Obesity Medicine: A New Frontier

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Pediatrics, Pediatric Endocrinology
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Disclosures

- Consultant - NovoNordisk Inc.
- Consultant - Medtronic
Overview

A. Obesity: a chronic disease
   - Impact on health
   - The role of the brain

B. Treatment of patients with obesity
   - A comprehensive approach - guidelines
   - Available treatments - focus on pharmacology
56 yo woman presents to clinic for a follow-up visit

- Blood pressure check, lab review, and medication refills; she does not have significant complaints
- **PmHx**: hypertension, hypercholesterolemia
- **Meds**: Lipitor, Lisinopril, multivitamin / **Allergies**: none
- **FmHx**: T2DM, HTN, and overweight/obesity

- Since the last visit you note she has gained 6-7 lbs and this looks to be a trend over the last several years, you now note that her weight is 205lbs (93.4kg)
- You have 12 minutes left but are likely double booked for your next patient…

*What do you do?*
56 yo woman presents to clinic for a follow-up visit

- Invite her to talk about her weight...
- Gained weight slowly over the years “especially after second pregnancy”. Tried Weight Watchers, Atkins, South Beach, etc. but has not been able to “stick with any one diet” for >6 weeks
- Peak weight: 212lbs / Her goal: lose 50lbs (~25% body weight)
- Diet history / physical activity / sleep / stress

- **PE:** Ht 5’6”, wgt 205lb, BMI 33kg/m², WC 43in, BP 120/78, P 75
  Gen: Pleasant, talkative women, slightly tearful when discussing her struggles with weight loss; HEENT: no thyromeg, no nodules, no moon facies; Abd: soft nt, obese, no striae, PE otherwise unremarkable
- **Labs:** TSH wnl, fasting glucose 113mg/dL, A1c 6.4%

56 yo woman with obesity, hypertension, hyperlipidemia, and prediabetes
AMERICAN BOARD of OBESITY MEDICINE
BMI $\geq 30$kg/m$^2$

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>$&lt;$18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25-29.9</td>
</tr>
<tr>
<td>Obese</td>
<td>$\geq 30$</td>
</tr>
</tbody>
</table>

- Obese 34%
- Overweight 33%
- "Normal weight" 32%
- Underweight 1%

The map shows the distribution of BMI categories across different states.
Obesity: a chronic disease

- excess fat accumulation that represents a risk to health

Adapted from: Daniel, Soleymani, Garvey, 2013 and slides Tim Garvey
What are the mechanisms underlying obesity?
Obesity pathophysiology

- We evolved during times food scarcity
- Body has a critical interest in carrying the "correct" amount of fuel
  
  **Set point**
- Fat mass is the logical regulated parameter
- Obesity results from **physiological dysfunction**
  (precipitated by modern society)
Obesity pathophysiology

Figure Adapted from Berthoud et al. Physiology. 2008;23 75-83.
Desirable food cues/stimuli

neural circuitry

altered neural response

altered food craving

altered eating behavior

weight gain

• Leptin/ghrelin
• Glucose levels
• Insulin & insulin resistance
• Cortisol
• GLP-1

Obesity

Biological factors driving eating behavior
Are brain responses to food stimuli different in individuals with obesity?
Measure brain response

Perfusion - Cerebral Blood Flow (CBF)
Activation - Blood Oxygen Level Dependent (BOLD) signal

↑ increased perfusion / activity
↓ decreased perfusion / activity
General study design: using fMRI to investigate brain response to food stimuli

- **Food Stimuli**
  - Food Pictures
  - Sugar Drinks

- **functional MRI scan**

- Hormones levels sampled at intervals throughout
Food Images: High-fat food vs. Non-food pictures
Obese vs. Lean

Obese adolescents: ↑ activation in regions of the brain involved in reward-motivation and emotion

Jastreboff et al, Diabetes Care, 2014
Food: drinking sugar
Obesity and sugar consumption

Johnson RJ, et al. AJCN, 2007
Brain response to drinking glucose

- Lean: ↑ activation in decision-making brain regions
- Obese: ↓ activation in decision-making cortical regions and ↑ activation in reward-motivation brain regions

Jastreboff et al, Diabetes, 2016
Many questions yet to be addressed…

• **Cause vs. effect?**
  – Are these differences in brain response due to obesity or do they themselves contribute to the development of obesity?

• **Timing?**
  – When do these changes occur? Long-term? Childhood? In utero?

• **Reversibility?**
  – Can these differences in brain response be reversed with weight loss?
  – If so, which type of treatment/weight loss? Over what period of time?
  – Sustainability?

• **Impact?**
  – What are the behavioral implications of the observed neural responses?
Obesity treatment: where are we now?

• Diabetes treatment >40 years ago…
  – Mechanism: ? relative lack of insulin
  – Medications: Insulin and sulfonylureas
  – Assessment: urine glucose testing

• **Obesity care is in its infancy, developing and evolving… the goal is to develop successful therapeutic options using rigorous scientific approach**

Glucometer circa late-1970s
Many treatment strategies for obesity

- Lifestyle change
- Meal-replacement
- Anti-obesity medications
- Endoscopic devices
- Weight-loss surgery
- Combination of therapies

Adapted from: Lee Kaplan, Blackburn Course in Obesity Medicine 2015
## Clinical practice guidelines for obesity

<table>
<thead>
<tr>
<th>Subject Area</th>
<th>Year</th>
<th>Society</th>
<th>Title</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obesity comprehensive care</strong></td>
<td>2016</td>
<td>AACE/ACE</td>
<td>The AACE/ACE Clinical Practice Guidelines for Comprehensive Medical Care of Patients with Obesity</td>
<td>Garvey et al, <em>Endocrine Practice</em>, 2016.</td>
</tr>
</tbody>
</table>
Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline

Caroline M. Apovian, Louis J. Aronne, Daniel H. Bessesen, Marie E. McDonnell, M. Hassan Murad, Uberto Pagotto, Donna H. Ryan, and Christopher D. Still

