CVD Prevalence and Costs Heading in the Wrong Direction

- According to a recent study by the American Heart Association, America’s Baby Boomers and Cardiovascular Disease (CVD) are on a collision course of alarming proportions.
- By 2030, it is projected that 40.5% of Americans—116 million people—will have some form of CVD.
- More than 787,000 people in the U.S. died from heart disease, stroke and other cardiovascular diseases in 2010. That’s about one of every three deaths in America.
- About 2,150 Americans die each day from these diseases, one every 40 seconds.
- In 2030, 39% of men and 42% of women will have some form of CVD, and blacks suffer at higher rates than whites and Hispanics.

Projections of Cardiovascular Disease Prevalence

<table>
<thead>
<tr>
<th>Year</th>
<th>2010</th>
<th>2015</th>
<th>2020</th>
<th>2025</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>36.9%</td>
<td>37.8%</td>
<td>38.7%</td>
<td>39.7%</td>
<td>40.5%</td>
</tr>
</tbody>
</table>

Assessing Obesity

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI (kg/m²)</th>
<th>Men &lt; 40 in</th>
<th>Women &lt; 35 in</th>
<th>Men &gt; 40 in</th>
<th>Woman &gt; 35 in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>≤18.5</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5-24.5</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
<td>Increased</td>
<td>High</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Obesity</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Class 1</td>
<td>30.0-34.9</td>
<td>High</td>
<td>Very High</td>
<td>High</td>
<td>Very High</td>
</tr>
<tr>
<td>Class 2</td>
<td>35.0-39.9</td>
<td>Very High</td>
<td>Very High</td>
<td>Extremely</td>
<td>Extremely</td>
</tr>
<tr>
<td>Class 3</td>
<td>≥40</td>
<td>Extremely</td>
<td>Extremely</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>
Update on Dyslipidemia: Assessing CHD Risk, Emerging Targets and New Treatments

Energy Partitioning in Gluteal-Femoral Fat:

Energy expenditure \(\downarrow\)

Energy intake \(\downarrow\)

Energy excess

ENough insulin-sensitive subcutaneous fat cells to clear plasma lipids and to store excess energy in AT?

1: YES

- e.g., premenopausal women with normal insulin sensitivity
- Normal metabolic risk profile

2: NO

- Impaired storage of excess energy in AT
- Limited storage in visceral AT, liver, pancreas, muscle
- Hypertriglyceridemia

AT = adipose tissue
CHD = coronary heart disease


Abdominal Fat Accumulation in Obese Women


Visceral Fat Is an Independent Predictor of All-Cause Mortality in Men

Visceral Adipose Tissue Area and Waist Girth according to CRP Quintiles

P<0.0001 vs. indicated quintiles

Central or Abdominal Obesity Is Associated With a Higher Level of Visceral Fat

White Adipose Tissue is a Metabolically Active Endocrine Organ

- Energy Metabolism (Storage)
- Cell Viability
- Control of Feeding
- Thermogenesis
- Neuroendocrine Function
- Reproduction
- Immunity
- Cardiovascular Function
Update on Dyslipidemia: Assessing CHD Risk, Emerging Targets and New Treatments

Secreted Adipose Proteins (Adipokines) with Important Roles in Metabolism

- Leptin
- Interleukin-6
- Adiponectin
- Adipin
- Plasminogen Activator Inhibitor-1
- TNFα
- Resistin
- Plasminogen
- Resistin
- TNF-α
- Chimerin
- TNF-α
- Adipsin
- Interleukin-6
- Visfatin

Co-Morbidities Related to Excessive Visceral Adiposity

- Type 2 DM
- Lipoprotein Lipoase
- Angiotensinogen
- Dislipidemia
- Lipoproprotein Lipoase
- FFA
- Insulin
- Type 2 diabetes
- Resistin
- Plasminogen Activator Inhibitor 1 (PAI-1)

Proposed Contribution of Ectopic Fat Deposition to the Cardiometabolic Risk Profile of Viscerally Obese Patients

- Systemic FFA
- UPL
- Insulin resistance
- FFA = Free Fatty Acids

Tissue Necrosis Factor-α (TNFα) is an adipose expressed protein which is a key driver of chronic inflammation and another of the candidate molecules inducing insulin resistance. Increased inflammation leads to increased cell infiltration. Proinflammatory cytokines and chemokines contribute to increased cell infiltration and acute phase response. Metalloproteinase synthesis, collagen production, and ion transport lead to tissue remodeling and increased permeability, compromising barrier function.

Stages of Type 2 Diabetes:

Dyslipidemia, proinflammatory, prothrombotic, and insulin resistance contribute to the progression of Type 2 diabetes. Postprandial hyperglycemia progresses to impaired glucose tolerance (IGT) and subsequently to Type 2 diabetes as phases I, II, and III.

Metabolic Syndrome

Abdominal obesity: waist circumference
- Men >40 in
- Women >35 in
- Children (>8 yr) 90th percentile for waist circum.

