Guidelines and the Practice of Obesity Medicine

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Disclosures

Consultant/Advisory Boards
Daiichi-Sankyo, Novo Nordisk, Janssen, Vivus, Takeda,
Liposcience, Eisai, Astra Zeneca, Boehringer-Ingelheim

Research
Merck, Astra Zeneca, Weight Watchers, Eisai, Sanofi,
Pfizer, Lexicon
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

Body Weight
Increase
Decrease

Cause of Obesity: Abnormal Energy Balance

Human being: biological and behavioral interface
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**

  - **Increased Hunger**
  - **Increased Calorie-dense food preferences**

- **Increased Appetite**
- **Decreased Energy Out**
- **Increased Energy In**

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

Garvey WT, 2014

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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

Medications approved for chronic weight management and how they work

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

<table>
<thead>
<tr>
<th>Agent</th>
<th>Action</th>
<th>Approval</th>
<th>Scheduled Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat Xenical®</td>
<td>• Peripheral pancreatic lipase inhibitor - blocks ingested fat absorption</td>
<td>Approved 1997</td>
<td>• No</td>
</tr>
<tr>
<td>Lorcaserin Belviq®</td>
<td>• 5-HT2c serotonin agonist • Little affinity for other serotonergic receptors</td>
<td>Approved 2012</td>
<td>• YES</td>
</tr>
<tr>
<td>Phentermine/Topiramate ER Qsymia™</td>
<td>• Sympathomimetic • Anticonvulsant (GABA receptor modulator carbonic anhydrase inhibitor, glutamate antagonist)</td>
<td>Approved 2012</td>
<td>• YES</td>
</tr>
<tr>
<td>Naltrexone SR/Bupropion SR Contrade®</td>
<td>• Opioid receptor antagonist • Dopamine/noradrenaline reuptake inhibitor</td>
<td>Approved 2014</td>
<td>• NO</td>
</tr>
<tr>
<td>Liraglutide 3.0 mg Saxenda®</td>
<td>• GLP-1 receptor agonist</td>
<td>Approved 2014</td>
<td>• No</td>
</tr>
</tbody>
</table>

ER: extended release; SR: sustained release; 5HT: serotonin; GABA: Gamma aminobutyric acid; GLP-1: Glucagon-like peptide 1

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

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

Plethora of Obesity Management Guidelines

NHLBI
AHA/ACC/TOS (Circulation, 2014)
ASBP
AACE (Endo Pract, 2014)
Endocrine Society (JCEM, 2015)
Canadian Task Force (CMAJ, 2015)
NICE 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>Diet, physical activity, and behavior</td>
<td>Appropriate NHLBI Guidelines</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>No</td>
<td>With comorbidities</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Surgery*</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>With comorbidities</td>
<td>+</td>
</tr>
</tbody>
</table>

*A Bariatric surgeries require lifestyle medical follow-up.
+FDA approved gastric band surgery for patients with BMI ≥30 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 ≥27 WITH COMPLICATIONS</td>
</tr>
<tr>
<td>BMI 25–26.9, or BMI ≥27</td>
<td>Stage Severity of Complications</td>
</tr>
<tr>
<td>LOW</td>
<td>MEDIUM</td>
</tr>
</tbody>
</table>

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

1. Lifestyle Modification: *MD/BD counseling; web/remote program; structured multi-disciplinary program |
2. Medical Therapy: phentermine; orlistat; lorcaserin; phentermine / topiramate ER |
3. 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.

No drugs are currently approved for the treatment of pre-diabetes.

Pre-diabetes Algorithm*:
AACE Comprehensive Diabetes Algorithms

Glycemic Control Algorithm

The Chronic Care Model of Weight Management by PCPs

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

TOS/AHA/ACC Guidelines

RECOMMENDATION 2

...Sustained weight loss of 3%–5% is likely to result in clinically meaningful reductions in triglycerides, blood glucose, hemoglobin A1c, and the risk of developing type 2 diabetes. Greater amounts of weight loss will reduce BP, improve LDL–C and HDL–C, and reduce the need for medications to control BP, blood glucose, and lipids as well as further reduce triglycerides and blood glucose.

