

Obesity Epidemic

Just how bad is it?
What can be done?

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Disclosures

- Consultant: Orexigen, Novonordisk, Zafgen, NPS, Eisai, Pathway Genomics, and Isis
- Research: Orexigen, Novonordisk, Enteromedics, NPS, Eisai, and Weight Watchers
- Speaker: NPS, AbbVie, Eisai, and Merck, Vivus

Obesity: Definition

- Obesity is now defined as “Chronic Disease”
 - American Medical Society 2013
- Associated with:
 - Ischemic heart disease and stroke
 - Diabetes and chronic kidney disease
 - Cancer
 - (liver, kidney, breast, endometrial, prostate, and colon)
 - Respiratory diseases
 - And a whole lot more
- Leading to increased mortality and morbidity
 - A shorter life span and a lot of medical problems

Prevalence

- Currently Americans and Californians
 - One in three American are obese
 - Approximately 30% to 35% are obese
 - Two in three Americans are obese or overweight
 - Approximately 60% to 67% are obese or overweight

Predicted Rates of Obesity 2015

- 75% of all Americans will be overweight or obese
 - California will be at this level
- 41% will be Obese
 - California may actually be above this
 - Due to high Asian and Hispanic populations
 - Hispanic 38.2%
 - Asian 13.9%
 - Caucasian 39.4%

Prevalence

- 78% of Mexican American women are overweight or obese
 - 60.3% non-Hispanic White women
- 81.3% Mexican American men are overweight or obese
 - 73.6% non-Hispanic White men
- 13.2% of Hispanics/Latino adults have diabetes
 - Compared to 7.6% of non-Hispanic White adults

Source: CDC 2012. Health United States, 2011. Table 74
<http://www.cdc.gov/nchs/data/hus/hus11.pdf>

(Source: CDC 2012. Summary Health Statistics for U.S. Adults: 2010.
Table8. http://www.cdc.gov/nchs/data/series/sr_10/sr10_252.pdf)

Asian Population

- See more medical problems at lower levels of weight gain
- Example:
 - Ideal weight for a male 5'9" is 140 to 155
 - American male height of 5'9" a weight of 195 pounds is obese
 - Japanese male height of 5'9" a weight of 165 pounds is obese
 - 2013 Japan society for the study of obesity

Medical Costs of Obesity:

- Average annual cost associated with the obese patient is \$656 higher than a normal weight patient
 - Old models just associated costs with weight
- Adjusting for diseases associated with obesity and reporting bias the cost may be closer to \$2741 annually
 - Diabetes is one of the main driving costs

What Can Be Done About This Obesity Epidemic?

- Lose weight
 - How much weight ?
- Maintain a lower weight
 - Prevention
 - Don't let the children get heavy
 - Obese children become obese adults
 - Very limited options for weight loss in Children
 - Diet and exercise
 - Bariatric surgery

It Only Takes Weight Loss of 5% to 10% to Get Great Benefit

- If BMIs were lowered by 5 percent (10 to 15 pounds), California could save 7.6 percent in health care costs, which would equate to savings of \$ 81,702,000,000 by 2030
- The number of California residents who could be spared from developing new cases of major obesity-related diseases includes:
 - 796,430 fewer people would get type 2 diabetes,
 - 656,970 fewer patients with coronary heart disease and strokes
 - 698,431 fewer patients with hypertension,
 - 387,850 fewer patients from arthritis
 - 52,769 fewer patients getting obesity-related cancers

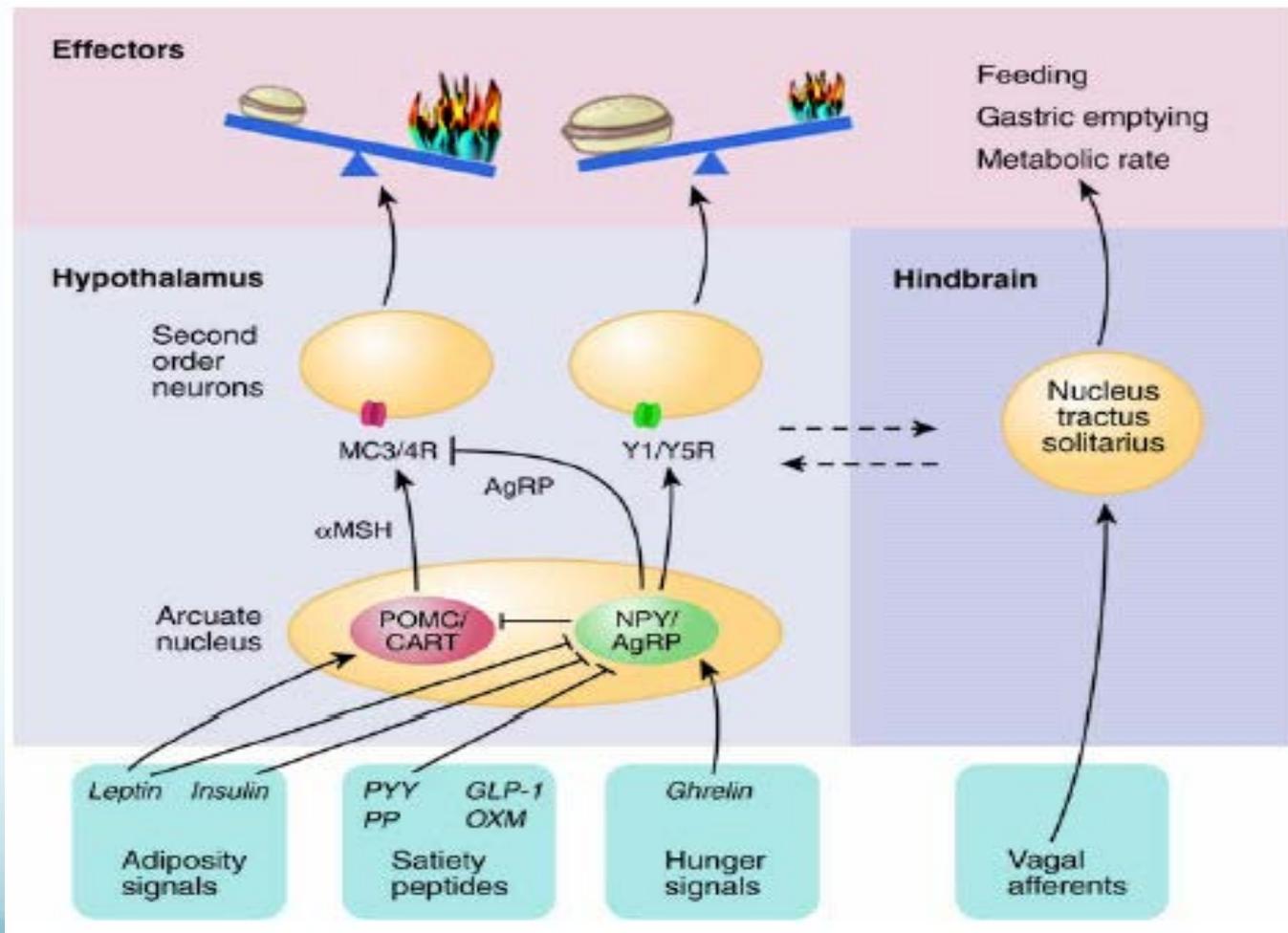
Barriers to Treating the Overweight Patient

- Lack of education
 - Physician level, health care givers and patients
- A lot of wrong information
 - Beliefs and misconceptions
 - Both doctors and patients
- Lack of treatment options
 - This is changing dramatically
- Americans live in an environment that promotes weight gain
 - Food availability and type of food available
 - Inability to burn calories (walking, biking etc.)

