Session 4: 
Obesity and Type 2 Diabetes: 
Understanding the Benefits of Weight Loss in the Diabetic Population

Learning Objectives

1. Recognize the impact of excess weight on overall patient health and the risk for developing type 2 diabetes.

2. Identify patients with prediabetes and provide strategies to engage patients in open dialogues about the benefits of weight reduction, including diabetes prevention, highlighting the essential components of weight management, and the importance of setting realistic weight-loss goals.

3. Describe the expected benefits of lifestyle change, structured weight-loss programs, and pharmacologic agents on achieving weight reductions in the diabetic obese patient.

4. Effectively manage antidiabetic medications and follow-up care as a result of patient weight loss.

Educational Partner:

CME • INCITE
Session 4: Obesity and Type 2 Diabetes: Understanding the Benefits of Weight Loss in the Diabetic Population

Learning Objectives

1. Recognize the impact of excess weight on overall patient health and the risk for developing type 2 diabetes
2. Identify patients with prediabetes and provide strategies to engage patients in open dialogues about the benefits of weight reduction, including diabetes prevention, highlighting the essential components of weight management and the importance of setting realistic weight loss goals
3. Describe the expected benefits of lifestyle change, structured weight loss programs, and pharmacologic agents on achieving weight reductions in the diabetic obese patient
4. Effectively manage antidiabetic medications and follow-up care as a result of patient weight loss

Nancy Bohannon, MD, FACP, FACE
Director of Clinical Research
Cardiovascular Risk Reduction Program
Saint Luke's Hospital
San Francisco, California

Dr. Nancy Bohannon is director of clinical research in the Cardiovascular Risk Reduction Program at Saint Luke’s Hospital in San Francisco. Dr. Bohannon earned her medical degree from the University of California (UC), Davis. Following her residency in internal medicine at the Children’s Hospital in San Francisco, she completed a clinical and research fellowship at the San Francisco Diabetes Association (SFDA) and the SFDA Dorothy Frank Research Fellowship at UC San Francisco.

Dr. Bohannon is active in both research and clinical projects. She has been in solo private practice of diabetes/endocrinology in San Francisco for 35 years. Her main interests include lipid disorders, components of the metabolic syndrome, and diabetes.

Dr. Bohannon is currently president of the Medical Society of the United States and Mexico. A fellow of the American College of Physicians and the American College of Endocrinology, she is a member of the American Medical Association, the professional sections of both the American Diabetes and the American Heart Associations, the Northern California Professional Diabetes Association, the American Federation for Clinical Research, and the Atherosclerosis Council.

Dr. Bohannon also serves on many editorial and review boards. She is a reviewer for *Patient Care, Diabetes Care and Endocrine Practice*, an editorial review panel member for *Postgraduate Medicine*; and an editorial board member for *Insulin and Primary Care Reports: The Practical Journal for Family Physicians*. Dr. Bohannon has published more than 75 research articles or abstracts in the *Journal of the American Medical Association, Diabetes Care, Postgraduate Medicine, Clinical Therapeutics*, and *Diabetes Technology & Therapeutics*, among others. She lectures extensively and internationally, most recently in India, Mexico, and Dubai, in 2011.

Patrick Mahlen O'Neil, PhD
Professor
Director, Weight Management Center
Department of Psychiatry and Behavioral Sciences
Medical University of South Carolina
Charleston, South Carolina

Patrick Mahlen O’Neil, PhD, is Professor of Psychiatry and Behavioral Sciences at the Medical University of South Carolina in Charleston, where he is also Director of the Weight Management Center. He earned his bachelor degree in economics from Louisiana State University in Baton Rouge and his master of science and doctorate degrees in clinical psychology from the University of Georgia in Athens. Since 1977, Dr. O’Neil has been professionally involved in numerous clinical, teaching, research, and public education roles concerning obesity. He directs a long-standing multidisciplinary weight management center offering services for people of all degrees overweight. His teaching activities include supervision of psychology interns on clinical rotations in the Center; lectures to medical students, residents, and other trainee groups; and invited continuing education lectures to physician and other practitioner audiences. He is and has been principal investigator for a number of externally funded clinical trials of weight-loss agents. He is the author of more than 100 professional publications, chapters, and presentations, primarily concerning psychological, behavioral, and other clinical aspects of obesity and its management. From 1987-1996, he authored *Weighing the Choices*, a weekly column on weight control in the Charleston, South Carolina, *Sunday Post and Courier*.

Session 4
Dr. O’Neil is Associate Editor of the journal *Surgery for Obesity and Related Diseases* and a member of the editorial boards of the journals *Obesity* (formerly *Obesity Research*), *Eating Behaviors*, and *International Journal of Obesity*. He is a long-standing active member of The Obesity Society (formerly the North American Association for the Study of Obesity [NAASO]), presently serving as Past President after terms as Councillor, Vice President, President Elect, and President. Previously, he was Editor of the NAASO Web site, Program Chair for the NAASO 1999 annual meeting in Charleston, a member of the Publications Committee, and a member of the National Institutes of Health/NAASO Ad Hoc Committee for Development of *The Practical Guide for the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. He is a former member of the Committee on Military Nutrition Research of the Institute of Medicine. In addition, he is former Chair of the Obesity and Eating Disorders Special Interest Group of the Association for the Advancement of Behavior Therapy.