Boston University School of Medicine and Boston Medical Center (C.M.A.), Boston, Massachusetts 02118; Weill-Cornell Medical College (L.J.A.), New York, New York 10065; Denver Health Medical Center (D.H.B.), Denver, Colorado 80204; Brigham and Women’s Hospital (M.E.M.), Boston, Massachusetts 02115; Mayo Clinic, Division of Preventative Medicine (M.H.M.), Rochester, Minnesota 55905; Alma Mater University of Bologna (U.P.), S. Orsola-Malpighi Hospital Endocrinology Unit, 40138 Bologna, Italy; Pennington Biomedical Research Center (D.H.R.), Baton Rouge, Louisiana 70808; and Geisinger Health Care System (C.D.S.), Danville, Pennsylvania 17822

J Clin Endocrinol Metab, February 2015, 100(2):342–362
2016 AACE Guidelines for the Comprehensive Medical Care of Patients with Obesity

AACE/ACE Algorithm for the Medical Care of Patients with Obesity

Patient Presentation
- Screen positive for overweight or obesity
- BMI ≥25 kg/m² (≥23 kg/m² in some ethnicities)
- Presence of weight-related disease or complication that could be improved by weight loss therapy

Evaluation
- Medical history
- Physical examination
- Clinical laboratory
- Review of systems, emphasizing weight-related complications
- Obesity history: graph weight vs age, lifestyle patterns/preferences, previous interventions

Anthropometric Diagnosis
- Confirm that elevated BMI represents excess adiposity
- Measure waist circumference to evaluate cardiometabolic disease risk

Clinical Diagnosis
- BMI kg/m²
  - <25 NORMAL WEIGHT
  - ≥23 in certain ethnicities
  - Waist circumference below regional/ethnic cutoffs

Checklist of Obesity-Related Complications
(Staging and risk stratification based on complication-specific criteria)
- None
- Mild to Moderate
- Severe
2016 AACE Guidelines for the Comprehensive Medical Care of Patients with Obesity

https://www.aace.com/publications/guidelines

- **Algorithm**: includes treatment goals based on weight-related diseases, guidance on initiation of pharmacotherapy, a comprehensive table of FDA approves anti-obesity medications, guidance on individualizing medication choice based on existing comorbidities

- **Executive summary**: context for the algorithm
<table>
<thead>
<tr>
<th>Anti-obesity Medication (Trade Name) Year of FDA Approval</th>
<th>Mechanism of Action, Study Name, Study Duration: % TBWL Greater Than Placebo</th>
<th>Dose</th>
<th>Common Side Effects</th>
<th>Contraindications, Cautions, and Safety Concerns</th>
<th>Monitoring and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat (Xenical™) (Alli™) 1999</td>
<td>Lipase inhibitor XENDOS</td>
<td>120 mg PO TID (before meals) OTC 60 mg PO TID (before meals)</td>
<td>Steatorrhea, Fecal urgency, Incontinence, Flatulence, Oily spotting, Frequent bowel movements, Abdominal pain, Headache</td>
<td>Pregnancy and breastfeeding, Chronic malabsorption syndrome, Olate nephrolithiasis, Rare severe liver injury, Cholelithiasis, Malabsorption of fat-soluble vitamins, Effects on other medications: • Warning, Safety Concern</td>
<td>Monitor for: • Cholelithiasis • Nephrolithiasis - Recommend standard multivitamin (to include vitamins A, D, E, and K) at bedtime or 2 hours after orlistat dose - Eating &gt;30% kcal from fat results in greater GI side effects - FDA-approved for children ≥12 years old - Administer levothyroxine and orlistat 4 hours apart</td>
</tr>
<tr>
<td>Lorcanerin (Belviq™) 2012</td>
<td>Serotonin (5HT2C) receptor agonist BLOSSOM BLOOM</td>
<td>10 mg PO BID</td>
<td>Headache, Nausea, Dizziness, Fatigue, Xerostomia, Dry eye, Constipation, Diarrhea, Back pain, Nasopharyngitis, Hyperprolactinemia</td>
<td>Pregnancy and breastfeeding, Serotonin syndrome or neuroleptic malignant syndrome, Safety data lacking in patients who have depression, Concomitant use of SSRI, SNRI, MAOI, bupropion, St. John’s wort as may increase risk of developing serotonin syndrome, Uncontrolled mood disorder, Cognitive impairment, Avoid in patients with severe liver injury or renal insufficiency, Caution with patients with bradycardia, heart block, or heart failure, Unproven concern for potential cardiac valvulopathy, Leukopenia</td>
<td>Monitor for: • Symptoms of cardiac valve disease • Bradycardia • Serotonin syndrome • Neuroleptic malignant syndrome • Depression • Severe mood alteration, euphoria, dissociative state • Confusion/somnolence • Priapism • Leukopenia • Euphoria at high doses could predispose to abuse • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas</td>
</tr>
<tr>
<td>Phentermine/Topiramate ER (Qsymia™) 2012</td>
<td>NE-releasing agent (phentermine) GABA receptor modulation (topiramate) EQUIP CONQUER SEQUEL</td>
<td>Starting dose: 1.75/23 mg PO QD for 2 weeks Recommended dose: 7.5/46 mg PO QD Escalation dose: 11.25/69 mg PO QD Maximum dose: 15/92 mg PO QD</td>
<td>Headache, Paresthesia, Insomnia, Decreased bicarbonate, Xerostomia, Constipation, Nasopharyngitis, Anxiety, Depression, Cognitive impairment (concentration and memory), Dizziness, Nausea, Dysgeusia</td>
<td>Pregnancy and breastfeeding (topiramate teratogenicity), Hypertyroidism, Acute angle-closure glaucoma, Concomitant MAOI use (within 14 days), Tachyarrhythmias, Decreased cognition, Seizure disorder, Anxiety and panic attacks, Nephrolithiasis, Hyperchloremic metabolic acidosis, Dose adjustment with hepatic and renal impairment, Concern for abuse potential, Combined use with alcohol or depressant drugs can worsen cognitive impairment</td>
<td>Monitor for: • Increased heart rate • Depressive symptomatology or worsening depression especially on maximum dose • Hypokalemia (especially with HCTZ or furosemide) • Acute myopia and/or ocular pain • Acute kidney stone formation • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas - Potential for lactic acidosis (hyperchloremic non-anion gap) in combination with metformin - MAOI (allow ≥14 days between discontinuation) - 15 mg/92 mg dose should not be discontinued abruptly (increased risk of seizure); taper over at least 1 week - Health care professional should check BHCQ before initiating, followed by monthly self-testing at home - Monitor electrolytes and creatinine before and during treatment - Can cause menstrual spotting in women taking birth control pills due to altered metabolism of estrogen and progestins</td>
</tr>
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<td>Anti-obesity Medication (Trade Name)</td>
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</table>
| **Naltrexone ER/Bupropion ER**      | Opiate antagonist (naltrexone) Reuptake inhibitor of DA and NE (bupropion) | **Titrate dose:**  
Week 1: 1 tab (8/90 mg) PO QAM  
Week 2: 1 tab (8/90 mg) PO BID  
Week 3: 2 tabs (total 16/180 mg) PO QAM and 1 tab (8/90 mg) PO QHS  
Week 4: 2 tabs (total 16/180 mg) PO QHS | • Nausea  
• Headache  
• Insomnia  
• Vomiting  
• Constipation  
• Diarrhea  
• Dizziness  
• Anxiety  
• Xerostomia | ✓ Pregnancy and breastfeeding  
✓ Uncontrolled hypertension  
✓ Seizure disorder  
✓ Anorexia nervosa  
✓ Bulimia nervosa  
✓ Severe depression  
✓ Drug or alcohol withdrawal  
✓ Concomitant MAOI (within 14 days)  
✓ Chronic opioid use  
• Cardiac arrhythmia  
• Dose adjustment for liver and kidney impairment  
• Narrow-angle glaucoma  
• Uncontrolled migraine disorder  
• Generalized anxiety disorder  
• Bipolar disorder  
• Safety data lacking in patients who have depression  
• Seizures (bupropion lowers seizure threshold) | Monitor for:  
• Increased heart rate and blood pressure  
• Worsening depression and suicidal ideation  
• Worsening of migraines  
• Liver injury (naltrexone)  
• Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas  
• Seizures (bupropion lowers seizure threshold)  
• MAOI (allow ≥14 days between discontinuation)  
• Dose adjustment for patients with renal and hepatic impairment  
• Avoid taking medication with a high-fat meal  
• Can cause false positive urine test for amphetamine  
• Bupropion inhibits CYP2D6 |
| **Liraglutide 3 mg**                 | GLP-1 analog  
SCALE Obesity & Prediabetes | **Titrate dose weekly by 0.6 mg as tolerated by patient (side effects):**  
0.6 mg SC QD→ 1.2 mg SC QD→ 1.8 mg SC QD→ 2.4 mg SC QD→ 3.0 mg SC QD | • Nausea  
• Vomiting  
• Diarrhea  
• Constipation  
• Headache  
• Dyspepsia  
• Increased heart rate | ✓ Pregnancy and breastfeeding  
✓ Personal or family history of medullary thyroid cancer or MEN2  
✓ Pancreatitis  
✓ Acute gallbladder disease  
✓ Gastroparesis  
✓ Severe renal impairment can result from vomiting and dehydration  
✓ Use caution in patients with history of pancreatitis  
✓ Use caution in patients with cholelithiasis  
✓ Suicidal ideation and behavior  
✓ Injection site reactions | Monitor for:  
• Pancreatitis  
• Cholelithiasis and Cholecystitis  
• Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas  
• Increased heart rate  
• Dehydration from nausea/vomiting  
• Injection site reactions  
• Titrate dose based on tolerability (nausea and GI side effects) |
Treatment strategies for obesity