How Do Humans Regulate their Weight and Food Intake

- Humans are wired to eat all the time
- The way we control food intake is to release hormones and send nerve signals up to the brain to stop eating (after a meal)
- Superimposed on this system is a learned system to respond to various cues to eat when food available
 - Example: if you eat lunch at noon then at 11:30 you will begin to increase the hormone ghrelin that will drive you to eat

Actions of Peripheral Hormones on the Hypothalamus



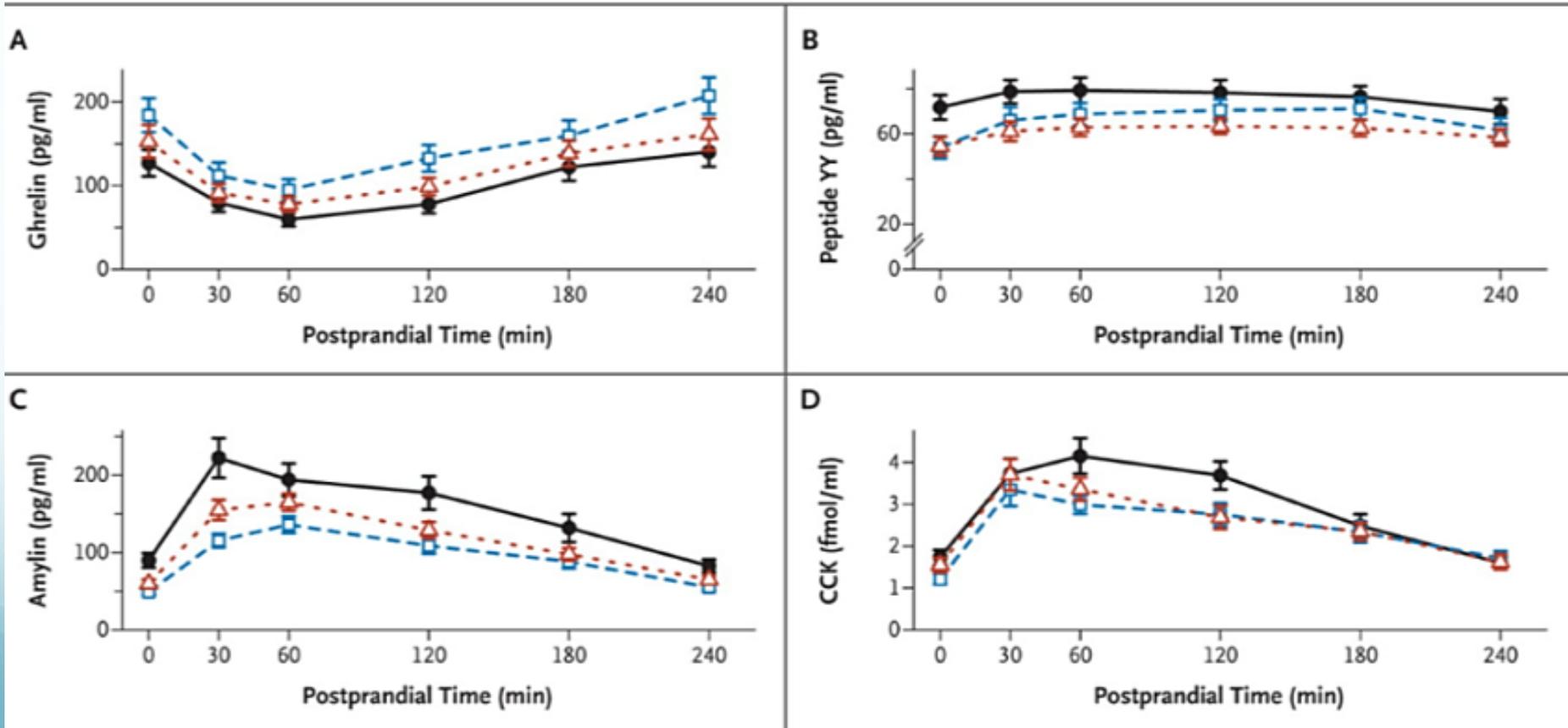
Why is Weight Loss So Difficult? You are Fighting Biology

- Patient X has gained 40 pounds and is now 200 pounds
- Patient X goes on a diet and loses 20 pounds (10% weight loss)
- The Human body will try to re-gain that 20 pounds.
 - Lower metabolism more than 10%
 - Change hormones to increase appetite

Fasting/Postprandial Hormone Levels

Mean (\pm SE) Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and CCK at Baseline, 10 Weeks, 62 Weeks