Closer to home, Dr. O’Neil served as a member of the Scientific Council of the South Carolina Nutrition Research Consortium throughout its existence. He participated as a member of a statewide committee that developed the Report on the Impact of Obesity on Health in South Carolina, in response to a mandate by the state General Assembly. He is also a former member and Chair of the South Carolina Board of Examiners in Psychology and Past President of the South Carolina Academy of Professional Psychologists. Since 2001, he has been a member of Town Council of the Town of Sullivan’s Island and, before that, was a member and Chair of the Town’s Planning Commission.

**Faculty Financial Disclosure Statements**

The presenting faculty reported the following:

Dr Bohannon receives grant research support from Calibra Medical, Inc.; Intuity Medical, Inc.; Eli Lilly and Company; Novartis Pharmaceuticals Corporation; sanofi-aventis U.S. LLC; Valeritas Inc.; and VIVUS, Inc.; and honoraria from Biodel Inc.; Calibra Medical, Inc.; Halozyme Therapeutics, Inc.; Johnson & Johnson; Eli Lilly and Company; MannKind Corporation; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Roche; Santaris Pharma A/S; sanofi-aventis U.S. LLC; Tethys Bioscience, Inc.; Valeritas Inc.; VeraLight, Inc.; and VIVUS, Inc.; and is a speaker for Amrylin Pharmaceuticals, Inc.; Eli Lilly and Company; Merck & Co., Inc.; Merck/Schering-Plough Pharmaceuticals; Novartis Pharmaceuticals Corporation; Qwest Diagnostics; sanofi-aventis U.S. LLC; Santaris Pharma A/S; and Tethys Bioscience, Inc. She is also a shareholder in Affymetrix, Inc.; Bristol-Myers Squibb; Johnson & Johnson; Eli Lilly and Company; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Genomic Health, Inc.; sanofi-aventis U.S. LLC; and VIVUS, Inc.

Dr O’Neil serves as an investigator for Novo Nordisk, Orexigen Therapeutics, and Weight Watchers International. He also serves on the advisory board for Orexigen Therapeutics.

**Education Partner Financial Disclosure Statement**

The content collaborators at CME Incite report the following:

Priya Wanchoo, MBBS, and Rose O’Connor, PhD, have no financial relationships to disclose.

**Suggested Reading List**

Garber AJ. Obesity and type 2 diabetes: which patients are at risk? *Diabetes Obes Metab*. 2012;14(5):399-408.


Obesity and Type 2 Diabetes: Understanding the Benefits of Weight Loss in the Diabetic Population
Patrick Mahlen O'Neil, PhD
Nancy Bohannon, MD, FACP, FACE

Learning Objectives
- Recognize the impact of excess weight on overall patient health and the risk for developing type 2 diabetes
- Identify patients with prediabetes and provide strategies to engage patients in open dialogues about the benefits of weight reduction, including diabetes prevention, highlighting the essential components of weight management and the importance of setting realistic weight loss goals
- Describe the expected benefits of lifestyle change, structured weight loss programs, and pharmacologic agents on achieving weight reductions in the diabetic obese patient
- Effectively manage antidiabetic medications and follow-up care as a result of patient weight loss

Pretest Question 1
Which of the following is the strongest predictor of developing T2DM?
1. Continued yearly excessive weight gain
2. Increase in waist circumference
3. Impaired glucose tolerance
4. All of the above

Pretest Question 2
In order to decrease an obese patient’s risk of developing type 2 diabetes, the minimum weight loss goal should be:
1. 5% to 10%
2. 20%
3. Depends on the initial BMI of the patient
4. High enough to lower the patient’s BMI to <30

Faculty Disclosures
- Patrick Mahlen O'Neil, PhD is on the advisory board for Orexigen Therapeutics, and is an investigator for Novo Nordisk, Orexigen Therapeutics, and Weight Watchers International.
- Dr Bohannon receives grant research support from Calibra Medical, Inc.; Intuity Medical, Inc.; Eli Lilly and Company; Novartis Pharmaceuticals Corporation; sanofi-aventis U.S. LLC; Valienta Inc.; and VIVUS, Inc.; and honoraria from Bodel Inc.; Calibra Medical, Inc.; Halozyme Therapeutics, Inc.; Johnson & Johnson; Eli Lilly and Company; MannKind Corporation; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Roche; Santaris Pharma A/S; sanofi-aventis U.S. LLC; Tethys Bioscience, Inc.; Valienta Inc.; Vasclairt, Inc.; and VIVUS, Inc.; and is a speaker for Amylin Pharmaceuticals, Inc.; Eli Lilly and Company; Merck & Co., Inc.; Merck/Schering-Plough Pharmaceuticals; Novartis Pharmaceuticals Corporation; Qwest Diagnostics; sanofi-aventis U.S. LLC; Santaris Pharma A/S; and Tethys Bioscience, Inc. She is also a shareholder in Affymetrix, Inc.; Bristol-Myers Squibb; Johnson & Johnson; Eli Lilly and Company; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Genomic Health, Inc.; sanofi-aventis U.S. LLC; and VIVUS, Inc.
Pretest Question 3

If an obese (BMI 32) person with hypertension and T2DM has been unsuccessful in his/her weight loss goals (5% reduction) after 6 months of lifestyle modification, what would be the next strategy to recommend for weight loss?