Triglycerides: ≥150 mg/dL
- Children >110 mg/dL

HDL cholesterol
- Men <40 mg/dL
- Women <50 mg/dL
- Children <40 mg/dL (boys and girls)

Blood pressure: ≥130/85 mm Hg
- Boys 120/80 mm Hg
- Girls 110/70 mm Hg

Fasting blood glucose: ≥110 mg/dL
- Children ≥110 mg/dL

NCEP=National Cholesterol Education Program

Factors Contributing to Cardiometabolic Risk

Overweight/Obesity
Insulin Resistance
Smoking, Physical Inactivity
Hypertension

Cardiometabolic Risk
Global Diabetes/CVD Risk

Abnormal Lipid Metabolism
- LDL
- ApoB
- HDL
- Triglycerides

Inflammation, Hypercoagulation

Age, Race, Gender, Family History

Metabolic syndrome contributes to accelerated CAD

Atherosclerosis is a form of hardening of the arteries in which a complex substance called plaque builds up in arteries eventually limiting blood flow.

Increasing Plaques

Decreasing flow

Normal Artery
Minimal Narrowing
Moderate Narrowing
Severe Narrowing
**Atherosclerotic plaque formation and unstable subendothelial atheroma**


**Angiographically Inapparent Atheroma**


**CAD Events and the Metabolic Syndrome**

- The metabolic syndrome confers a 2 – 5 fold increased risk of developing cardiovascular disease and at least a 4 fold risk of developing type 2 diabetes
- Women with type 2 diabetes have a 3- to 9-fold increased risk of cardiovascular disease and events

CAD Events and the Metabolic Syndrome

- Less likely to be associated with high-grade obstructive coronary lesions
- Less likely to be symptomatic prior to event
- Characterized by smaller, diffuse, unstable, lesions, endothelial dysfunction, and increased inflammatory and thrombogenic potential

1998 Executive Summary NIH Guidelines for Obesity Management Intervention

<table>
<thead>
<tr>
<th>BMI</th>
<th>18.5-24.9 Lean</th>
<th>25-29.9 Overweight</th>
<th>30-34.9 Obesity Class I</th>
<th>35-39.9 Obesity Class II</th>
<th>≥40 Obesity Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of complications</td>
<td>Very low</td>
<td>Mild</td>
<td>Moderate</td>
<td>High</td>
<td>Extreme</td>
</tr>
<tr>
<td>Nutrition</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Behavioral Management</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Medication</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Common clinical scenarios: Spectrum of Obesity Risk

- 34 y/o female, BMI = 36, works, 2 school-aged children, PMHX of "white coat" blood pressure elevations (high 140 to mid-150s SBP), mild dyslipidemia (TGs 170, HDL 39, LDL 126), FBG 102 mg/dL, Depression on SSRI, OA, too busy to exercise, exhausted by the time children are put to bed....
- 42 y/o male, BMI = 30, small business owner, PMHX insomnia, HTN, ED, smoker .....increased work and home related stressors, no time to exercise but gets "plenty of exercise at work"....
- 28 y/o African-American female, BMI 28.5, PMHX includes well-controlled T2DM on monotherapy, reports 15 lb weight increase over the past 6 months, stopped usual exercise program due to life circumstances, before she started her regular exercise routine, reports a history of elevated blood pressure, wants medication to help her lose weight....
- 48 y/o female, BMI = 52, PMHX chronic left knee pain, fatigue, steady weight gain since puberty and worsening with each pregnancy (2), chronic dieter, minimal success with weight loss......
Obesity and Cardiometabolic Disease

- Not all overweight / obese patients have metabolic disease
- Not all patients with metabolic disease are overweight / obese
- Improved outcomes for the treatment of obesity may depend on stratification of patients by metabolic risk

Are these recommendations now outdated?

EBP: an extensive PubMed literature search using the search term “bariatric surgery” identified a total of 14,287 publications with approximately 6,800 citations from 2008 to 2012.

Complication-Centric Approach to the Management of Cardiometabolic Risk and Obesity

- Complications can be categorized to identify patients most likely to benefit from weight loss and the intensity of treatment strategies
  - Cardiometabolic
  - Mechanical
  - Functional Impairment
  - Edmonton Obesity Staging System
**Edmonton Obesity Staging System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Obesity-Related Risk Factors</th>
<th>Physical Symptoms, Psychopathology, Functional Limitations, and Impairment of Well-being</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None (blood pressure, serum lipids, fasting glucose, etc)</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Subclinical (borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc)</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Established (hypertension, type 2 diabetes mellitus, sleep apnea, osteoarthritis, renal disease, polycystic ovary syndrome, anxiety disorder, etc)</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Established end-organ damage (myocardial infarction, heart failure, diabetic complications, inoperable osteoarthritis, etc)</td>
<td>Significant</td>
</tr>
<tr>
<td>4</td>
<td>Severe disabilities (potentially end-stage disabilities, etc)</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Sharma & Kushner, 2009

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**What can bariatric surgery teach us about the pathophysiology of metabolic dysregulation?**

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**Anatomical Manipulation of Surgical Bariatric Procedures**

- a. Roux-en-Y gastric bypass
- b. adjustable gastric banding
- c. vertical sleeve gastrectomy

MIRI 455.3 Barou D.St. Online Edition 2014 MIRI 455.3
Lessons from Bariatric Surgery

Through the study of RYGB effects, important reprogramming of gut hormones and adipocyte regulation have been identified which impact glucose homeostasis, and that this affect is more important than those on body weight.

