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
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Donna H. Ryan, MD
Professor Emeritus
Pennington Biomedical Research Center
Baton Rouge, Louisiana

Dr Donna H. Ryan is Professor Emeritus at the Pennington Biomedical Research Center in Baton Rouge, Louisiana, where she served as associate executive director for clinical research for more than 20 years. She has been actively engaged in obesity and nutrition research for the last 20 years.

Dr Ryan served as 2009–2010 president of The Obesity Society, an organization of more than 2000 North American scientists. She co-chairs the panel that is currently revising the National Institutes of Health (NIH)–sponsored Guidelines for the Evaluation and Management of Overweight and Obesity, or Obesity II.

Dr Ryan’s research interests include many aspects of obesity management and prevention, including obesity pharmacotherapy, evaluation of weight-loss diets of different macronutrient composition, practical or pragmatic clinical trials to evaluate primary care approaches to obesity management, and translational research engaging third-party payors in obesity intervention.

Dr Ryan was funded for more than 20 years by the United States Department of Defense to oversee a military nutrition research project in which she collaborated with the US Army Research Institute for Environmental Medicine’s Military Nutrition Division. She was co-principal investigator for the NIH-funded Clinical Nutrition Research Center at Pennington and co-principal investigator for the National Institute of Diabetes and Digestive and Kidney Diseases–sponsored Look AHEAD (Action for Health in Diabetes) study that addresses weight loss in persons with type 2 diabetes. Dr Ryan conceived a statewide Clinical Translational Science Center, awarded in 2012, that encompasses 9 Louisiana research institutions. She inaugurated LSU ICON (Improving Clinical Outcomes Network), a project to improve clinical outcomes in 11 Louisiana State University hospitals.

Since retiring from active service in February 2012, Dr Ryan continues her public service around obesity issues with the NIH and nonprofits, consults with the drug and device industry, and is actively engaged in continuing medical education.

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

Dr Patrick Mahlen O’Neil 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’s 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 of 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. Dr O’Neil 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 to 1996, he authored *Weighing the Choices*, a weekly column on weight control in the Charleston *Sunday Post and Courier*.

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*, *Eating Behaviors*, and the *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]), and is the organization’s past president after having served terms as councilor, vice president, president elect, and president. Previously, Dr O’Neil was editor of the NAASO Web site, program chair of the NAASO 1999 annual meeting in Charleston, a member of the NAASO’s publications committee, and a member of the National Institutes of Health (NIH)/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, Dr O’Neil 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 has been a member of the Scientific Council of the South Carolina Nutrition Research Consortium since its inception. He served 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. Dr O’Neil 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 town council member of Sullivan’s Island and, prior to that, a member and chair of the town’s planning commission.

**Faculty Financial Disclosure Statements**
The presenting faculty reported the following:

Dr Ryan serves as an advisor to Arena Pharmaceuticals, Inc.; Eisai Co., Ltd.; and Novo Nordisk Inc.; and as a consultant for Scientific Intake Limited Co.

Dr O’Neil serves as an investigator for Novo Nordisk Inc.; Weight Watchers International, Inc.; and Orexigen Therapeutics, Inc., for which he also serves as an advisor.

**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
Donna Ryan, MD

Session 4
12:20 PM – 1:50 PM

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.
- Donna Ryan, MD is on the scientific advisory board for Arena, Eisai, Novo Nordisk, and a consultant for Scientific Intake.

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
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

Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults Aged 18 Years or Older

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

The Tar Heel State
State Obesity Rate: 27.8%
State Diabetes Rate: 9.6%
We have work to do…!
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

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?

Let's move on... We will come back at the end

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

![Graph showing the relationship between BMI and risk of Type 2 DM for men and women.](Link to graph)


Age-Adjusted Relative Risk

<table>
<thead>
<tr>
<th>Body Mass Index (kg/m²)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;22</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>22-25</td>
<td>2.9</td>
<td>1.8</td>
</tr>
<tr>
<td>25-30</td>
<td>4.3</td>
<td>2.1</td>
</tr>
<tr>
<td>30-35</td>
<td>8.1</td>
<td>4.4</td>
</tr>
<tr>
<td>35-40</td>
<td>15.8</td>
<td>6.1</td>
</tr>
<tr>
<td>40-45</td>
<td>27.8</td>
<td>11.6</td>
</tr>
<tr>
<td>45-50</td>
<td>40.3</td>
<td>21.3</td>
</tr>
<tr>
<td>50-55</td>
<td>54.0</td>
<td>42.1</td>
</tr>
<tr>
<td>55+</td>
<td>93.2</td>
<td></td>
</tr>
</tbody>
</table>