1. Lifestyle change
2. Meal-replacement
3. Anti-obesity medications
4. Endoscopic devices
5. Weight-loss surgery
6. Combination of therapies

Adapted from: Lee Kaplan, Blackburn Course in Obesity Medicine 2015
Treatment strategies for obesity

- Lifestyle change
- Meal-replacement
- Anti-obesity medications
- Endoscopic devices
- Weight-loss surgery
- Combination of therapies

Adapted from: Lee Kaplan, Blackburn Course in Obesity Medicine 2015
Lifestyle

1) Reduced-calorie diet:
   • Energy deficit of $\geq 500$ kcal/day
     - Women 1200-1500 kcal/day
     - Men 1500-1800 kcal/day

2) Increased physical activity:
   • Aerobic activity (brisk walking) for $\geq 150$ min/wk
     (30 minutes/day on most days)
   • Weight loss maintenance - 200-300 min/wk to prevent weight regain over $>1$ year

3) Behavior therapy:
   • Comprehensive lifestyle intervention, structural behavior change program, includes regular self-monitoring
Diabetes Prevention Program: reduction in incidence of Type 2 Diabetes

- N = 3,234
- IFG or IGT
- Mean age: 51 years old
- Mean BMI: 34 kg/m²
- 68% women / 45% minority

**Randomized to one of three arms:**
1) Intensive Lifestyle Intervention (ILI) diet, exercise, & behavior change
2) Metformin 850mg twice daily
3) Placebo

**Cumulative Incidence of Diabetes**

- 1 kg weight lost = ↓ incidence of T2D by 16%

Compared to placebo:
- **Metformin** ↓ incidence of T2D by 31%
- **Lifestyle** ↓ incidence of T2D by 58%

Treatment strategies for obesity

- Lifestyle change
- Meal-replacement
- Anti-obesity medications
- Endoscopic devices
- Weight-loss surgery
- Combination of therapies

Adapted from: Lee Kaplan, Blackburn Course in Obesity Medicine 2015
Timeline of anti-obesity medications

- **1959**: Phentermine
- **1997**: Fenphen
- **1999**: Orlistat (Xenical)
- **2008**: Rimonabant
- **2010**: Sibutramine
- **2012**: Phentermine/Topiramate (Qsymia)
- **2014**: Lorcaserin (Belviq)
- **2014**: Naltrexone/Bupropion (Contrave)
- **2010**: Liraglutide (Saxenda)
Mechanisms of action of anti-obesity medications

**CNS**
- phentermine
- lorcaserin
- phentermine/topiramate
- naltrexone/bupropion
- liraglutide (GI)

**GI**
- orlistat
- liraglutide (also CNS)
Indications for treatment with anti-obesity medications

- BMI >30 kg/m²
- BMI >27 kg/m² with co-morbidities
  - such as T2D, HTN, hyperlipidemia, NAFLD
- Prescribe medication in the context of lifestyle intervention
Phentermine resin (Adipex-P™) or Diethylpropion (Tenuate™)