Our challenge is to develop non-surgical interventions that mimic the metabolic benefits of bariatric surgery.
Update on Dyslipidemia: Assessing CHD Risk, Emerging Targets and New Treatments

Pharmacologic Strategies Based on Assessment of Metabolic Health: Management Strategies for Obesity

**Metabolically Healthy**

**Stepwise approach**
- Assess complications
- Assess BMI and treatment criteria
- Behavioral interventions
- Self-selected Diet
- Assess and treat mood disorders
- Primary Medications
  - Phentermine (Adipex)
  - Topiramate (Topamax)
  - Zonasmide (Zonegran)
  - Buproprion (Wellbutrin)
  - Lorcaserin (Belviq)
- BMI > 40 Bariatric Surgical Procedure

**Metabolic Risk Factors**

**Simultaneous approach**
- Assess Complications
  - Contemporary
  - Weight loss
  - Behavioral interventions
  - Multimodal Diet
- Target mood disorder treatment
- Assist and treat sleep apnea
- Combination Medications
  - Phentermine (Adipex) + Orlistat (Xenical)
  - Topiramate (Topamax) + Metformin (Glucophage)
  - Zonasmide (Zonegran) + GLP-1 (Byetta)
  - Buproprion (Wellbutrin) + Pramlintide (Amylin)
  - Phentermine/Topiramate (Qysmia)
  - Lorcaserin (Belviq)
- BMI > 35 with DM - Lap Band
- BMI > 30 with DM - Sleeve Gastrectomy

Examples of novel therapeutic targets include:
- Appetite as well as taste/food preferences
- Energy expenditure
- Inflammation
- Preservation of β-cell function
- Hepatic glucose output

Clinical Management of Metabolic Dysregulation in the Obese Patient

Intensive management of comorbidities
- IFG/IGT/DMT2
- Sedentary lifestyle
- Dyslipidemia
- Pre- and hypertension
- Obesity

How much weight loss is needed to improve metabolic dysregulation and CV risk?
Update on Dyslipidemia: Assessing CHD Risk, Emerging Targets and New Treatments

Diabetes Prevention Program Change in Body Weight

<table>
<thead>
<tr>
<th>Base BW (kg)</th>
<th>Year 0</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>94.3</td>
<td>94.3</td>
<td>94.1</td>
<td>94.1</td>
<td>94.1</td>
<td>94.1</td>
</tr>
</tbody>
</table>

Change from Baseline Body Weight (kg)

0                  1                  2                  3                 4

Years after Randomization


“Normal” Weight (BMI=25 kg/m²) but Viscerally Obese Patient...

Before

After... a weight loss of 5 kg

• Moderate weight loss (5–10%) by diet and/or exercise can induce a substantial (~30%) loss of atherogenic visceral fat and substantially improve the risk profile status of these patients

• Thus, the importance of *waist* rather than weight management is emphasized


Clinical Management of Metabolic Dysregulation in the Obese Patient

Intensive management of comorbidities

- IFG/IGT/DMT2
- Dyslipidemia
- Pre- and hypertension
- Sedentary lifestyle
- Obesity

How much exercise is needed to improve CV risk?
Acute and Chronic Effects of Regular Physical Activity/Exercise

Sedentary Viscerally Obese

- Improvements of lipoprotein-lipid profile and insulin/glucose metabolism
- Mobilization of visceral AT without significant changes in adiposity

Physically Active Viscerally Obese

- Additional physical and metabolic improvements
- Mobilization of visceral AT and significant weight loss

Physically Active Nonviscerally Obese

Effect of Exercise on Lipoprotein Profiles

- Manson et. al. (2002). Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *NEJM, 37 (10).*
- Kraus et al. (2002). Effects of the amount and intensity of exercise on plasma lipoprotein. *NEJM, 37 (10).*

Clinical Management of the Metabolic Dysregulation in the Obese Patient

Intensive management of comorbidities

- IFG/IGT/DMT2
- Dyslipidemia
- Pre- and hypertension
Update on Dyslipidemia: Assessing CHD Risk, Emerging Targets and New Treatments

Major Clinical Trials Show That Intensive Glucose Control Does Not Decrease Cardiovascular Events

- Action to Control Cardiovascular Risk in Diabetes (ACCORD)
- Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE)
- VA Diabetes Trial (VADT)


Main Findings from the ACCORD and ADVANCE Studies

**ACCORD**
- 10,251 participants
- Mean age: 62 years
- Median duration of diabetes mellitus: 10 years
- Mean A1C at entry: 8.3%
- Known heart disease or at least 2 risk factors

**ADVANCE**
- 11,140 participants
- Mean age: 66 years
- Mean duration of diabetes mellitus: 8 years
- Mean A1C at entry: 7.48%
- History of major CV event or at least 1 risk factor


**CONCLUSION:** Intensive glucose-lowering did not significantly reduce CVD events (primary outcome) may cause harm in high-risk patients with type 2 diabetes (increased mortality).