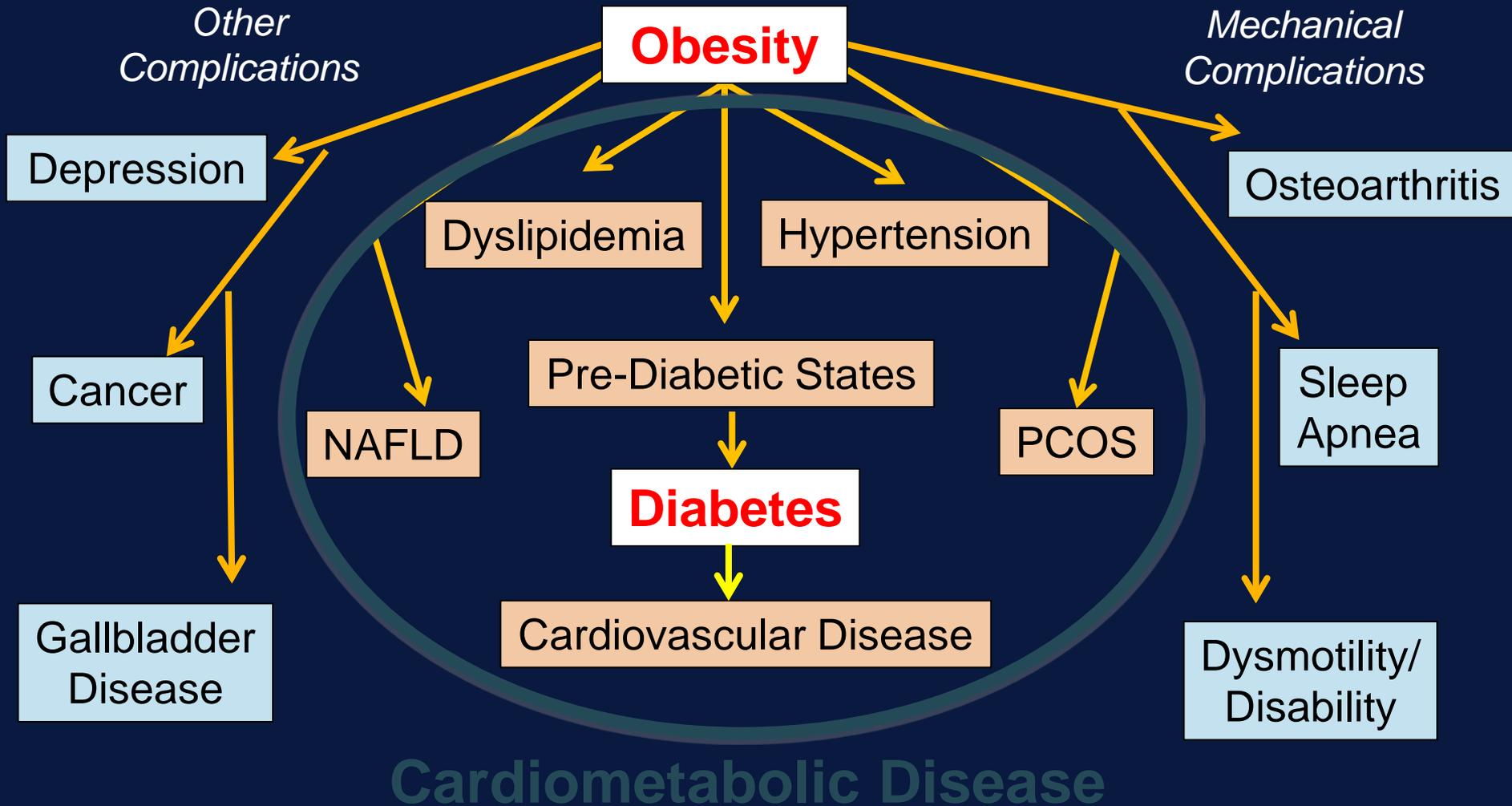
—●— Baseline -□- Week 10 -△- Week 62



Approaches for Staging Cardiometabolic Disease Risk in Obesity

- Clinically identifiable Risk States
 - Prediabetes¹
 - Metabolic Syndrome²
- Indices
 - Framingham Risk Score³
 - Reynolds Risk Score⁴
 - ADA Diabetes Risk Score⁵
- Commercial Diagnostic Products
 - PreDX (Tethys Bioscience)⁶
 - LP-IR score (Liposcience)⁷
- Clinical Staging Paradigms
 - Edmonton Obesity Staging System (EOSS)⁸
 - Cardiometabolic Disease Staging (CMDSt)⁹

Medical Complications of Obesity



Cardiometabolic Disease

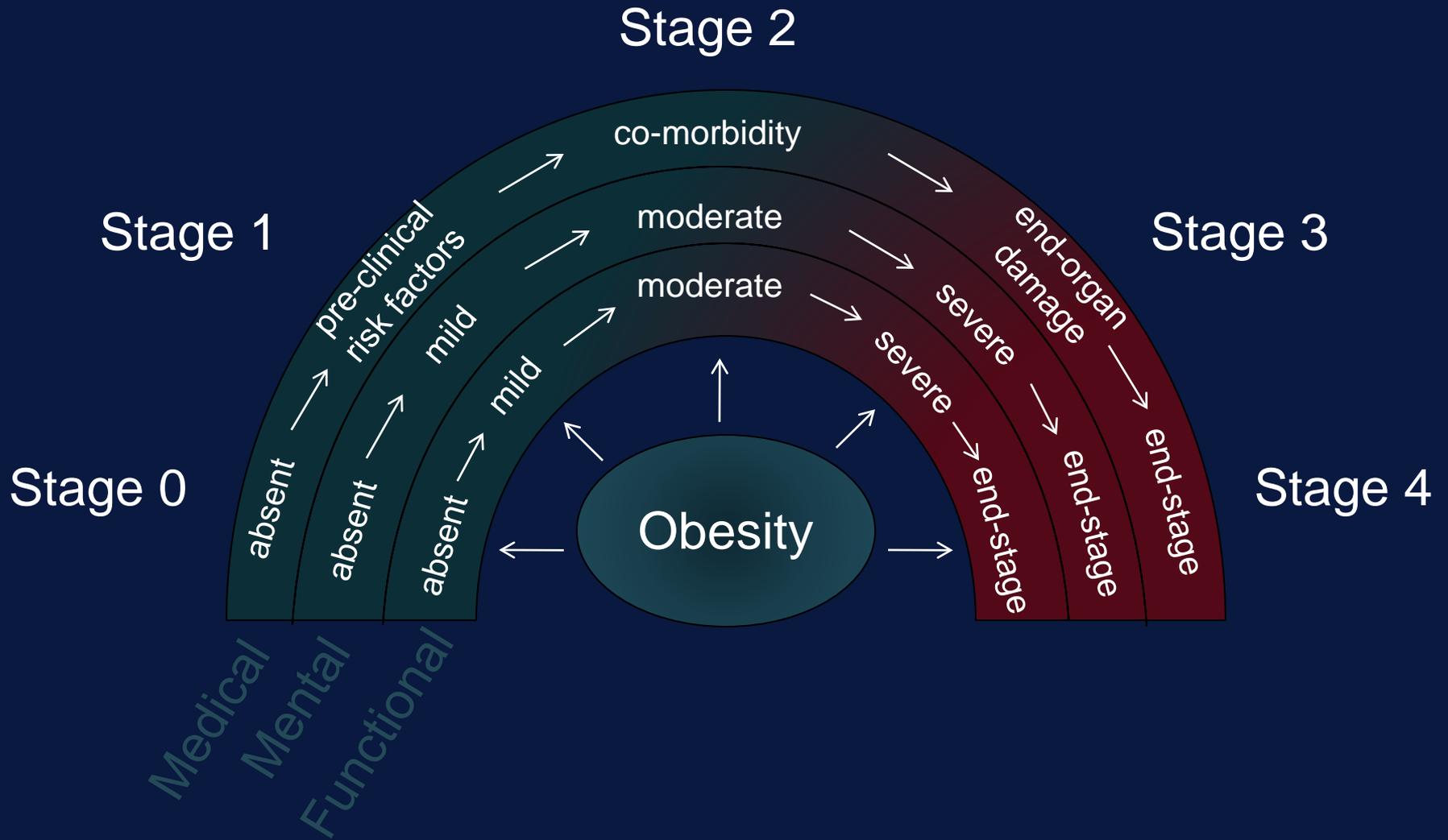
Courtesy of WT Garvey, 2011. NAFLD = nonalcoholic fatty liver disease; PCOS = polycystic ovary syndrome

Adapted from Pi-Sunyer X. *Postgrad Med.* 2009 Nov;121(6):21-33.