1. Confirm FDA prescribing information
   - Assess efficacy and safety at 3 months,
   - Avoid off-label use of medications
   - Apply “off-ramp” if <5% weight loss
   - Prescribing indications

<table>
<thead>
<tr>
<th>1</th>
<th>Heart disease, uncontrolled HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoid sympathomimetics (phenetermine, diethylpropion)</td>
</tr>
<tr>
<td></td>
<td>Prefer orlistat, lorcaserin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2</th>
<th>Depression &amp; Psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoid lorcaserin especially if on serotonergic medications</td>
</tr>
<tr>
<td></td>
<td>Prefer phentermine-topiramate ER, orlistat</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoid diabetes meds producing weight gain</td>
</tr>
<tr>
<td></td>
<td>Prefer metformin, GLP-1RAs, SGLT2i,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2</th>
<th>HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoid Beta blockers</td>
</tr>
<tr>
<td></td>
<td>Prefer ACEIs, ARBs, Ca channel blockers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoid paroxetine, amitriptyline, mirtazapine</td>
</tr>
<tr>
<td></td>
<td>Prefer fluoxetine, bupropion, sertraline,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2</th>
<th>Psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoid clozapine, olanzapine, risperidone, quetiapine</td>
</tr>
<tr>
<td></td>
<td>Prefer ziprasidone, aripiprazole</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3</th>
<th>Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoid gabapentin, pregabalin, valproic acid, carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Prefer felbamate, topiramate, zonisamide</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3</th>
<th>Contraception</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoid progestin-only preparations</td>
</tr>
<tr>
<td></td>
<td>Prefer estrogen/progestin combinations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3</th>
<th>Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoid glucocorticoids</td>
</tr>
<tr>
<td></td>
<td>Prefer NSAIDs, sulfasalazine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3</th>
<th>Antihistamines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoid H1 antihistamines</td>
</tr>
<tr>
<td></td>
<td>Prefer decongestants</td>
</tr>
</tbody>
</table>

Spectrum of Obesity Guidelines

**BMI Centric**
1. Treatment indications based on BMI
2. Goal of therapy is to lose a given amount of weight (e.g., 5-10%)

**Complications-Centric**
1. Treatment indications based on risk, presence, and severity of obesity related complications
2. Goal of therapy is to treat or prevent the complication

All patients treated who meet BMI criteria
- More aggressive treatments targeted to those patients who will derive highest benefit
- High benefit/risk
- High cost effectiveness

Low benefit/risk
- Low cost effectiveness

Low cost effectiveness
Limitations of Obesity Guidelines regarding the promotion of high quality and rational care for the patient with obesity

1. Multiple guidelines create confusion among health professionals
2. Not all guidelines are comprehensive
3. Evidence-based guidelines built around selected questions that may not be meaningful or translatable to actual patient care
4. Guidelines may not consider the totality of evidence pertinent to management issues
5. Obesity Medicine lacks a comprehensive evidence-based guidelines that is translatable to real-world clinical care of patients with obesity

NICE Guidelines
National Clinical Guideline Centre -- United Kingdom
National Institute for Health and Care Excellence
November 2014
http://www.nice.org.uk/guidance/ph53

Consider pharmacological treatment only after dietary, exercise and behavioural approaches have been started and evaluated.

Consider drug treatment for people who have not reached their target weight loss or have reached a plateau on dietary, activity and behavioural changes.
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

AACE Consensus Conference on Obesity

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

Four Pillars

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.
Emergent Concept 1.
“The imprecision and uncertainties regarding the current diagnosis of obesity based solely on BMI, and the need for a diagnosis that was more medically meaningful and actionable, clearly emerged as major impediments to concerted action, and were responsible for a degree of immobilization across pillars.

“….the framework for a medical definition of obesity would consist of the continued use of BMI together with….an assessment of the presence and severity of obesity-related complications.”


DIAGNOSIS = Anthropometric Measure of Adiposity + Indication of the Impact on Health

DIAGNOSIS = BMI + Presence and Severity of Obesity-related Complications

**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


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**Chronic Disease Model**

(ie, obesity, diabetes, asthma, hypertension, lupus, etc.)

[Diagram showing the Chronic Disease Model with connections between Genetics, Environment, DISEASE, and Complications/Disease Severity.]
### Advanced Framework for a New Diagnosis of Obesity as a Chronic Disease

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>ANTHROPO-METRIC COMPONENT</th>
<th>CLINICAL COMPONENT</th>
<th>Prevention/Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>BMI &lt; 25</td>
<td>Normal BMI</td>
<td>Primary</td>
</tr>
<tr>
<td>Overweight Stage 0</td>
<td>BMI 25-29.9</td>
<td>No obesity-related complications</td>
<td>Secondary</td>
</tr>
<tr>
<td>Obesity Stage 0</td>
<td>BMI ≥ 30</td>
<td>No obesity-related complications</td>
<td></td>
</tr>
<tr>
<td>Obesity Stage 1</td>
<td>BMI ≥ 25</td>
<td>Presence of 1 or more mild-to-moderate obesity-related complications</td>
<td>Tertiary</td>
</tr>
<tr>
<td>Obesity Stage 2</td>
<td>BMI ≥ 25</td>
<td>Presence of 1 or more severe obesity-related complications</td>
<td></td>
</tr>
</tbody>
</table>