**A1C <7.0% Is Appropriate for Most Patients with Diabetes**

- An A1C value of <7.0% is appropriate and well supported by clinical trial results:
  - There are no data to support an A1C goal of <7.0% for reducing cardiovascular risk
- For individual patients, intensifying the regimen should be weighed by the potential risks and benefits:
  - History of severe hypoglycemia
  - Limited life expectancy
  - Children
  - Comorbid conditions
  - Longstanding diabetes and minimal or stable microvascular complications

Diabetes Management

- Less emphasis on glycemic targets for prevention of CVD
- Glycemic targets to reduce microvascular complications
- Clinical management targeting the preservation or rejuvenation of beta-cell function
- Aggressive management of CV morbidities

Clinical management targeting the preservation or rejuvenation of Beta Cell Function

- Progressive deterioration in cell function and mass with duration of diabetes (Approx. 50% loss of normal at the time of diagnosis, and a reduction in beta-cell mass of about 60% at necropsy)
- The reduction of cell mass is thought to be attributable to accelerated apoptosis.
- The major clinical factors for progressive loss of beta-cell function and mass are:
  - Glucotoxicity
  - Lipotoxicity
  - Adipocyte-secreted cytokines and hormones
    - Proinflammatory cytokines (TNF-, IL-6, and IL-1 receptor antagonist) are produced and secreted by fat tissue, increased in obesity, and have been causally linked to insulin resistance
    - Letpin
  - Beta cell amyloid deposition
- Impaired cell function and possibly cell mass appear to be reversible, particularly at early stages of the disease where the limiting threshold for reversibility of decreased beta-cell mass has probably not been passed.


Interventions found to preserve or rejuvenate beta cell function

Emerging evidence suggests that several medical therapies could offer specific benefits by preventing or delaying the decline in cell mass/function, thereby representing a substrate for early intervention efforts to lower the burden of DM2.

- In individuals with established DM2, the inhibition of the increased apoptosis may lead to restoration of beta-cell mass because islet neogenesis appeared to be unaffected.
- Short-term initiation of intensive insulin therapy in newly diagnosed DM (temporary remission time)
- Induction of beta-cell "rest" by selective activation of ATP-sensitive K (KATP) channels, using drugs such as diazoxide (Pruglycem)
- Use of antiapoptotic drugs such as the thiazolidinediones (TZDs) and incretin mimetics and enhancers
- Short acting insulin secretagogues meglitinide (Prandin)
Update on Dyslipidemia: Assessing CHD Risk, Emerging Targets and New Treatments

### Oral Medications for Diabetes Mellitus and Weight Change

<table>
<thead>
<tr>
<th>Medication</th>
<th>Weight: Positive change (lb/yr)</th>
<th>Weight: Negative change (lb/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>1 – 3</td>
<td>0 – 6</td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td>0 – 10</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>Neutral</td>
<td>0 – 10</td>
</tr>
<tr>
<td>TZD’s</td>
<td>1 – 13</td>
<td></td>
</tr>
<tr>
<td>GLMides</td>
<td>1 – 3</td>
<td></td>
</tr>
<tr>
<td>Exenatide*</td>
<td></td>
<td>1.75 (15-month RCT)</td>
</tr>
<tr>
<td>Sitagliptin†</td>
<td>Neutral (24-week RCT)</td>
<td>0 (24-week RCT)</td>
</tr>
<tr>
<td>Pramlintide‡</td>
<td></td>
<td>3.7 (16-week RCT)</td>
</tr>
</tbody>
</table>

TZD=thiazolidinedione; RCT=randomized controlled trial

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**Weight Gain Can Originate From Frequently Prescribed Drugs**

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**When Considering Drug Related Weight Gain**

- Depending on the clinical situation, the benefits of taking a medication may exceed the risks of weight gain.
- Before prescribing a drug, discuss the potential risks of weight gain, and attempt to minimize it by recommending appropriate lifestyle changes.
- For patients who already are overweight, there may be alternative medicines that do not seem to be associated with weight gain.
Insulin Sensitizers

Biguanides: Metformin (Glucophage)
- reduces hepatic glucose production in the presence of insulin, increases peripheral insulin sensitivity
- associated with weight loss
- reduces carbohydrate absorption from the GI track
- circulating insulin levels decline
- lowers LDL and triglycerides
- lowers PAI-1
- ameliorates endothelial function
- lowers blood pressure

Insulin Sensitizers

Thiazolidinediones (TZD): Rosiglitazone (Avandia) and pioglitazone (Actos)
- insulin-stimulated glucose uptake by skeletal muscle cells, insulin resistance in peripheral tissues
- insulin levels (greater extent than with metformin)
- lipolysis and enhances adipocyte differentiation
- microalbumin excretion
- HDL, triglyceride levels, Alters LDL phenotype
- blood pressure, enhances fibrinolysis and improves endothelial function
- Weight gain, mostly peripheral subcutaneous sites, decreases visceral fat deposition (remodeling)