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Mean weight loss (in excess of placebo)</th>
<th>Dose</th>
<th>Side effect</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (NE) -releasing agent (adrenergic)</td>
<td>5%-7.8%</td>
<td>Adipex-P 15-37.5 mg/d</td>
<td>headache, increased BP, anxiety, palpitations, tachycardia, ischemic events</td>
<td>h/o heart disease, uncontrolled HTN, hyperthyroidism, anxiety, glaucoma, h/o drug abuse, anxiety d/o MAOi, pregnancy, breastfeeding, sympathomimetic amines</td>
</tr>
<tr>
<td></td>
<td>7.9lbs / 3.6kg study duration: 2-24 wks</td>
<td>Tenuate 75 mg/d</td>
<td>dry mouth, insomnia, tremor, psychosis, diarrhea, constipation, urticaria, impotence, euphoria, dysphoria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.6lbs / 3.0kg study duration: 6-52 wks</td>
<td></td>
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<tr>
<td></td>
<td>FDA approved: 1959 only for short term use (3 months)</td>
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</tr>
</tbody>
</table>

Most commonly prescribed weight loss medication in America!

Apovian, et al., Endo Society CPG, JCEM, 2015
<table>
<thead>
<tr>
<th>Mechanism</th>
<th><strong>Mean weight loss</strong> (in excess of placebo)</th>
<th>Dose</th>
<th>Side effect</th>
<th>Contraindications /caution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipase inhibitor</td>
<td><strong>2.9-3.4%</strong> 6.5-7.5lbs / 2.9-3.4kg</td>
<td>60-120mg TID</td>
<td>steatorrhea, fecal urgency, incontinence, oily spotting, flatulence, decreased absorption of vit. A,D,E,K</td>
<td>pregnant, breast feeding, cholestasis, malabsorption, syndrome, warfarin, antiepileptic drugs</td>
</tr>
<tr>
<td></td>
<td>study duration: 1-4yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FDA approved: 1999</td>
<td></td>
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</tr>
</tbody>
</table>
**Lorcaserin** (Belviq™)

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Mean weight loss (in excess of placebo)</th>
<th>Dose</th>
<th>Side effect</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>5HT&lt;sub&gt;2c&lt;/sub&gt; receptor agonist (serotonergic)</td>
<td>3.6% 7.9lbs / 3.6kg study duration: 1-2yr FDA approved: 2012</td>
<td>10 mg BID</td>
<td>headache, nausea, dry mouth, dizziness, fatigue, constipation</td>
<td>pregnant breast feeding caution: SSRI, SNRI, MAOI, bupropion, St. John’s wort</td>
</tr>
</tbody>
</table>
Lorcaserin: BLOOM - behavioral modification and lorcaserin for overweight and obesity treatment – year 2
<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Mean weight loss (in excess of placebo)</th>
<th>Dose</th>
<th>Side effect</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE releasing agent (phentermine) / GABA receptor modulation (topiramate)</td>
<td>6.6-8.6% 14.5-18.9lbs / 6.6-8.6 kg</td>
<td>titrate to dose: 3.75mg/23mg QD (starting dose) to 15mg/92mg QD (high dose)</td>
<td>nausea constipation headache vomiting dizziness metal fog</td>
<td>pregnancy breast feeding hyperthyroidism glaucoma MAOi inhibitors severe depression sympathomimetic amines</td>
</tr>
<tr>
<td></td>
<td>study duration: 1yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FDA approved: 2012</td>
<td></td>
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</tbody>
</table>

Apovian, et al., Endo Society CPG, JCEM, 2015
SEQUEL: Phentermine/topiramate ER - weight loss at 2 years

- N=676
- BMI >27 <45 with 2 or more comorbidities
- mean BMI 36 kg/m²
- mean age 51-52 yrs / 68-70% women / 82-86% white

SEQUEL: Phentermine/topiramate ER - prevention of diabetes

Compared to placebo:
7.5/46 $\rightarrow$ 54% reduction in progression to T2D
15/92 $\rightarrow$ 76% reduction in progression to T2D

Garvey, et al., Diabetes Care, 2014
Phentermine/topiramate: CONQUER - patients with significant comorbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with T2D</td>
<td>Placebo</td>
</tr>
<tr>
<td>Pts with preDM</td>
<td>Phentermine 7.5 mg plus topiramate 46.0 mg</td>
</tr>
<tr>
<td>Pts with hyperTG</td>
<td>Phentermine 15.0 mg plus topiramate 92.0 mg</td>
</tr>
</tbody>
</table>

### Naltrexone/bupropion (Contrave™)

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Mean weight loss (in excess of placebo)</th>
<th>Dose</th>
<th>Side effect</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>opiate antagonist (naltrexone) / reuptake inhibitor of DA and NE (bupropion) (opioid antagonism/ CNS)</td>
<td>4.8%-6.0% study duration: 1yr FDA approved: 2014</td>
<td>Titrate to dose: 8mg/90mg QD to 16mg/180mg BID</td>
<td>nausea constipation headache vomiting dizziness</td>
<td>uncontrolled HTN seizure d/o anorexia nervosa bulimia nervosa drug or alcohol withdrawal MAOi inhibitors</td>
</tr>
</tbody>
</table>

COR-DM: Naltrexone/bupropion

- N=505 pt with T2D
  - HgbA1c 8.0%
    - Metformin 78%
    - Sulfonylurea 49%
    - TZD 31%
- mean BMI 36kg/m²
- mean age 54 yo
- 54% women
- 80% white

Weight loss

<table>
<thead>
<tr>
<th>Weight Loss at Week 56</th>
<th>Placebo (% subjects)</th>
<th>NB (% subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 5%</td>
<td>18.9</td>
<td>44.5***</td>
</tr>
<tr>
<td>≥ 10%</td>
<td>5.7</td>
<td>18.5***</td>
</tr>
</tbody>
</table>
COR-DM: Naltrexone/bupropion

HgbA1c Reduction

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>naltrexone/bupropion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.0</td>
<td>0.1%</td>
</tr>
<tr>
<td>16</td>
<td>-0.2</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>-0.4</td>
<td>0.6%</td>
</tr>
<tr>
<td>32</td>
<td>-0.6</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>-0.8</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>-1.0</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>-1.2</td>
<td></td>
</tr>
</tbody>
</table>