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### STEP 3: Staging using Complication-Specific Criteria

**Step 1** Anthropometric Component

- **BMI ≥ 25**: Overweight or Obesity
- **BMI < 25**: Normal Weight – No Obesity

**Step 2** Clinical Component

- **Overweight or Obesity Stage 0**: No obesity related complications
- **Overweight or Obesity Stage 0**: One or more obesity related complications

**Step 3** Complications Staging

- **Obesity Stage 1**: No obesity related complications
- **Obesity Stage 1**: Evaluation using complications-specific criteria
- **Obesity Stage 2**: One or more complications mild to moderate in severity and/or can be treated effectively with a moderate degree of weight loss
- **Obesity Stage 2**: At least one complication that is severe and/or requires more aggressive weight loss therapy for effective treatment
### Checklist of Obesity Related Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Tests/Exams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic Syndrome</td>
<td>Waist, BP, HDL, TG, FPG</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>FPG</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>FPG</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Lipid panel</td>
</tr>
<tr>
<td>Hypertension</td>
<td>BP</td>
</tr>
<tr>
<td>NAFLD</td>
<td>Exam, LFTs</td>
</tr>
<tr>
<td>PCOS</td>
<td>Exam, ROS</td>
</tr>
<tr>
<td>Sleep Apnea</td>
<td>Exam, ROS</td>
</tr>
<tr>
<td>osteoarthritis</td>
<td>Exam, ROS</td>
</tr>
<tr>
<td>GERD</td>
<td>Exam, ROS</td>
</tr>
<tr>
<td>Disability/Immobility</td>
<td>Exam, ROS</td>
</tr>
<tr>
<td>Psychological Disorder</td>
<td>Exam, ROS</td>
</tr>
<tr>
<td>Secondary: genetic syndromes, hormonal disease, iatrogenic</td>
<td>Exam, ROS, med review, family hx</td>
</tr>
</tbody>
</table>

### Obesity Management: Intensity Based on Disease Severity

**Step 4**
Treatment based on clinical judgment

<table>
<thead>
<tr>
<th>Chronic Disease Management</th>
<th>Primary</th>
<th>Secondary</th>
<th>Tertiary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment/Prevention</td>
<td>Treatment/Prevention</td>
<td>Treatment/Prevention</td>
<td>Treatment/Prevention</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

Goals of Therapy for Cardiometabolic Disease (Metabolic Syndrome and Prediabetes)

1. Prevent Progression to Type 2 Diabetes
2. Lower Blood Pressure
3. Correct Dyslipidemia
Long-Term Weight Loss Is Difficult to Maintain

DPP Outcomes Study (N = 2766)


Weight Loss Reduces Long-Term Incidence of T2DM

DPP Outcomes Study (N = 2766)

How much weight loss is needed to prevent type 2 diabetes? the DPP experience

![Graph showing incidence rate per 100 person-years vs. change in weight from baseline (kg).]


Weight Loss Induced by Phentermine/Topiramate ER Prevents Diabetes in Patients With Metabolic Syndrome and/or Prediabetes: SEQUEL Study

![Graph showing cumulative incidence rate of type 2 diabetes over weeks.]

Dose-Response for Weight Loss and Diabetes Prevention due to Phentermine/Topiramate ER Treatment: SEQUEL

Garvey et al, Diabetes Care, 37:912, 2014

Incidence of Diabetes after Bariatric Surgery#: UK population-based matched* cohort study

Booth H et al, Lancet Diabetes Endocrinol E-pub Nov 3, 2014

*Matched for BMI, age, gender, index year, HbA1c
# banding>bypass>sleeve
hide slide - hold data for later FMA trainings

LMNN (Linda Shapiro Manning), 11/11/2013
Change in risk factors by weight loss categories for the Look AHEAD cohort.

