The Evolution of Cardiometabolic Risk Reduction and Mixed Dyslipidemia: Examining the Role of Chronic Obesity Management

A podcast educational activity based on a live program conducted December 8-10, 2008 in Orlando, Florida
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The Evolution of Cardiometabolic Risk Reduction and Mixed Dyslipidemia: Examining the Role of Chronic Obesity Management

P R O G R A M   A G E N D A

Management of Cardiometabolic Risk: Evidence-Based Treatment Strategies
Joseph Saseen, Pharm.D., FCCP, BCPS, CLS

Chronic Obesity Management: Current Strategies and Future Development
Carrie M. Maffeo, Pharm.D., BCPS, CDE

P R O G R A M   F A C U L T Y

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The faculty and planners report the following relationships:

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PROGRAM OVERVIEW

In 2004, one in five deaths in the United States was attributed to coronary heart disease (CHD). The estimated direct and indirect costs of CHD in the United States will amount to more than $156 billion in 2008. Efforts to reduce CHD risk have focused on obesity and mixed dyslipidemia because of the high prevalence of these conditions, their substantial contribution to CHD risk, and the difficulty managing the conditions.

Nearly half of adults and one in ten adolescents have high cholesterol, and approximately 17% of American adults (more than 44 million Americans) have low concentrations of high-density lipoprotein (HDL) cholesterol, which protects against CHD. Abdominal obesity (a large waist circumference), low HDL cholesterol, and elevated triglycerides are components of the metabolic syndrome, a constellation of interrelated cardiometabolic risk factors that contribute to CHD. Other cardiometabolic risk factors include elevated blood glucose and elevated blood pressure. Nearly one in four Americans—an estimated 47 million United States residents—have the metabolic syndrome. The metabolic syndrome manifests at increasingly young ages; roughly one in ten American adolescents has the syndrome.

Lifestyle modification (dietary changes and increased physical activity) is the intervention of choice to address obesity, but it is notoriously unsuccessful. The usefulness of currently available anti-obesity agents is limited by adverse effects. The benefit of raising HDL cholesterol and reducing elevated triglycerides along with reducing elevated low-density lipoprotein (LDL) cholesterol in decreasing CHD risk is well established. Raising HDL cholesterol also has been shown to reduce the progression of atherosclerosis.

Attendees will learn about trends in the prevalence and the clinical and economic impact of coronary heart disease (CHD), obesity, mixed dyslipidemia, and the metabolic syndrome in the United States. Current recommendations for managing obesity and mixed dyslipidemia will be reviewed briefly. Limitations of lifestyle modification and currently available anti-obesity and antilipemic drug therapies, and the mechanisms of action and possible benefits of new drug therapies in development will be discussed. Case studies will be used to illustrate the decision-making process for patients at risk for CHD because of obesity or mixed dyslipidemia.
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PROGRAM OBJECTIVES

At the conclusion of this educational activity, participants should be able to

- Discuss trends in the prevalence and the clinical and economic impact of coronary heart disease (CHD), obesity, mixed dyslipidemia, and the metabolic syndrome in the United States.
- Outline current recommendations for managing obesity and mixed dyslipidemia, as well as the limitations and benefits of lifestyle modification and currently available drug therapies for the treatment of these conditions.
- Recommend an appropriate therapeutic strategy to reduce CHD risk in a patient with obesity or mixed dyslipidemia.
- Discuss the pharmacist's role in reducing cardiovascular risk and promoting a healthy lifestyle.

CONTINUING EDUCATION ACCREDITATION

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program provides 1 hour (0.1 CEU) of continuing education credit (program number 204-000-08-469-H01P).

