appetite&lt;br&gt;-Changes in serotonin may also lead to increase in appetite and decrease satiety</td>
</tr>
<tr>
<td>Contraceptives</td>
<td>The progestin-only injectable&lt;br&gt;-<strong>depo medroxyprogesterone</strong></td>
<td>-*<em>DMPA users increased their weight (+5.1 kg), body fat (+4.1 kg), percent body fat (+3.4%) more than OC and NH users</em>&lt;br&gt;- Weight gain has not been consistent with OCPs</td>
</tr>
</tbody>
</table>

## Weight centric approach to treat DMII

<table>
<thead>
<tr>
<th>Intervention</th>
<th>A1C reduction expected %</th>
<th>Weight effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1-2</td>
<td>Loss 0.6-2.7 Kg</td>
</tr>
<tr>
<td>GLP-1 analogs (Liraglutide, Exenatide)</td>
<td>0.5-1.5</td>
<td>Loss 1.8-6.0 kg</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>0.5-0.7</td>
<td>Loss 1.5 Kg</td>
</tr>
<tr>
<td>DPP-4 inhibitor (Januvia)</td>
<td>0.5-0.8</td>
<td>Neutral</td>
</tr>
<tr>
<td>Sulfonylureas (Glipizide, glimepiride)</td>
<td>1-2</td>
<td>Gain 1.8-5.0 Kg</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.5-1.5</td>
<td>Gain 1.3-4.8 Kg</td>
</tr>
<tr>
<td>Insulin</td>
<td>1.5-3.5</td>
<td>Gain (variable) up to 10 kg</td>
</tr>
<tr>
<td>Intense Lifestyle intervention</td>
<td>0.6</td>
<td>Loss 8.6 % of body weight</td>
</tr>
</tbody>
</table>
NEW AACE Guidelines – Weight Loss or Weight Neutral Medications FIRST

1st Line
- Metformin

2nd Line
- GLP-1 receptor agonist
- SGLT2 inhibitor
- DPP-4 inhibitor

Last
- Insulins – cause weight gain
Requires Comprehensive Treatment Approach

- **Foundation of all weight management approaches**
- **Lifestyle Modification**
  - Diet + Physical Activity + BH
  - Devices
  - Pharmacotherapy
    - BMI ≥27 w/ comorbidities or BMI ≥30
  - Anti-obesity: Phentermine, Qsymia, Contrave, Belviq, Saxenda
- **Surgery**

For pts with BMI ≥35 w/ DM II or BMI >40
The Challenge

85% of patients that diet and exercise fail....

What do you offer your patients for whom diet, exercise and behavioral therapy alone has not resulted in sustained weight loss?

Target underlying pathways that contribute to hunger, satiety, and reward

Anti-obesity Medications

Medications plus lifestyle changes can result in weight loss of about 3.5-10kg more than lifestyle interventions alone.

AHA/TOS/ACC Guidelines for Selecting Treatment

- Non-drug interventions should be attempted for at least 6 months before considering pharmacotherapy
- For patients with BMI $\geq 30$
- For patients with BMI $\geq 27$ w/ concomitant risk factors or diseases (hypertension, dyslipidemia, CHD, type 2 diabetes, sleep apnea)

Agents may be used in those $>18$ yo. There is a lack of clinical trial data to support use in patients $>65$ yo

## Comparison of Obesity Treatments

<table>
<thead>
<tr>
<th>Agent</th>
<th>Brand Name</th>
<th>Drug (kg)</th>
<th>Placebo (kg)</th>
<th>Net Weight Loss (kg)</th>
<th>Duration</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>Adipex</td>
<td>12.2</td>
<td>4.8</td>
<td>7.4</td>
<td>36 weeks</td>
<td>1959</td>
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<tr>
<td>Orlistat</td>
<td>Xenical</td>
<td>5.8</td>
<td>3.0</td>
<td>2.8</td>
<td>4 years</td>
<td>1999</td>
</tr>
<tr>
<td>Phentermine Topiramate</td>
<td>Qsymia</td>
<td>10.2</td>
<td>1.4</td>
<td>8.8</td>
<td>56 weeks</td>
<td>2012</td>
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<tr>
<td>Lorcanerin</td>
<td>Belviq</td>
<td>8.2</td>
<td>3.4</td>
<td>4.8</td>
<td>52 weeks</td>
<td>2012</td>
</tr>
<tr>
<td>Buproprion Naltrexone</td>
<td>Contrave</td>
<td>8.2</td>
<td>1.9</td>
<td>6.2</td>
<td>48 weeks</td>
<td>2014</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Saxenda</td>
<td>7.2</td>
<td>2.8</td>
<td>4.4;5.8</td>
<td>20;56 weeks</td>
<td>Sept 2014</td>
</tr>
</tbody>
</table>
Phentermine

- Sympathomimetic; controls appetite
- Schedule IV; approved for short term use (3 months)
- **COST $6-40/month**
- **Dose:** 15mg or 37.5mg can be given daily, or 8mg BID or TID to control hunger.
  