Wing R R et al. Diabetes Care 2011;34:1481-1486

HbA1c (Δ%)

DBP and SBP (Δ mmHg)

HDL and LDL (Δ mg/dl)

Fasting Glucose (Δ mg/dl)

Triglycerides (Δ mg/dl)

HDL and LDL no lipid meds (Δ mg/dl)

Varady KA et al, Lipids Health Dis. 10:119, 2011

Effects of Weight Loss and Exercise on Lipid panel Parameters

- 12 week study
- Weight Loss ~5% in diet groups
**Meta-Analysis of Low Carb vs Low Fat Weight Loss Diets: Effects on Lipids**

**WEIGHT LOSS**
- Low carb better at 6 mo
- No difference at 12 mo

**LDL-c**
- Low fat better at 6 & 12 mo

**HDL-c**
- Low carb better at 6 & 12 mo

**TRIGLYCERIDES**
- Low carb better at 6 & 12 mo

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Nordmann et al., JAMA Int Med. 166:285, 2006

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Calculated LDL cholesterol values in the conventional lipid panel do not reveal effects of insulin sensitivity on LDL subclass particle concentrations.

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Correlations between GDR (insulin sensitivity) and selected lipoprotein subclass particle concentrations and particle sizes.


Correlation between the percentage changes in plasma TG and percentage changes in number of large VLDL particles (panel A) and LDL particle diameters (panel B) in men who consumed a reduced calorie diet for 12 wk.

**Prevalence of LDL subclass pattern B as a function of dietary carbohydrate before and after weight loss**

![Graph](image)


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**Macronutrient Diet Composition:**

**Effect on Insulin Sensitivity in Isocaloric Substitution Experiments**

- Diets enriched in the following are associated with a *decrease* in insulin sensitivity
  - Total fat
  - Saturated fat
  - *trans*-fat
  - Refined grains

- Diets enriched in the following are associated with an *increase* in insulin sensitivity
  - Fiber
  - Fruits/Vegetables
  - Polyunsaturated fats
  - Monounsaturated fats
  - Whole grain

Lara-Castro C and Garvey WT, JCEM 89:4197, 2004
Lifestyle Therapy Based on the Characteristics of the Dyslipidemia

**Low Fat Diets**
- Saturated fats < 10%
- No trans fat
- High Fiber
- Exercise

**Low Carbohydrate Diets**
- Mediterranean Diet
  - Emphasize MUFAs and PUFAs
  - High Fiber and whole grains
  - Exercise

**Hypercholesterolemia**
- Elevated LDL-c
- Elevated TG > 500 mg/dl

**Dyslipidemia of Insulin Resistance**
- Elevated TG 150-500 mg/dl
- Low HDL-c
- More small dense LDL particles

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
Cardiometabolic Disease Staging (CMDS)\(^8\)

<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

Guo F, Moellering DR, Garvey WT. Obesity, In Press, 2013
CMDS Predicts T2DM Independent of BMI in CARDIA

Guo F, Moellering DR, Garvey WT. Obesity 22:110, 2014

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

Guo F, Moellering DR, Garvey WT. Obesity, In Press, 2013
SUMMARY

A complications-centric approach to the management of obesity, together with a diagnosis that reflects both the degree of adiposity and the presence/severity of obesity related complications (i.e., impact on health), can promote:

• A medical model for care of obesity as a chronic disease
• Optimal benefitted/risk ratio that targets more aggressive treatments to those patients who will derive the highest benefit
• Cost effectiveness
• High quality care: a structured approach to comprehensive evaluation and therapeutic decisions
• Coverage and accessibility of treatment options by re-assuring regulators, administrators, payers, employers, and benefit managers
Thank You

RESERVE SLIDES
Survival Probability and Incident CHD in the ARIC Study
Lean, Overweight, and Obese Subjects who were either metabolically healthy or had the Metabolic Syndrome

CONCLUSIONS: 1. BMI has relatively small impact on T2DM risk in insulin sensitive individuals.
2. BMI has larger impact on T2DM risk in insulin resistant individuals

Incident T2DM in the ARIC Study
Lean, Overweight, and Obese Subjects who were either metabolically healthy or had the Metabolic Syndrome

Note: Lean MS subjects have much higher rate of T2DM than metabolically healthy obese

### AACE Guidelines for Obesity Management

**Diagnosis Complications**

<table>
<thead>
<tr>
<th>STEP 1</th>
<th>STEP 2</th>
<th>STEP 3</th>
<th>STEP 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthropometric Component, BMI</td>
<td>Clinical Component</td>
<td>Staging</td>
<td>Suggested Interventions</td>
</tr>
</tbody>
</table>

#### 25 - 29.9
- Overweight, Stage 0
  - Checklist: Presence or absence of weight-related complications
  - Lifestyle modification
  - Reduced-calorie healthy meal plan
  - Physical activity