HgbA1c Target at Week 56:
- < 7%
  - Placebo: 26.3%
  - NB: 44.1***%
- < 6.5%
  - Placebo: 10.2%
  - NB: 20.7**%

Hollander, et al., Diabetes Care, 2013
# Liraglutide (Saxenda™)

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Mean weight loss (in excess of placebo)</th>
<th>Dose</th>
<th>Side effect</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 agonist</td>
<td>7%</td>
<td>3mg SC QD</td>
<td>nausea vomiting pancreatitis risk</td>
<td>medullary thyroid CA, MEN2</td>
</tr>
<tr>
<td></td>
<td>12.8lbs / 5.8kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>study duration: 1yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FDA approved: 2014</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Apovian, et al., Endo Society CPG, JCEM, 2015
Liraglutide 3mg: SCALE – 1 & 2 years

Astrup, et al., Int J of Obesity, 2012
SCALE: Liraglutide 3mg – decreased progression to T2D

Progression to Diabetes

P<0.001

Cumulative No. of Patients Receiving a Diagnosis of Diabetes over 56 Weeks (No. at Risk)

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 (2219)</td>
<td>1 (1225)</td>
</tr>
<tr>
<td>2</td>
<td>2 (2210)</td>
<td>2 (1210)</td>
</tr>
<tr>
<td>3</td>
<td>3 (2137)</td>
<td>3 (1204)</td>
</tr>
<tr>
<td>4</td>
<td>4 (2130)</td>
<td>4 (1096)</td>
</tr>
<tr>
<td>5</td>
<td>5 (1035)</td>
<td>8 (984)</td>
</tr>
<tr>
<td>6</td>
<td>9 (911)</td>
<td>9 (911)</td>
</tr>
<tr>
<td>7</td>
<td>10 (908)</td>
<td>10 (908)</td>
</tr>
<tr>
<td>8</td>
<td>11 (818)</td>
<td>11 (818)</td>
</tr>
<tr>
<td>9</td>
<td>12 (817)</td>
<td>12 (817)</td>
</tr>
<tr>
<td>10</td>
<td>13 (816)</td>
<td>13 (816)</td>
</tr>
<tr>
<td>11</td>
<td>14 (813)</td>
<td>14 (813)</td>
</tr>
</tbody>
</table>

Pi-Sunyer, et al., *NEJM*, 2015
Efficacy of anti-obesity drugs

- Phentermine/topiramate ER (Gadde et al. 2011)
  - 7.5/46 mg for 1 year
- Phentermine (Aronne et al. 2013)
  - 15 mg daily for 28 weeks
- Naltrexone SR/bupropion SR (Greenway et al. 2010)
  - Maximum dose for 56 weeks
- Liraglutide (Saxenda [liraglutide] package insert 2014)
  - 3.0 mg for 56 weeks
- Lorcaserin (Smith et al. 2010)
  - 10 mg twice daily for 1 year
- Orlistat (Aronne et al. 2013)
  - 120 mg thrice daily for 1 year

% estimated weight loss (drug minus placebo)
Weight loss required to prevent/treat weight-related diseases

- Male hypogonadism, urinary stress incontinence: 5 to 10%
- T2D, dyslipidemia, HTN, PCOS, NAFLD: 5 to 15%
- Asthma/reactive airway disease: 7 to 8%
- Obstructive sleep apnea: 7 to 11%
- Prediabetes, metabolic syndrome, female infertility: 10%
- Osteoarthritis, GERD: 10 to 40%
- Steatohepatitis: 10%
Treatment strategies for obesity

1. Lifestyle change
2. Meal-replacement
3. Anti-obesity medications
4. Endoscopic devices: intragastric balloon
5. Weight-loss surgery
6. Combination of therapies

Adapted from: Lee Kaplan, Blackburn Course in Obesity Medicine 2015
Indications for treatment with intragastric balloon

- BMI 30-40kg/m²
- In conjunction with diet/lifestyle intervention
Endoscopic procedure: Intragastric balloon

- FDA approved 2015
- Endoscopic – placement and removal
- 450-900cc saline
- 6 months
- ~12% body weight loss
- Cost is not covered by insurance
AspireAssist®

• FDA approved June 2016
• “reverse PEG”
• Aspirate 1/3 of stomach content after meals
• 1-2 lb weight loss per week
• Up to 40% excess weight loss
Treatment strategies for obesity

- Lifestyle change
- Meal-replacement
- Anti-obesity medications
- Endoscopic devices
- Weight-loss surgery
- Combination of therapies

Adapted from: Lee Kaplan, Blackburn Course in Obesity Medicine 2015
Indications for treatment with bariatric surgery

- BMI >40kg/m²
- BMI >35kg/m² with co-morbidities
  - such as T2D, sleep apnea, etc.
  - some insurance carriers: BMI >30kg/m² in patients with T2D
- Patient is well-informed and motivated with acceptable risk for surgery
Bariatric surgery

- Laparoscopic
- 10-15 lbs/mo for first 6 months
- 5-7 lbs/mo for subsequent 6 months
- ~100-120 lbs at 1 year
- Life-long vitamin supplementation (Fe, B12, Ca, vitamin D, MVI)
- Weight regain does occur

Gastric Banding

Gastric Sleeve

RYGB

50-60% excess weight loss

60-70% excess weight loss
Bariatric surgery and diabetes control

**BMI**

<table>
<thead>
<tr>
<th>Value at Visit</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical therapy</td>
<td>36.4</td>
<td>34.6</td>
<td>34.2</td>
<td>35.0</td>
<td>34.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeve gastrectomy</td>
<td>36.1</td>
<td>28.3</td>
<td>27.1</td>
<td>27.9</td>
<td>29.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>37.1</td>
<td>28.2</td>
<td>26.7</td>
<td>27.3</td>
<td>27.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HgbA1c**

<table>
<thead>
<tr>
<th>Value at Visit</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical therapy</td>
<td>9.0 (8.5)</td>
<td>7.1 (6.8)</td>
<td>7.5 (6.9)</td>
<td>7.7 (7.3)</td>
<td>8.4 (7.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeve gastrectomy</td>
<td>9.5 (8.9)</td>
<td>6.7 (6.4)</td>
<td>6.6 (6.4)</td>
<td>6.8 (6.8)</td>
<td>7.0 (6.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>9.3 (9.2)</td>
<td>6.3 (6.2)</td>
<td>6.3 (6.1)</td>
<td>6.5 (6.4)</td>
<td>6.7 (6.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