Edmonton Obesity Staging System (EOSS)

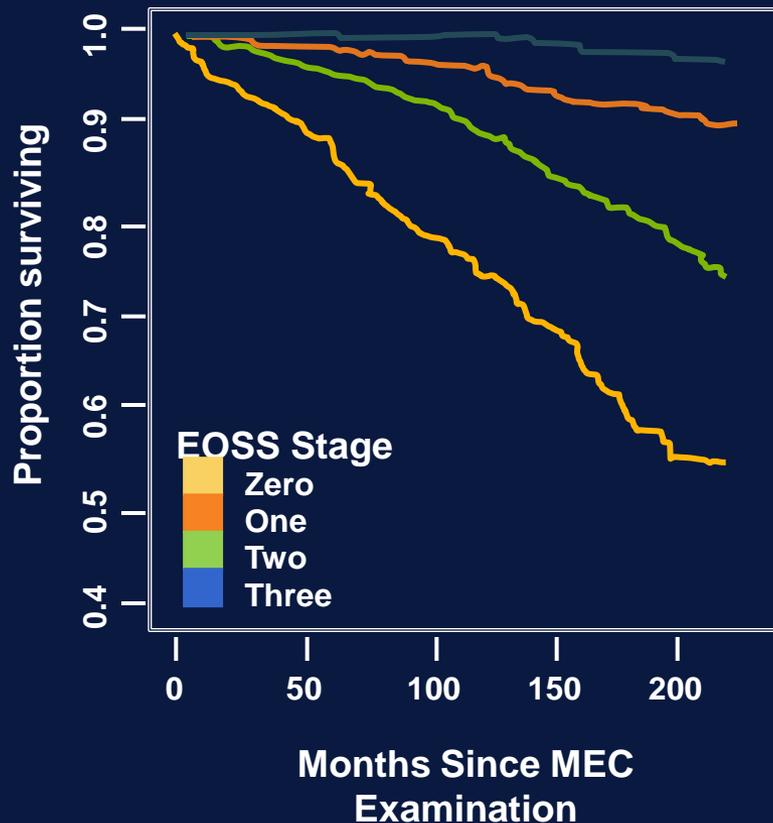
Stage	Cardiometabolic	Mechanical/Functional
0	No Risk Factors	No functional impairments or impairments in well-being
1	Sub-clinical Risk Factors: Prediabetes, metabolic syndrome, NAFLD	Mild limitations and impairment of well-being
2	End-Stage Metabolic Disease: T2DM, hypertension, sleep apnea	Moderate limitations and impairment of well-being
3	End-Stage CVD Disease: MI, heart failure, stroke	Significant limitations and impairment of well-being
4	End-Stage Disabilities	Severe limitations and impairment of well-being

Edmonton Obesity Staging System (EOSS)

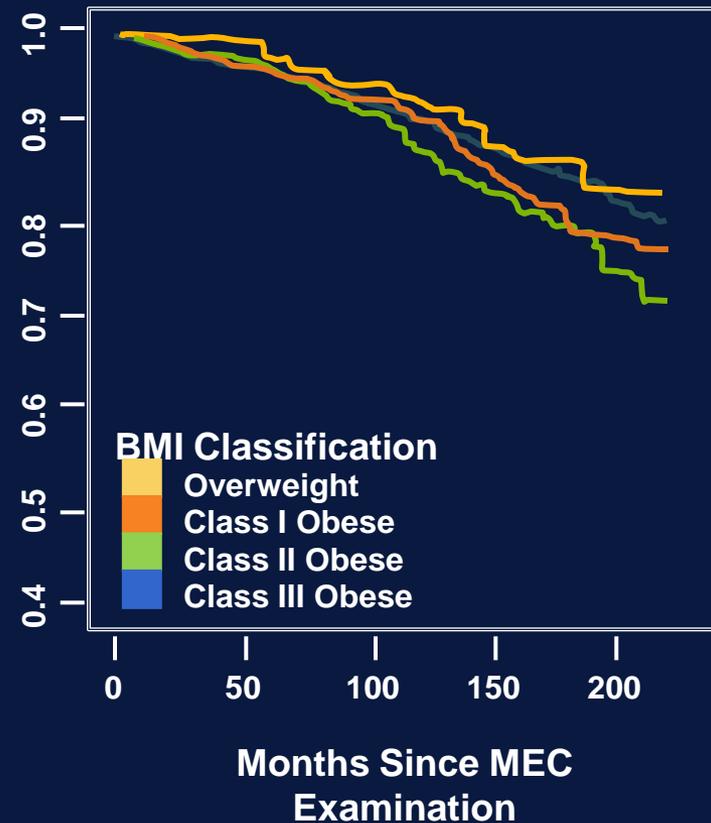


EOSS Predicts Mortality in NHANES III

NHANES III (1988-1994)



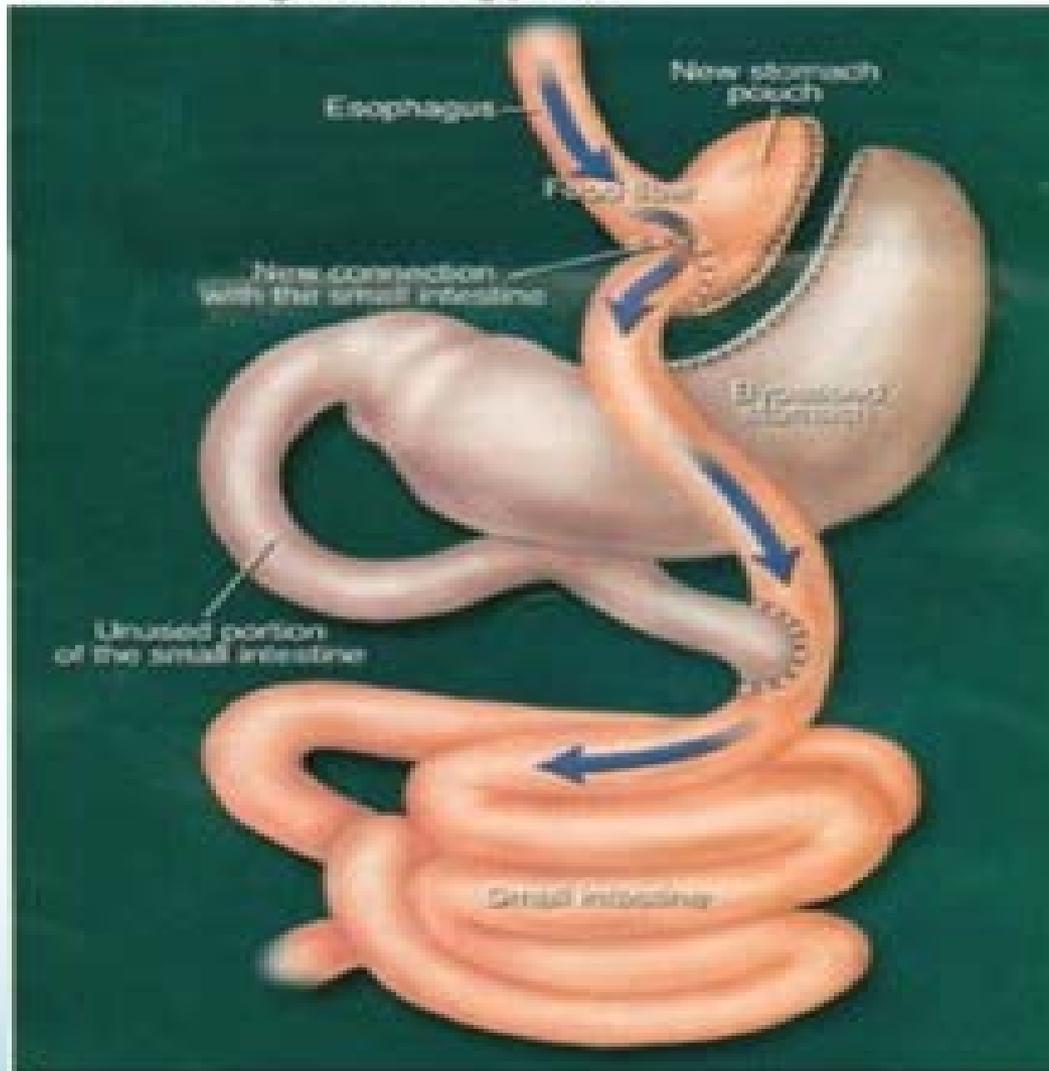
NHANES III (1988-1994)