Metformin (Glucophage)
- Metformin, increasingly used in patients with prediabetes and other insulin-resistant states for the management of obesity
- produces small sustained weight losses of about 2% relative to placebo
- has a good safety profile, and long-term clinical experience
- because weight loss attributable to metformin is small, its usefulness as monotherapy for obesity treatment is limited, but its salutary effects on body weight make it a good choice when other indications warrant its prescription
- Metformin has also been used to prevent or ameliorate weight gain with atypical antipsychotic agents and mood stabilizers.
- A meta-analysis examining the effect of medications for attenuation of antipsychotic weight gain found an approximate 3 kg additional weight loss relative to placebo attributable to metformin
Trends in Obesity Management: Targeting Gut Hormones

- In combination, represents a strategy to improve weight loss efficacy closer to the weight loss efficacy of metabolic surgical procedures
- Metabolic surgery modulates a number of anorectic gut hormones
- Has been studied in both diabetic and metabolically health samples
- Limited by delivery method

Physiological changes after the most commonly performed bariatric surgery procedures and modern obesity and type 2 diabetes mellitus pharmacotherapy

<table>
<thead>
<tr>
<th></th>
<th>RYGB</th>
<th>VSG</th>
<th>AGB</th>
<th>Orlistat</th>
<th>Lorcaserin</th>
<th>Phentermine/ topiramate</th>
<th>GLP-1 agonists</th>
<th>DPP-4 inhibitors</th>
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</thead>
<tbody>
<tr>
<td>Appetite</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma GLP-1</td>
<td>↓/↑</td>
<td>↔</td>
<td>↔</td>
<td>/↑</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Plasma PYY</td>
<td>↑↑</td>
<td>↔/↑</td>
<td>↔/↑</td>
<td>/↓</td>
<td>?</td>
<td>?</td>
<td>?</td>
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<tr>
<td>Plasma leptin</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>?</td>
<td>↓</td>
<td>?</td>
<td>?</td>
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<tr>
<td>Gastric emptying</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>?</td>
<td>↓</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Caloric malabsorption</td>
<td>Minimal for fat only</td>
<td>?</td>
<td>?</td>
<td>↑</td>
<td>?</td>
<td>↓</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Food preferences</td>
<td>↓</td>
<td>Consumption of fat and sugar</td>
<td>↓</td>
<td>Consumption of fat and sugar</td>
<td>↓</td>
<td>?</td>
<td>Consumption of fat and sugar</td>
<td>↓</td>
</tr>
<tr>
<td>Glycaemic improvements</td>
<td>Early and gradual, weight-dependent and -independent</td>
<td>Gradual</td>
<td>Gradual</td>
<td>Gradual</td>
<td>Gradual</td>
<td>Gradual</td>
<td>Early and gradual, weight-dependent and -independent</td>
<td>Early and gradual</td>
</tr>
<tr>
<td>Early postprandial insulin release</td>
<td>Early and gradual</td>
<td>Gradual</td>
<td>Gradual</td>
<td>Gradual</td>
<td>Gradual</td>
<td>Gradual</td>
<td>Early and gradual, weight-dependent and -independent</td>
<td>Early and gradual</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>?</td>
</tr>
<tr>
<td>Pancreatic stress</td>
<td>↑</td>
<td>▶</td>
<td>▶</td>
<td>▶</td>
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<td>▶</td>
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<tr>
<td>Other measures</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>?</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Miras and Le Roux (2013). Can medical therapy mimic the clinical efficacy or physiological effects of bariatric surgery?
GLP-1 Agonists

Approved GLP-1 agonists:
- Exenatide (Byetta/Bydureon)
- Liraglutide (Victoza)
- Albiglutide (Tanzeum), licensed in 2014 by GSK

- Enhances glucose-dependent insulin secretion by pancreatic β-cell proliferation
- Reduces adiposity
- Increases insulin sensitivity
- Suppresses inappropriately high glucagon secretion
- Slows gastric emptying, reduces food intake, mild anorexic
- Weight loss

Exenatide (Byetta)

![Graph: Weight Change During Treatment with Exenatide]


DPP IV Inhibitors

- Sitagliptin (Januvia)
- Vildagliptin (Galvus)
- Saxagliptin (Onglyza)
- Linagliptin (Trajenta)
DPP IV Inhibitors

- Used in combination with oral agents, insulin or monotherapy
- In clinical trials, GLP-1 receptor agonists have tended to produce greater blood glucose-lowering effects than DPP-4 inhibitors
- GLP-1 inhibitors consistently decreased weight, while the DPP-4 inhibitors have been weight-neutral
- These differences are probably explained by the fact that GLP-1 receptor agonists are dosed to produce pharmacologic concentrations, whereas the level of GLP-1 receptor stimulation that can be achieved with DPP-4 inhibitors is limited by endogenous GLP-1 secretion