#### ≥ 30
- Obesity, Stage 0
  - Lifestyle modification/ Reduced-calorie meal plan/ Physical activity
  - Intensive behavioral and lifestyle therapy

#### ≥ 25
- Obesity Stage 1
  - 1 or more mild-moderate complications
  - Intensive behavioral and lifestyle therapy
  - Consider adding weight loss medication if BMI ≥ 27

- Obesity Stage 2
  - at least 1 severe complication
  - Intensive behavioral and lifestyle therapy
  - Add weight loss medication if BMI ≥ 27
  - Consider bariatric surgery in T2DM if BMI 35-39.9
  - Consider bariatric surgery if BMI ≥ 40

#### 4-step approach is recommended for all patients

**STEP 1: Screening**

**AACE/ACE Diagnostic Algorithm for the Disease of Obesity**

- **Step 1** Anthropometric Component

- **BMI ≥ 25**
  - BMI 23-25 and waist circumference above risk threshold in certain ethnicities
  - Overweight or Obesity

- **BMI < 25**
  - BMI 23-25 and waist circumference below risk threshold in certain ethnicities
  - Normal Weight – No Obesity
4-step approach, STEP 2: Evaluate for presence of obesity related complications

Endocrine Society Guidelines

RECOMMENDATION 1.2

In order to promote long-term weight maintenance, we suggest the use of approved weight loss medications to ameliorate comorbidities and amplify adherence to behavior changes .... in individuals with a BMI ≥ 30 kg/m2 or in individuals with a BMI of ≥ 27 kg/m2 and at least one associated comorbid medical condition such as hypertension, dyslipidemia, T2DM, and obstructive sleep apnea.

AACE Plans

1. Evidence based guidelines
   - Assess evidence to justify complications-centric approach to care
   - Comprehensive
   - Totality of evidence
   - Address practical management issues

2. White Paper and Tool Kit
   - Based on the evidence-based guidelines that describes their practical application in patient care,
   - Provides a ‘tool kit’ for establishing an obesity medicine practice
   - Lowers the ‘activation energy’ for the practice of obesity medicine for motivated professionals

3. CME programs
   - Based on the principles in the white paper

4. Second consensus conference on obesity
   - Will include professional societies and patients in an effort to harmonize existing guidelines around a practical and actionable plan for patient care

Medications approved for chronic weight management – Dosing and Response Evaluation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
<th>Response Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>120 mg orally with each meal</td>
<td>Not addressed in label</td>
</tr>
<tr>
<td>Lorcanerin</td>
<td>10 mg orally twice daily</td>
<td>Stop if &lt;5% loss at 12 weeks</td>
</tr>
<tr>
<td>Phentermine/ Topiramate ER</td>
<td>Orally in am; 3.75 mg/23 mg x 14 days; Then, 7.5/46 mg x14 days.</td>
<td>At 12 weeks, option to ↑ to 11.25 mg/69 mg x 14 days, then 15 mg/96 mg; Stop if &lt;5% loss at 12 weeks on top dose</td>
</tr>
<tr>
<td>Naltrexone SR/ Bupropion SR</td>
<td>Orally; Wk 1 -1 tab (8 mg/90 mg) in am ; Wk 2 - 1 in am 1 in pm; Wk 3 - 2 in am 1 in pm; Wk 4 - 2 in am 2 in pm.</td>
<td>Stop if &lt;5% loss at 12 weeks</td>
</tr>
<tr>
<td>Liraglutide 3 mg</td>
<td>Inject subcutaneously (any time of day); Wk 1 - 0.6 mg; increase dose by 0.6 mg weekly until dose is 3.0 mg (Wk 5)</td>
<td>Stop if &lt;4% weight loss at 16 weeks</td>
</tr>
</tbody>
</table>

All data from product label
### Medications Approved for Chronic Weight Management – Safety and Contraindications