1. Continue lifestyle modifications for another 6 months
2. Increase daily exercise time
3. Consider pharmacotherapy
4. Schedule bariatric surgery
5. Unsure

Pretest Question 4

Which pharmacotherapy(ies) for chronic weight management has the FDA approved in 2012?

1. Liraglutide
2. Phentermine/topiramate ER
3. Liraglutide and phentermine/topiramate ER
4. Lorcaserin and phentermine/topiramate ER
5. Combination naltrexone and bupropion
6. All of the agents listed

Type 2 Diabetes as a Complication of Obesity: Understanding the Link

Patrick Mahlen O’Neil, PhD
Professor
Director, Weight Management Center
Department of Psychiatry and Behavioral Sciences
Medical University of South Carolina
Charleston, South Carolina

Obesity (BMI ≥ 30 kg/m²)

<table>
<thead>
<tr>
<th>Year</th>
<th>Data</th>
<th>14.0%</th>
<th>16.0-17.9%</th>
<th>18.0-21.9%</th>
<th>22.0-25.9%</th>
<th>&gt;26.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>No Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diabetes

<table>
<thead>
<tr>
<th>Year</th>
<th>Data</th>
<th>&lt;4.5%</th>
<th>4.5-5.9%</th>
<th>6.0-7.4%</th>
<th>7.5-8.9%</th>
<th>≥9.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>No Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Meet Mary

History
- 46 years old, diagnosed with T2DM 5 yrs ago, with an A1c of 7.8%
- She was 5’6”, 282 pounds; BMI 48.4
- Started on metformin 500 mg
- Recommended lifestyle changes: diet and exercise regimen

Chief Complaint
- Comes to the office because of shortness of breath and feeling tired all day
- Further evaluation shows:
  – Her A1c now is at 8.4%
  – Weight gain of 15 pounds
  – Lipid profile is moderately elevated across all parameters

Concerned that she will need to start on insulin because she is scared of shots, or that she will potentially need to take more pills
Meet Larry

History

- 36-year-old man
- History of poorly controlled hypertriglyceridemia
  - His initial fasting serum cholesterol was 299 mg/dL
  - Triglycerides were 235 mg/dL and high-density lipoprotein (HDL) cholesterol was 30 mg/dL before treatment
- His height and weight at the time of initial diagnosis were 5’11” and 215 pounds
  - BMI of 30
- Now, he weighs 255 pounds and his BMI is 36
  - Waist circumference is now over 40

Chief Complaint

- Presented with polyuria, polydipsia, and "feeling dry" during the past 2 months

Meet Larry (continued)

Current Medications

- He was treated with gemfibrozil 600 mg twice daily and told to watch his diet and exercise
- Was not given any tools on how to actually lose weight and wasn’t referred to a dietician

To Think About…

- Is this what you typically see in your practice?
- What is your next course of action for this patient? (Please write down notes in your workbook)
- Any other concerns?

Meet Larry

To Think About…

- Is this what you typically see in your practice?
- What is your next course of action for this patient? (Please write down notes in your workbook)
- Any other concerns?

Let’s move on…We will come back at the end

The Twin Epidemic: Relationship Between BMI and Risk of Type 2 DM

<table>
<thead>
<tr>
<th>Age-Adjusted Relative Risk</th>
<th>Body Mass Index (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>&lt;22</td>
<td>1.0</td>
</tr>
<tr>
<td>22-25</td>
<td>1.0</td>
</tr>
<tr>
<td>25-26</td>
<td>1.0</td>
</tr>
<tr>
<td>26-27</td>
<td>1.0</td>
</tr>
<tr>
<td>27-28</td>
<td>1.0</td>
</tr>
<tr>
<td>28-29</td>
<td>1.0</td>
</tr>
<tr>
<td>29-30</td>
<td>1.0</td>
</tr>
<tr>
<td>30-32</td>
<td>1.0</td>
</tr>
<tr>
<td>33-34</td>
<td>1.0</td>
</tr>
<tr>
<td>35+</td>
<td>1.0</td>
</tr>
</tbody>
</table>


The Twin Epidemic: Relationship Between BMI and Risk of Type 2 DM

- OBESITY
- INSULIN RESISTANCE
- INSULIN SECRETION DEFECT
- GENETIC PREDISPOSITION

GLUCO- AND LIPO- TOXICITY

Genes

Liver

Muscles

IGT

FFA

TNF-a, resistin, leptin, adiponectin ...

Vicious circle

Genes

INSULIN MELLITUS
Impact of Different Fat Depots on Insulin Sensitivity

- Obesity plays an important role in the pathogenesis of insulin resistance and type 2 diabetes
- The amount of total body fat, as well as its distribution in different body compartments, is an important factor in the development of the disease
  - High visceral fat and liver fat are found to be strongly associated with insulin resistance after weight has plateaued

Abdominal Obesity Is Associated With Increased Risk of Developing Diabetes

<table>
<thead>
<tr>
<th>Waist Circumference (cm)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;27.9 in)</td>
<td></td>
</tr>
<tr>
<td>(27.9–29.8 in)</td>
<td>4.8</td>
</tr>
<tr>
<td>(29.9–31.9 in)</td>
<td>7.8</td>
</tr>
<tr>
<td>(32–33.9 in)</td>
<td>11.1</td>
</tr>
<tr>
<td>(34–35.8 in)</td>
<td>15.3</td>
</tr>
<tr>
<td>(35.9–37.9 in)</td>
<td>20.3</td>
</tr>
<tr>
<td>(&gt;38 in)</td>
<td>24</td>
</tr>
</tbody>
</table>


