Emerging Pharmacologic Treatments & Strategies in the Management of Obesity

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Outline

• Rationale for long-term therapy: obesity is a chronic disease
• Pathophysiological mechanisms that necessitate long-term medical therapy
• Compare and contrast the safety and efficacy of emerging pharmacologic therapies in the management of obesity
• Discuss the metabolic effects, adverse effects, and drug-drug interactions associated with anti-obesity medications
• Examine models of medical care for obese patients, evidenced-based approaches for diagnosis and stratification of disease severity, and the utility of established obesity treatment guidelines
1. “It is the strong contention of AACE that the view of obesity as a behavioral decision is debunked by biomedical evidence.”

2. “…obesity is a primary disease, and the full force of our medical knowledge should be brought to bear on the prevention and treatment of obesity as a primary disease entity.”

3. “…obesity is an altered physiological and metabolic state, with genetic, environmental, and behavioral determinants, which results in increased morbidity and mortality.”

The American Medical Association designates obesity as a disease.
June 18, 2013, AMA House of Delegates


Initializing Concepts: The AACE Position

Is Obesity a Disease?

Concordance of Body Type between Dizygotic or Fraternal Twins

Concordance of Body Type between Monozygotic or Identical Twins
Polygenic Diseases: Susceptibility Genes Interact with Each Other and the Environment

Gene 1

Gene 2

Environment & Behavior

Individuals with Disease

Determinants of Body Weight

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
Energy intake
Ingestion of:
Proteins
Fats
Carbohydrates

Energy expenditure
Basal metabolic rate
Physical activity
Energy to metabolized food

Human being: biological and behavioral interface

Body Weight
Increase
Decrease

Cause of Obesity: Abnormal Energy Balance

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


Available at: http://www.ama-assn.org/resources/doc/csaph/a05csa4-fulltext.pdf
**BMI Review**

<table>
<thead>
<tr>
<th>BMI Class</th>
<th>BMI Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
</tr>
<tr>
<td>Obesity class 1</td>
<td>30.0-34.9</td>
</tr>
<tr>
<td>Obesity class 2</td>
<td>35.0-39.9</td>
</tr>
<tr>
<td>Obesity class 3 (severe)</td>
<td>≥40.0</td>
</tr>
</tbody>
</table>

*World Health Organization defines overweight as BMI ≥25 kg/m² and obese as BMI ≥30 kg/m².*


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**Medical Complications of Obesity**

- **Obesity**
  - Dyslipidemia
  - Hypertension
  - Prediabetic States
  - NAFLD
  - PCOS
  - Diabetes
  - CVD

- **Other Complications**
  - Depression
  - Cancer
  - Gallbladder Disease

- **BioMechanical Complications**
  - Sleep Apnea
  - Osteoarthritis
  - Stress Incontinence
  - GERD
  - Dismobility/Disability

**Cardiometabolic Disease**

PCOS: Polycystic ovary syndrome; NAFLD: Non-alcoholic fatty liver disease

In Obesity, fat tissue can be inflamed (i.e., “sick fat”) and function abnormally

Fat Tissue Inflammation

Central Adiposity

ABNORMAL SECRETION OF ADIPOCYTE FACTORS

LIPIDS in BLOOD
Dyslipidemia

BLOOD VESSEL
Hypertension Atherosclerosis

MUSCLE
Insulin resistance Glucose intolerance

Garvey WT, 2013

Secreted Adipocyte Factors

Insulin Resistance/Adipocyte Size
- Free Fatty Acids
- Leptin
- Adiponectin
- Resistin

Dysfibrinolysis
- PAI-1

Vascular Reactivity
- Free Fatty Acids
- Angiotensinogen (RAAS)
- Inflammation

Lipids/Lipoproteins
- Acylation Stimulation Protein
- Cholesterol Ester Transfer Protein
- Phospholipid Transfer Protein

Inflammation
- TNF alpha
- IL-1, IL-6, IL-8, IL-10
- MCP-1
- MIF

RAAS, renin–angiotensin–aldosterone system; TNF, tumor necrosis factor; IL, interleukin; MCP-1, monocyte chemotactic protein-1; MIF, macrophage migration inhibiting factor.
Pre-diabetic State

- Overt Diabetes

- Late-phase Insulin Secretion
- First-phase Insulin Secretion
- Insulin Sensitivity
- Fasting Glucose

Pre-diabetic State
Overt Diabetes

WT Garvey, 2011.