56 yo woman with obesity hypertension, hyperlipidemia, and prediabetes

- Started on metformin
  - HbA1c 6.4% → 6.0%
  - 5 lbs weight loss
  - GI side-effects from metformin

- Started on liraglutide (Saxenda)
  - 17 lbs weight loss over 3 months (~8% of her body weight) dose 2.4 mg daily
  - HgbA1c 5.5%

- Return in 3 months to reassess progress
Concluding thoughts and considerations

• Goal to match each individual patient with the most effective treatment(s)
  – Contraindications, comorbidities, in the setting of patient’s life must be considered

• Response to any treatment is highly variable
  – With medications, assess at 1 month and 3 months

• Long-term RCT are needed for all treatment modalities

• Future… new treatments and using combinations of treatment modalities

A comprehensive treatment approach is critical and compassion is paramount
Thank you

- Bob Sherwin, MD
- Rajita Sinha, PhD
- Sonia Caprio, MD
- Todd Constable, PhD
- Michelle Van Name, MD
- Mary Savoye, RD
- Nicola Santoro, MD, PhD
- Jagriti Arora, MS
- Cheryl Lacadie, BS
- Silvio Inzucchi, MD
- Lee Kaplan, MD, PhD
- Glenda Calendar, MD
- Sherwin Lab
- Yale Stress Center

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- EFF Award (Jastreboff)
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- DRC P30DK045735 (Sherwin)
- R01 DK085577 (Caprio)
- K12 DK094714 (Tamborlane)
- UL1 DE019586 (Sinha)
- PL1 DA024859 (Sinha)
Weight loss varies widely among patients

**Diet (Low-carbohydrate)**

**Device (Duodenal liner)**

**Drug (Liraglutide)**

**Surgery (Gastric Bypass)**

Patients (%)

- % total body weight lost:
  - 0-5
  - 5-10
  - 10-15
  - 15-20
  - 20-25
  - 25-30
  - 30-35
  - 35-40
  - 40-45
  - >50

Slide: Lee Kaplan, Blackburn Course in Obesity Medicine 2015
## Summary: Anti-obesity medications for long-term treatment of obesity

<table>
<thead>
<tr>
<th>Obesity Drug</th>
<th>Trade Name</th>
<th>Mechanism</th>
<th>Proposed Dosage</th>
<th>Pivotal Clinical Trials</th>
<th>Weight change relative to placebo</th>
<th>Most Common Adverse Events</th>
<th>Safety Concern Raised by the FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>Xenical, (Alli)</td>
<td>Inhibits lipase, 30% less fat absorbed</td>
<td>120mg, (60mg OTC) TID before meals</td>
<td>XENDOS</td>
<td>1yr: 4.0% 4yr: 2.6%</td>
<td>GI side-effects (flatulence, fecal urgency, oily spotting, etc)</td>
<td>Rare severe liver injury (post marketing) and oxalate-kidney injury</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Belviq</td>
<td>Selective serotonergic 2C receptor agonist</td>
<td>10 mg po BID</td>
<td>BLOSSOM, BLOOM, BLOOM-DM</td>
<td>1yr: 3.0-3.6% 2yr: 3.1%</td>
<td>Headache, nausea, dizziness, fatigue</td>
<td>Carcinogenicity, valvulopathy, cardiovascular risk</td>
</tr>
<tr>
<td>PHEN/TPM (phentermine/topiramate)</td>
<td>Qsymia</td>
<td>Sympathomimetic amine and anticonvulsant agent</td>
<td>Low, 3.75/23 mg; mid, 7.5/46 mg; high,15/92 mg po QD</td>
<td>EQUIVATE, EQUIP, CONQUER, SEQUEL</td>
<td>1yr: 8.6-9.3% 2yr: 8.7%</td>
<td>Headache, paresthesia, dry mouth, altered taste, dizziness</td>
<td>Depression, cognitive issues, cardiovascular risk from increased heart rate, birth defects</td>
</tr>
<tr>
<td>Bupropion SR/ naltrexone SR (FDA 2014)</td>
<td>Contrave</td>
<td>Dopamine and norepinephrine reuptake inhibitor and opioid receptor antagonist</td>
<td>Sustained release Titrate dose: 8mg/90mg QD - 16mg/180mg BID</td>
<td>COR I, COR-II, COR-BMOD, COR-Diabetes</td>
<td>1yr: 4.8% 2yr: 6.0%</td>
<td>Nausea, headache, insomnia, constipation, tremor</td>
<td>Cardiovascular risk from increased blood pressure and heart rate</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Saxenda</td>
<td>GLP-1 analog</td>
<td>3mg QD SC</td>
<td>SCALE</td>
<td>1yr: 5.9% 2yr: 6.0%</td>
<td>Nausea, vomiting, diarrhea, headache</td>
<td>Pancreatitis, gallbladder dz, hypoglycemia</td>
</tr>
</tbody>
</table>

Wyatt, JCEM, 2013; Yanovski, JAMA, 2014; Garvey Endocrine Practice, 2014
Anti-obesity medication studies

Khera, et al., JAMA, 2016
Study participants: lean adults and adolescents

<table>
<thead>
<tr>
<th></th>
<th>Adults (N=20)</th>
<th>Adolescents (N=14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>31 ± 1.7</td>
<td>15.9 ± 0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>10/10</td>
<td>10/4</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>22.6 ± 0.6</td>
<td>21.8 ± 0.6</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Fasting Glucose (mg/dL)</strong></td>
<td>96 ± 2.4</td>
<td>87 ± 1.4</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Fasting Insulin (uU/mL)</strong></td>
<td>9.7 ± 0.6</td>
<td>14.5 ± 1.6</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Hormones in lean adults vs. adolescents

<table>
<thead>
<tr>
<th></th>
<th>Adults (N=20)</th>
<th>Adolescents (N=14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HOMA-IR</strong></td>
<td>2.3 ± 0.2</td>
<td>3.9 ± 0.9</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Leptin (ng/mL)</strong></td>
<td>7.3 ± 1.3</td>
<td>8.3 ± 2.5</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Ghrelin (pg/mL)</strong></td>
<td>848.9 ± 64.2</td>
<td>817.6 ± 69.1</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>GLP-1 (pg/mL)</strong></td>
<td>2.3 ± 0.6</td>
<td>1.5 ± 0.6</td>
<td>0.39</td>
</tr>
</tbody>
</table>