  (start at low dose either 8mg, 15 mg or 18.25mg)

- **Contraindications:** CVD, uncontrolled HTN, tachycardia, CKD, hyperthyroidism, agitation, angle-closure glaucoma, pulmonary HTN, Hx of drug abuse/dependence, bipolar, mania

Common SE: dry mouth, constipation, insomnia, palpitations, anxiety, euphoria

- Monitor BP and HR, baseline creatine

Phentermine / Topiramate

- Approved July 2012
- Once a day combination of phentermine and extended release topiramate
- **REMS program, only available by registered pharmacies**
- **Cost of $150/month**
- Use of two existing medications
  - Phentermine
  - Topiramate approved for seizure and migraine ppx

Dose has to be titrated up and max dose of 15mg/92 mg

Topiramate

- Reduction in compulsive or addictive food cravings via antagonism of AMPA receptors
- Decreased lipogenesis and modification of food taste via inhibition of carbonic anhydrase
- Increased energy expenditure via activation of GABA receptors
- Off label for binge eating

Phentermine

- Reduction in hunger via sympathomimetic signals

**Full-dose**

15 mg phentermine/92 mg topiramate

-13.2%, 30 lbs
10% more than placebo
Phentermine / Topiramate

- **Contraindications:** Hyperthyroidism, tachycardia, SI, angle-closure glaucoma, cognitive impairment, metabolic acidosis, hypokalemia, MAOIs

- **SE:** paresthesia, dizziness, taste alteration, insomnia, constipation, dry mouth, memory or cognitive changes. HR increase due to phentermine

- **Topiramate can cause HYPOKALEMIA**
  - if pt is on potassium wasting diuretic (i.e. HCTZ)
  - consider more frequent lab monitoring

**Teratogenic Risk** - Women of child bearing potential should have pregnancy test and ensure adequate contraception (2 forms of birth control)

Phentermine/Topiramate

CONQUER Trial: Weight Loss Over Time

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<tr>
<th>Weeks</th>
<th>Placebo</th>
<th>Mid-dose</th>
<th>Full-dose</th>
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<tr>
<td>8</td>
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Mean % Weight Loss

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<tr>
<th>Weeks</th>
<th>Patients</th>
<th>Placebo</th>
<th>Mid-dose</th>
<th>Full-dose</th>
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<tr>
<td>8</td>
<td>564</td>
<td>344</td>
<td>634</td>
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Completers (% of randomized)

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<tr>
<th>Weeks</th>
<th>Placebo</th>
<th>Mid-dose</th>
<th>Full-dose</th>
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<tr>
<td>8</td>
<td>57%</td>
<td>69%</td>
<td>64%</td>
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1. Statistically greater number of patients completing study on Qnexa vs. placebo, p<0.0001

* Data from patients that completed 56 weeks on treatment

Gadde, Kishore M et al. The Lancet, Volume 377, Issue 9774, 1341 - 1352
Lorcaserin (Belviq)

- Approved in 2012
- **Selective** 5-HT2c receptor agonist → improves **satiety**
- 1997 - Fenfluramine withdrawn
- Nonspecific 5HT receptor agonist
  5-HT2b receptor subtype on cardiac valves → valvulopathy
- Lorcaserin has 11x affinity toward 2C than 2B

Lorcaserin

- Dosing 10mg BID; no titration
- New dose of 20mg ER once daily
- **Most common side effects**: headache, nausea, fatigue and dizziness
- **Contraindications**: Avoid concurrent use of SSRI- risk of serotonin syndrome. Caution with those who have valvular heart disease

At Week 52, the mean weight loss was 8.0% with BELVIQ vs 3.7% with placebo

Response to therapy should be evaluated by **Week 12. If a patient has not lost at least 5% body weight, discontinue BELVIQ**

BLOOM-DM (ITT population)*

BELVIQ Provided Improvement in Glycemic Control Parameters Compared to Placebo

<table>
<thead>
<tr>
<th></th>
<th>HbA1c</th>
<th>Fasting Plasma Glucose</th>
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<tbody>
<tr>
<td><strong>Baseline (%)</strong></td>
<td>8.1</td>
<td>163.3</td>
</tr>
<tr>
<td><strong>Change From Baseline (%)</strong></td>
<td>-0.9‡</td>
<td>-27.4‡</td>
</tr>
<tr>
<td><strong>BELVIQ (N=256)</strong></td>
<td></td>
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<tr>
<td><strong>Placebo (N=252)</strong></td>
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</table>