OBESITY

INSULIN RESISTANCE

INSULIN SECRETION DEFECT

High energy intake

FFA

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

Genes

GLUCOS- AND LIPO- TOXICITY

Liver

Muscles

Vicious circle

Genetic predisposition

Insulin resistance
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</td>
<td>1</td>
</tr>
<tr>
<td>27.9–29.8</td>
<td>1.6</td>
</tr>
<tr>
<td>29.9–31.9</td>
<td>2.0</td>
</tr>
<tr>
<td>32–33.9</td>
<td>2.9</td>
</tr>
<tr>
<td>34–35.8</td>
<td>4.0</td>
</tr>
<tr>
<td>35.9–37.9</td>
<td>5.0</td>
</tr>
<tr>
<td>&gt;38</td>
<td>7.0</td>
</tr>
</tbody>
</table>

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<td>1.6</td>
</tr>
<tr>
<td>29.9–31.9</td>
<td>2.0</td>
</tr>
<tr>
<td>32–33.9</td>
<td>2.9</td>
</tr>
<tr>
<td>34–35.8</td>
<td>4.0</td>
</tr>
<tr>
<td>35.9–37.9</td>
<td>5.0</td>
</tr>
<tr>
<td>&gt;38</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Waist Circumference (WC) as a Predictor of Diabetes

5882 adults from 1999-2004 NHANES grouped into sex-specific WC and BMI tertiles. Other cardiometabolic risk factors = BP, TG, LDLc, HLCc, and glucose

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

Early Intervention Needed for Prevention of Type 2 Diabetes

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

Weight Loss and Diabetes

- Weight loss can reduce the risk of significant comorbidities like T2DM
- By lowering weight, patients with impaired glucose intolerance 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


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

- Log rank test: P=0.001 (Relative risk reduction, 38%) median follow-up 7.4 years

Diabetes Prevention Program (DPP) 4-Year Study Results: Progression From IGT to T2DM

- 58% reduction in diabetes incidence per 100 person-years
  - Diet + Exercise
    - n=1079
  - Metformin
    - n=1073
  - Placebo
    - n=1082


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

Look AHEAD Changes in Risk Factors at 4 years

- Weight Loss Benefits: Effect on Cardiovascular and Diabetes Measures: 1-Year Data
- DSE (diabetes support and education)
- ILI (intensive lifestyle intervention)

<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>HbA1c (%)</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>-2.8</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>-30.3</td>
</tr>
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<th>ILI  (8.6% loss)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>-0.2</td>
<td>-0.08</td>
</tr>
<tr>
<td>% on insulin, none at BL</td>
<td>7%</td>
<td>11%</td>
</tr>
<tr>
<td>% on insulin, BL use</td>
<td>77%</td>
<td>87%</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>-4.66</td>
<td>-3.41</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>-3.44</td>
<td>-3.19</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>-18.88</td>
<td>-22.77</td>
</tr>
<tr>
<td>LDL (mg/dL) corrected</td>
<td>-12.71</td>
<td>-13.78</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>+3.95</td>
<td>+2.58</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>-22.91</td>
<td>-27.61</td>
</tr>
</tbody>
</table>


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

How Do We Assess Our Diabetic, Overweight Patients?

1) Assess cardiometabolic disease risk (e.g., future T2DM and CVD)
   - waist circumference, blood pressures, fasting and 2-hr glucose, lipid panel
2) Evaluate for other medical complications of obesity
   - urinary incontinence, restless legs, sleep apnea, NASH, GERD, asthma, pseudotumor cerebri
3) Evaluate for genetic and endocrine causes of obesity

Cardiometabolic Risk Stratification for Overweight and Obese

<table>
<thead>
<tr>
<th>Low Metabolically Healthy</th>
<th>Moderate 1 or 2 ATP III Risk Factors</th>
<th>High Prediabetes IFG or IGT</th>
<th>Very High Prediabetes + Metabolic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM</td>
<td>Prediabetes IFG or IGT</td>
<td>Prediabetes + Metabolic Syndrome</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>Extreme Obesity</td>
<td>≥ 35.0</td>
<td>Extremely high</td>
<td>Extremely high</td>
</tr>
</tbody>
</table>