<table>
<thead>
<tr>
<th>Agent</th>
<th>Safety</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>Warning: ↑ cyclosporine exposure; rare liver failure; multivit advised</td>
<td>Chronic malabsorption; gall bladder disease</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Warnings: serotonin syndrome; valvular heart disease; cognitive impairment; depression; hypoglycemia; priapism</td>
<td>Do not use with MAOIs. Use with “extreme caution” with serotonergic drugs (SSRIs, SNRIs); Pregnancy</td>
</tr>
<tr>
<td>Phentermine/Topiramate ER</td>
<td>Warning: fetal toxicity; acute myopia; cognitive dysfunction; metabolic acidosis; hypoglycemia</td>
<td>Glaucma; hyperthyroidism; MAOIs; Pregnancy</td>
</tr>
<tr>
<td>Naltrexone SR/Bupropion SR</td>
<td>Boxed warning: suicidal; BP, HR; ↑ seizure risk; glaucoma; hepatotoxicity</td>
<td>Seizure disorder; uncontrolled HTN; chronic opioid use; MAOIs; Pregnancy</td>
</tr>
<tr>
<td>Liraglutide 3.0 mg</td>
<td>Boxed warning: rodent thyroid c-cell tumors. Warnings: acute pancreatitis, acute gallbladder disease, hypoglycemia, heart rate increase; renal impairment; suicidal behavior</td>
<td>Patients with a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia; Pregnancy</td>
</tr>
</tbody>
</table>

*All data from product label*

### Medications Approved for Chronic Weight Management – Tolerability

<table>
<thead>
<tr>
<th>Agent</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>All the symptoms of steatorrhea (fatty discharge, etc.)</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Headache, dizziness, fatigue</td>
</tr>
<tr>
<td>Phentermine/Topiramate ER</td>
<td>Paresthesias, dysgeusia; dizziness, dry mouth</td>
</tr>
<tr>
<td>Naltrexone SR/Bupropion SR</td>
<td>Nausea, vomiting, headache, dizziness, insomnia</td>
</tr>
<tr>
<td>Liraglutide 3 mg</td>
<td>Nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain.</td>
</tr>
</tbody>
</table>

*All data from product label*
• The patient asks, “Which drug is the best drug for me?”

## Medications for Chronic Weight Management and the Patient

<table>
<thead>
<tr>
<th>Condition</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who could become pregnant</td>
<td>Do NOT prescribe. Obtain negative pregnancy test before prescribing PHEN/TPM and monthly while on therapy.</td>
</tr>
<tr>
<td>Who is breast feeding</td>
<td>Do NOT prescribe.</td>
</tr>
<tr>
<td>With history of seizure</td>
<td>NB is contraindicated. Taper PHEN/TPM slowly when discontinuing to avoid precipitating seizure.</td>
</tr>
<tr>
<td>With history of kidney stones</td>
<td>Avoid: PHEN/TPM, Orlistat.</td>
</tr>
<tr>
<td>With glaucoma</td>
<td>Contraindicated: PHEN/TPM. (angle closure glaucoma associated with NB)</td>
</tr>
<tr>
<td>With hypertension</td>
<td>NB,</td>
</tr>
<tr>
<td>With arrhythmia</td>
<td>NB, PHEN/TPM, liraglutide can increase heart rate.</td>
</tr>
</tbody>
</table>

Data from product label. NB: Naltrexone SR/Bupropion SR. PHEN/TPM: Phentermine/Topiramate ER
### Medications for Chronic Weight Management and the Patient

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| With moderate renal impairment                 | Do not exceed 7.5/46 mg PHEN/TPM  
Do not exceed 16/180 mg NB  
Use with caution: Liraglutide, Lorcaserin  
No information: Orlistat |
| With moderate hepatic impairment               | Do not exceed 7.5/46 mg PHEN/TPM  
Do not exceed 8/90 mg NB  
Use with caution: Liraglutide, Lorcaserin  
No information: Orlistat |
| With depression receiving SSRIs                | Extreme caution: Lorcaserin  
(PHEN/TPM has been studied in phase III) |
| With depression                                | (PHEN/TPM has been studied in phase III)                                    |
| Age >65 years                                   | Limited experience for NB, PHEN/TPM, Liraglutide, Lorcaserin; none for Orlistat |

Data from product label.  
NB: Naltrexone SR/Bupropion SR.  
PHEN/TPM: Phentermine/Topiramate ER

### Medications for Chronic Weight Management: Contraindications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal or family history; medullary thyroid cancer</td>
<td>Liraglutide</td>
</tr>
<tr>
<td>Chronic malabsorption</td>
<td>Orlistat</td>
</tr>
<tr>
<td>Cholestatic</td>
<td>Orlistat</td>
</tr>
<tr>
<td>Chronic opioid use</td>
<td>NB</td>
</tr>
<tr>
<td>Seizures</td>
<td>NB</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
<td>NB</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>PHEN/TPM</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>PHEN/TPM</td>
</tr>
<tr>
<td>Within 14 days of MAOI use</td>
<td>NB, PHEN/TPM</td>
</tr>
</tbody>
</table>