Treatment Options:

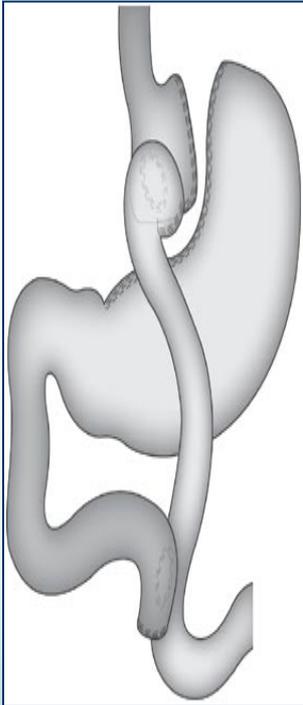
- Diet and Exercise (behavior modification)
 - 5 % weight loss
- Medications with Diet and Exercise
 - 5% to 10% weight loss
- Bariatric Surgery for Morbid obesity
 - 10% to 35% weight loss
 - This applies to about 7% of the population
 - For the right patient it has been shown to have tremendous benefit (diabetic patient)

Roux-en-Y gastric bypass

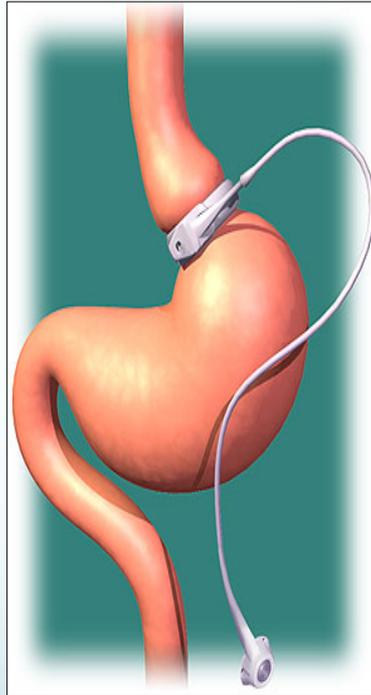


Current Surgical Options

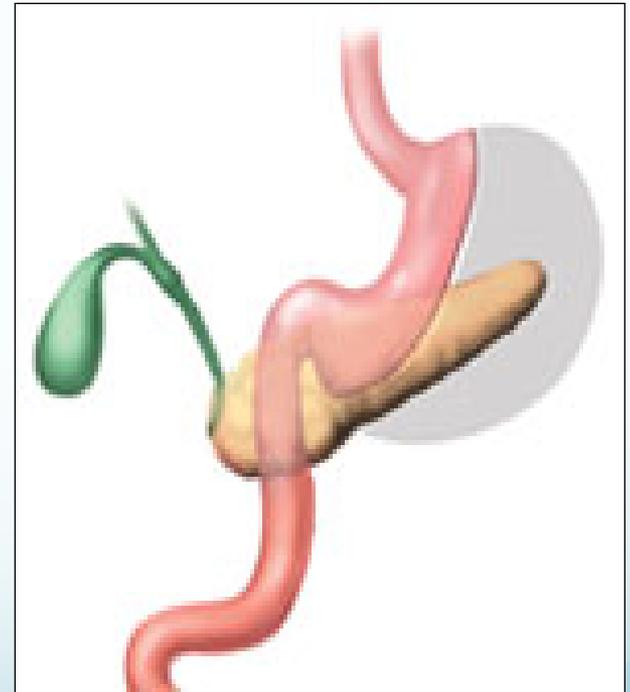
**Laparoscopic
Gastric Bypass**



**Laparoscopic
Gastric Band**



**Laparoscopic
Sleeve
Gastrectomy**



Bariatric Surgery Works

- Up to 80 percent of diabetics have dramatic improvement in their diabetes
- The Sleeve gastrectomy and the gastric bypass both change the hormones that control weight
 - Resulting in improved weight loss
 - Better long term weight loss
 - The gastric band has no effect on the hormones that control weight
 - Currently see more
 - Gastric bypass and Sleeve gastrectomy

Bariatric Surgery: Is it Worth it?

- Health care costs of bariatric surgery
 - Bariatric Surgery \$15,000 to \$28,000
 - Decrease in the number of chronic medications after bariatric surgery
 - Increased use of hospital resources after surgery
- Various studies looked at costs of care over 6 to 20 years and could not demonstrate a cost benefit for weight loss surgery
- Bariatric surgery did benefit **Some** patients
 - Diabetics
 - Osteoarthritis

Medications

- Up to 2012 physicians and other health care givers had one or two medications to use for weight loss
- In 2012 two medications approved
 - Last time we had a medication approved for weight loss was in late 1990s
- 2013 to 2014 expect to see two more medications approved
- This is an area of obesity medicine with the biggest changes

Older Medication Treatment Options

- Phentermine
 - Approved for Short term use (12 weeks)
 - \$15 monthly
 - Stimulant with known effects
 - Increase in heart rate
 - Increase in blood pressure
 - In California the most missed used weight loss medication
 - Physicians can sell this out of their office
 - The usual dose is above the FDA recommended dose

Orlistat

- Alli (over the counter) or Xenical (Rx)
 - Blocks the absorption of fat in humans
 - Very minimal amount is absorbed into the blood stream
 - Stays in the Gastrointestinal tract
 - Gastrointestinal side effects
 - Oil leakage, passing gas with a surprise etc.
 - Not a whole lot of weight loss in clinical practice

New Medications

- Phentermine with Topiramate ER
 - Combination of two older medications
- Lorcaserin
 - New medication that works on satiety
- Potential Future weight loss medications
 - Bupropion/naltrexone
 - Liraglutide

Phentermine/Topiramate ER Approved 2012

- Combination of two older medications
- Phentermine –
 - Reduces appetite by stimulation of various regions of the hypothalamus to release norepinephrine
- Topiramate – unknown
 - Suppresses appetite and promotes satiety
- Schedule IV and Category X

ER = extended release; QOD = every other day,.