Summary of effects of GLP-1 and DPP IV

<table>
<thead>
<tr>
<th>GLP-1</th>
<th>DPP-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>injection</td>
</tr>
<tr>
<td>GLP-1 concentrations</td>
<td>pharmacological</td>
</tr>
<tr>
<td>Mechanism of actions</td>
<td>GLP-1</td>
</tr>
<tr>
<td>Activation of the portal glucose sensor</td>
<td>no</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Glucagon secretion</td>
<td>↓</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>↓</td>
</tr>
<tr>
<td>Weight reduction</td>
<td>yes</td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>↓</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>yes (approx 45%)</td>
</tr>
<tr>
<td>Expansion of β cell mass</td>
<td>yes</td>
</tr>
<tr>
<td>Potential immunogenicity</td>
<td>yes</td>
</tr>
</tbody>
</table>

Drucker DJ. Mechanisms in Medicine Inc., 2006 (222)

Gut Hormone Combination Therapies

- Approach to overcoming the tolerability issues with single agent hormones
- May improve weight loss outcomes

Tolerability issues:
- Side effects (especially nausea) dose related
- Increased risk for acute pancreatitis with high dose single agent (liraglutide or exenatide)
- Risk increased if patient used tobacco, consumed ET0H or had BMI > 30
- Concern has also been raised that GLP-1 therapy could lead to an increase in pancreatic and thyroid cancer incidence.

There are currently nine ongoing, prospective, controlled trials of GLP-1 based therapy with over 65,000 subjects, which should provide answers to these important safety questions from patient compliance to offering a much more practical way of achieving combinations that should increase efficacy and reduce side effects.
Sodium–glucose co-transporter-2 inhibitors: an emerging new class of oral antidiabetic drug:
Dapagliflozin (Farxiga); Canagliflozin (Invokana)

- **A Study of Dapagliflozin in Patients With Type 2 Diabetes on High Doses of Insulin Plus Insulin Sensitizers: Applicability of a Novel Insulin-Independent Treatment**

  - Objective - To determine if dapagliflozin, which selectively inhibits renal glucose reabsorption, lowers hyperglycemia in type 2 diabetes patients poorly controlled with high insulin doses plus oral antidiabetic agents (OADs)
  - Conclusions - In patients on high insulin doses plus insulin sensitizers who had their baseline insulin reduced by 50%, dapagliflozin decreased A1C, produced better FPG and PPG levels, and lowered weight more than placebo.
  - Main considerations: glucosuria, hypotension (dehydration) increased risk of UTIs and yeast infections

Diazoxide (Proglycem)

- Selective beta-cell K+ ATP channel opener
- Inhibits insulin secretion to "rest" the beta cell
- Preserves insulin stores and pulsatile insulin secretion
- Possible antiapoptotic effect by blocking glucose-induced cytosolic Ca2 increase secondary to the beta cell KATP channel closure with the rise in plasma glucose (in vitro studies have shown that glucose induced apoptosis is Ca2 dependent)

Orlistat (Xenical)

Orlistat is a gastrointestinal lipase inhibitor
- Works in the lumen of the stomach and small intestine
- Prevents conversion of dietary fats into absorbable fatty acids

*Approved April 1999*

- Major advantage: Inhibits approximately 30% of dietary fat intake
  - Can help with further reductions in caloric restriction without feelings of deprivation.

Alli: A half-dose version of prescription Orlistat (Xenical) is available as a new "over-the-counter" drug.
**Update on Dyslipidemia:**
Assessing CHD Risk, Emerging Targets and New Treatments

---

**Effect of Long-Term Orlistat (Xenical) Therapy on Body Weight**

- **Change in Weight (kg)**
  - Placebo: -4.1 kg
  - Orlistat: -6.9 kg

![Graph showing weight change over weeks](Torgeson-et-al-Diabetes-Care-2004-27-155)

---

**Gastrointestinal Side Effects of Orlistat (Xenical) Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Orlistat</td>
</tr>
<tr>
<td>Fatty/oily stool</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>Increased defecation</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Liquid stools</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Fecal urgency</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Fecal urgency</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Oily evacuation</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Low plasma vitamin conc.</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>0.6</td>
<td>5.1</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>0.9</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Values are percentage of subjects.


---

**Orlistat (Xenical)**

- 120 mg TID with each meal (during or up to one hour post meal)
- Excretes in stool ~ 30% of ingested fats
- 1 year data: 9% weight loss vs. 5.8% placebo

**Major Advantages:**
- Slows the rate of weight regain
- Improved metabolic indicators
- In T2 DM, decreased need for sulfonylurea drugs
- No drug interactions

**Disadvantages:**
- Watch vitamin supplementation
- Side effects decrease over time; decrease with fiber tablets (lubricate fiber/metamucil or calcium carbonate to reduce GI side effects)
Clinical Management of the Obese Patient with Metabolic Syndrome

Pharmacologic
- ACE/ARB
- Statins
- Fish oil, policosanol, etc
- Nutritional therapeutics
- Antiobesity medications (prescriptions/OTC)

Clinical Management of the Metabolic Syndrome

Intensive management of comorbidities
- IFG/IGT/DMT2
- Dyslipidemia
- Pre- and hypertension
- Obesity

Clinical Implications

- Mean weight loss generally modest
- Medications double the number of patients who lose 5-10% of their pre-intervention weight.
- First 4 weeks predicts success
- If not 2 kg weight loss in the first 4 weeks, consider:
  - Titrating medication
  - Change in medication
  - Combination therapies (off label: currently, emerging evidence to support combination therapies)
Clinical Implications