FORMAT AND METHODS

This is an online activity consisting of two audio presentations with slides, a post-test, and an activity evaluation tool. Participants must listen to all presentations, take the activity post-test, and complete the course evaluation to receive continuing education credit. A minimum score of 70% is required on the test for credit to be awarded, and participants may print their official statements of continuing education credit immediately. The estimated time to complete this activity is one hour. This activity is provided free of charge.
Joseph Saseen, Pharm.D., FCCP, BCPS, CLS
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University of Colorado Denver
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Joseph Saseen, Pharm.D., FCCP, BCPS, CLS, is Associate Professor of Clinical Pharmacy and Family Medicine at the University of Colorado Denver. Dr. Saseen is a Board Certified Pharmacotherapy Specialist with added qualifications in cardiology, is certified as a Clinical Lipid Specialist, and is a Fellow of the American College of Clinical Pharmacy.

Dr. Saseen received both his B.S. Pharmacy and Pharm.D. from the State University of New York at Buffalo and then completed an ambulatory care research fellowship at the University of Illinois at Chicago. In his current position, Dr. Saseen practices as a clinical pharmacy specialist at the University of Colorado’s Family Medicine Center, and he educates pharmacy and medical students. His research and other scholarly endeavors focus on cardiovascular pharmacotherapy. Dr. Saseen is a member of the Board of Directors for the National Lipid Association’s Accreditation Council for Clinical Lipidology. He has won several teaching awards, and most recently was the recipient of the Doctor of Pharmacy Class of 2009 Outstanding Instructor Award.
Learning Objectives

- Discuss trends in the prevalence and clinical and economic impact of coronary heart disease (CHD), obesity, mixed dyslipidemia, and the metabolic syndrome in the United States
- Outline current recommendations for managing obesity and mixed dyslipidemia and the limitations of lifestyle modification and currently available drug therapies for the treatment of these conditions and the benefits
- Recommend an appropriate therapeutic strategy to reduce CHD risk in a patient with obesity or mixed dyslipidemia
- Discuss the pharmacist’s role in reducing cardiovascular risk and promoting a healthy lifestyle

Costs of CVD in 2008

- Direct costs: $296.4 billion
- Indirect costs: $152.1 billion

What is the comparative magnitude of direct costs?
- Hospital > Physicians > Drugs
- Hospital > Drugs > Physicians
- Physicians > Hospital > Drugs

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AHA/NHLBI Scientific Statement
Metabolic Syndrome Diagnostic Criteria

Criteria (3 of 5 needed for diagnosis)

- Elevated waist circumference (in) ≥40 (men), ≥35 (women)
- Elevated triglycerides (mg/dL) ≥150 or drug therapy
- Reduced HDL cholesterol (mg/dL) <40 (men), <50 (women) or drug therapy
- Elevated BP (mm Hg) ≥130/85 or drug therapy
- Elevated fasting glucose (mg/dL) ≥100 or drug therapy


Mortality in the United States
Adults 30-75 years old

Causes of CV Morbidity & Mortality

- Atherosclerotic vascular disease (AVD)
  - Coronary heart disease
    - Chronic stable angina
    - Acute coronary syndrome (e.g., MI)
    - Sudden cardiac death
  - Symptomatic carotid artery disease
    - Ischemic stroke
    - Transient ischemic attack
  - Peripheral arterial disease
  - Abdominal aortic aneurysm


7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)

- Primary goal: ↓ CV morbidity/mortality
- Blood pressure goals
  - <140/90 mm Hg for most patients
  - <130/80 mm Hg for diabetes or chronic kidney disease


2007 AHA Scientific Statement

<table>
<thead>
<tr>
<th>Area</th>
<th>Blood Pressure Target (mm Hg)</th>
<th>Specific Drug Indications</th>
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</thead>
<tbody>
<tr>
<td>General CAD Prevention</td>
<td>&lt;140/90</td>
<td>Monotherapy or combination therapy</td>
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<tr>
<td>High CAD risk1</td>
<td>&lt;130/80</td>
<td>• ACEI (or ARB), CCB, or thiazide</td>
</tr>
<tr>
<td>CAD2</td>
<td>&lt;130/80</td>
<td>• blocker and ACEI or ARB</td>
</tr>
<tr>
<td>LVD</td>
<td>&lt;120/80</td>
<td>ACEI or ARB and β-blocker and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>aldosterone antagonist and diuretic</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; LVD = left ventricular dysfunction (i.e., systolic heart failure)
1= diabetes, chronic kidney disease, CAD equivalent (carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm), or 10-yr Framingham score ≥20%
2= stable angina, unstable angina/NSTEMI, or STEMI