The Spectrum of Cardiometabolic Disease

**Prediabetic States**

1. Prediabetes
   i. IFG
   ii. IGT
2. Metabolic Syndrome
   - Waist
   - Blood pressure
   - Fasting glucose
   - Triglycerides
   - HDL-cholesterol

**Type 2 Diabetes**

**Cardiovascular Disease**

Garvey WT, 2013

Obesity

Insulin Resistance
Environmental and Genetic Factors Contributing to Excess Fat Storage and Metabolic Complications

**Environment**
- Increased Energy Intake
- Decreased Energy Expenditure
- Excess Fat Storage

**Genetics**
- Osteoarthritis
- Sleep Apnea
- Disability
- Urinary Incontinence

**Complications**
- BIOMECHANICAL Complications
- CARDIOMETABOLIC Complications

**Conditions**
- Diabetes
- Metabolic Syndrome
- Prediabetes
- NAFLD
- HTN
- CVD

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**Regulation of Energy Intake**

**Peripheral Signals**
- GHRELIN
- LEPTIN
- CCK
- GLP-1
- PEPTIDE YY
- AMYLIN
- INSULIN

**Hypothalamic Pathways**
- Arcuate Nucleus
- PVN, LHA, DMN

**Higher Cortical Centers**
- MCH1R
- MCH
- BDNF
- NTRK2

**Molecules and Pathways**
- POMC/CART
- Leptin
- Glucagon-like peptide-1 (GLP-1)
- Peptide YY (PYY)
- Amylin
- Insulin

**Signaling Receptors**
- MC4R
- Y1R
- Y5R
- GSHR
- LepR
- GHSR

**Orexigenic Pathway**
- NPY
- AgRP

**Anorexigenic Pathway**
- AGRP
- αMSH

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Domenica M. Rubino, MD.

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Courtesy of Dr. W. Timothy Garvey, 2013.
The Pathophysiology of Obesity: Why do patients so frequently regain weight following lifestyle therapy

It is difficult for patients to maintain their weight loss over time.

- ↑ Ghrelin
- ↓ Leptin, PYY, CCK, Amylin
- ↓ Resting energy expenditure
- ↑ Hunger
- ↑ Calorie-dense food preferences

In Obesity, biology protects against weight loss and maintains a high body weight

Equilibrium Weight
Baseline weight
250 lbs

Weight Loss

Weight Gain

Increased Appetite
Decreased Energy Out
Increased Energy In

Sacks FS. et al. NEJM 2009;360(9) 859-873.

Garvey WT, 2014
Chronic Disease Model
(ie, obesity, diabetes, asthma, hypertension, lupus, etc.)

Genetics

Environment

DISEASE

Genetics

Complications/
Disease Severity

Environment

Obese persons face discrimination in ....

- EMPLOYMENT
- COLLEGE ADMISSION
- ROMANCE
- MEDICAL CARE
- INCOME
- AIRLINE SEATING

• >90% of obese persons have attempted to lose weight
• >50% are currently trying to lose weight

Lifestyle Modification in the Treatment of Obesity: evidence-based essentials

- Reduced calorie diet – 500 kcal energy deficit/day
- Healthy meal plan (e.g., low carb, low fat, DASH, Mediterranean)
- Very Low Calorie Diets
- Use of meal replacements (at least once a day)
- Behavioral intervention (education, motivational interviewing, portion control, resolve psychological problems, etc.)
- Increase voluntary physical activity; reduce sedentary behavior
- Aspects associated with success in the National Weight Control Registry
  - self monitoring,
  - lots of physical activity,
  - low levels of sedentary behavior,
  - healthy eating patterns
Intensification of Lifestyle Therapies to Achieve Weight Loss Goals

**Lifestyle Therapy**
- Simple advice to lose weight in doctor’s office
- Internet programs or self-help books
- Advice from dietitian
- Structured programs (Weight Watchers, YMCA, tele-communication)
- Multidisciplinary structured programs
- Physician-driven individualized structured programs

**Mean Weight Change in the Diabetes Prevention Program**

![Graph showing mean weight change over years from randomization for Placebo, Metformin, and Lifestyle interventions. The graph indicates that the Lifestyle intervention results in a significant weight loss compared to Placebo and Metformin.]

Incident Diabetes During the DPP

All Participants

- Placebo (n=1082)
- Metformin (n=1073)
- Lifestyle (n=1079)

Risk reduction
31% by metformin
58% by lifestyle


Long-term Weight Loss Is Difficult to Maintain

DPP Outcomes Study (N=2766)

DPP, Diabetes Prevention Program; T2DM, type 2 diabetes mellitus.

Weight Loss Reduces Long-term Incidence of Type 2 Diabetes

DPP Outcomes Study (N=2766)

DPP, Diabetes Prevention Program; T2DM, type 2 diabetes mellitus.


Intensive Intervention in T2DM: Weight Regain over 4 Years in Look AHEAD

Look AHEAD Trial (N=5145)

ILI, intensive lifestyle intervention; DSE, diabetes support and education.

Effect of Weight Loss in T2DM on CV Risk Factors and Diabetes Measures

Look AHEAD Trial \( (N=5145) \)

<table>
<thead>
<tr>
<th></th>
<th>At 1 year</th>
<th>DSE</th>
<th>ILI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (%)</td>
<td>-0.7</td>
<td>-8.6</td>
<td></td>
</tr>
<tr>
<td>A1C (%)</td>
<td>-0.14</td>
<td>-0.64*</td>
<td></td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>-7.2</td>
<td>-21.5*</td>
<td></td>
</tr>
<tr>
<td>% on diabetes medications</td>
<td>2.2</td>
<td>-7.8*</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>-2.8</td>
<td>-6.8*</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>-1.8</td>
<td>-3.0*</td>
<td></td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>-5.7</td>
<td>-5.2</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>1.4</td>
<td>3.4*</td>
<td></td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>-14.6</td>
<td>-30.3*</td>
<td></td>
</tr>
</tbody>
</table>

*\( P \leq 0.001 \); † \( P = 0.01 \) vs customary support.