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

Retention:
ILI=94.2%
DSE=93.3%
Getting Started

Identify barriers to success

<table>
<thead>
<tr>
<th>Medications that promote weight gain</th>
<th>Safety issues in weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sulfonylureas, TZDs</td>
<td>• Insulin and insulin secretagogues must be reduced or stopped</td>
</tr>
<tr>
<td>• Antidepressants (except venlafaxine, bupropion, desvenlafaxine)</td>
<td>• Risk of developing gallstones with rapid weight loss</td>
</tr>
<tr>
<td>• Glucocorticoids</td>
<td></td>
</tr>
<tr>
<td>• Beta blockers</td>
<td></td>
</tr>
</tbody>
</table>

Getting Started (continued)

Improve Patient Communication

Can I talk about your health and how your lifestyle 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."

Getting Started (continued)

• Agreement to at least 5% weight loss, with a goal of 10% within 6 months
• Stress to your patient that even modest weight loss has significant effect in overall health improvement

Assist
• Assist by providing tools, advice, treatment referral
• Assess and support your patient along the way

Set a realistic goal

Set follow-up appointments

Obesity Treatment Guidelines

A Guide to Selecting Treatment

<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>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet, physical activity and behavior</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Surgery*</td>
<td>Not appropriate</td>
<td>Not appropriate</td>
<td>Not appropriate</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

Initiate weight loss recommendations on the basis of potential for health improvement

Tools We Have to Support Weight Loss

Donna H. Ryan, MD
Professor Emeritus
Pennington Biomedical Research Center
Baton Rouge, Louisiana

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

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

Watch <10 hours of TV per week

Engage in at least 200 minutes of mild/moderate exercise per week

- 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 Noradrenergic</td>
<td>Peripheral Pancreatic lipase inhibitor</td>
</tr>
<tr>
<td>Approval</td>
<td>Short-term use Class II-IV</td>
<td>Long-term use Not scheduled</td>
</tr>
<tr>
<td>Cost</td>
<td>$</td>
<td>$$$$</td>
</tr>
<tr>
<td>Common Adverse Effects</td>
<td>Restlessness, Insomnia, Increase in pulse, Increase in blood pressure</td>
<td>GI symptoms including oily spotting, fatus with discharge, fecal urgency, fatty/oily stool, and others less frequently Increase in urinary oxalate</td>
</tr>
</tbody>
</table>

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

Completers Data

Week

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

-12 -10 -8 -6 -4 -2 0 2 4 6 8 10 12
0 2 4 6 8 10 12 14 16 18 20

P=0.001 vs placebo


There is concern about fat-soluble vitamin absorption.

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</th>
<th>Lorcaserin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Status</td>
<td>Approved July 2012</td>
<td>Approved June 2012</td>
</tr>
<tr>
<td>Mechanism</td>
<td>PHEN stimulates norepinephrine release from hypothalamic neurons; TPM is an anticonvulsant (MOA unclear)</td>
<td>Selectively targets the 5-HT2C receptor</td>
</tr>
<tr>
<td>Follow-up Duration</td>
<td>56 (108) weeks</td>
<td>52 (104) weeks</td>
</tr>
<tr>
<td>Common Adverse Effects</td>
<td>Dry mouth, Tingling, Constipation, Altered taste sensation</td>
<td>Headache, Dizziness, Nausea</td>
</tr>
</tbody>
</table>

PHEN/TPM ER: phentermine plus topiramate extended release

Study Design: 56-Week Study Followed by 52-Week Extension

Placebo-controlled, double-blind

**Treatment (56 weeks)**

- Placebo
  - n=994
- 7.5 mg phentermine/46 mg topiramate (PHEN/TPM ER 7.5/46)
  - n=498
- 15 mg phentermine/92 mg topiramate (PHEN/TPM ER 15/92)
  - n=995

**Continuation of Original Treatment**

- Placebo
  - n=227
- 7.5 mg phentermine/46 mg topiramate (PHEN/TPM ER 7.5/46)
  - n=153
- 15 mg phentermine/92 mg topiramate (PHEN/TPM ER 15/92)
  - n=295

All subjects participated in a lifestyle modification program

This study was conducted between December 2008 and June 2010, registered at clinicaltrials.gov as NCT00796367.