Evidence-Base for Drug Therapy
General Prevention of CAD

- The choice of drugs remains controversial
- General consensus that BP reduction, rather than the choice of drug, is the major determinant of CV risk reduction
- However, sufficient evidence from comparative clinical trials support:
  - ACEI (or ARB), CCB, or thiazide diuretic as first-line therapy
  - Supplemented by a second drug if BP control is not achieved with monotherapy


Overview of Cholesterol

- Total Cholesterol = LDL-C + HDL-C + TG/5
- Which of the following lipoprotein changes is associated with the highest CV risk?
  - Elevated LDL-cholesterol (LDL-C)
  - Low HDL-cholesterol (HDL-C)
  - Elevated triglycerides (TG)

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Dyslipidemia Targets of Treatment

- Primary Target: LDL-C
  - Goal value based on CV risk
- Secondary Target: Non-HDL-C
  - Only after LDL-C goal met and TG ≥200 mg/dL
  - Goal is always the LDL-C goal + 30
- Tertiary Target: HDL-C
  - Only for metabolic syndrome after other targets met
  - Goal >40 mg/dL in men, >50 mg/dL in women


LDL-Cholesterol Goal Values

- AVD
- Diabetes
- Baseline LDL-C <100 mg/dL
- 2 or more CV risk factors
- Framingham: >10%
- <70 mg/dL
- <100 mg/dL
- <130 mg/dL
- <180 mg/dL


Lipoprotein Management in Patients With Cardiometabolic Risk

Consensus statement from ADA and ACC

Goal Values (mg/dL)

- Highest Risk:
  - CVD or DM with ≥1 major risk factor
  - LDL-C <70 Non-HDL-C <100 ApoB <80

- High Risk:
  - No CVD, no DM with ≥2 major risk factors
  - DM with no major risk factors
  - LDL-C <100 Non-HDL-C <130 ApoB <90

Other major risk factors (beyond dyslipidemia) include cigarette smoking, hypertension, and family history of premature coronary artery disease.

Lipid-Lowering Therapies

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
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<tbody>
<tr>
<td><strong>Statins</strong></td>
<td>↓↓↑↓</td>
<td>↑↑↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>(atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bile acid sequestrants</strong></td>
<td>↓↓↑↓</td>
<td>↑↑↓↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>(colesevelam, cholestyramine, colestipol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nicotinic acid</strong></td>
<td>↓↓↑↑</td>
<td>↑↑↓↑</td>
<td>↓↓</td>
</tr>
<tr>
<td><strong>Fibric acid derivatives</strong></td>
<td>↓↓↑↑</td>
<td>↑↑↓↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>(gemfibrozil, fenofibrate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cholesterol absorption inhibitor</strong></td>
<td>↓↓↑↑</td>
<td>↑↑↓↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>(acetimide)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Omega-3 fatty acids</strong></td>
<td>↑↑↓↓</td>
<td>↓↓↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>(eicosapentaenoic acid)</td>
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</table>

LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; TG: Triglycerides

Cholesterol Treatment Trialists’ Collaborators
- Meta-analysis, 14 randomized controlled trials (n=90,056)
- Major Vascular Events per 1-mmol/L (38.7-mg/dL) LDL-C Reduction

AHA/ACC Guidelines:
Secondary Prevention for Patients With Coronary and Other AVD
- LDL-C goal values
  - 100 mg/dL
  - Further reduction to 70 mg/dL is reasonable
  - 70 mg/dL if baseline LDL-C is 70-100 mg/dL
- If < LDL-C 70 mg/dL is not possible because of a high baseline LDL-C:
  - Achieve LDL-C reduction of 50% with statins or combination regimens