- HOMA-IR (Homeostatic Model Assessment) - fasting insulin and glucose

Jastreboff et al, ADA Abstract, 2014
### Adolescent participants in glucose/fructose study

<table>
<thead>
<tr>
<th></th>
<th>Lean (N=14)</th>
<th>Obese (N=24)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>15.8</td>
<td>15.3</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Race (AA/C/H)</strong></td>
<td>4/5/5</td>
<td>8/8/8</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Sex (% male)</strong></td>
<td>71</td>
<td>46</td>
<td>ns</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>21.8</td>
<td>34.4</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>% Body Fat</strong></td>
<td>22.2</td>
<td>40.9</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
## Fasting metabolic profile

<table>
<thead>
<tr>
<th></th>
<th>Lean (N=14)</th>
<th>Obese (N=24)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting Glucose</strong> (mg/dL)</td>
<td>88</td>
<td>91</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Fasting Insulin</strong> (uU/mL)</td>
<td>14.6</td>
<td>33.5</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>WBISI</strong></td>
<td>3.7</td>
<td>2.1</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>HOMA-IR</strong></td>
<td>3.9</td>
<td>9.6</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Fasting Leptin</strong> (ng/mL)</td>
<td>8.3</td>
<td>37.1</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

- WBISI (Whole Body Insulin Sensitivity Index) - calculated from OGTT
- HOMA-IR (Homeostatic Model Assessment) - fasting insulin and glucose
Cerebral blood flow response to glucose ingestion

Lean Adults

Page et al, JAMA, 2013

Lean Adolescents

Jastreboff et al, in preparation

$z = 9$

$z = -4$

$z = 1$

$z = -4$

$z = 1$

$z = 6$

$p < 0.05$, whole brain corrected
Brain response to drinking glucose and fructose in obese and lean adolescents

8 AM fasting
Fasting plasma sample

8 AM fasting
Baseline fMRI

Fasting

or

post-drink

fMRI perfusion scan

Plasma glucose & insulin levels sampled at 10 min intervals over 60 mins

<table>
<thead>
<tr>
<th></th>
<th>Lean (N=14)</th>
<th>Obese (N=24)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>15.8</td>
<td>15.3</td>
<td>ns</td>
</tr>
<tr>
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<td>4/5/5</td>
<td>8/8/8</td>
<td>ns</td>
</tr>
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<td>46</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.8</td>
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<td>0.0001</td>
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<tr>
<td>% Body Fat</td>
<td>22.2</td>
<td>40.9</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
Obesity treatment recommendations

- Diet and lifestyle
- Anti-obesity medications
- Endoscopic procedures
- Bariatric surgery

**Table 1.** Obesity Treatment Options Based on the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: Evidence Report Released in 1998

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Potential Treatment Risk</th>
<th>Current Patient Risk (BMI Range, kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>25–26.9 +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27–29.9 +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–34.9 +</td>
</tr>
<tr>
<td>Diet, exercise, and behavioral therapy</td>
<td>Low</td>
<td>35–39.9 +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36–39.9 +</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥40</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>↓</td>
<td>With a comorbidity +</td>
</tr>
<tr>
<td>Surgery</td>
<td>High</td>
<td>With a comorbidity +</td>
</tr>
</tbody>
</table>

(Wyatt, JCEM, 2013)
An fMRI study neural response to drinking glucose in adults vs. adolescents

- **8 AM fasting**
- **Baseline fMRI**
- **Fasting plasma sample**
- **Glucose**
- **Post-drink**

<table>
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<td>0.38</td>
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</table>

Plasma glucose & insulin levels sampled at 10 min intervals over 60 mins

**fMRI perfusion scan**
Hypothesized schematic diagram: Altered regional perfusion response to glucose in obese adolescents.
Hypothesized schematic diagram:
Altered regional perfusion response to glucose in obese adolescents

Lean

Obese

PFC
striatum
hypothalamus

Sugar (glucose)

Decision-making
(prefrontal cortex)

Reward/motivation
(striatum)

Hunger/satiety
(hypothalamus)

Sugar (glucose)
Obesity
Edmonton Obesity Staging System (EOSS)

Stage 0
- Absent
- Absent
- Absent

Stage 1
- Pre-clinical risk factors
- Mild
- Mild

Stage 2
- Co-morbidity
- Moderate

Stage 3
- End-organ damage
- Severe
- End-stage

Stage 4
- End-stage

Obesity

Sharma AM & Kushner RF, *Int J Obes* 2009
**EOSS: EDMONTON OBESITY STAGING SYSTEM - Staging Tool**

### STAGE 0
- **No** sign of obesity-related risk factors
- **No** physical symptoms
- **No** psychological symptoms
- **No** functional limitations

**Case Example:**
Physically active female with a BMI of 32 kg/m², no risk factors, no physical symptoms, no self-esteem issues, and no functional limitations.

**Class I, Stage 0 Obesity**

**WHO Obesity Classification (BMI kg/m²):**
- Obese Class I: 30 - 34.9
- Obese Class II: 35 - 39.9
- Obese Class III: ≥40

### STAGE 1
- Patient has obesity-related **SUBCLINICAL** risk factors (borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.) - **OR** -
- **MILD** physical symptoms - patient currently not requiring medical treatment for comorbidities (dyspnea on moderate exertion, occasional aches/pains, fatigue, etc.) - **OR** -
- **MILD** obesity-related psychological symptoms and/or mild impairment of well-being (quality of life not impacted)

**Case Example:**
38 year old female with a BMI of 59.2 kg/m², borderline hypertension, mild lower back pain, and knee pain. Patient does not require any medical intervention.