All Patients Received Lifestyle Modification Counseling

BELVIQ (N=256)  Placebo (N=252)

Buproprion/Naltrexone (Contrave)

- Approved, Sept 10, 2014
- **Naltrexone** - opioid receptor antagonist
  
  May reduce preference for highly palatable foods, especially foods that are high in fat and sugar

- **Buproprion**
  
  norepinephrine - dopamine reuptake inhibitor;

Buproprion/Naltrexone (Contrave)

- **Dosing**
  - 8mg Naltrexone HCL/90mg Buproprion HCL
  - Therapeutic dose of 32mg/360 mg

- **Common side effects:** Nausea (29%), constipation (19%), headache (17%), dizziness (9%), vomiting (10%), dry mouth
  - No increased risk of SI/Depression

- Weight loss of 8.2% vs. 1.4% placebo

Apovian, Aronne, et al Obesity (Silver Spring) 2013 May; 21(5): 935–943
COR-I/II Trials: 56 week Completer Data

- 3 Phase III Trials
- NB32 (Naltrexone SR 32mg, Bupropion SR 360mg)

Liraglutide (Saxenda™)

- September 11, 2014
- Glucagon-Like Peptide 1 Analog
- Secreted in L cells of the intestine
- delays gastric emptying and enhances satiety
- binds and activates GLP-1 receptor in hypothalamus involved in appetite regulation

Image from Shashikiran Umakanth, Published on Dec 13, 2015 Health and Medicine
Liraglutide 3 mg - SCALE Obesity and Prediabetes study

- 3,731 patients with BMI>30 or BMI>27 with 1 co-morbidity

24-year-old female with past medical history of PCOS, Impaired glucose tolerance, HTN, and overweight with BMI of 29 comes to discuss her weight. 

**WEIGHT HISTORY:**

She has struggled with her weight since she “can remember” and had multiple prior weight loss attempts including several years in Weight Watchers and working out with a trainer which have been unsuccessful. She feels that she loses and regains the same 10 lbs over the years.

- Her BP has been well controlled on Hydrochlorothiazide
- On Metformin 1500mg daily for PCOS and IGT

She is interested in starting medication for weight loss. Her insurance does not cover these medications, and she has limited financial resources since she is a student.

What would you recommend for this patient?

A) Advice on diet and exercise changes to help with weight loss and recommend that she follows-up in 6 months

B) Place referral to nutrition

C) Start patient on phentermine 37.5mg once daily for only 3 months

D) Start patient on phentermine 15 mg once daily. Have patient return every 4 weeks for follow-up. Keep her on this medication and/or add topiramate until she reaches her goal weight

E) Both B and D


Thomas et al. 2014 – National Weight Control Registry
Weight Loss Devices: BMI <40

- **Endogastric Balloons**
- **Vagal Nerve Stimulator**
- **Oral Device**
- **Aspire-Stomach Pump**
BARIATRIC SURGERY: BMI >35 W/ COMPLICATIONS/ BMI >40

Adjustable Gastric Band (Lap Band)
- Stomach pouch
- Adjustable band
- Port placed under skin

Roux-en-Y Gastric Bypass (RNY)
- Bypassed portion of stomach
- Bypassed duodenum
- Gastric pouch
- Jejunum
- Food, digestive juice

Vertical Sleeve Gastrectomy
- Gastric sleeve (new stomach)
- Removed portion of stomach

Percent Comorbidity Resolution

<table>
<thead>
<tr>
<th></th>
<th>6 Months</th>
<th>1 Year</th>
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<tbody>
<tr>
<td>Sleep Apnea</td>
<td>10%</td>
<td>78%</td>
</tr>
<tr>
<td>GERD</td>
<td>5%</td>
<td>56%</td>
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<tr>
<td>Hyperlipidemia</td>
<td>22%</td>
<td>33%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49%</td>
<td>78%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>72%</td>
<td>78%</td>
</tr>
</tbody>
</table>
Weight Loss with bariatric surgery

HR adjusted for sex, age, and risk factors was 0.71 for surgery compared to the control (P=0.01)

How can we help?

◆ Be non-judgmental

Obese patients who experience stigma in health-care settings may delay or forgo age-appropriate screenings

◆ Discuss how this is a chronic disease and offer treatment

◆ Set realistic expectations

weight loss 5-10% will lead to significant health improvements
In Summary

- Obesity is a complex chronic disease that is difficult to treat
- It requires a multidisciplinary comprehensive approach with multiple options of treatment
- **Even a small amount of weight loss 5-10% will lead to significant health improvements**
- Anti-obesity medications in addition to lifestyle changes can result in more significant weight loss (3.5-10kg > lifestyle interventions alone)
- Surgical options are now safer, leading to many comorbidity resolution and long term weight loss
QUESTIONS AND COMMENTS?