Need for Combination Therapy
- Mixed dyslipidemia
  - Combination therapy to attain both LDL-C and non-HDL-C goal values
    - Statin with fibric acid derivative
    - Statin with niacin
    - Statin with omega-3 fatty acids
- Very high LDL-C (≥ 190 mg/dL)
  - Statin with ezetimibe
  - Statin with bile acid sequestrant

Special Issues and Controversies
- Drug interactions
  - Fenofibrate + statin safer than gemfibrozil + statin
- Adherence and persistence with treatment
- Outcomes data limited for some circumstances
  - Combination therapy approaches
  - Metabolic syndrome and mixed dyslipidemia
  - Primary prevention in the very elderly
  - Primary prevention in women
A 39-year-old Hispanic man has metabolic syndrome. He also has hypertension and dyslipidemia (both controlled with drug therapy), his BMI is 31 kg/m$^2$ (i.e., he is obese), and he has prediabetes. What is the optimal treatment to prevent progression to type 2 diabetes?

- Metformin
- Pioglitazone
- Intensive lifestyle modification

**Elevated Fasting Glucose**

- $\geq 100$ mg/dL is cutoff for prediabetes
- **CONUNDRUM:** Pharmacotherapy reduces progression of prediabetes to type 2 diabetes
  - Metformin, acarbose, and thiazolidinediones delay progression in high-risk patients
  - Preventive effect dissipates when drug is stopped
  - Used clinically, but are not FDA approved

**ADA Consensus Statement**

**Impaired Fasting Glucose and Impaired Glucose Tolerance**

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>Impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)</td>
<td>Lifestyle modification (i.e., 5–10% weight loss and moderate-intensity physical activity ~30 min/day) and/or Metformin (850 mg twice daily)</td>
</tr>
<tr>
<td>IFG or IGT with 1 of the following:</td>
<td>Lifestyle modification (as above) and/or Metformin (850 mg twice daily)</td>
</tr>
<tr>
<td>• Age $&lt;60$ years of age</td>
<td></td>
</tr>
<tr>
<td>• BMI $\geq 25$ kg/m$^2$</td>
<td></td>
</tr>
<tr>
<td>• Family history of diabetes (first-degree relative)</td>
<td></td>
</tr>
<tr>
<td>• ↑ Triglycerides</td>
<td></td>
</tr>
<tr>
<td>• ↓ HDL-C</td>
<td></td>
</tr>
<tr>
<td>• Hypertension</td>
<td></td>
</tr>
<tr>
<td>• HbA1C $&gt;6.5%$</td>
<td></td>
</tr>
</tbody>
</table>

**Abdominal Obesity**

- Visceral fat
  - Mostly located in the abdominal cavity
  - Buried beneath muscle and surrounds and protects organs
  - More metabolically active than subcutaneous fat
- Abdominal obesity is more closely correlated with cardiometabolic risk and risk factors than total body fat

**Other Risk-Reduction Strategies**

- Antiplatelet therapy
  - Low-dose aspirin (81 mg daily) when Framingham risk score $\geq 10\%$
  - Clopidogrel for aspirin intolerance or contraindications
- Smoking cessation
- Influenza vaccination?

**Summary**

- Target cardiometabolic parameters to reduce CV risk
  - Most proven
    - Hypertension
    - Dyslipidemia (especially to ↓ LDL-C)
    - Antiplatelet therapy
  - Highly recommended
    - Intervention for prediabetes
    - Minimizing abdominal obesity
### Appendix

#### Men

<table>
<thead>
<tr>
<th>Age</th>
<th>Points</th>
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<td>45-49</td>
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<td>50-54</td>
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<td>70-74</td>
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<td>75-79</td>
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<table>
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<th>Total Cholesterol</th>
<th>Age 20-39</th>
<th>40-49</th>
<th>50-59</th>
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<th>70-79</th>
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<tr>
<td>280</td>
<td>11</td>
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<td>5</td>
<td>3</td>
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<th>70-79</th>
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<th>Systolic BP (mmHg)</th>
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<th>Treated</th>
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<th>Point Total</th>
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<td>0-4</td>
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**10-Year risk ____ %**

#### Women

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<th>Points</th>
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<tr>
<td>20-34</td>
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<td>&lt;160</td>
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<td>160-199</td>
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<td>2</td>
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<td>200-239</td>
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<td>4</td>
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<td>240-279</td>
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<td>8</td>
<td>5</td>
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<td>280</td>
<td>13</td>
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<table>
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<tr>
<th>Points</th>
<th>Age 20-39</th>
<th>40-49</th>
<th>50-59</th>
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<td>Smoker</td>
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<table>
<thead>
<tr>
<th>HDL (mg/dL)</th>
<th>Points</th>
<th>Systolic BP (mmHg)</th>
<th>Untreated</th>
<th>Treated</th>
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<tbody>
<tr>
<td>60</td>
<td>-1</td>
<td>&lt;120</td>
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<td>0</td>
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<tr>
<td>50-59</td>
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<td>120-129</td>
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<td>40-49</td>
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<td>130-139</td>
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<td>2</td>
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<tr>
<td>&lt;40</td>
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<td>140-159</td>
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<td>2</td>
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<tr>
<td></td>
<td></td>
<td>160</td>
<td>2</td>
<td>3</td>
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<table>
<thead>
<tr>
<th>Point Total</th>
<th>10-Year Risk %</th>
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<tbody>
<tr>
<td>&lt;9</td>
<td>&lt;1</td>
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<tr>
<td>9-12</td>
<td>1</td>
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<tr>
<td>13-14</td>
<td>2</td>
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<tr>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>16</td>
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<td>18</td>
<td>6</td>
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<td>19</td>
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<td>20</td>
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<td>21</td>
<td>14</td>
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<td>24</td>
<td>27</td>
</tr>
<tr>
<td>25</td>
<td>30</td>
</tr>
</tbody>
</table>

**10-Year risk ____ %**

The Evolution of Cardiometabolic Risk Reduction and Mixed Dyslipidemia: Examining the Role of Chronic Obesity Management

Carrie M. Maffeo, Pharm.D., BCPS, CDE
Director, Health Education Center
Assistant Professor of Pharmacy Practice
Butler University College of Pharmacy and Health Sciences
Indianapolis, Indiana

Carrie M. Maffeo, Pharm.D., BCPS, CDE, is Director of the College of Pharmacy and Health Sciences Health Education Center and an Assistant Professor in the Department of Pharmacy Practice, Butler University. Dr. Maffeo received her Pharm.D. from Butler University. She completed a Primary Care Specialty Residency at the University of Southern California. Dr. Maffeo’s post-graduate residency program served the residents in downtown, South Central and East Los Angeles.

Prior to her arrival at Butler University in the fall of 2003, Dr. Maffeo spent five years at the University of Colorado Hospital and Health Sciences School of Pharmacy teaching and practicing in the areas of primary care for the medically indigent and clinical community pharmacy. Her experiences subsequently led her to focus on underserved and diverse patient populations. Dr. Maffeo is a Certified Diabetes Educator and Board Certified Pharmacotherapy Specialist. She is an active member of the American Society of Health-System Pharmacists, American Pharmacists Association, and American Association of Colleges of Pharmacy. Her areas of clinical practice include health promotion, weight management, diabetes prevention, and cardiovascular risk reduction.
Chronic Obesity Management: Current Strategies and Future Direction

Carrie Maffeo, Pharm.D., BCPS, CDE
Butler University College of Pharmacy and Health Sciences

Learning Objectives

- Outline current recommendations for managing obesity and mixed dyslipidemia and the limitations of lifestyle modification and currently available drug therapies for the treatment of these conditions and the benefits.
- Recommend an appropriate therapeutic strategy to reduce coronary heart disease (CHD) risk in a patient with obesity or mixed dyslipidemia.
- Discuss the pharmacist’s role in reducing cardiovascular risk and promoting a healthy lifestyle.

POP QUIZ!

What are the two leading causes of preventable death in the United States?

1. Smoking-related illness
2. Poor diet and physical inactivity

What are the two leading causes of preventable death in the United States?


Chronic Diseases

Childhood Obesity

Cover Story: July 3rd, 2000
Medical costs attributable to obesity were $75 billion in 2003; half of these costs were paid by taxpayers.

Obese adults have 36-39% higher health care costs.

Estimated 365,000 deaths annually in United States due to obesity.

Impact of Overweight and Obesity

Weight Status and BMI (Ages 2 to 20)

<table>
<thead>
<tr>
<th>Weight Status and BMI (Ages 2 to 20)</th>
<th>BMI-for-Age</th>
<th>Weight Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>5th percentile to &lt;85th percentile</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>85th to less than 95th percentile</td>
<td>At Risk of Obese</td>
<td></td>
</tr>
<tr>
<td>At or above 95th percentile</td>
<td>Overweight or Obese</td>
<td></td>
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BMI is calculated then graphed on CDC gender-specific growth charts for those ages 2 to 20 years (http://www.cdc.gov/growthcharts)


Social Commentaries/Documentaries

Assessment of Overweight & Obesity: Adults

<table>
<thead>
<tr>
<th>Weight Status</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5–24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25–29.9</td>
</tr>
<tr>
<td>Obesity</td>
<td>30.0–34.9</td>
</tr>
<tr>
<td>Extreme Obesity</td>
<td>≥35.0</td>
</tr>
</tbody>
</table>

- Increased waist circumference (assesses abdominal fat) associated with increased relative risk for the development of obesity-associated complications & metabolic syndrome
  - Men >40 inches (102 cm)
  - Women >35 inches (88 cm)


Assessment of Overweight and Obesity: Children

<table>
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BRFSS: Obesity Prevalence 1995

Percentage of adults aged >18 years who were obese,* by state - Behavioral Risk Factor Surveillance System, United States, 1995, 2000, and 2005


BRFSS: Obesity Prevalence 2000

Percentage of adults aged >18 years who were obese,* by state - Behavioral Risk Factor Surveillance System, United States, 1995, 2000, and 2005

BRFSS: Obesity Prevalence 2005

Percentage of adults aged >18 years who were obese, by state — Behavioral Risk Factor Surveillance System, United States, 1995, 2000, and 2005

BRFSS: Obesity Prevalence 1995-2005

Percentage of adults aged >18 years who were obese, by state — Behavioral Risk Factor Surveillance System, United States, 1995, 2000, and 2005

National Health and Nutrition Examination Survey (NHANES): Adults

The 2003-2004 data on adults demonstrated:

- 65% of U.S. adults had a BMI >25 kg/m²
- 32.2% of adults (>66 million) were obese
- The prevalence of obesity among men demonstrated a significant increase from 27.5% to 31.1%.
  - 70.8% of men >20 years old were overweight or obese
  - 78.2% of men 40-59 years old were overweight or obese


National Health and Nutrition Examination Survey (NHANES): Children & Adolescents

The 2003-2004 data on children show:

- 17.1% of children and adolescents 2-19 years of age (>12.5 million) were overweight
- Between 1999 and 2004, there was a significant increase in the prevalence of overweight among girls and boys:
  - Girls: from 13.8% in 1999 to 16.0% in 2004
  - Boys: from 14.0% in 1999 to 18.2% in 2004
- Adolescents were more likely to be overweight than were younger children


Pop Quiz

- What is the average annual weight gain for adults in the United States?
  - 0.25 to 0.5 kg
  - 0.5 to 1.0 kg
  - 1.0 to 1.5 kg

Factors Contributing to Obesity

- Obesity being overweight are a result of an imbalance between food consumed and physical activity.
- National data have shown an increase in the calorie consumption of adults and no change in physical activity patterns.
- Obesity is a complex issue related to lifestyle, environment, and genetics.


What is an Obesogenic Environment?

Consists of:

- Calorie-dense foods that are readily available
  - increasing portion sizes
  - eating out more often
  - increased consumption of sugar-sweetened drinks
- Low-energy expenditure is common
  - increased time spent on television, computer, & electronic games
  - changing labor markets
  - fear of crime, which deters outdoor exercise

FRENCH FRIES

20 Years Ago

210 calories
2.4 ounces

Today

How many calories are in today’s portion of fries?

210 calories
2.4 ounces

Calorie difference: 400

Maintaining a Healthy Weight is a Balancing Act

Calories In = Calories Out

How long will you have to walk leisurely in order to utilize those extra 400 calories?*

*Based on 160-lb person

Calories In = Calories Out

If you walk leisurely for 1 hour and 10 minutes you will burn approximately 400 calories.*

*Based on 160-lb person
Treatment and Prevention of Obesity

First-Line Treatment

- Lifestyle changes to generate a negative energy balance and produce a healthy gradual, consistent weight loss
  - Healthy eating
  - Regular physical activity
- On average, a deficit of 250 calories/day or 1750 calories per week is needed to produce a 0.5-lb loss of fat/week
  - This can be achieved through diet, exercise, or both
  - Initial goal: decrease initial body weight by 10%
  - Continue with additional weight loss if needed
  - Once goal weight achieved, implement weight maintenance plan

Obtaining a Healthy Weight Through Positive Lifestyle Choices

- Behavior change programs
  - Goal setting, self-monitoring, problem-solving techniques, estimating energy needs
- Healthy eating
  - Dietary Guidelines for Americans & American Heart Association diet & lifestyle recommendations
  - Diet rich in fruits, vegetables, & whole grains; consume low-fat dairy products; limit intake of saturated & trans fats, high-calorie foods with low nutritional value, & sweetened or sugary drinks
- Physical activity
  - 2008 Physical Activity Guidelines for Americans
  - American College of Sports Medicine & AHA: Physical Activity & Public Health

Pop Quiz

- What percentage of American adults do not engage in any regular physical activity?
  - 40%
  - 50%
  - 60%

2008 Physical Activity Guidelines for Americans

- First step: meet minimum level of recommended activity
  - 150 min/wk of moderate-intensity or 75 min/wk of vigorous
- Then monitor body weight and, if necessary, increase amount of activity to a point that is individually effective in achieving a healthy body weight
  - Some people require 300+ minutes of moderate-intensity activity/week
  - All activities that expend calories help control body weight
  - Vigorous-intensity activity is a much more time-efficient way to achieve NET increases in caloric expenditure
  - “The good news for people needing to lose weight is that regular physical activity provides major health benefits, no matter how their weight changes over time.”

Pharmacotherapy for Obesity

- Drug therapy may be a helpful component of the treatment regimen for obese patients in addition to lifestyle therapy
  
- Drug therapy can be considered for those with:
  - BMI >30 kg/m²
  - BMI 27-30 kg/m² with comorbid condition (type 2 diabetes, hypertension, CHD, dyslipidemia, sleep apnea)
- American College of Physicians recommends drug therapy for BMI >30 kg/m²

Pharmacotherapy Overview

- Centrally-acting medications
  - Anorexiants/appetite suppressants
    - Increase the availability of anorexogenic neurotransmitters (norepinephrine, serotonin, dopamine) in the CNS
  - Endocannabinoid system (ECS)
    - Cannabinoid receptors (CB1) regulate food intake and influence use and storage of fat
    - CB1 receptor antagonists suppress food intake and inhibit hepatic and adipose tissue lipogenesis

- Peripherally-acting medications
  - Lipase inhibitors
    - Form covalent bonds with gastric and pancreatic lipases in the stomach and small intestine
    - The enzymes become unavailable to hydrolyze dietary triglycerides into free fatty acids and monoglycerides, reducing fat absorption
  - Anorexiants/appetite suppressants
    - Increase the availability of anorexigenic neurotransmitters (noradrenaline, serotonin, dopamine) in the CNS
    - CB1 antagonists suppress food intake and inhibit hepatic and adipose tissue lipogenesis
    - GI peptides with anorexiant effects (amylin, glucagon-like peptide-1, leptin)

Investigational Pharmacotherapy

- Lipase inhibitor
  - Fat absorption by 25-30%

- Anorexiant
  - (5-HT & NE
    - Reuptake inhibitor
  - CB1, receptor antagonist

- CB2 receptor antagonist

- Orlistat
  - BMI >30 kg/m²
  - Flatulence

- Naltrexone SR
  - BMI >30 kg/m²
  - Oily stools/spotting, fecal urgency, increased HTN, tachycardia

- Bupropion SR
  - BMI >30 kg/m² or >27 kg/m²
  - Cognitive dulling

- Phentermine
  - BMI >30 kg/m² or >27 kg/m²
  - Weight loss agent

- Metformin
  - BMI >30 kg/m² or >27 kg/m²
  - No published data

- Sacubitril/valsartan
  - BMI >30 kg/m² or >27 kg/m²
  - No published data

Off-Label Pharmacotherapy

- Norepinephrine & appetite suppressants
- First class of medications approved by FDA in patients with BMI >30 kg/m² or >27 kg/m² with risk factors
- Short-term use (generally interpreted as 12 weeks)
- Potential for addiction, abuse, and side effects limits use
- Expected weight loss: 3-3.6 kg

Schedule

<table>
<thead>
<tr>
<th>Medication</th>
<th>C IV</th>
<th>C III</th>
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<tbody>
<tr>
<td>Phentermine, diethylpropion</td>
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<td></td>
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<tr>
<td>Benzphetamine, phenetermine</td>
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Investigational Combination Pharmacotherapy

<table>
<thead>
<tr>
<th>Bupropion SR/ Naltrexone SR (Contrave)</th>
<th>Bupropion SR/ Zonisamide (Empatic)</th>
<th>Phentermine/ Topiramate (Qnexa)</th>
<th>Pramlintide/ Meterleptin</th>
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<tbody>
<tr>
<td>Status</td>
<td>Phase III</td>
<td>Phase III</td>
<td>Phase II</td>
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<tr>
<td>Mechanism</td>
<td>DA &amp; NE receptor inhibitor opioid antagonist</td>
<td>DA &amp; NE receptor inhibitor anticonvulsant</td>
<td>Anorexiant &amp; anticonvulsant</td>
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<tr>
<td>Preliminary Weight Loss Data</td>
<td>Tx group ↓ 5.4% vs. 0.8% in placebo group</td>
<td>Tx group ↓ 8.6% vs. 1.1% in placebo group</td>
<td>Tx group ↓ 11.4 kg vs. 2.2 kg in placebo group</td>
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<tr>
<td>Comments</td>
<td>Motivation &amp; reinforcement of food &amp; pleasure of eating</td>
<td>Zonisamide has serotonergic &amp; dopaminergic activity</td>
<td>Mild stimulant cognitive dulling effect</td>
</tr>
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</table>

Approved Pharmacotherapy

- Antidepressants
  - SSRI (Selective Serotonin Reuptake Inhibitors)
  - SNRI (Serotonin Norepinephrine Reuptake Inhibitors)
  - MAOI (Monoamine Oxidase Inhibitors)

- Weight loss data
  - Phase II: 4.1-5.3 kg
  - Phase III: 4.2 kg

- Approved ≥18 years
  - Approved ≥16 years

- Depressant
  - Mild cognitive dulling

- Antidepressant
  - Mild to moderate GI side effects

- Anticonvulsant
  - No effect on heart rate observed

- Antidepressant
  - No depression, anxiety, aggression, seizures, suicidal thoughts

- Antidepressant
  - Flatulence

- Antidepressant
  - Dry mouth, nausea, insomnia

- Antidepressant
  - No published data available

- Antidepressant
  - Metabolism of fluphenazine as an anti-obesity drug at a dose of 60 mg/day generated a variable weight change from 14.5 kg lost to 0.40 kg gained

- Antidepressant
  - Limited utility as a long-term anti-obesity drug

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  - Limited utility as a long-term anti-obesity drug
“If exercise could be purchased in a pill, it would be the single most widely prescribed and beneficial medicine in the nation.”

—Robert H. Butler
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SELECTED REFERENCES


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