BP, blood pressure; CV, cardiovascular; DSE, diabetes support and education; ILI, intensive lifestyle intervention; T2DM, type 2 diabetes mellitus.


Rationale for Using Medications

- Help patients who are struggling to achieve health benefits through weight loss.
- Use as an adjunct to a lifestyle intervention program that includes a reduced calorie diet.
- Addition of a weight-loss medication consistently achieves greater weight loss than that achieved by the lifestyle intervention alone.
- Can help sustain weight loss. Obesity is a life-long disease and requires long-term treatment and follow-up.
- The ASBP, AACE and 2013 AHA/ACC/TOS Obesity Guidelines all advise use of medications for patients who have sufficient health risk, not for cosmetic reasons.
Obesity Medications: Prescribing Principles

- Indications: (i) BMI 25-29.9 with at least one obesity related complication; (ii) BMI ≥ 30.
- FDA “off-ramp”: Discontinue medication if weight loss is <5% on maximal dose of drug after 12 weeks.
- In the case of primary failure, can try another medication
- Medications vary regarding efficacy, warnings, cautions, and side effect profile; this is important regarding individualization of therapy.
- CVOTs pending
- Additional data is required for optimal use of medications in long term treatment.

Obesity Pharmacotherapy

<table>
<thead>
<tr>
<th>Agents</th>
<th>Action</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phentermine</td>
<td>Sympathomimetic</td>
<td>• 1959</td>
</tr>
<tr>
<td>Orlistat</td>
<td>GI lipase inhibitor</td>
<td>• 1997</td>
</tr>
<tr>
<td>Recently Approved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phentermine/Topiramate ER</td>
<td>Sympathomimetic/Anticonvulsant (GABA receptor modulation?)</td>
<td>• Approved, Summer 2012</td>
</tr>
<tr>
<td>Lorcarisin</td>
<td>5-HT2C serotonin receptor agonist</td>
<td>• Approved, Summer 2012</td>
</tr>
<tr>
<td>NaltrexoneSR/Bupropion SR</td>
<td>Dopamine/noradrenaline reuptake inhibitor/Opioid receptor antagonist</td>
<td>• Approved, September 2014</td>
</tr>
<tr>
<td>Hopefully Available in Future (2014?)</td>
<td>GLP-1 receptor agonist</td>
<td>• Pending FDA decision</td>
</tr>
</tbody>
</table>
Actions of Recently Approved Weight-Loss Medications

Arcuate Nucleus

- POMC/CART
- GLP-1 R
- μ-OR
- 5-HT2C
- Naltrexone
- Lorcaserin

Paraventricular Nucleus

- MC4R
- α-MSH
- GABA?
- Topiramate
- Bupropion

Higher Cortical Centers

- Decreased Appetite
- Dopamine/NE reuptake

MC4R, melanocortin 4 receptor.
GABA, gamma-aminobutyric acid.
POMC/CART, pro-opiomelanocortin/cocaine- and-amphetamine-regulated transcript.

Approved by FDA 1998; 120 mg po tid with meals

Orlistat: Use in Clinical Practice

Contraindications
✓ Pregnancy
✓ Malabsorption syndrome
✓ Cholestasis

Warnings
✓ Drug interactions: cyclosporine, levothyroxine, warfarin
✓ Rare severe liver injury
✓ Oxalate renal stones
✓ Need to restrict dietary fat (<30% of calories)
✓ Need for daily vitamin (especially fat soluble)
✓ Risk of hypoglycemia with diabetes meds

**Benefits of Medication Use: 4-Year Randomized Controlled Trial of Orlistat as an Adjunct to Lifestyle for the Prevention of T2DM in Obese At-risk Patients**

![Graph showing weight change over time for placebo and orlistat + lifestyle interventions.](image)

- Placebo + lifestyle: Change in Body Weight (kg)
- Orlistat + lifestyle: Change in Body Weight (kg)

- **P < 0.001**
- Orlistat + “DPP-type” intervention: −5.8 kg
- “DPP-type” intervention: −3.0 kg

**Change in Body Weight (kg)**

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo + lifestyle</th>
<th>Orlistat + lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>52</td>
<td>−3.0</td>
<td>−3.0</td>
</tr>
<tr>
<td>104</td>
<td>−3.0</td>
<td>−3.0</td>
</tr>
<tr>
<td>156</td>
<td>−3.0</td>
<td>−3.0</td>
</tr>
<tr>
<td>208</td>
<td>−3.0</td>
<td>−3.0</td>
</tr>
</tbody>
</table>

DPP = Diabetes Prevention Program.