Bays HE, Gadde KM. *Drugs Today*. 2011;47:903-914; Bays HE. *Expert Rev Cardiovasc Ther*. 2010 8;12:1777-1801; Qsymia [prescribing Information]. Mountain View, CA: Vivus, Inc.; 2012.

Risk Evaluation and Mitigation Strategies (REMS) for Phentermine/Topiramate ER

- Purpose of the REMS
 - To counsel patients that have the potential to get pregnant
 - Recommended to get pregnancy test before and monthly while on phentermine/topiramate ER
 - Topiramate associated with oral cleft lip or palate
 - Thus this drug is only available through “Certified Pharmacies”
 - Vivus.com accessed May 16, 2013

How will Phentermine /Topiramate ER be used ?

- The obese patient with morbid obesity or with multiple medical problems
 - High risk patient
- Very good weight loss: over 80% of patients will achieve 5% or better weight loss
- Higher side effect profile
- REMS program: Use with caution in women who can get pregnant

Lorcaserin Approved 2012

- Serotonin 5HT_{2c} receptor agonist
- Works primarily on satiety
 - Fullness after a meal
- Very selective for the 2c receptor
 - Did echocardiograms to show no significant effect on 2b receptors on the heart valves
 - 2.4% Lorcaserin vs. 2.0% for placebo

Lorcaserin

- Dose: 10 mg BID
- Very low side effect profile
 - 8.6% for Lorcaserin vs. 6.7% placebo prematurely discontinued due to adverse events
- 47% of patients that start Lorcaserin will lose 5% or more of their weight
 - If they do not lose 5% of their weight at 3 months stop the medication (they are a non-responder)

Lorcaserin: How Will it Be Used

- Well studied in the average female who is overweight or obese that needs to lose weight.
- Had a particularly good effect in overweight and obese diabetics.
- Due to the fact that it has no stimulant properties should be good in the cardiac patient, insomniacs, and anxious patients.
 - (The drug will probably need to be studied in a large scale cardiac study in the future)

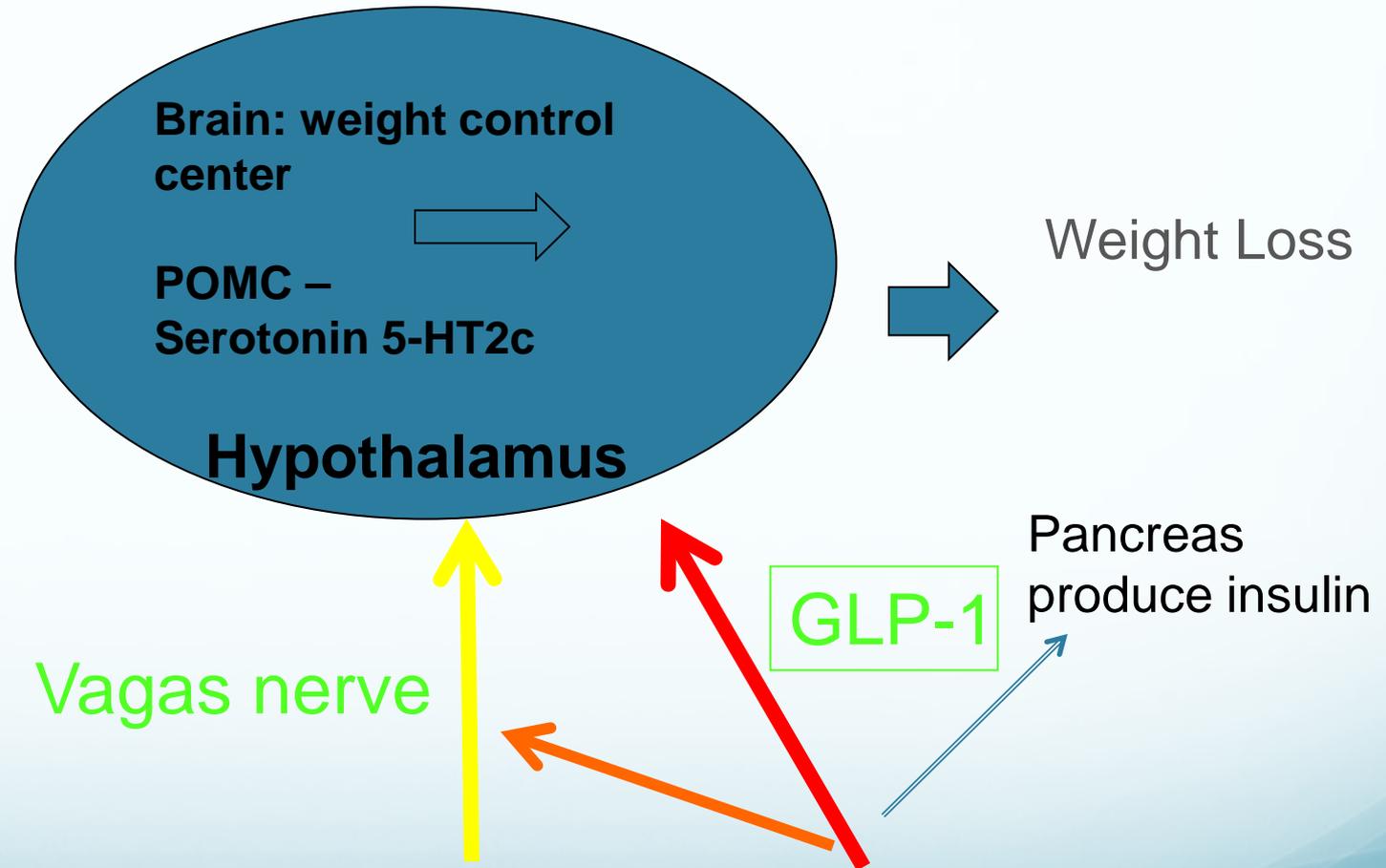
Bupropion SR and Naltrexone ER Combination Medication

- Bupropion: approved for depression and smoking cessation
 - Appears to decrease the “reward system” that various foods can induce
- Naltrexone – pure opioid antagonist
 - An opioid pathway is known that tries to stop or slow weight loss – naltrexone blocks this pathway
- Undergoing review for CV safety; resubmission to FDA planned later in 2013/2014

MOA = mechanism of action.

Padwal R. *Curr Opin Investig Drugs*. 2009;10:1117-1125.

GLP-1 Hormones



Intestines, Liver, Pancreas and the rest of the body sending up signals to stop eating (hormonal and neurologic)

GLP-1 Liraglutide for Diabetes

- Long-acting analog of glucagon-like-peptide-1 (GLP-1)
 - Secreted by intestinal cells in response to food
 - Satiety Hormone: Decreases food intake by activating GLP-1 receptors in the brain and vagal afferent nerves
- Approved dosage for diabetes: 1.8 mg/d SC
- Dose used in obesity trials: 3.0 mg
- Not yet approved as stand-alone drug for obesity

Sugar Sweetened Beverages

- Sugar sweetened beverages
 - Drinks that contain sucrose (table sugar)
 - High fructose corn syrup
 - Fruit-juice concentrate
 - All have the same metabolic effects
- This does not include
 - Non-calorie sweetened drinks (example diet sodas)
 - Bottle water

Sugar Sweetened Beverages

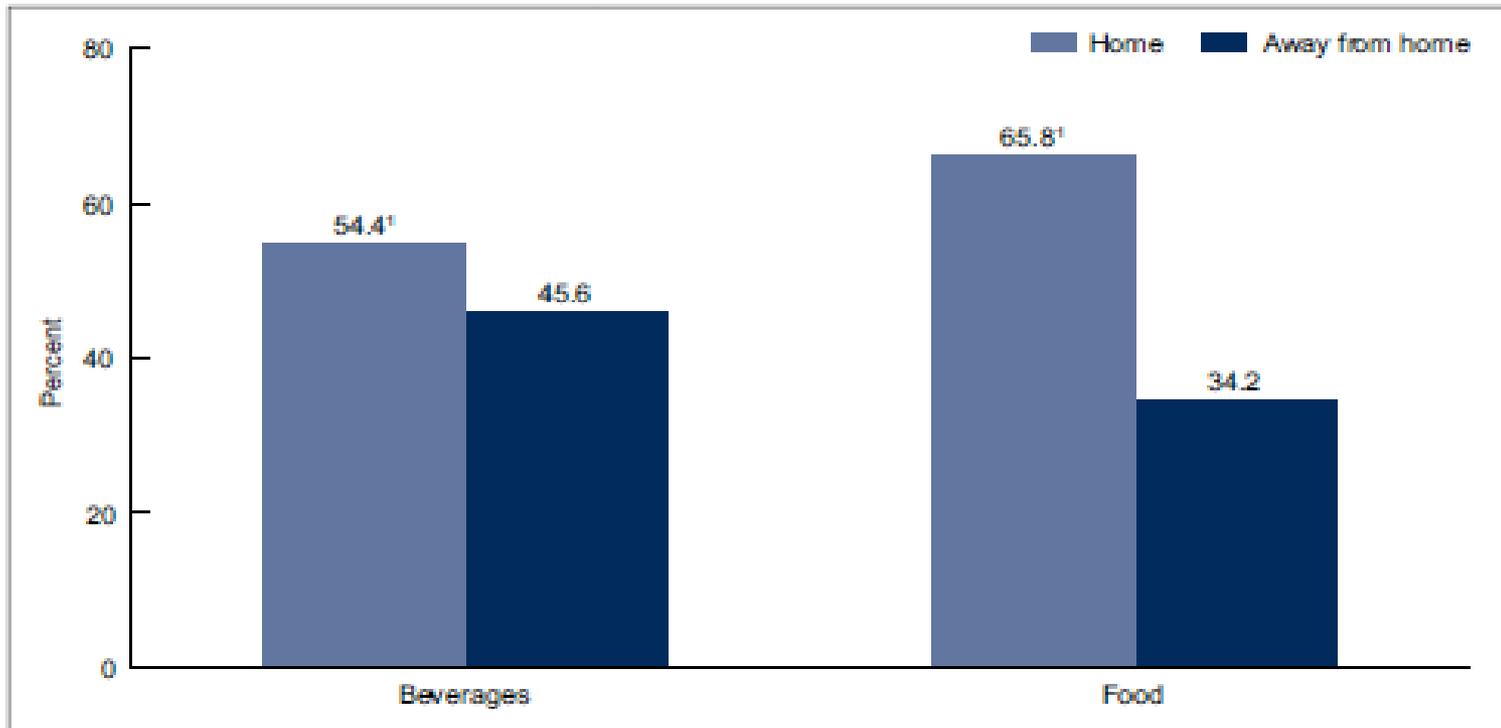
- Associated with
 - Increased weight (very strong evidence)
 - Risk of Coronary artery disease
 - Diabetes
- NEJM Health Policy Report The public health and economic benefits of Taxing Sugar-sweetened beverages KD Brownell 2009

Where Added Sugars Come From

What Types of Foods?

NCHS Data Brief ■ No. 87 ■ March 2012

Figure 5. Percentage of kilocalories from added sugars among children and adolescents aged 2–19 years, by type of food and location food was consumed: United States, 2005–2008



*Significantly different from kilocalories from added sugars consumed away from home, $p < 0.05$.
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2005–2008.

Replacing Caloric Beverages for Weight loss (Choice Study)

- Recruited 318 persons that regularly consumed sugar sweetened drinks
- Patients enrolled in a 6 month weight loss program
 - Group WA: switch sugar drinks to water
 - Group DB: switch sugar drinks to diet beverage
 - Group AC: control group no switch just regular weight loss program

Replacing Caloric Beverages for Weight loss (Choice)

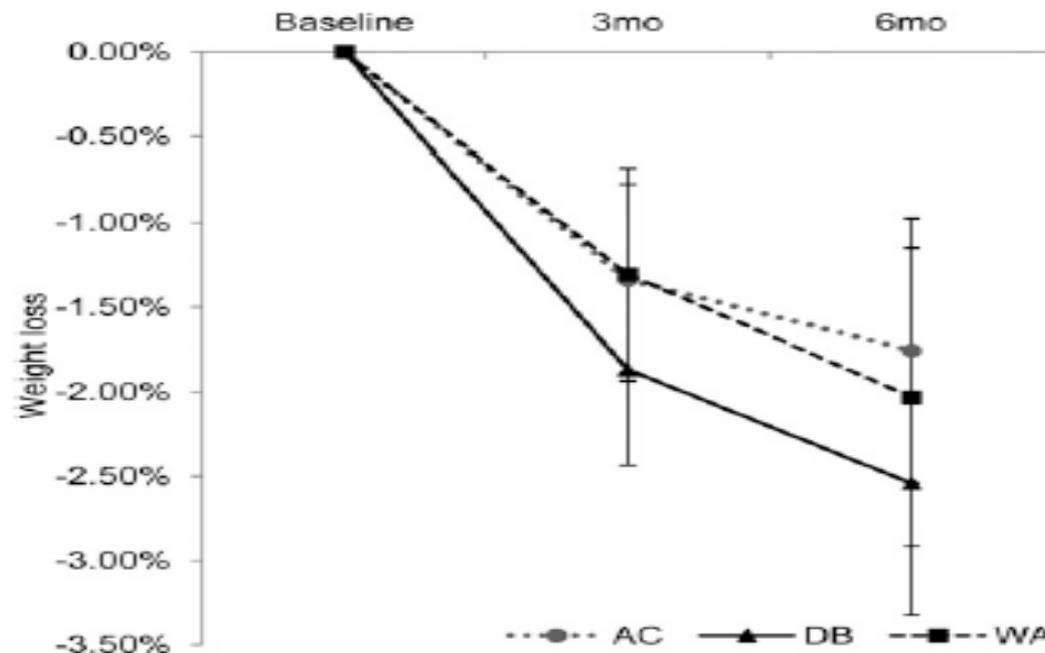
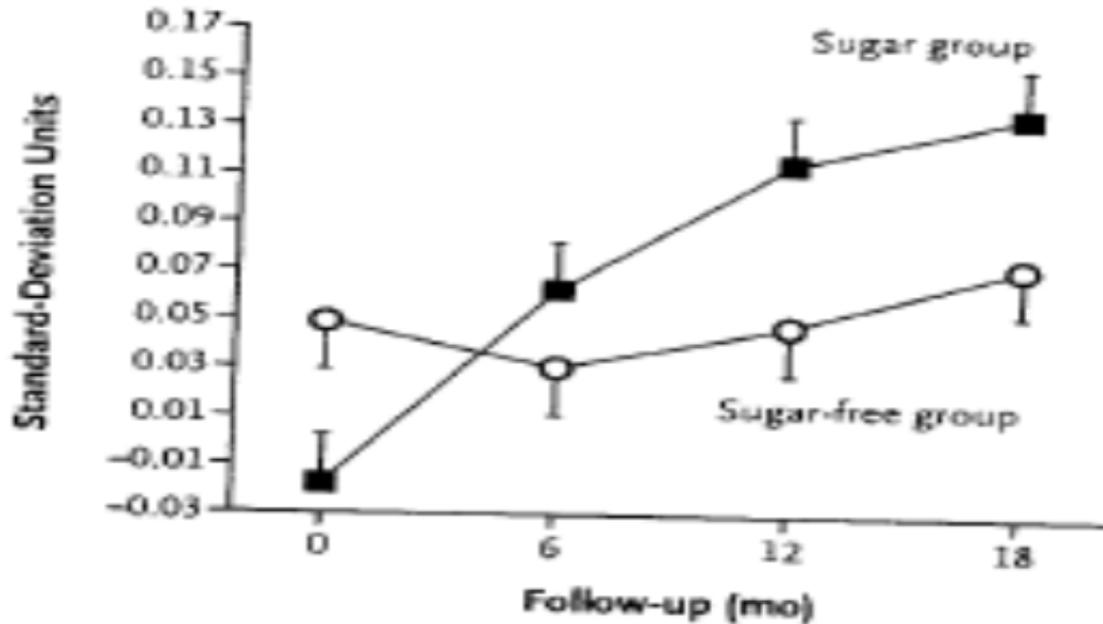


FIGURE 3. Means (95% CIs) estimated by using an intention-to-treat analysis with multiple imputation. A repeated-measures mixed model was used to examine time, group, and treatment \times time interaction at each time point. A significant effect of time was observed for the DB ($n = 105$), WA ($n = 108$), and AC ($n = 105$) groups at 0–3 mo ($P < 0.001$) and 0–6 mo ($P < 0.001$). There were no significant treatment \times time interactions between the WA and AC groups or between the DB and AC groups at any time. AC, attention control; DB, diet beverage; WA, water.

NEJM Sept 18th 2012

A Trial of Sugar-free or sugar-sweetened beverages and body weight in Children JC de Ruyter, MR Olthof, JC Seidell, and MB Katan

A BMI z Score as a Function of Time



Activity and Exercise

- Exercise is probably the best indicator of who keeps the weight off
- The best exercise is felt to be a combination of
 - Aerobic
 - Resistance training
- Time needed to exercise per week can vary but is around 3 to 5 hours per week
- Yes: exercise can increase the desire to eat (appetite) but most humans still burn more calories than consumed with the increased appetite

Moderate to Vigorous Activity in Children Ages 9 to 15

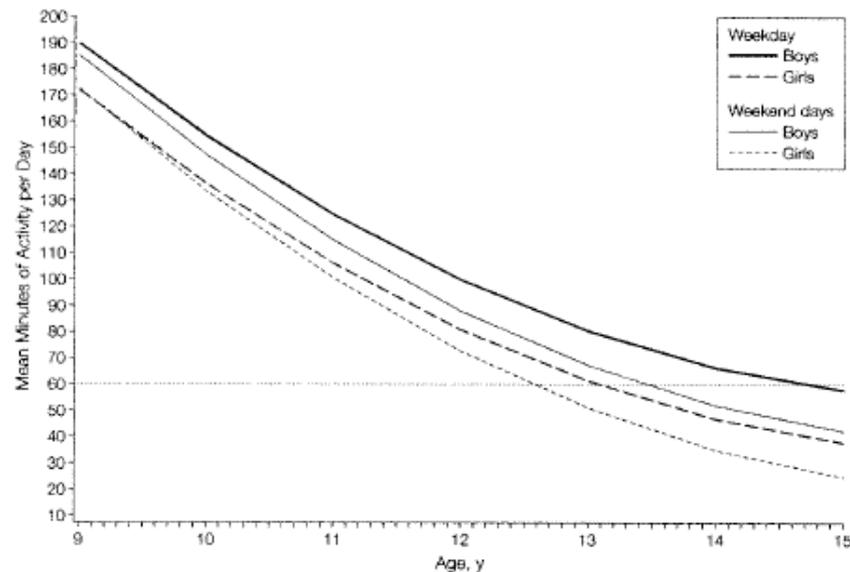
MODERATE-TO-VIGOROUS PHYSICAL ACTIVITY IN CHILDREN AGED 9 TO 15 YEARS

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Figure 3. Average Weekday and Weekend Minutes of MVPA by Sex



MVPA indicates moderate-to-vigorous physical activity. Dotted horizontal line indicates the recommended 60 minutes per day of MVPA for children.¹⁰ Graphs were generated from estimates obtained from growth curve model 2, which included intercepts, age, sex, age \times sex, and age \times age to describe change in MVPA on weekdays and weekends between ages 9 and 15 years. Girls cross below the recommended 60 minutes of MVPA per day at approximately 13.1 years (95% CI, 12.9-13.3) for weekday activity and 12.6 years (95% CI, 12.3-12.8) for weekend activity; boys cross below the recommended 60 minutes of MVPA per day at approximately 14.7 years (95% CI, 14.3-15.3) for weekday activity and 13.4 years (95% CI, 13.2-13.7) for weekend activity.

My Policy Wish List

- Strongly consider regulation of sugary drinks (Soda, juice etc.)
 - Please do not include diet sodas or non-calorie drinks in this regulation
- Keep kids active especially as they age
 - Biggest drop off in physical activity is in middle school and High School
 - Particularly for the non-athletes
 - Particularly Girls

My Policy Wish List

- There is a strong need to educate health care givers and in particular physicians
 - Start in the state medical schools
 - Make it mandatory CME (continuing medical education)
- View Obesity as a chronic disease
 - Public education about discrimination of the over weight patient (over weight minority female)
 - Like any chronic disease it will need a long term chronic treatments available
 - Weight loss medications have arrived
 - Safer – the testing of the newer medications is high level
 - REMS (risk evaluation management strategy)

Reimbursement for Weight Loss Medications and Bariatric Surgery

- Bariatric Surgery:
 - Still the best treatment option for the morbidly obese
 - Has significant risks and should reserved for morbidly obese patients with
 - Diabetes
 - Osteoarthritis
 - Other appropriately selected cases
- Medications
 - Very useful in the obese patient with medical problems or significant risk factors
 - Example: Diabetics or Pre-diabetics