Measuring Waist Circumference

- Locate upper hip bone and top of right iliac crest
- Place measuring tape around abdomen at level of iliac crest, keeping it parallel to the floor
- Ensure tape is snug but not compressing the skin


Weight Loss and Diabetes

- Weight loss can reduce the risk of significant comorbidities like T2DM
- By lowering weight, patients with impaired glucose tolerance benefit
  - DPP
  - Look AHEAD Trial

Diabetes Prevention Program (DPP)

- Can a 7% reduction in initial weight, combined with increased physical activity, reduce the risk of developing type 2 diabetes in at-risk individuals?
- 3234 patients; BMI = 34.0 kg/m²; impaired glucose tolerance (95-125 mg/dL)
- Randomly assigned to 4-year trial
  - Placebo
  - Metformin (850 BID)
  - Lifestyle intervention

Diabetes Incidence per 100 Person-Years

- Diet + Exercise: n=1079, 4.8
- Metformin: n=1073, 7.8
- Placebo: n=1082, 11

The goal of intensive lifestyle intervention was a 7% reduction in baseline body weight through low-calorie, low-fat diet and moderate-intensity exercise for ≥150 minutes per week.

IGT=impaired glucose tolerance; T2DM=type 2 diabetes mellitus; DPP=Diabetes Prevention Program.


7-Year Follow-up of the Finnish Diabetes Prevention Study

Total N=522
n=172 (men)
n=350 (women)

*Relative risk reduction.

Intensive lifestyle intervention: 5% weight reduction, diet (<30% calories from fat, ≤15 mg fiber intake), exercise ≥ 30 minutes/day.

Look AHEAD Study: Design

Purpose: Examine the long-term effects (<13.5 years) of an intensive lifestyle intervention program on cardiovascular morbidity and mortality in overweight or obese persons with type 2 diabetes.

- 5145 overweight subjects with type 2 diabetes
- 2 arms:
  - Usual care (diabetes support and education)
  - Usual care + intensive lifestyle intervention
- Study duration: up to 13.5 years (with 4 years of intensive lifestyle intervention to achieve 7% loss)
- Primary outcome: cardiovascular death (fatal MI and stroke), nonfatal MI, and stroke; hospitalization for angina


Lifestyle Intervention: Conclusion

- The intervention induced clinically significant weight loss in all subsets of a demographically and ethnically diverse population
- Nearly 50% of ILI participants achieved a loss ≥5% of initial weight


Retention:
ILI=94.2%
DSE=93.3%


Percentage of Participants Meeting Different Weight Loss Criteria at 1 Year

- ILI: 92.7% 55.6% 68.0% 55.1%
- DSE: 20.1% 25% 27% 210%


Percentage Reduction in Initial Weight Over 4 Years in ILI and DSE Groups

- ILI: -4.7% -4.5%
- DSE: 1.0% -0.1%

Weight Loss Benefits: Effect on Cardiovascular and Diabetes Measures: 1-Year Data

<table>
<thead>
<tr>
<th>Measure</th>
<th>DSE (0.7% weight loss)</th>
<th>ILI (8.6% weight loss)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c (%)</td>
<td>-0.14</td>
<td>-0.64*</td>
</tr>
<tr>
<td>Glucose (mg %)</td>
<td>-7.2</td>
<td>-21.5</td>
</tr>
<tr>
<td>% on diabetes meds</td>
<td>-2.2</td>
<td>-7.8</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>-2.6</td>
<td>-6.8</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>-1.8</td>
<td>-3.0</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>-5.7</td>
<td>-5.2</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>+1.4</td>
<td>+3.4*</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>-14.6</td>
<td>-36.3*</td>
</tr>
</tbody>
</table>

DSE=diabetes support and education; ILI=intensive lifestyle intervention.
Look AHEAD Changes in Risk Factors at 4 years

<table>
<thead>
<tr>
<th></th>
<th>DBE (1.0% loss)</th>
<th>ILI (4.7% loss)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 C (%)</td>
<td>-0.08</td>
<td>-0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>% on insulin, none at Bl.</td>
<td>11%</td>
<td>7%</td>
<td>0.001</td>
</tr>
<tr>
<td>% on insulin, BL use</td>
<td>87%</td>
<td>77%</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>-3.41</td>
<td>-4.66</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>-3.19</td>
<td>-3.44</td>
<td>0.29</td>
</tr>
<tr>
<td>LDL (mg/dl) corrected</td>
<td>-22.77</td>
<td>-18.88</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>+2.58</td>
<td>+3.95</td>
<td>0.001</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>-27.51</td>
<td>-22.91</td>
<td>0.13</td>
</tr>
</tbody>
</table>

How Do We Assess Our Diabetic, Overweight Patients?