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**Lorcaserin: Use in Clinical Practice**

Approved by FDA June 2012  10 mg po bid, schedule pending (IV)

**Contraindications**

- Pregnancy

**Warnings**

- Coadministration with other serotonergic or antidopaminergic agents
- Valvular heart disease
- Cognitive impairment
- Psychiatric disorders (euphoria, suicidal thoughts, depression)
- Priapism
- Risk of hypoglycemia with diabetes meds

Lorcaserin 10 mg bid: BLOOM Study
Weight Change Over Two Years


Lorcaserin – BLOOM Study: Key Secondary Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Lorcaserin</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>↓</td>
<td>−6.8</td>
<td>−3.9</td>
</tr>
<tr>
<td>SBP/DBP (mm Hg)</td>
<td>↓</td>
<td>−1.4/−1.1</td>
<td>−0.8/−0.6</td>
</tr>
<tr>
<td>Cholesterol (% Δ)</td>
<td></td>
<td>−0.90</td>
<td>0.57</td>
</tr>
<tr>
<td>Total</td>
<td>↓</td>
<td>−2.87</td>
<td>4.03</td>
</tr>
<tr>
<td>LDL</td>
<td>↓</td>
<td>0.05</td>
<td>−0.21</td>
</tr>
<tr>
<td>HDL</td>
<td>↓</td>
<td>−0.90</td>
<td>−0.14</td>
</tr>
<tr>
<td>Triglycerides (%)</td>
<td>↓</td>
<td>−6.15</td>
<td>−0.14</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>↓</td>
<td>−0.41</td>
<td>−0.17</td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td>−2.0</td>
<td>−1.6</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>↓</td>
<td>−1.1</td>
<td>−0.9</td>
</tr>
<tr>
<td>Beck depression II</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Intention-to-Treat Analysis with LOCF Imputation
HOMA-IR, homeostasis model assessment of insulin resistance
Lorcaserin: Adverse Events Reported by 5% or More in Any Group

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Lorcaserin (N=3195)</th>
<th>Placebo (N=3185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>537 (16.8)</td>
<td>321 (10.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>270 (8.5)</td>
<td>122 (3.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>264 (8.3)</td>
<td>170 (5.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>186 (5.8)</td>
<td>125 (3.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>229 (7.2)</td>
<td>114 (3.6)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>169 (5.3)</td>
<td>74 (2.3)</td>
</tr>
</tbody>
</table>


Phentermine/Topiramate ER: Use in Practice

Approved by FDA in July 2012, schedule IV
- Initiation X 2 weeks: phentermine 3.25mg/topiramate ER 23 mg
- Treatment dose daily: phentermine 7.5 mg/topiramate ER 46 mg
- Maximum dose daily: phentermine 15 mg/ topiramate ER 92 mg

**Contraindications**
- Pregnancy, glaucoma, hyperthyroidism, MAOIs

**Warnings**
- Fetal toxicity
- Increased heart rate
- Suicide and mood and sleep disorders
- Acute myopia and glaucoma
- Cognitive impairment
- Metabolic acidosis
- Creatinine elevations
- Hypoglycemia with diabetes medications

Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 2 Years: SEQUEL Study


Phentermine/Topiramate ER Effect on Risk Factors: CONQUER Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Phentermine 7.5 mg/Topiramate 46 mg ER</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>↓ -7.6</td>
<td>-2.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>↓ -4.7</td>
<td>-2.4</td>
<td>0.0008</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>↓ -3.4</td>
<td>-2.7</td>
<td>0.1281</td>
</tr>
<tr>
<td>Triglycerides (%)</td>
<td>↓ -8.6</td>
<td>4.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL–C (%)</td>
<td>↓ -3.7</td>
<td>-4.1</td>
<td>0.7391</td>
</tr>
<tr>
<td>HDL–C (%)</td>
<td>↑ 5.2</td>
<td>1.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>↓ -2.49</td>
<td>-0.79</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>↑ 1.40</td>
<td>0.33</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Changes from baseline to week 56 in secondary endpoints

**Phentermine/Topiramate ER: EQUIP and CONQUER – Most Commonly Reported Treatment Emergent Adverse Events Occurring More Commonly In Patients Receiving Medication**

<table>
<thead>
<tr>
<th>Adverse Event (%) (N=3749)</th>
<th>Placebo</th>
<th>PHEN/TPM ER Low</th>
<th>PHEN/TPM ER Mid</th>
<th>PHEN/TPM ER Top</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesia</td>
<td>1.9</td>
<td>4.2</td>
<td>13.7</td>
<td>19.9</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2.8</td>
<td>6.7</td>
<td>13.5</td>
<td>19.1</td>
</tr>
<tr>
<td>Constipation</td>
<td>6.1</td>
<td>7.9</td>
<td>15.1</td>
<td>16.1</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1.1</td>
<td>1.3</td>
<td>7.4</td>
<td>9.4</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8.0</td>
<td>12.5</td>
<td>10.6</td>
<td>9.4</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.7</td>
<td>5.0</td>
<td>5.8</td>
<td>9.4</td>
</tr>
</tbody>
</table>

Sources:

**Effect of Weight Loss Induced by Phentermine/Topiramate ER on the Prevention of Diabetes in Patients With Metabolic Syndrome and/or Prediabetes: SEQUEL Study**

![Graph showing cumulative incidence rate of type 2 diabetes over weeks for different treatment groups.]