- None of the medications need to be tapered before discontinuing
- Medications can be used for the prevention of weight regain
- Medications can be prescribed for intermittent use

PHENTERMINE (Adipex)

FDA approved since 1972
- Induces feelings of satiety by modulating central norepinephrine and dopamine receptors (increases the availability of anorexigenic neurotransmitters: dopamine, serotonin, norepinephrine)
- By far the most widely prescribed obesity medication in the United States
  - 25.3 million prescriptions dispensed to an estimated 6.2 million users between 2008-2011
- Appetite Suppression
  - Feeling satisfied with less food
  - Less preoccupation with food
  - Greater control of food intake
- FDA Approved for 12 weeks or less
- Expected weight loss: 2 – 10 kg (5%) weight loss
- Schedule IV

Other Advantages:
- once daily, with or without food
- tablets are scored
- low cost (approx. $15.00 - $40.00/month)

Disadvantages:
- Tolerance develops after 2-3 months
- monitor BP
- should have eye exam within one year, avoid with poorly controlled glaucoma
- watch drug interactions
Update on Dyslipidemia: Assessing CHD Risk, Emerging Targets and New Treatments

**Effect of Continuous and Intermittent Phentermine (Adipex) Therapy on Body Weight**


<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Continuous</th>
<th>Alternate</th>
<th>Dummy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-20</td>
<td>-20</td>
<td>-20</td>
</tr>
<tr>
<td>2</td>
<td>-16</td>
<td>-16</td>
<td>-14</td>
</tr>
<tr>
<td>4</td>
<td>-12</td>
<td>-14</td>
<td>-14</td>
</tr>
<tr>
<td>6</td>
<td>-10</td>
<td>-12</td>
<td>-14</td>
</tr>
<tr>
<td>8</td>
<td>-8</td>
<td>-14</td>
<td>-14</td>
</tr>
<tr>
<td>10</td>
<td>-6</td>
<td>-14</td>
<td>-14</td>
</tr>
<tr>
<td>12</td>
<td>-4</td>
<td>-16</td>
<td>-14</td>
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<tr>
<td>14</td>
<td>-2</td>
<td>-18</td>
<td>-16</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>-20</td>
<td>-20</td>
</tr>
</tbody>
</table>

**Topiramate (Topamax)**

Carbonic anhydrase inhibitor anticonvulsant which is thought to suppress appetite, impact satiety, and stimulate thermogenesis.

- **Topiramate (Topamax) effective in the treatment of binge-eating disorder**
Topiramate (Topamax): Clinical Information

- Mechanism for weight loss not well understood
- Appears to affect early satiety, mild anorexic effects and increased basal metabolic rate, reduces binge eating behavior
- Appropriate dose as a single agent not well documented
- Initial dose: 25 mg q hs and titrate by 25 mg q week to 50 mg BID or effects observed
- Major side effects: Sedation, episodic paraesthesias in extremities, taste perversion, cognitive changes at higher doses – word searching, poor concentration
- Generic formulations available but still expensive

Phentermine/Topiramate (Qysmia)

Once daily combination therapy: topiramate and phentermine in extend release formulation

Vivos Pharmaceuticals

Dosage:
- 3.75/23
- 7.5/46
- 15/92
Phentermine/Topiramate (Qysmia): Clinical Information

- Advantage: extend release formulation associated with fewer side effects compared to prescribing each generic component
- Approved for long-term management of obesity
- No titration schedule and once per day dosing is an advantage for adherence
- Cost is a limiting factor: 30 tablets range from $150.00 – 240.00 per month

<table>
<thead>
<tr>
<th>Clinical Trials Approved for Qysmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial name</td>
</tr>
<tr>
<td>EQUIP</td>
</tr>
<tr>
<td>EQUIATE</td>
</tr>
<tr>
<td>CONQUER</td>
</tr>
<tr>
<td>SEQUEL</td>
</tr>
</tbody>
</table>

Weight loss at largest dose 15/92

Common Adverse Events in 1-year Trials of Phentermine/Topiramate (Qysmia)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo N = 1,561</th>
<th>Treatment group N = 1,580</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>2.6 6.7 13.5 19.1</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>6.1 7.9 15.1 16.1</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4.4 5.6 5.6 7.2</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.9 5.0 5.4 5.8</td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0.1 0.2 0.3 0.3</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>5.1 10.4 7.6 10.6</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>1.1 1.3 1.4 1.4</td>
<td></td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>0.6 0.4 2.0 3.5</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4.7 5.0 5.8 9.4</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>3.3 2.8 4.3</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.9 2.9 1.8 4.1</td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>0.7 1.7 2.6 3.7</td>
<td></td>
</tr>
</tbody>
</table>
Lorcaserin (Belviq)