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

![Graph showing weight loss over 1 year](image)

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

![Graph showing blood pressure and lipid levels](image)
Effect of Phentermine/Topiramate ER on Glucose Levels in Obese Adults With Type 2 Diabetes After 1 Year


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


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%, −9.3%, and −10.5% for placebo, 7.5/46, and 15/92, 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


Weight Change Over 52 Weeks With Lorcaserin Therapy

MITT/LOCF Population Placebo Lorcaserin 10 mg BID Lorcaserin 10 mg QD P Value

| PCT (%) of patients with ≥5% wt loss | 40 (16.1) | 94 (37.3) | <0.001 | 42 (44.7) | <0.001 |
| PCT (%) of patients with ≥10% wt loss | 11 (4.6) | 41 (16.3) | <0.001 | 17 (18.1) | <0.001 |

### Effect of Lorcaserin in Metabolic Measures

#### Parameters

<table>
<thead>
<tr>
<th>Lorcaserin 10 mg (n=251)</th>
<th>Placebo (n=248)</th>
<th>P Value</th>
<th>Lorcaserin 10 mg (n=256)</th>
<th>Placebo (n=252)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>36.8±4.5</td>
<td></td>
<td>36.4±4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.4±1.1</td>
<td></td>
<td>-1.7±1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>146.0±13.5</td>
<td></td>
<td>146.9±12.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.5±0.9</td>
<td></td>
<td>-1.0±0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>77.9±9.0</td>
<td></td>
<td>76.6±8.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.7±0.9</td>
<td></td>
<td>-1.0±0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>180.6±30.1</td>
<td></td>
<td>183.0±30.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change</td>
<td>-1.6±0.7</td>
<td></td>
<td>-2.3±1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>45.7±12.7</td>
<td></td>
<td>45.3±11.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change</td>
<td>-0.7±0.6</td>
<td></td>
<td>-0.9±0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>94.6±30.2</td>
<td></td>
<td>95.0±30.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change</td>
<td>4.8±3.8</td>
<td></td>
<td>5.2±3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>126.5±13.5</td>
<td></td>
<td>126.6±12.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change</td>
<td>-78.7±7.9</td>
<td></td>
<td>-77.9±8.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>162.0±35.7</td>
<td></td>
<td>172.1±103.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change</td>
<td>172.0±35.7</td>
<td></td>
<td>173.9±37.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting insulin (µU/mL)</td>
<td>160.0±41.6</td>
<td></td>
<td>163.6±48.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change</td>
<td>-11.9±2.3</td>
<td></td>
<td>-27.4±2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (%)</td>
<td>110±8.9</td>
<td></td>
<td>109±8.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change</td>
<td>-1.0±0.6</td>
<td></td>
<td>-1.0±0.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*LS mean change from baseline for lorcaserin 10 mg BID compared to control for continuous variables. Fisher’s exact test for categorical variables.

#### Methods

As an antagonist of the 5-HT2C receptor, lorcaserin decreases appetite and increases satiety, leading to weight loss.

#### Adverse Events

- Nausea
- Headache
- Constipation
- Vomiting
- Dry mouth

**Common AEs**

- Nausea
- Headache
- Constipation
- Vomiting
- Dry mouth

**Liver AEs**

- Nausea
- Vomiting
- Constipation
- Effects

### Emerging Pharmacotherapy

#### Agent

<table>
<thead>
<tr>
<th>Naltrexone/BupSR1</th>
<th>Liraglutide2,3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Status</td>
<td>FDA requested additional Phase 3 data</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Naltrexone, opioid receptor antagonist; Bupropion, norepinephrine-dopamine reuptake inhibitor</td>
</tr>
<tr>
<td>Follow-up Duration</td>
<td>Phase 3 clinical trials</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 analogue</td>
<td></td>
</tr>
</tbody>
</table>

**Common AEs**

- Nausea
- Headache
- Constipation
- Vomiting
- Dry mouth

**Liver AEs**

- Nausea
- Vomiting
- Constipation
- Effects

### 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></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>Newest</td>
</tr>
</tbody>
</table>


### Decreased Mortality in Extremely Obese Patients After Bariatric Surgery

![Graph](image-url)


### 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

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

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

Opportunity
Use every office visit as an opportunity to counsel patients on the benefits of weight loss if applicable

Consider weight loss drugs

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

10%
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?