Sources:
Naltrexone ER/Bupropion ER: Use in Practice

Approved by FDA Sept 2014
Initiation: Begin with 1 pill each AM and escalate dose over 4 weeks to 2 pills bid
Treatment: 2 pills bid, each containing 8 mg naltrexone/90 mg bupropion

Contraindications
- Pregnancy
- Uncontrolled HTN
- Seizure disorder
- Chronic opioid use
- MAOIs

Warnings
- Angle closure glaucoma
- Suicidal behavior/ideation
- Increased BP and HR
- Seizures
- Risk of hypoglycemia with diabetes medications
- Note: high fat meal increases blood levels

Naltrexone SR/Bupropion SR: Observed Change in Body Weight Over 56 Weeks (COR-I)

MITT, LOCF analysis
Naltrexone/Bupropion ER Effect on Risk Factors: COR-I Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Naltrexone/Bupropion ER 32/360 mg</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist (cm)</td>
<td>↓</td>
<td>-6.2</td>
<td>-2.5</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>↑</td>
<td>-0.1</td>
<td>-1.9</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>↑</td>
<td>0</td>
<td>-0.9</td>
</tr>
<tr>
<td>Pulse rate (bpm)</td>
<td>↑</td>
<td>0.4</td>
<td>-1.0</td>
</tr>
<tr>
<td>TG (%)</td>
<td>↓</td>
<td>-12.7</td>
<td>-3.1</td>
</tr>
<tr>
<td>LDL-c (%)</td>
<td></td>
<td>-2.0</td>
<td>-0.5</td>
</tr>
<tr>
<td>HDL-c (%)</td>
<td>↑</td>
<td>8.0</td>
<td>0.8</td>
</tr>
<tr>
<td>CRP (%)</td>
<td>↓</td>
<td>-29.0</td>
<td>-16.7</td>
</tr>
<tr>
<td>Fasting insulin (%)</td>
<td>↓</td>
<td>-17.1</td>
<td>-4.6</td>
</tr>
</tbody>
</table>

Changes from baseline to week 56 in secondary endpoints

Naltrexone/Bupropion ER: COR-I Study – Most Commonly Reported Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event (%) (N = 573)</th>
<th>Placebo</th>
<th>Naltrexone/Bupropion 32/360 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5.3</td>
<td>29.8</td>
</tr>
<tr>
<td>Headache</td>
<td>9.3</td>
<td>13.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>6.1</td>
<td>7.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.6</td>
<td>9.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.5</td>
<td>9.8</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1.9</td>
<td>7.5</td>
</tr>
<tr>
<td>Hot flush</td>
<td>1.2</td>
<td>5.2</td>
</tr>
</tbody>
</table>

On the Horizon: Medications Considered for US Approval in 2014

<table>
<thead>
<tr>
<th>Agents</th>
<th>Site of Action</th>
<th>Phase 3 Studies</th>
<th>Approval/Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide3,4</td>
<td>• GLP-1 receptor agonist</td>
<td>• SCALE-Maintenance</td>
<td>• NDA submitted</td>
</tr>
<tr>
<td></td>
<td>• 3 mg qd</td>
<td>• SCALE-Sleep Apnea</td>
<td>• Panel review in 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SCALE-DM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SCALE-Obesity and Pre-DM</td>
<td></td>
</tr>
</tbody>
</table>


Ability of Liraglutide 3 mg to Maintain and Promote Additional Weight Loss After Low-calorie Diet: SCALE Maintenance Study

![Graph showing weight changes over time for Liraglutide and Placebo groups.]

Mean ± SD weight at run-in (week -12): 105.9 ± 22.1 kg

F = follow-up period; S = screening period.
### Comparative Efficacy of Weight-Loss Medications

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

<table>
<thead>
<tr>
<th>Medication</th>
<th>% Weight Loss After 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine/Topiramate</td>
<td>0</td>
</tr>
<tr>
<td>Liraglutide* 3 mg</td>
<td>1</td>
</tr>
<tr>
<td>Naltrexone/Bupropion*</td>
<td>2</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>3</td>
</tr>
<tr>
<td>Orlistat</td>
<td>4</td>
</tr>
<tr>
<td>Phentermine</td>
<td>5</td>
</tr>
</tbody>
</table>

*Not approved for the treatment of obesity.


---

### Surgical Options

**Gastric Restriction Procedures**
- Laparoscopic Adjustable Gastric Band (LABG)
- Gastric Plication

**Metabolic Procedures**
- Laparoscopic Sleeve Gastrectomy (LSG)
- Roux-en-Y Gastric Bypass (RYGB)
- Biliopancreatic Diversion

---

*EQUILA, CONVERG, SCALE, COMBINE, ECLIPSE, EQUITE, G-YPEN.*
Weight Regain After Bariatric Surgery SOS Study: Mean Percent Weight Over 15 Years

No. patients
Control  
2037 1768 1660 1553 1490 1281 982 886  
190
BANDING  
376 383 357 328 333 298 267 237 52
Vertical-banded gastroplasty 1369 1236 1244 1121 1086 1004 899 746 108
Gastric bypass  
286 245 245 211 209 166 92 58 10

Bariatric Surgery Reduces Mortality in Severely Obese Patients

Swedish Obese Subjects Study (N=4047)

Fatal CV Events: Control (49 events)  
HR, 0.56; 95% CI, 0.35-0.88; Log-rank P = 0.01
Surgery (28 events)  
HR, 0.83; 95% CI, 0.69-1.00; Log-rank P = 0.05

Total CV Events: Control (49 events)  
HR, 0.83; 95% CI, 0.69-1.00; Log-rank P = 0.05
Surgery (28 events)  
HR, 0.83; 95% CI, 0.69-1.00; Log-rank P = 0.05

Dr. Garvey, are you nuts? 35% of America is obese and another 35% is overweight. We can’t pay for treatment for all these folks? We will go broke !!!

How Do We Use Available Treatment Modalities for Overweight and Obese Patients?

- Balance efficacy, safety, and cost
- Optimize benefit: risk ratio
- Achieve best outcomes
- Cost-effectiveness of care
### NHLBI Obesity Treatment Guidelines

**A Guide to Selecting Treatment**

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>25–26.9</th>
<th>27–29.9</th>
<th>30–34.9</th>
<th>35–39.9</th>
<th>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet, physical activity, and behavior</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate NHLBI Guidelines</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Pharmacotherapy</strong></td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With comorbidities</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Surgery</strong>*</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAGB only</td>
<td></td>
<td></td>
<td></td>
<td>With comorbidities</td>
<td>+</td>
</tr>
</tbody>
</table>

* *Bariatric surgeries require lifestyle medical follow-up.*

\[FDA\text{ approved gastric band surgery for patients with BMI } \geq 30\text{ and one weight related medical condition (February 2011).}

LAGB, laparoscopic adjustable gastric banding


### AACE Complication-Centric Model for Care of the Overweight/Obese Patient

**STEP 1**  **EVALUATION FOR COMPLICATIONS AND STAGING**

<table>
<thead>
<tr>
<th>CARDIOMETABOLIC DISEASE</th>
<th>BIOMECHANICAL COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO COMPLICATIONS</td>
<td>BMI 25–26.9, or BMI ≥ 27</td>
</tr>
<tr>
<td><strong>BMI 27</strong></td>
<td>WITH COMPLICATIONS</td>
</tr>
<tr>
<td>Stage Severity of Complications</td>
<td>LOW</td>
</tr>
</tbody>
</table>

**STEP 2**  **SELECT:**

- Lifestyle Modification: MD/BD counseling, web/remote program; structured multi-disciplinary program
- Medical Therapy: phentermine, orlistat, lorcaserin, phentermine / topiramate ER
- Surgical Therapy (BMI ≥ 35): Lap band, gastric sleeve, gastric bypass

**STEP 3**  If therapeutic targets for improvements in complications not met, Intensify lifestyle and/or medical and/or surgical treatment modalities for greater weight loss

Therapeutic Weight Loss

<table>
<thead>
<tr>
<th>OBESITY COMPLICATION</th>
<th>% weight loss required for therapeutic benefit</th>
<th>Notes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Prevention</td>
<td>3% to 10%</td>
<td></td>
<td>DPP (Lancet, 2009) SEQUEL (Garvey et al, 2013)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5% to &gt;15%</td>
<td></td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3% to &gt;15%</td>
<td></td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>3% to &gt;15%</td>
<td></td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>10%</td>
<td></td>
<td>Sleep AHEAD (Foster, 2009)</td>
</tr>
<tr>
<td>Sleep Apnea (AHI)</td>
<td>10%</td>
<td></td>
<td>Winslow et al, 2012</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>5-10%</td>
<td></td>
<td>Christensen et al, 2007; Felson et al, 1992; Aaboe et al, 2011</td>
</tr>
<tr>
<td>Stress Incontinence</td>
<td>5-10%</td>
<td></td>
<td>Burgst et al, 2007; Leslie et al, 2009</td>
</tr>
<tr>
<td>GERD</td>
<td>5-10% women 10% men</td>
<td></td>
<td>Singh et al, 2013; Tutupan R, 2011</td>
</tr>
<tr>
<td>PCOS</td>
<td>5-15% (&gt;10% optimal)</td>
<td></td>
<td>Pandas D et al, 2006; Norman et al, 2002; Moran et al, 2013</td>
</tr>
</tbody>
</table>

The Spectrum of Cardiometabolic Disease

Prediabetic States
1. Prediabetes
   i. IFG
   ii. IGT
2. Metabolic Syndrome
   • Waist
   • Blood pressure
   • Fasting glucose
   • Triglycerides
   • HDL-cholesterol

Type 2 Diabetes

Cardiovascular Disease

Insulin Resistance

Obesity

Garvey WT, 2013
Prevalence of Metabolically Healthy Obese vs. Insulin Resistant Obese as a Function of Weight Class