Patient Encounter

1) Assess cardiometabolic disease risk (ie, future T2DM and CVD) (waist circumference, blood pressures, fasting and 2-hr glucose, lipid panel)
2) Evaluate for other medical complications of obesity (polycythemia vera, osteoarthritis, sleep apnea, NASH, GERD, asthma, venous stasis, pseudotumor cerebri)
3) Evaluate for genetic and endocrine causes of obesity

Cardiometabolic Risk Stratification for Overweight and Obese

<table>
<thead>
<tr>
<th>Metabolically Healthy</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>Highest</th>
<th>End Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 2 ATP III Risk Factors</td>
<td>Prediabetes</td>
<td>IFG or IGT</td>
<td>T2DM and/or CVD</td>
<td>CVD</td>
<td></td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>Prediabetes + Metabolic Syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risks

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
<th>Obesity Class</th>
<th>Disease Risk Relative to Normal Weight and Waist Circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 – 24.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 – 29.9</td>
<td>Increased</td>
<td>High</td>
</tr>
<tr>
<td>Obesity</td>
<td>30.0 – 34.9</td>
<td>High</td>
<td>Very high</td>
</tr>
<tr>
<td>35.0 – 39.9</td>
<td>II</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td>Extreme Obesity</td>
<td>40.0†</td>
<td>III</td>
<td>Extremely high</td>
</tr>
</tbody>
</table>

* Disease risk for type 2 diabetes, hyperlipidemia, and CVD.
† Increased waist circumference also can be a marker for increased risk, even in persons of normal weight.


Getting Started

Improve Patient Communication

Can I talk about your health and how your weight is affecting it? Can we talk about your weight?

NO... “The single best thing you can do to improve your health is to make some changes in your diet and other lifestyle factors. Let’s talk about this at the next visit.”

YES... “Great. The single best thing you can do to improve your health is to make some changes in your diet and other lifestyle factors. Let’s see what might work to help you do this.”
Obesity Treatment Guidelines

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>Treatment 25-26.9</th>
<th>27-29.9</th>
<th>30-34.9</th>
<th>35-39.9</th>
<th>&gt;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>Pharmaco-therapy</td>
<td>Not appropriate</td>
<td>With comorbidities</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Surgery*</td>
<td>Not appropriate</td>
<td>Not appropriate</td>
<td>With comorbidities</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm

*Bariatric surgeries require lifestyle medical follow-up.

Tools We Have to Support Weight Loss

Nancy Bohannon, MD, FACP, FACE
Director of Clinical Research
Cardiovascular Risk Reduction Program
Saint Luke’s Hospital
San Francisco, California

Match Patients and Treatments on Risk/Benefit Assessment

Interventions for Weight Loss

**Lifestyle modification**
- Changes in nutrition and physical activity

**Pharmacotherapy**
- Review of currently available treatment options

**Bariatric surgery**
- Realistic expectations and risk/benefit ratio

Lifestyle Modification for Weight Control

- Reduce energy intake by 500 to 1000 kcal/day
  - Reduce portion size, fat, and sugar
- Exercise ≥180 minutes/week
  - Use of pedometer
- Record food intake, physical activity, and weight
- Set realistic goals for weight loss/behavior change
  1. 5% weight loss in 3 months and reassess
  2. When 5% to 10% weight loss achieved: enter maintenance
  3. Close follow-up with patient: visits/phone
  4. Provide tips for weight loss from National Weight Registry
  5. If no weight loss in 3 months, modify plan to include pharmacotherapy

Tips From National Weight Registry

<table>
<thead>
<tr>
<th>Watch &lt;10 hours of TV per week</th>
<th>Low-calorie (&lt;1400 calories) diet with &lt;30% fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engage in at least 200 minutes of mild/moderate exercises per week</td>
<td></td>
</tr>
</tbody>
</table>
  - Maintain discipline over what you eat
  - Do not overeat
  - Keep your diet consistent

Weigh in at least weekly
- Always record what you eat and your activities

Brown Medical School/The Miriam Hospital National Weight Control Registry http://www.nwcr.ws
An adjunct to lifestyle modification
• Not a substitute
Can increase chances of meaningful weight loss
Until recently, only 2 agents FDA approved
• One approved for short-term use
• One approved for long-term use
In 2012, 2 new drugs granted FDA approval

Older Approved Pharmacotherapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>PHENTERMINE</th>
<th>ORLISTAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Central</td>
<td>Peripheral</td>
</tr>
<tr>
<td>Portion</td>
<td>Noradrenergic</td>
<td>Pancreatic lipase inhibitor</td>
</tr>
<tr>
<td>Approval</td>
<td>Short-term use</td>
<td>Long-term use</td>
</tr>
<tr>
<td>Class</td>
<td>II-IV</td>
<td>Not scheduled</td>
</tr>
<tr>
<td>Cost</td>
<td>$</td>
<td>$555</td>
</tr>
<tr>
<td>Common Adverse Effects</td>
<td>Restlessness</td>
<td>GI symptoms including oily spotting, flatulence, fecal urgency, fatty/oily stool, and others less frequently</td>
</tr>
</tbody>
</table>

Tips for Managing Patients on Orlistat*

• Discuss potential bowel effects and mechanism with patient
• Start at 120 mg before each meal
• Prescribe a moderate-fat diet (35% of energy)
  – Caution patients about high-fat meal or snack
• Metamucil has been shown to reduce bowel effects
• For long-term use, prescribe a multivitamin
• Orlistat can interfere with cyclosporin absorption
• Encourage long-term use
• Monitor renal function