- Eisai Pharmaceuticals
- Lorcaserin, a new selective serotonin 5-HT2C receptor agonist
  - Increases satiety by stimulating parts of the 5-HT 2C serotonin receptor in the hypothalamus and thus affecting appetite and metabolism.
- Similar to fenfluramine (5 HT serotonin 2b receptor) which was associated with damage to the heart valves
- Preferential affinity to 5-HT2C receptors provides lorcaserin the efficacy of previous serotonergic antiobesity treatments without the undesirable safety concerns that led to their withdrawal.2
- Approved at a dose of 10 mg twice daily in patients with a BMI of 30 or 27 kg/m² with at least 1 weight-related comorbidity, such as hypertension, type 2 diabetes, or dyslipidemia

Drugs With US Food and Drug Administration–Approved Indication for Obesity

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Placebo</th>
<th>Intervention</th>
<th>Placebo</th>
<th>Intervention</th>
<th>Placebo</th>
<th>Intervention</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorcaserin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith et al. 2010</td>
<td>-5.8</td>
<td>-2.2</td>
<td>-4.8</td>
<td>-2.2</td>
<td>41.5</td>
<td>20.3</td>
<td>32.6</td>
</tr>
<tr>
<td>O'Neil et al. 2012</td>
<td>-5.0</td>
<td>-2.9</td>
<td>-5.8</td>
<td>-2.8</td>
<td>40.2</td>
<td>47.2</td>
<td>25.0</td>
</tr>
<tr>
<td>Fidler et al. 2011</td>
<td>-4.7</td>
<td>-2.8</td>
<td>-4.7</td>
<td>-2.8</td>
<td>40.2</td>
<td>47.2</td>
<td>22.6</td>
</tr>
</tbody>
</table>

Long-term Drug Treatment for Obesity
Yanovski, Yanovski, JAMA 2013

Lorcaserin (Belviq): Clinical Information

- Approved for long-term management of obesity
- Twice daily dosing (10 mg tablets)
- CV effects still under review
- Cost: 60 tablets $125.00 to 200.00 per month
**Bupropion (Wellbutrin)**

- A norepinephrine and dopamine reuptake inhibitor
- Research supports monotherapy for as long as 1 year as a weight loss medication
- A pooled analysis of 3 studies ranging from 6 to 12 months showed additional weight loss relative to placebo of 2.8 kg in patients receiving 400 mg per day of bupropion, with total weight loss of 4.4 kg

![Effect on body weight of bupropion in a randomized, placebo-controlled clinical trial. Adapted from Anderson et al. (2002)](image)

**Zonisamide (Zonegran)**

- **Zonisamide in the treatment of binge eating disorder with obesity: a randomized controlled trial.**

- **Zonisamide for weight loss in obese adults: a randomized controlled trial.**
  - Gadde et al., *J Fam Pract* 2003, 52 (8): 600-1
**Update on Dyslipidemia: Assessing CHD Risk, Emerging Targets and New Treatments**

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**Zonisamide (Zonegran)**

![Graph showing weight loss over weeks](image)


---

**Combination: Empatic (Bupropion/Zonisamide)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent with 8% Weight loss</th>
<th>Percent with 10% weight loss</th>
<th>Weight loss (kg)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empatic 360</td>
<td>82.5</td>
<td>47.7</td>
<td>9.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bupropion 360</td>
<td>2.3</td>
<td></td>
<td>2.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Zonisamide 360</td>
<td></td>
<td>5.3</td>
<td>5.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>placebo</td>
<td>18.9</td>
<td>5.7</td>
<td>1.7</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

24-week, double-blind, randomized trial evaluated 729 patients and incorporated a typical diet and exercise regimen. Patients enrolled in this trial had a body mass index (BMI) of 30 to 45, or as low as 27 in the presence of hypertension or dyslipidemia.

---

**Combination: Empatic (Bupropion/Zonisamide)**

- Empatic patients experienced significant weight loss as early as their first post-baseline visit at week four
- Empatic patients continued to lose weight through the end of the trial period, with no evidence of a weight loss plateau
- Improvements were observed in key markers of cardiometabolic risk such as waist circumference, triglycerides, fasting insulin and blood pressure
Contrave (Bupropion/Naltrexone)

- During phase 2 testing different dosages were used in a once daily formula these include:
  - 16 mg naltrexone *IR - 400 mg bupropion *SR
  - 32 mg naltrexone *IR - 400 mg bupropion *SR
  - 48 mg naltrexone *IR - 400 mg bupropion *SR
- 32 mg naltrexone *SR / 400 mg bupropion *SR: on average showed the best benefit to risk ratio thus making it the preferred dose.
- More tolerable in SR formulation
- Contrave works in the brain or hypothalamus where the control center for one's appetite
- On average, the participants lost between 9% to 15% of their body weight

SUMMARY

- Pharmacotherapy may be indicated in patients with BMI >30, or > 27 with comorbidities
- Phentermine, an appetite suppressant is presently the most frequently used anti-obesity drugs
- New drugs under investigation have been targeted at the gut-brain fat tissue interaction that regulate appetite and energy metabolism in humans
- Combination therapies represent the trend in obesity management for patients with and without metabolic complications and moves toward a personalized approach
- Weight Gain is among side effects listed in official information sheets for some of the most frequently prescribed drugs in the United States

Questions?