Men

<table>
<thead>
<tr>
<th>Weight Class</th>
<th>Metabolically Healthy</th>
<th>Metabolically Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>69.9</td>
<td>30.1</td>
</tr>
<tr>
<td>Overweight</td>
<td>51.2*</td>
<td>48.8</td>
</tr>
<tr>
<td>Obese</td>
<td>29.2</td>
<td>70.8*</td>
</tr>
</tbody>
</table>

Women

<table>
<thead>
<tr>
<th>Weight Class</th>
<th>Metabolically Healthy</th>
<th>Metabolically Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>78.9</td>
<td>21.1</td>
</tr>
<tr>
<td>Overweight</td>
<td>64.6*</td>
<td>35.4</td>
</tr>
<tr>
<td>Obese</td>
<td>57.0</td>
<td>43.0*</td>
</tr>
</tbody>
</table>


Insulin Resistance Is a More Important Contributor than Obesity to Cardiovascular Risk

<table>
<thead>
<tr>
<th>BMI Status</th>
<th>Metabolic Status</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight</td>
<td>Normal</td>
<td>120</td>
</tr>
<tr>
<td>Obese</td>
<td>Normal</td>
<td>77</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>132</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI Status</th>
<th>Metabolic Status</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight</td>
<td>Dysmetabolic</td>
<td>250</td>
</tr>
<tr>
<td>Obese</td>
<td>Dysmetabolic</td>
<td>149</td>
</tr>
<tr>
<td>Normal</td>
<td>Dysmetabolic</td>
<td>52</td>
</tr>
</tbody>
</table>

MACE = death, nonfatal MI, stroke, congestive heart failure.
Approaches for Staging Cardiometabolic Disease Risk in Obesity

Clinically identifiable Risk States

- Prediabetes
- Metabolic Syndrome

Indices

- Framingham Risk Score
- Reynolds Risk Score
- ADA Diabetes Risk Score

Commercial Diagnostic Products

- PreDX® (Tethys Bioscience)
- LP-IR score® (Liposcience)
- Quantose IR (Metabolon)

Clinical Staging Paradigms

- Edmonton Obesity Staging System (EOSS)
- Cardiometabolic Disease Staging (CMDS)

Cardiometabolic Disease Staging (CMDS)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Risk Factors</td>
<td>Healthy Obese 1</td>
</tr>
<tr>
<td>1</td>
<td>1 or 2 Risk Factors (waist, blood pressure, triglycerides, HDL-c)</td>
<td>Metabolic Syndrome has low sensitivity for CMD, and 1 or 2 risk factors elevates risk of future T2DM and CVD 2,3</td>
</tr>
<tr>
<td>2</td>
<td>Metabolic Syndrome OR Prediabetes (i) Metabolic Syndrome alone, OR (ii) IFG, OR (iii) IGT</td>
<td>Both Metabolic Syndrome and Prediabetes confer increased risk of T2DM and CVD 3,4</td>
</tr>
<tr>
<td>3</td>
<td>Metabolic Syndrome plus Prediabetes 2 or more out of 3: Metabolic Syndrome, IFG, IGT</td>
<td>Risk of future T2DM is double in patients with both Metabolic Syndrome and Prediabetes compared with either alone 3,6</td>
</tr>
<tr>
<td>4</td>
<td>End-Stage Cardiometabolic Disease Type 2 Diabetes and/or CVD</td>
<td>T2DM is CVD risk equivalent 7</td>
</tr>
</tbody>
</table>

Cumulative Diabetes Incidence as a Function of Increasing CMDS Risk Stage: CARDIA Study Cohort

Survival Probability as a Function of Increasing CMDS Risk Stage: NHANES

Guo F, Moellering DR, Garvey WT. Obesity, In Press, 2013
**Pre-diabetes Algorithm**:
AACE Comprehensive Diabetes Algorithms


---

**Glycemic Control Algorithm**

---

* Order of medications listed in a suggested hierarchy of usage
** Based upon phase 3 clinical trial data

---

**Progression of Disease**

---

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Paradox

We have more effective tools to treat obesity than ever before,

Yet:

- Overweight, Obesity, and the resulting suffering and social costs of the disease are mounting
- There is limited availability and access to many effective therapies
Four Pillars

Concerted Action Plan for Obesity

AACE Consensus Conference on Obesity

Building an Evidence Base for Comprehensive Action
March 23-24, 2014 Washington, DC

5 Questions
1. What is obesity?
2. What options are available for obesity management?
3. What is the optimal use of therapeutic modalities?
4. Can the optimal framework be cost-effective?
5. What are the knowledge gaps and how can they be filled?

AACE Consensus Conference on Obesity.

AACE Consensus Conference on Obesity
Comprehensive Plan for Treatment/Prevention of Obesity

Primary
• Prevent obesity

Secondary
• Treat obesity to prevent disease complications

Tertiary
• Treat obesity to ameliorate disease complications

### AACE Consensus Conference on Obesity: Diagnosis Must Integrate 2 Components

- **Diagnosis**
- **BMI**
- **Anthropometric Measure of Adiposity**
- **Indication of the Impact on Health**
- **Presence and Severity of Obesity-related Complications**


### Advanced Framework for a New Diagnosis of Obesity as a Chronic Disease

<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</td>
<td>BMI 25-29.9</td>
<td>No obesity Related Complications</td>
<td>Secondary</td>
</tr>
<tr>
<td>Obesity</td>
<td>BMI ≥ 30</td>
<td>No obesity Related Complications</td>
<td>Secondary</td>
</tr>
<tr>
<td>Obesity Stage 1</td>
<td>BMI ≥ 25</td>
<td>Presence of one or more mild-moderate obesity related complications</td>
<td>Tertiary</td>
</tr>
<tr>
<td>Obesity Stage 2</td>
<td>BMI ≥ 25</td>
<td>Presence of one or more severe obesity related complications</td>
<td>Tertiary</td>
</tr>
</tbody>
</table>

Obesity Management: Intensity Based on Disease Severity

**Step 4**
Treatment based on clinical judgment

<table>
<thead>
<tr>
<th>Overweight/Obesity Stage 0</th>
<th>Obesity Stage 1</th>
<th>Obesity Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy meal pattern, Calorie reduction, Physical activity</td>
<td>Intensive Lifestyle/Behavioral Therapy ± Medications</td>
<td>Intensive Lifestyle/Behavioral Therapy + medications; Consider Bariatric Surgery</td>
</tr>
</tbody>
</table>

**Chronic Disease Management**

**Primary**
Treatment/Prevention

**Secondary**
Treatment/Prevention

**Tertiary**
Treatment/Prevention

Rationale for a Complications-Centric Model as opposed to decisions based primarily on BMI level

1. Nearly 70% of American Adults are overweight or obese, and it is not safe or fiscally feasible to treat everyone with medications or surgery.

2. Risk staging and assessment of obesity-related complications (presence and severity) can identify those patients who will most benefit from weight loss therapy.

3. Emphasize medical rather than cosmetic outcome because medications + lifestyle often achieve ~10% weight loss.

4. 10% weight loss is sufficient to improve insulin sensitivity, glucose homeostasis, lipid levels, blood pressure, diabetes prevention, CVD risk factors, and glucose & blood pressure control in T2DM.

5. Benefit/risk and cost effectiveness are increased when medical and surgical interventions are targeted to obese patients with complications.

6. Optimal benefit / risk occurs when weight loss is used as a tool to treat the complications of obesity.

THANK YOU
Liraglutide Dose-Response Effect on Body Weight Over 20 Weeks: Nondiabetic Obese Adults

**New Obesity Diagnosis: Staging for Cardiometabolic Disease**

*ATP III Risk Factors Evaluated: Waist, BP, HDL, TG, Fasting Glucose*

<table>
<thead>
<tr>
<th>STAGE</th>
<th>CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>No Risk Factors</td>
</tr>
<tr>
<td>Stage 1</td>
<td>1 or 2 risk factors</td>
</tr>
</tbody>
</table>
| Stage 2 | • Metabolic Syndrome  
            • Prediabetes  
            • Type 2 Diabetes |

**Obesity Diagnosis: Staging of Diabetes Risk:**
10 year incident diabetes in the ARIC study

![Graph showing diabetes progression over follow-up years for different stages](image-url)

The Chronic Care Model of Weight Management by PCPs

The 2013 TOS/AHA/ACC Guidelines Include a Treatment Algorithm

1. Evaluation: BMI ≥25
2. Treat complications up front “regardless of weight loss efforts”
3. Assess lifestyle choices and readiness to change, and set weight-loss goals with patient
4. Comprehensive lifestyle intervention with goal of 5-10% weight loss
5. If weight loss is not ≥5%, add medications
6. Consider bariatric surgery
7. Long-term follow-up

Prediabetes Algorithm

LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

OTHER CVR RISK FACTORS

ANTI-OBESEITY THERAPIES

ANTIHYPERGLYCEMIC THERAPIES

FPG, fasting plasma glucose; GLP-1 RA, long-acting glucagon-like peptide 1 receptor agonist; PG, plasma glucose; TZD, thiazolidinedione.

CMDS Predicts T2DM Independent of BMI in CARDIA

**Model 1**
No Adjustment for BMI

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 3</td>
<td>21.9 (11.2-43.0)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>9.73 (5.17-18.3)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>3.32 (1.80-6.15)</td>
</tr>
<tr>
<td>Metabolically Healthy</td>
<td>1[Reference]</td>
</tr>
</tbody>
</table>

**Model 2**
Adjustment for BMI

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 3</td>
<td>11.7 (5.69-24.2)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>6.10 (3.14-11.9)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>2.38 (1.26-4.50)</td>
</tr>
<tr>
<td>Metabolically Healthy</td>
<td>1[Reference]</td>
</tr>
</tbody>
</table>

Guo F, Moellering DR, Garvey WT. Obesity, In Press, 2013
Improvements in Sleep Apnea (Apnea/Hypopnea Index) with Phentermine/Topiramate ER Therapy

Winslow DH et al, Sleep, 35:1529, 2012