Recently Approved Pharmacotherapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>PHEN/TPM ER 1,2 Lorcaserin 3,4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval</td>
<td>Approved July 2012</td>
</tr>
<tr>
<td>Mechanism</td>
<td>PHEN stimulates norepinephrine release from hypothalamic neurons; TPM is an anticonvulsant (MOA unclear)</td>
</tr>
<tr>
<td>Follow-up Duration</td>
<td>56 (108) weeks</td>
</tr>
<tr>
<td>Common Adverse Effects</td>
<td>Dry mouth, Tingling, Constipation, Altered taste sensation</td>
</tr>
</tbody>
</table>

Orlistat: Safety

<table>
<thead>
<tr>
<th>AEs at 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, n=943</td>
</tr>
<tr>
<td>31%</td>
</tr>
<tr>
<td>7%</td>
</tr>
<tr>
<td>20%</td>
</tr>
<tr>
<td>1%</td>
</tr>
</tbody>
</table>

PHEN/TPM ER: phentermine plus topiramate extended release

Tips for Managing Patients on Orlistat* has been sourced.

PLACEBO, n=340
Orlistat, n=343

Effect of Long-term Treatment With Orlistat (the XENDOS Study)

Completers Data

Orlistat + lifestyle (n=853)
Placebo + lifestyle (n=557)

Weight Change (kg)

Week

0  52  104  156  208

-12  -6.9  -4.1  0  3  6  9  12

P<0.001 vs placebo

There is concern about fat-soluble vitamin absorption.


Recently Approved Pharmacotherapy

Tips for Managing Patients on Orlistat*

*Orlistat is available as an OTC treatment at a dosage of 60 mg.

Tips for Managing Patients on Orlistat*

*Orlistat is available as an OTC treatment at a dosage of 60 mg.

Tips for Managing Patients on Orlistat*

*Orlistat is available as an OTC treatment at a dosage of 60 mg.

Tips for Managing Patients on Orlistat*

*Orlistat is available as an OTC treatment at a dosage of 60 mg.

Tips for Managing Patients on Orlistat*

*Orlistat is available as an OTC treatment at a dosage of 60 mg.

Tips for Managing Patients on Orlistat*

*Orlistat is available as an OTC treatment at a dosage of 60 mg.

Tips for Managing Patients on Orlistat*

*Orlistat is available as an OTC treatment at a dosage of 60 mg.

Tips for Managing Patients on Orlistat*

*Orlistat is available as an OTC treatment at a dosage of 60 mg.

Tips for Managing Patients on Orlistat*

*Orlistat is available as an OTC treatment at a dosage of 60 mg.

Tips for Managing Patients on Orlistat*

*Orlistat is available as an OTC treatment at a dosage of 60 mg.

Tips for Managing Patients on Orlistat*

*Orlistat is available as an OTC treatment at a dosage of 60 mg.

Tips for Managing Patients on Orlistat*

*Orlistat is available as an OTC treatment at a dosage of 60 mg.

Tips for Managing Patients on Orlistat*

*Orlistat is available as an OTC treatment at a dosage of 60 mg.
Study Design: 56-Week Study Followed by 52-Week Extension

Placebo-controlled, double-blind

Treatment (56 weeks)

Placebo
n=994

7.5 mg phenetermine/46 mg topiramate (PHEN/TPM ER 7.5/46) n=426

15 mg phenetermine/92 mg topiramate (PHEN/TPM ER 15/92) n=995

Continuation of Original Treatment (56 weeks)

Placebo
n=227

7.5 mg phenetermine/46 mg topiramate (PHEN/TPM ER 7.5/46) n=153

15 mg phenetermine/92 mg topiramate (PHEN/TPM ER 15/92) n=295

All subjects participated in a lifestyle modification program.

Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults After 1 Year


Comparison of mean placebo-subtracted changes from baseline in weight loss between Placebo and treatment groups. Data are based on least squares mean (95% CI) ANCOVA on week 12 values. *P < 0.0001 vs placebo.

Effect of Phentermine/Topiramate ER on Blood Pressure and Lipid Levels in Obese Adults Over 2 Years


Comparison of mean placebo-subtracted changes from baseline in blood pressure and lipid levels between Placebo and treatment groups. Data are based on least squares mean (95% CI) ANCOVA on week 24 values. All P values are vs placebo.

Effect of Phentermine/Topiramate ER on Glucose Levels in Obese Adults With Type 2 Diabetes After 1 Year


Comparison of mean placebo-subtracted changes from baseline in glucose levels between Placebo and treatment groups. Data are based on least squares mean (95% CI) ANCOVA on week 12 values. All P values are vs placebo.