Data from product label.  
NB: Naltrexone SR/Bupropion SR.  
PHEN/TPM: Phentermine/Topiramate ER
Evaluation of Obesity Complications and Clinical Decisions Regarding Therapy

1. Non-Alcoholic Fatty Liver Disease
2. Cardiometabolic Disease
   • Prediabetes
   • Metabolic Syndrome
   • Type 2 Diabetes
   • Cardiovascular Disease

Progression of NAFLD
### Changes in Body Weight and Liver after 6 Weeks treatment with Lifestyle plus Orlistat

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight (kg)</td>
<td>120</td>
<td>110</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>44</td>
<td>40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver Volume by MRI (ml)</td>
<td>2,199</td>
<td>1,934</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver Fat by 1H-NMR Spectroscopy (AU)</td>
<td>0.07</td>
<td>0.03</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Lewis MC et al, Obesity Surgery 16:697-701, 2006

### Histological Results from Paired Biopsies Before and After Weight Loss

<table>
<thead>
<tr>
<th>Score</th>
<th>Number Before</th>
<th>Number After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis Score</td>
<td>9 severe</td>
<td>4 severe</td>
</tr>
<tr>
<td></td>
<td>1 moderate</td>
<td>1 A2</td>
</tr>
<tr>
<td></td>
<td>4 mild</td>
<td>1 A2</td>
</tr>
<tr>
<td>Inflammation Score</td>
<td>1 A4</td>
<td>1 A2</td>
</tr>
<tr>
<td></td>
<td>1 A3</td>
<td>1 A2</td>
</tr>
<tr>
<td></td>
<td>9 A2</td>
<td>2 A2</td>
</tr>
<tr>
<td></td>
<td>4 A1</td>
<td>2 A2</td>
</tr>
<tr>
<td></td>
<td>3 A0</td>
<td>3 A0</td>
</tr>
<tr>
<td></td>
<td>3 A1</td>
<td>1 A1</td>
</tr>
<tr>
<td></td>
<td>2 A0</td>
<td>2 A0</td>
</tr>
<tr>
<td>Fibrosis Score</td>
<td>1 F3</td>
<td>1 F1</td>
</tr>
<tr>
<td></td>
<td>8 F2</td>
<td>1 F4; 1 F2; 2 F0</td>
</tr>
<tr>
<td></td>
<td>5 F1</td>
<td>2 F1; 3 F0</td>
</tr>
</tbody>
</table>

Mean 5.4% weight loss after 6 months on lifestyle plus orlistat

**Randomized Controlled Trial Assessing Lifestyle-Induced Weight Loss on NAFLD Histology**

NASH Activity Score: steatosis, lobular inflammation, hepatocyte ballooning. Improvement = change in 3 points

Promrat K et al, Hepatology 51:121-129, 2010

---

**Gastric Bypass Surgery and NAFLD**

18 months after Roux-en-Y, weight loss 50 kg

<table>
<thead>
<tr>
<th>Histological Finding</th>
<th>Prevalence Before</th>
<th>Prevalence After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis</td>
<td>89.7%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Hepatocellular Ballooning</td>
<td>58.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Centrilobular Fibrosis</td>
<td>50%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Note: no improvements in portal tract inflammation and fibrosis

**Weight Loss Therapy: NAFLD**

**Liver Biopsy**

<table>
<thead>
<tr>
<th>No Steatosis</th>
<th>Steatosis Only</th>
<th>Inflammation and/or fibrosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight/Obesity Stage 0</td>
<td>Obesity Stage 1</td>
<td>Obesity Stage 2</td>
</tr>
</tbody>
</table>

**Step 4**
Treatment based on clinical judgment.

**Management**

* Lobular inflammation and ballooning degeneration, Mallory Bodies and/or fibrosis

---

**Effects of Commercial Weight Loss Programs on Lipid panel Parameters**

<table>
<thead>
<tr>
<th>Program</th>
<th>TG</th>
<th>LDL-c</th>
<th>HDL-c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkins</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Weight-Watchers</td>
<td>a</td>
<td>b</td>
<td>b</td>
</tr>
<tr>
<td>Slim-Fast</td>
<td>ab</td>
<td>ab</td>
<td>ab</td>
</tr>
<tr>
<td>Rosemary Conley</td>
<td>b</td>
<td>b</td>
<td>b</td>
</tr>
<tr>
<td>Control</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
</tbody>
</table>

Effects of Weight Loss on Lipids and Lipoproteins (alternate day fasting)

- Weight Loss 6 kg
- LDL size
- LDL large
- LDL small
- Changes correlated with decrease WC and weight