**Class III, Stage 1 Obesity**

### STAGE 2
- Patient has an **ESTABLISHED** obesity-related comorbidities requiring medical intervention (HTN, Type II Diabetes, sleep apnea, PCOS, osteoarthritis, reflux disease) - **OR** -
- **MODERATE** obesity-related psychological symptoms (depression, eating disorders, anxiety disorder) - **OR** -
- **MODERATE** functional limitations in daily activities (Quality of life is beginning to be impacted)

**Case Example:**
32 year old male with a BMI of 36 kg/m² who has primary hypertension and obstructive sleep apnea.

**Class II, Stage 2 Obesity**

### STAGE 3
- Patient has **significant** obesity-related end-organ damage (myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis) - **OR** -
- **SIGNIFICANT** obesity-related psychological symptoms (major depression, suicide ideation) - **OR** -
- **SIGNIFICANT** functional limitations (eg: unable to work or complete routine activities, reduced mobility)
- **SIGNIFICANT** impairment of well-being (quality of life is significantly impacted)

**Case Example:**
49 year old female with a BMI of 67 kg/m² diagnosed with sleep apnea, CV disease, GERD, and suffered from stroke. Patient's mobility is significantly limited due to osteoarthritis and gout.

**Class III, Stage 3 Obesity**

### STAGE 4
- **SEVERE** (potential end stage) from obesity related comorbidities - **OR** -
- **SEVERELY** disabling psychological symptoms - **OR** -
- **SEVERE** functional limitations

**Case Example:**
45 year old female with a BMI of 54 kg/m² who is in a wheelchair because of disabling arthritis, severe hyperpnoea, and anxiety disorder.

**Class III, Stage 4 Obesity**

_Sharma AM & Kushner RF, Int J Obes 2009_
## Comprehensive guidelines (AACE)

### Diagnostic Categories
- **NORMAL WEIGHT** (no obesity)
  - No complications
  - **OVERWEIGHT** BMI 25–29.9
  - **OBESITY** BMI ≥30

### Stages
- **STAGE 0**
  - One or more mild-to-moderate complications or may be treated effectively with moderate weight loss
- **STAGE 1**
  - At least one severe complication or requires more aggressive weight loss for effective treatment
  - BMI ≥25
- **STAGE 2**
  - BMI ≥25

### Phases of Chronic Disease Prevention and Treatment Goals
- **PRIMARY**
  - Prevent overweight/obesity
- **SECONDARY**
  - Prevent progressive weight gain or achieve weight loss to prevent complications
- **TERTIARY**
  - Achieve weight loss sufficient to ameliorate the complications and prevent further deterioration

### Treatment Based on Clinical Judgment
- **Primary Prevention**
  - Healthy meal plan
  - Physical activity
  - Health education
  - Built environment
- **Secondary Prevention**
  - Lifestyle/behavioral therapy
  - Consider pharmacotherapy if lifestyle alone not effective
- **Tertiary Prevention**
  - Lifestyle/behavioral therapy
  - Consider pharmacotherapy (BMI ≥27)
  - Add pharmacotherapy (BMI ≥27)
  - Consider bariatric surgery (BMI ≥35)
Comparative efficacy of anti-obesity medications

All data placebo-subtracted, maximal dose, ITT-LOCF, 1 year, unless otherwise indicated

Garvey, Endocrine Practice, 2014; Wadden et al, Int J Obesity, 2013
BMI ≥30kg/m²

**Edmonton Obesity Staging System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>medical</th>
<th>psychological</th>
<th>functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>Pre-clinical risk factors</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Co-morbidities</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>End-organ damage</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>End-stage</td>
<td>End-organ</td>
<td>End-organ</td>
</tr>
</tbody>
</table>

**Classification**

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25-29.9</td>
</tr>
<tr>
<td>Obese (class 1)</td>
<td>≥ 30</td>
</tr>
<tr>
<td>Obese (class 2)</td>
<td>≥ 35</td>
</tr>
<tr>
<td>Obese (class 3)</td>
<td>≥ 40</td>
</tr>
</tbody>
</table>
General study design: using fMRI to investigate brain response to food stimuli

Food Stimuli

- Food Stories
- Food Pictures
- Sugar Drinks

Brain response in both adults & adolescents

functional MRI scan

Hormones levels sampled at intervals throughout
“...All you can think about is having that cheesecake. Your mouth waters. You can’t wait to taste that creamy sweet bite of heaven!... Your heart beats faster... Your eyes scan the cheesecake. Your mouth is watering... You cut a huge piece!... It all looks so good. You can’t wait to taste the sweet creamy texture and soft buttery crust... You cut a piece with your fork. It is dense and creamy. You raise the fork to your lips...”
Favorite food story vs. neutral-relaxing story

• Obese: ↑ activation in motivation & emotion brain regions

Jastreboff et al, Diabetes Care, 2013
• Individuals with obesity have different/altered brain responses to:
  – thinking about food (specifically favorite or desired food)
  – looking at food (high-calorie vs. non-food)
  – consuming food (sugar, specifically glucose)
BMI $\geq 30$ kg/m$^2$
BMI ≥30kg/m²

1986

No Data  <10%  10%-14%
BMI ≥30kg/m²

1988

No Data
<10%
10%–14%

Yale SCHOOL OF MEDICINE
BMI $\geq 30$kg/m$^2$
BMI ≥30kg/m²

1990

No Data          <10%           10%–14%

Yale SCHOOL OF MEDICINE
BMI ≥30 kg/m²

1992

- No Data
- <10%
- 10%-14%
- 15%-19%
BMI ≥30 kg/m²

1994

No Data  <10%  10%-14%  15%-19%

Yale SCHOOL OF MEDICINE
BMI ≥30 kg/m²

1999

No Data  <10%  10%–14%  15%–19%  20%–24%
BMI ≥30 kg/m²

2004

No Data
<10%
10%–14%
15%–19%
20%–24%
25%–29%

Yale SCHOOL OF MEDICINE
No Data          <10%           10% – 14%           15% – 19%           20% – 24%          25% – 29%          ≥30%

BMI ≥30kg/m²
Brain region of interest: the hypothalamus

- **hypothalamus**
- hunger & satiety
Brain regions of interest relating to reward, motivation, emotion, and decision-making

**cortical**
- Prefrontal cortex
- Anterior cingulate cortex
- Insula

**striatal**
- Putamen
- Caudate

**limbic**
- Amygdala
- Thalamus

**hypothalamus**
- Hunger & satiety

Regions include:
- Hypothalamus: hunger & satiety
- Thalamus: emotion & memory
- Amygdala: emotion & memory
- Insula: processing & executive function
- Prefrontal cortex
- Anterior cingulate cortex
- Putamen
- Caudate
- Hypothalamus: hunger & satiety
- Thalamus: emotion & memory
- Amygdala: emotion & memory