Phentermine/Topiramate ER Safety Data

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=993)</th>
<th>PHEN/TPM ER 7.5/46 (n=498)</th>
<th>P Value</th>
<th>PHEN/TPM ER 15/92 (n=994)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>2 (2%)</td>
<td>13 (26%)</td>
<td>&lt;0.0001</td>
<td>21 (2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>2 (2%)</td>
<td>14 (28%)</td>
<td>&lt;0.0001</td>
<td>21 (2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (6%)</td>
<td>15 (30%)</td>
<td>&lt;0.0001</td>
<td>17 (2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>13 (13%)</td>
<td>12 (24%)</td>
<td>0.7422</td>
<td>13 (1%)</td>
<td>0.7906</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9 (9%)</td>
<td>11 (22%)</td>
<td>0.2204</td>
<td>10 (1%)</td>
<td>0.3947</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1 (1%)</td>
<td>7 (14%)</td>
<td>&lt;0.0001</td>
<td>10 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (5%)</td>
<td>6 (12%)</td>
<td>0.3832</td>
<td>10 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (9%)</td>
<td>7 (14%)</td>
<td>0.1983</td>
<td>10 (1%)</td>
<td>0.4467</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (3%)</td>
<td>7 (14%)</td>
<td>0.0005</td>
<td>10 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>7 (7%)</td>
<td>7 (14%)</td>
<td>1.0000</td>
<td>9 (1%)</td>
<td>0.1511</td>
</tr>
<tr>
<td>Back pain</td>
<td>5 (5%)</td>
<td>6 (12%)</td>
<td>0.6199</td>
<td>7 (1%)</td>
<td>0.0386</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (4%)</td>
<td>4 (8%)</td>
<td>0.6754</td>
<td>7 (1%)</td>
<td>0.0139</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (5%)</td>
<td>4 (8%)</td>
<td>0.7010</td>
<td>7 (1%)</td>
<td>0.1270</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5 (5%)</td>
<td>6 (12%)</td>
<td>0.2229</td>
<td>6 (1%)</td>
<td>0.3690</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>4 (4%)</td>
<td>4 (8%)</td>
<td>0.7729</td>
<td>6 (1%)</td>
<td>0.0157</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 (4%)</td>
<td>5 (10%)</td>
<td>0.1753</td>
<td>5 (1%)</td>
<td>0.0855</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5 (5%)</td>
<td>5 (10%)</td>
<td>0.5373</td>
<td>4 (1%)</td>
<td>0.3025</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4 (4%)</td>
<td>4 (8%)</td>
<td>1.0000</td>
<td>5 (1%)</td>
<td>0.4004</td>
</tr>
</tbody>
</table>

*P* values are vs placebo.
# Results Summary

- Overall, 84% of subjects completed the study.
- Subjects in the PHEN/TPM ER treatment group showed:
  - Significant, sustained weight loss (intent-to-treat with last observation carried forward, $P<0.0001$ compared with placebo).
  - Greater LS mean change in body weight (−1.8%, −8.3%, and −10.5% for placebo, 7.5/46, and 10/92, respectively).
- In the PHEN/TPM ER treatment group, there were significantly higher numbers of subjects with:
  - ≥5%, ≥10%, ≥15%, and ≥20% weight loss compared with placebo ($P<0.001$) at each dose.
  - Improved cardiovascular and metabolic variables and decreased rates of incident diabetes in comparison with placebo.
  - Reduced rates of adverse events between 56 and 108 weeks compared with rates between 0 and 56 weeks.

## REMS Training for PHEN/TPM ER
- PHEN/TPM ER is contraindicated during pregnancy.
- PHEN/TPM ER has been approved with a REMS training program to inform clinicians and patients about:
  - Increased risk of congenital malformation, specifically orofacial clefts, in infants exposed to PHEN/TPM ER during the first trimester of pregnancy.
  - Importance of pregnancy prevention for females of reproductive potential receiving PHEN/TPM ER.
  - Need to discontinue PHEN/TPM ER immediately if pregnancy occurs.

# Effect of Lorcaserin in Metabolic Measures

### Weight Change Over 52 Weeks With Lorcaserin Therapy

### Effect of Lorcaserin in Glycemic Parameters

### Weight Change Over 104 Weeks With Lorcaserin Therapy
Lorcaserin Safety Data

<table>
<thead>
<tr>
<th>Event</th>
<th>Lorcaserin 10 mg BID, n=256</th>
<th>Lorcaserin 10 mg QD, n=95</th>
<th>Placebo n=252</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>37 (14.5)</td>
<td>16 (16.8)</td>
<td>18 (7.1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>30 (11.7)</td>
<td>8 (8.4)</td>
<td>22 (8.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>29 (11.3)</td>
<td>22 (22.2)</td>
<td>25 (9.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (9.4)</td>
<td>8 (8.4)</td>
<td>20 (7.9)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>23 (8.8)</td>
<td>9 (9.3)</td>
<td>15 (5.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>21 (8.2)</td>
<td>5 (5.3)</td>
<td>11 (4.4)</td>
</tr>
<tr>
<td>Syncope, hypotension</td>
<td>19 (7.4)</td>
<td>14 (14.5)</td>
<td>16 (6.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (7.0)</td>
<td>5 (5.3)</td>
<td>11 (4.4)</td>
</tr>
<tr>
<td>Gastroenteritis, gastrointestinal</td>
<td>18 (7.0)</td>
<td>5 (5.3)</td>
<td>11 (4.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (5.8)</td>
<td>8 (8.4)</td>
<td>13 (5.1)</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>14 (5.4)</td>
<td>14 (14.5)</td>
<td>16 (6.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (4.7)</td>
<td>10 (10.5)</td>
<td>8 (3.2)</td>
</tr>
<tr>
<td>Osteoarthritis, pain</td>
<td>8 (3.1)</td>
<td>5 (5.3)</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>8 (3.1)</td>
<td>5 (5.3)</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Depression</td>
<td>6 (2.3)</td>
<td>5 (5.3)</td>
<td>5 (2.0)</td>
</tr>
</tbody>
</table>

Emerging Pharmacotherapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Naltrexone/BupSR&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Liraglutide&lt;sup&gt;2,3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Status</td>
<td>FDA requested additional Phase 3 data</td>
<td>In Phase 3 clinical trials</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Naltrexone, opioid receptor antagonist; Bupropion, norepinephrine reuptake inhibitor</td>
<td>Glucagon-like peptide-1 analogue</td>
</tr>
<tr>
<td>Follow-up Duration</td>
<td>56 weeks</td>
<td>56 weeks</td>
</tr>
<tr>
<td>Common AEs</td>
<td>• Nausea</td>
<td>• Nausea</td>
</tr>
<tr>
<td></td>
<td>• Headache</td>
<td>• Vomiting</td>
</tr>
<tr>
<td></td>
<td>• Constipation</td>
<td>• Dry mouth</td>
</tr>
<tr>
<td></td>
<td>• Dizziness</td>
<td>• Gastrointestinal effects</td>
</tr>
</tbody>
</table>

Bariatric/“Metabolic” Surgeries

- **Indications**
  1. BMI >40 kg/m² or BMI 35-39.9 kg/m² and life-threatening cardiopulmonary disease, severe diabetes, or lifestyle impairment
  2. Failure to achieve adequate weight loss with nonsurgical treatment

- **Contraindications**
  1. History of noncompliance with medical care
  2. Certain psychiatric illnesses: personality disorder, uncontrolled depression, suicidal ideation, substance abuse
  3. Unlikely to survive surgery

Current Bariatric Surgical Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Gastric Band</th>
<th>Gastric Sleeve</th>
<th>Gastric Bypass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversible?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Weight loss</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Safety</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Other issues</td>
<td>Requires compliance for greatest efficacy</td>
<td>Newest</td>
<td></td>
</tr>
</tbody>
</table>

Bariatric Surgery and T2DM Outcomes

Following bariatric surgery, significant improvements are seen for those patients with T2DM
- 87% achieve better glucose control and need fewer antidiabetic medications
- Average of 78% achieve normal glycemic control without taking any antidiabetic medications for a period of time

Decreased Mortality in Extremely Obese Patients After Bariatric Surgery

![Graph showing decreased mortality in extremely obese patients after bariatric surgery](image)

P<0.04

<table>
<thead>
<tr>
<th>Remission of type 2 diabetes</th>
<th>Adjustable Gastric Banding</th>
<th>Roux-en-Y Gastric Bypass</th>
<th>Bilopancreatic Diversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>56.7%</td>
<td>80.3%</td>
<td>95.1%</td>
<td></td>
</tr>
</tbody>
</table>

Potential Complications of Surgical Weight Loss

- Postoperative mortality and morbidity
- Acute complications
  - Hemorrhage, leaks, obstruction, infection
- Long-term complications
  - Nutritional deficiency
  - Potential weight regain (can be up to 20% weight regain in 60% of patients)
  - Internal hernias

Case Discussion

Let’s Go Back to Our Patients

- T2DM
- HTN
- Lipids elevated
- Severely obese

History

- Elevated TG
- Increased WC
- Obese
- New onset DM

History

Case Studies: Management

- Are we concerned about sleep apnea occult CVD, metabolic syndrome?
- How effective is a low-carb diet in reducing TG?
- How often do you see a midlife weight gain in your practice?
- How do we support and reinforce these to lose weight?
- Are they candidates for pharmacotherapy?

Adjusting Antidiabetic Medications After Weight Loss

Takeaways for Your Practice

- Use every office visit as an opportunity to counsel patients on the benefits of weight loss if applicable
- Weight loss drugs may be used as part of a comprehensive weight loss program, including dietary therapy and physical activity, for:
  - Patients with a BMI of 30 with no concomitant obesity-related risk factors or diseases
  - Patients with a BMI of 27 with concomitant obesity-related risk factors or diseases
  - Weight loss drugs should never be used without concomitant lifestyle modifications
- Losing 10% of initial body weight can significantly decrease the severity of obesity-associated risk factors
Post-test Question 1
Which of the following is the strongest predictor of developing T2DM?
1. Continued yearly excessive weight gain
2. Increase in waist circumference
3. Impaired glucose tolerance
4. All of the above

Post-test Question 2
In order to decrease an obese patient’s risk of developing type 2 diabetes, the minimum weight loss goal should be:
1. 5% to 10%
2. 20%
3. Depends on the initial BMI of the patient
4. High enough to lower the patient’s BMI to <30

Post-test Question 3
If an obese (BMI 32) person with hypertension and T2DM has been unsuccessful in his/her weight loss goals (5% reduction) after 6 months of lifestyle modification, what would be the next strategy to recommend for weight loss?
1. Continue lifestyle modifications for another 6 months
2. Increase daily exercise time
3. Consider pharmacotherapy
4. Schedule bariatric surgery
5. Unsure

Post-test Question 4
Which pharmacotherapy(ies) for chronic weight management has the FDA approved in 2012?
1. Liraglutide
2. Phentermine/topiramate ER
3. Liraglutide and phentermine/topiramate ER
4. Lorcaserin and phentermine/topiramate ER
5. Combination Naltrexone and Bupropion
6. All of the agents listed

THANK YOU!
QUESTIONS?