Criteria: (i) Blood pressure < 130/85; (ii) Fasting glucose < 100 mg/dl; (iii) HDL ≥ 40 mg/dl men or ≥ 50 mg/dl women

Metabolically Healthy meet all 3 criteria
Metabolically Suboptimal fail 1 or 2 criteria
Metabolically Unhealthy fail all 3 criteria

Guo F and Garvey WT, unpublished data, 2014
Differences in Response to Commercial Weight Loss Programs in Pattern B vs Pattern A Lipid Phenotype

<table>
<thead>
<tr>
<th>Mean weight loss at 6 mo (kg)</th>
<th>Pattern A</th>
<th>Pattern B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>-0.9</td>
<td>-0.9</td>
</tr>
<tr>
<td>Atkins</td>
<td>-8.9</td>
<td>-8.9</td>
</tr>
<tr>
<td>Weight Watchers</td>
<td>-8.0</td>
<td>-8.0</td>
</tr>
<tr>
<td>Slim-Fast</td>
<td>-6.7</td>
<td>-6.7</td>
</tr>
<tr>
<td>Rosemary Conley</td>
<td>-8.8</td>
<td>-8.8</td>
</tr>
</tbody>
</table>


Complications-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 ≥ 27 WITH COMPLICATIONS</td>
</tr>
<tr>
<td>BMI 25-26.9, or BMI ≥ 27</td>
<td>Stage Severity of Complications</td>
</tr>
<tr>
<td>LOW</td>
<td>MEDIUM</td>
</tr>
<tr>
<td>MEDIUM</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

**Step 2**
SELECT:

Therapeutic targets for improvement in complications

- Treatment modality
- Treatment intensity for weight loss based on staging

- Lifestyle Modification: MD/RD counseling; web/remote program; structured multidisciplinary program
- Medical Therapy: phentermine; orlistat; lorcaserin; phentermine/topiramate ER; metformin/buproprion; lorcaserin
- 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>Maximum benefit 10%</td>
<td>DPP (Landel, 2009) SEQUEL (Garvey et al, 2013)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5% to &gt;15%</td>
<td>BP still decreasing &gt;15%</td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3% to &gt;15%</td>
<td>TG still decreasing at &gt;15%</td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>3% to &gt;15%</td>
<td>HbA1c still decreasing at &gt;15%</td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>10%</td>
<td>Improves steatosis, inflammation, mild fibrosis</td>
<td>Assy et al, 2007; Green et al, 2004; Anish et al, 2009</td>
</tr>
<tr>
<td>Sleep Apnea (AHI)</td>
<td>10%</td>
<td>Little benefit at ≤5%</td>
<td>Sleep AHEAD (Foster, 2009)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>5-10%</td>
<td>Improves symptoms and joint stress mechanics</td>
<td>Christiansen et al, 2007; Faoro et al, 1992; Ashik et al, 2011</td>
</tr>
<tr>
<td>Stress Incontinence</td>
<td>5-10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GERD</td>
<td>5-10% women vs. 10% men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCOS</td>
<td>5-15% (&gt;10% optimal)</td>
<td>Lowers androgens, improves ovulation, increases insulin sensitivity</td>
<td>Panidis D et al, 2008; Norman et al, 2002; Moran et al, 2013</td>
</tr>
</tbody>
</table>

### Effects of Mediterranean Diet with and without Weight Loss on Lipoproteins and Lipoprotein Turnover

<table>
<thead>
<tr>
<th></th>
<th>MD-WL</th>
<th>MD+WL</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>-5%</td>
<td>-29%</td>
</tr>
<tr>
<td>LDLc</td>
<td>-10%</td>
<td>-13%</td>
</tr>
<tr>
<td>Apo-B100</td>
<td>-10%</td>
<td>-15%</td>
</tr>
<tr>
<td>LDL % small</td>
<td>-12%</td>
<td>-15%</td>
</tr>
<tr>
<td>LDL % medium</td>
<td>+11%</td>
<td>+15%</td>
</tr>
<tr>
<td>LDL % large</td>
<td>+1%</td>
<td>+1%</td>
</tr>
<tr>
<td>CETP</td>
<td>-7%</td>
<td>-7%</td>
</tr>
<tr>
<td>Hepatic Lipase</td>
<td>-7%</td>
<td>-12%</td>
</tr>
<tr>
<td>Insulin</td>
<td>-17%</td>
<td>-31%</td>
</tr>
</tbody>
</table>

FCR = fractional catabolic rate; PS = Pool size; PR = production rate
When individual weight loss is displayed, it looks like this: