

The Skinny on Obesity

Current Medical Management of Obesity

Susan Reeds MD, FACP

Assistant Professor of Medicine

Geriatrics and Nutritional Science/ Weight Management

Washington University in St. Louis School of Medicine

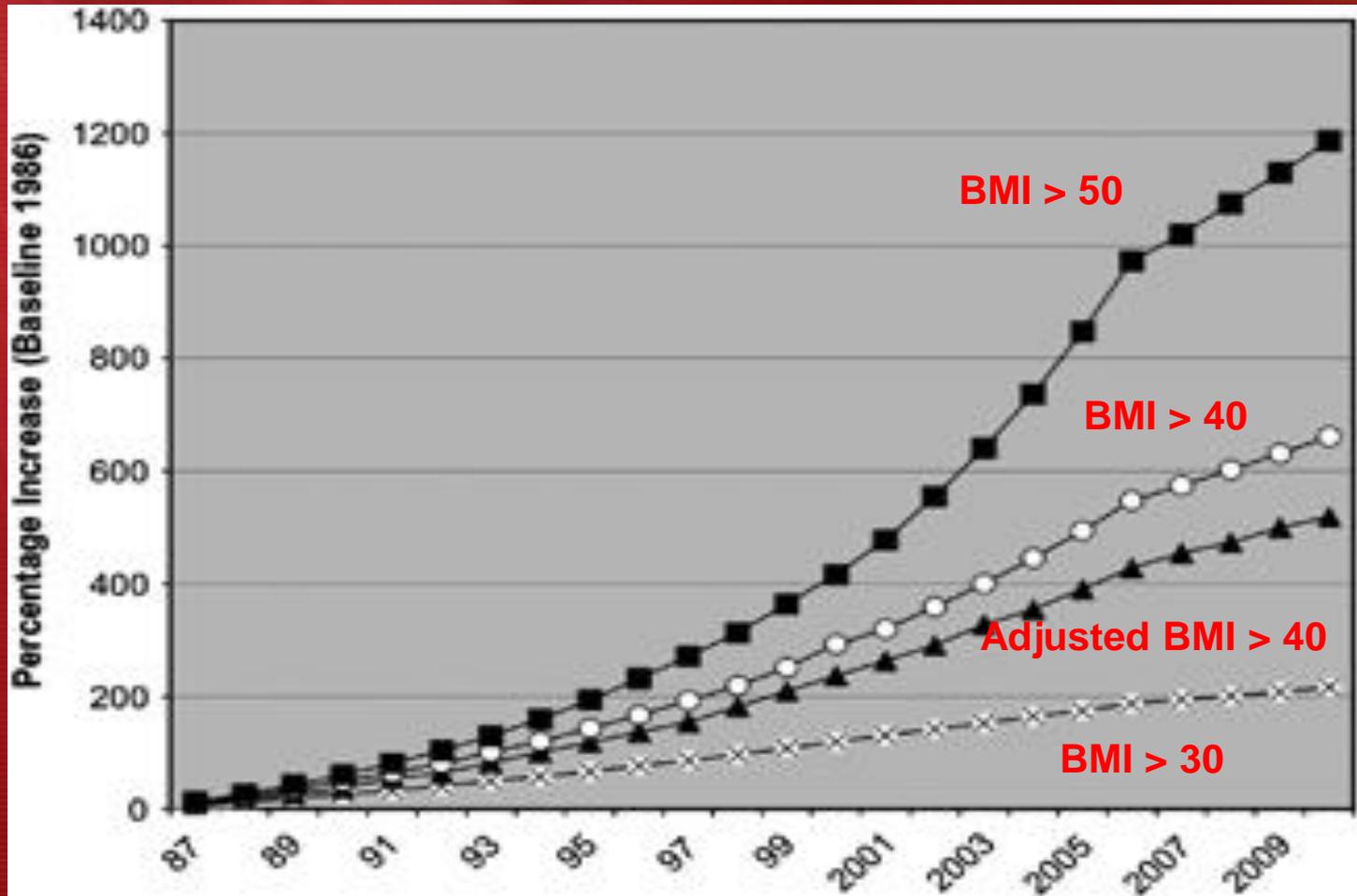
Objectives

- Review the current prevalence of obesity in the US
- Understand the effects of obesity on morbidity and mortality
- Be able to identify individuals requiring treatment for obesity
- Understand the currently available medical treatment strategies for obesity

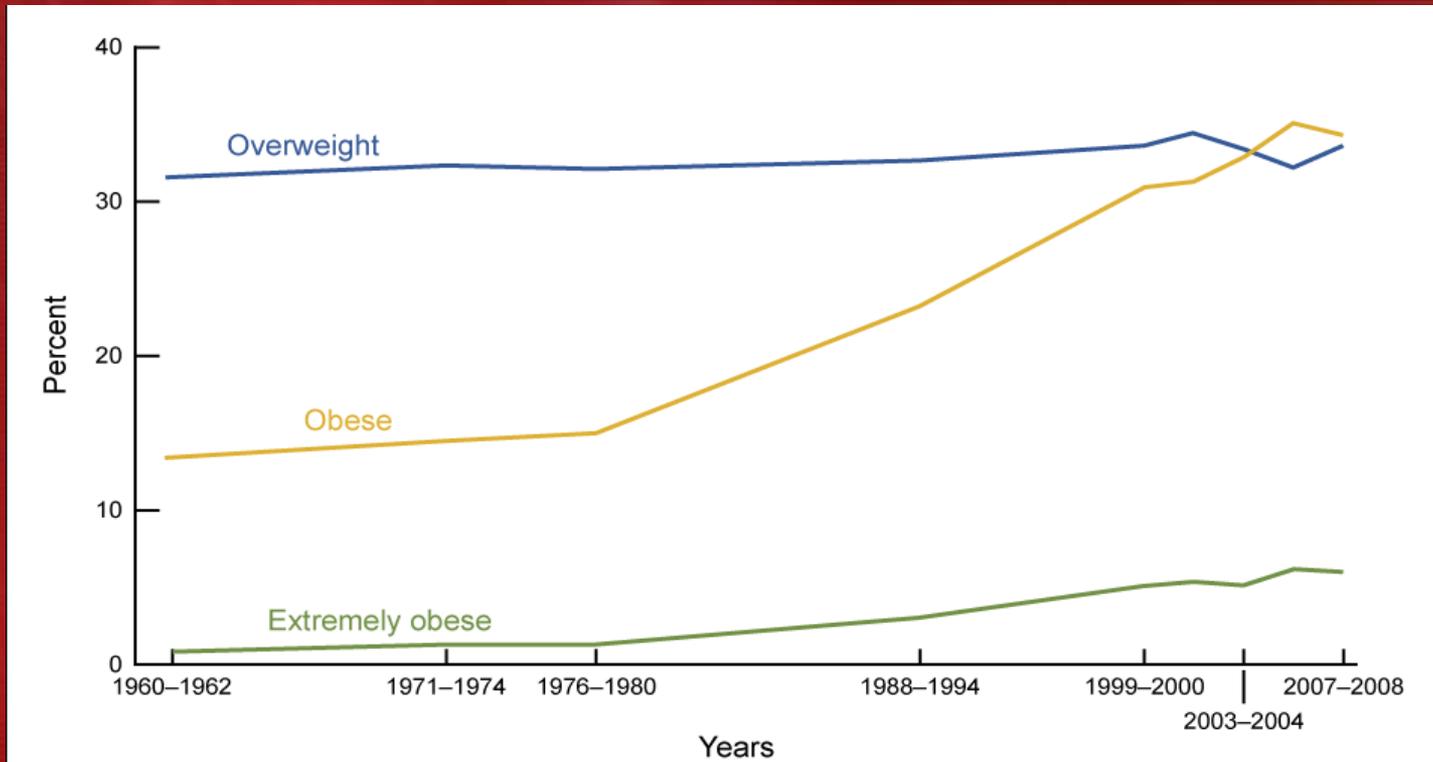
Adult Obesity Facts -- US

- 68.5% of adults overweight or obese
- 34.1% obese
 - Non-Hispanic blacks > Hispanic > Non-Hispanic Whites >> Non-Hispanic Asians
 - Female > male (except 40-59yo range; greatest in >60yo)
 - Higher in low vs high-income (in all ♀ and in NHB and MA ♂)
 - Lower in college educated ♀ (no dif. in ♂)

Rapid rise in Morbid Obesity



Trends in overweight, obesity, and extreme obesity in adults: 1960-2008



Ogden, CL et al. Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults: United States, Trends 1976-1980 Through 2007-2008. NCHS Study Brief. Hyattsville, MD, national Center for health Statistics. 2010
http://www.cdc.gov/NCHS/data/hestat/obesity_adult_07_08/obesity_adult_07_08.pdf

Medical Complications of Obesity

Pulmonary disease

abnormal function
obstructive sleep apnea
hypoventilation syndrome

Nonalcoholic fatty liver disease

steatosis
steatohepatitis
cirrhosis

Gall bladder disease

Gynecologic abnormalities

abnormal menses
infertility
polycystic ovarian syndrome

Osteoarthritis

Skin

Gout

Idiopathic intracranial hypertension

Stroke

Cataracts

Coronary heart disease

Diabetes

Dyslipidemia

Hypertension

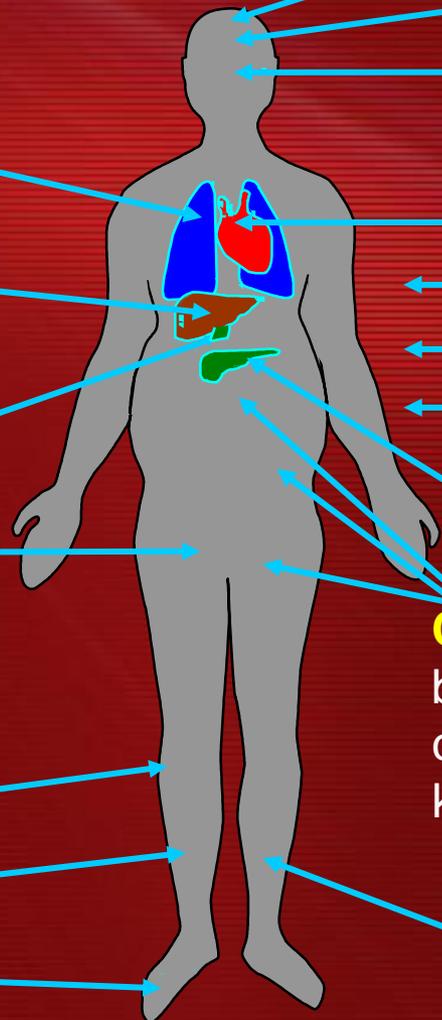
Severe pancreatitis

Cancer

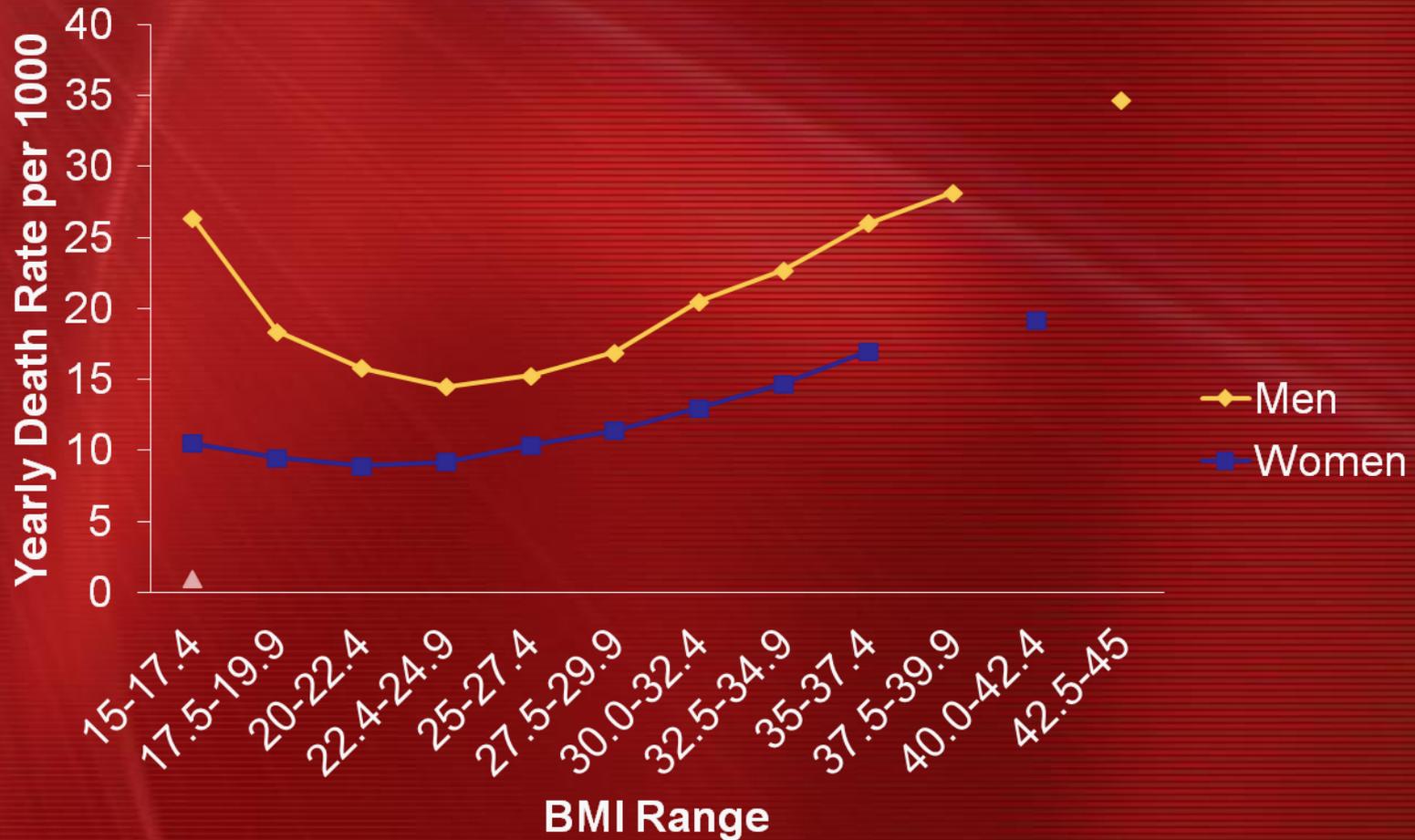
breast, uterus, cervix
colon, esophagus, pancreas, liver
kidney, prostate

Phlebitis

venous stasis



All Cause Mortality and BMI



Key Principles of Obesity Care

- Obesity is a chronic disease
- It is a heterogeneous condition
- Etiology is multifactorial
- Obese patients may be less likely to seek routine medical care and have recommended screenings

Screening

- Measure weight and height and calculate BMI annually:
 - Underweight < 18.5
 - Normal 18.5 – 24.9
 - Overweight 25 – 29.9
 - Obesity Class 1 30 – 34.9
 - Obesity Class 2 35 – 39.9
 - Obesity Class 3 ≥ 40

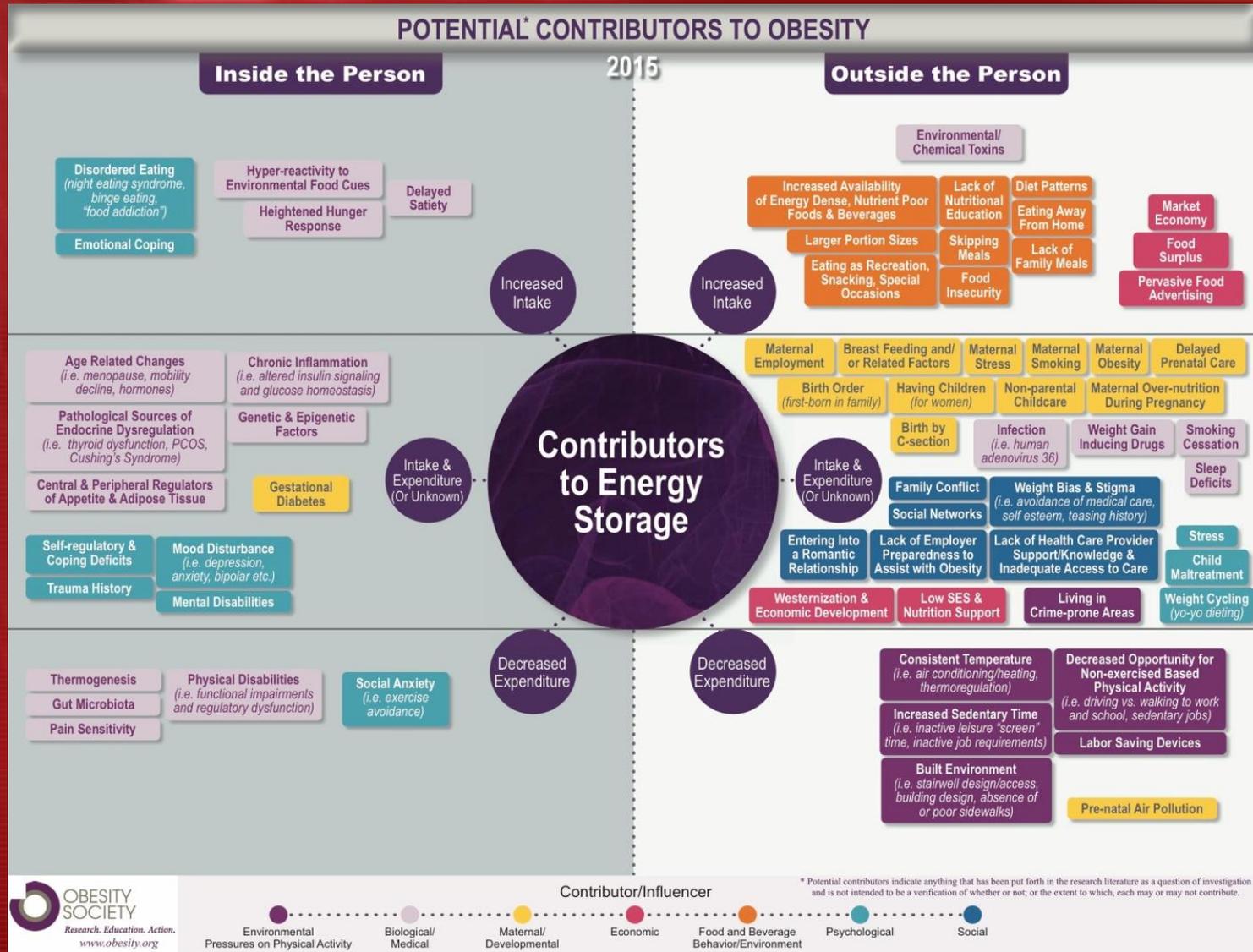
Waist Circumference

- High waist circumference indicative of increased CVD risk
 - For women >35 inches, 88 cm
 - For men >40 in., 102 cm
- Measure if BMI 25 – 35 kg/m²

Assess Need for Treatment

- Assess for CVD risk factors – HTN, dyslipidemia, impaired fasting glucose, diabetes
- BMI ≥ 30 or 25 – 30 with increased CVD risk → treatment for obesity indicated
- BMI < 25 or 25 – 30 w/out increased CVD risk → advise to avoid weight gain

Contributors to Obesity



Approach to the Patient

- Weight history –
 - Age/stage of onset of weight gain
 - Trajectory over time – high/low adult weights
 - Prior weight loss attempts and response
 - Family history of overweight/obesity
 - Outside influences

Modifiable Contributors

- Medications that promote weight gain
- Diet
- Physical activity/exercise habits
- Stress
- Sleep quality and quantity
- Schedule, circadian rhythms

Medication-induced Weight Gain

Classes most commonly implicated:

- Antipsychotics, Antidepressants, Antiepileptics, Anti-diabetic (insulin, sulfonylureas, TZDs), Corticosteroids
- ? -- Antihistamines, β blockers, OCPs, anti-retrovirals

Drug	Weight change, kg	Drug	Weight change, kg
Amitriptyline	1.8	Gabapentin	2.2
Mirtazapine	1.5	Pioglitazone	2.6
Olanzapine	2.4	Glimepiride	2.1
Quetiapine	1.1	Glyburide	2.6
Risperidone	0.8	Glipizide	2.2

Dietary History

- Meal timing
- Food preferences, intolerances
- Cravings
- Hunger vs non-hunger-related
- Cultural/religious influences
- Who is at home and who does the cooking

Initial Evaluation

Labs: CBC, CMP, fasting lipids, A1c, TSH

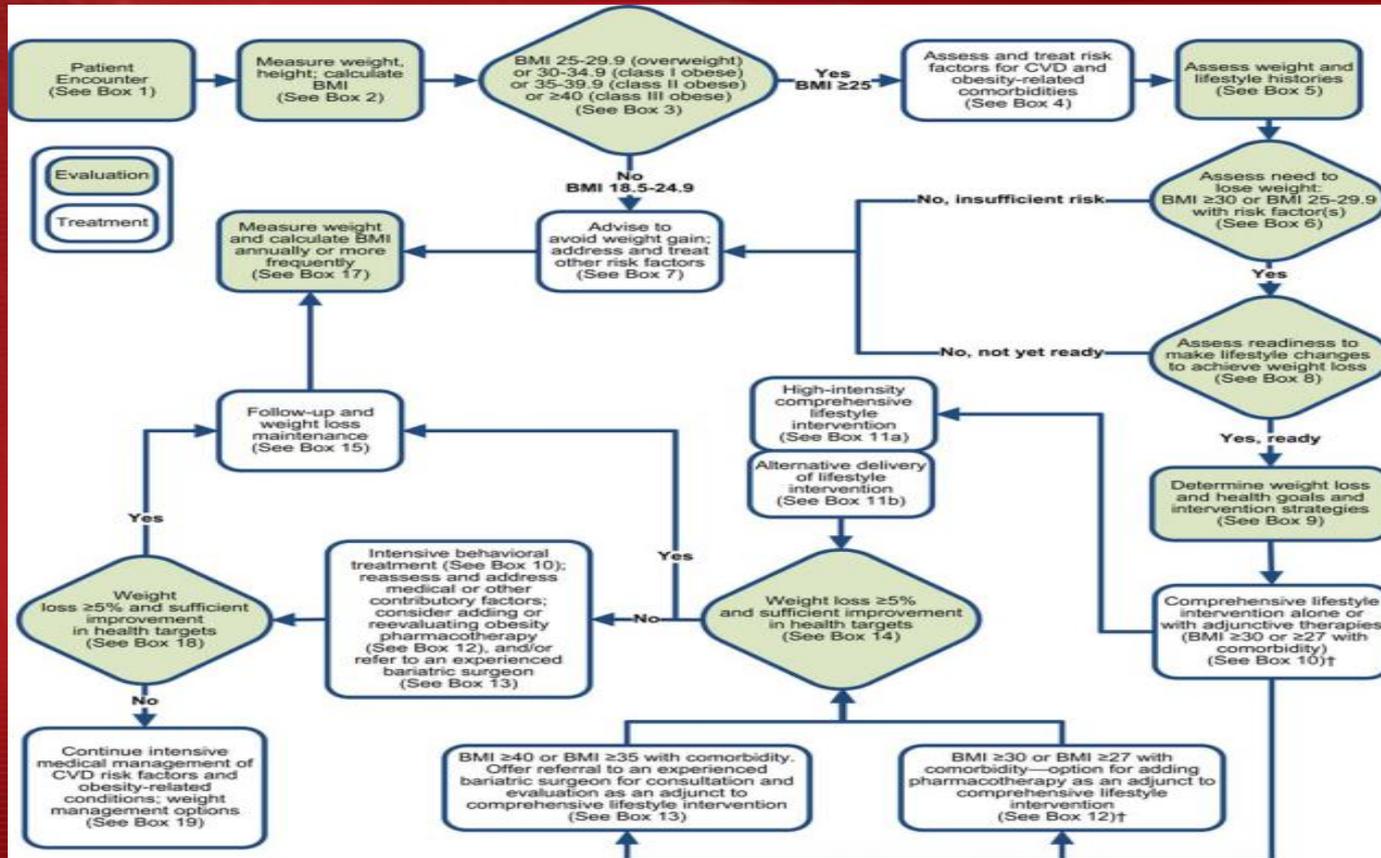
Key Physical Exam Points:

- Fat distribution
- Signs of androgen excess – acne, facial hair
- Signs of insulin resistance – acanthosis, tags
- Evidence for other specific conditions – striae, thyroid enlargement, signs of R heart failure, stigmata of chronic liver disease

Weight Loss and Health Goals

- Sustained weight loss of 3-5% may lead to clinically meaningful reductions in some CVD risk factors
- Larger weight losses produce greater benefits
- Guidelines recommend an initial goal of 5-10% of baseline weight within 6 months

Executive summary: 2013 AHA/ACC/TOS Guidelines for the management of overweight and obesity in adults



High-Intensity, Comprehensive Programs

- \geq 14 sessions in 6 months
- Individual or Group Sessions
- Moderately reduced calorie diet
- Increased activity
- Behavioral component

Treatment

- Therapeutic Lifestyle Changes
 - Diet
 - Exercise
 - Behavior Modification
- Pharmacotherapy
- Surgical/Endoscopic therapies

All of these diets are effective if a reduction in caloric intake is achieved:

- European Association for the Study of Diabetes Guidelines
- High-protein (25% protein/30% fat/ 45% carb) with food provided
- Higher –protein Zone-type (30% protein/30% fat/ 40% carb)
- Lacto-ovo vegetarian
- Low-calorie with prescribed calorie restriction
- Low carb (initially <20g/day)
- Vegan-style low-fat (10-25% calories from fat)
- Low-fat (20%)
- Lower fat (<30%) high dairy (4 servings/day) diets with or without increased fiber, and with or without low-glycemic-index/load foods
- Macronutrient targeted (15 or 25% protein, 20-40% fat, 35/45/55/65% carb)
- Mediterranean
- Moderate –protein (12% protein, 30% fat, 58% carb)
- High-glycemic load or low-glycemic load – with prescribed energy deficit
- AHA step 1-style (1500-1800 cal/day, <30% total cal from fat, <10% from sat fat)

Low-Fat vs Low-Carbohydrate: Weight Loss at 24 months



Comparison of Varying Macronutrient Composition



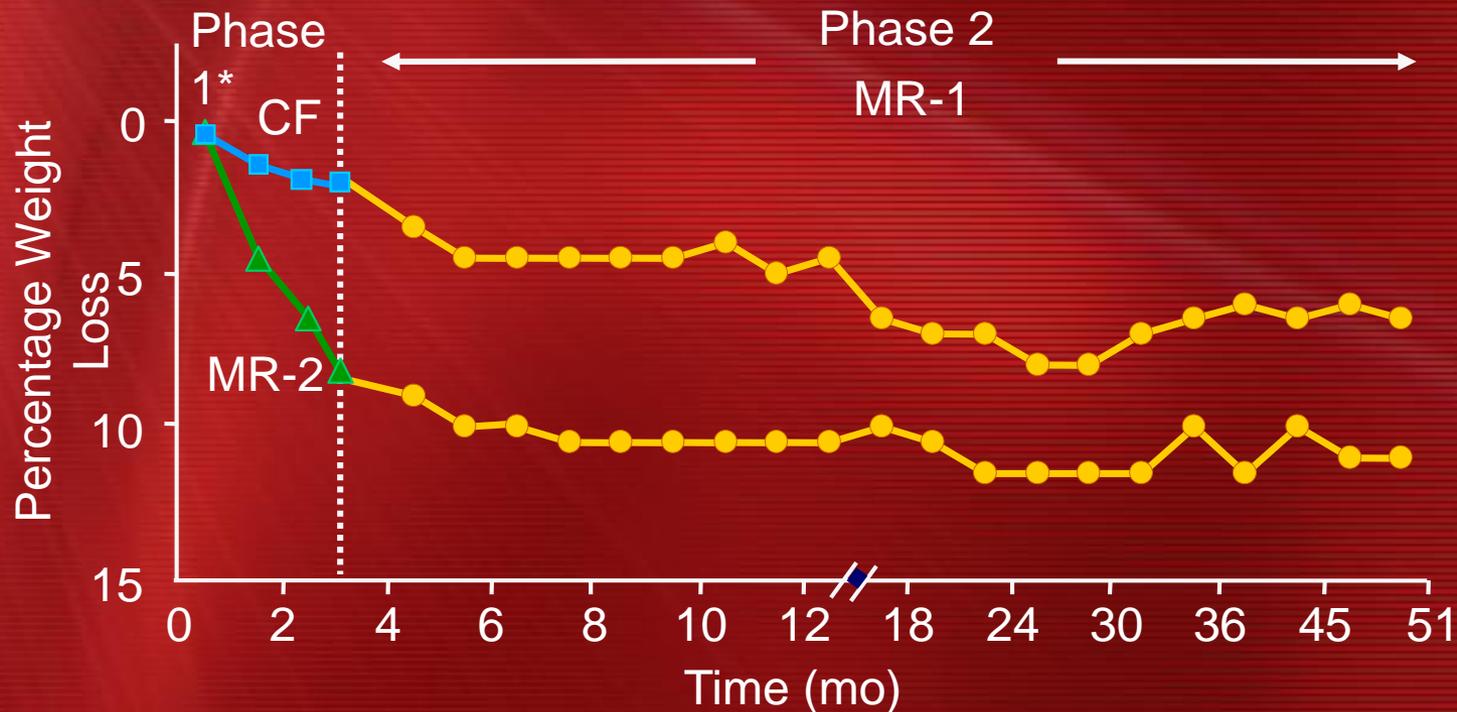
Energy deficit is required for weight loss

- Energy deficit may be prescribed or realized
- How to determine energy deficit/ calories recommended:
 - 1200-1500 kcal/day for women; 1500-1800 kcal/day for men
 - 500-750 kcal/day or 30% deficit in estimated energy requirements

Estimating Energy Requirements

- **Resting Metabolic Rate (RMR) -- Mifflin St. Jeor Equation**
 - For men: $(10 \times w) + (6.25 \times h) - (5 \times a) + 5$
 - For women: $(10 \times w) + (6.25 \times h) - (5 \times a) - 161$
- **Total Energy Expenditure (TEE) = RMR x physical activity level – Harris Benedict Equation**
 - Multipliers for RMR based on activity level – sedentary, lightly active, moderately active, very active, extra active

Meal Replacements Enhance Initial and Long-term Weight Loss



*1200–1500 kcal/d diet prescription. CF=conventional foods.

MR-2=replacements for 2 meals, 2 snacks daily. MR-1=replacements for 1 meal, 1 snack daily.

Ditschuneit et al. *Am J Clin Nutr* 1999;69:198.
Fletcher-Mors et al. *Obes Res* 2000;8:399.

Very Low Calorie Diets

- <800 kcal/day
- Require close medical supervision
- Contraindications: pregnancy, renal insufficiency, T1DM, ESLD, pancreatitis
- Adverse effects: gallstones, fatigue, hair loss, irregular menses

VLCD

- Tsai AG; Ann Int Med 2005 – Optifast
 - 12-15% wt loss at 3-6 months
 - Maintenance: 8-9% at 1 yr, 7% 3 yrs, 5% 4 yrs
- Vink, et al; Obesity Jan 2016 – 9kg wt loss at 5 weeks on 500kcal/day diet; 4.5 kg regain at 9 months – both similar to LCD (1250 kcal/day)
- May be appropriate in certain settings where rapid wt loss is a priority such as prior to joint replacement surgery

Special Situations

- CVD/CVD Risk
 - Low fat/higher carb
 - Modified DASH diet
- Diabetes/Metabolic syndrome
 - Low glycemic index/glycemic load diet

Expected Weight Loss with Diet

- With dietary intervention aimed at reducing daily energy intake:
 - weight loss is maximal at 6 months
 - smaller losses maintained for up to 2 years
- Typical weight loss is:
 - 4-12 kg at 6-months
 - 4-10 kg at 1 year
 - 3 kg to 4 kg at 2 years

Exercise

- Definitions:
 - Low Intensity – 1.1-2.9 METS
 - Able to sing the alphabet
 - Moderate Intensity – 3.0-5.9 METS
 - Can talk but not sing
 - Vigorous Intensity – ≥ 6 METS
 - Cannot say more than 1 or 2 words at a time, gasping for air
 - “Lifestyle physical activity”

Weight Effects of Exercise

- Inverse relationship between physical activity level and body weight or BMI
- To maintain health/prevent weight gain → 150-250 minutes per week moderate intensity exercise, or 75 min/wk vigorous exercise

ACSM physical activity guidelines -- Medicine and Science in Sports and Exercise, 2009

DHSS 2008 Physical Activity Guidelines for Americans

Weight Effects of Moderate Exercise

- < 150 min/week likely to result in minimal to no weight loss
- >150 minutes per week may result in modest weight loss (2-3 kg over time)
- 225-420 min/wk (or 115-210 min/wk vigorous) may result in significant weight loss (5-7.5 kg)

ACSM physical activity guidelines -- Medicine and Science in Sports and Exercise, 2009

DHSS 2008 Physical Activity Guidelines for Americans

Exercise for overweight or obesity. Cochrane Database Syst Rev. 2006

Weight Effects of Exercise

- Physical activity in association with moderate calorie restriction produces a small but significant increase in weight loss vs diet alone
- Increased lifestyle PA is likely beneficial
- Resistance exercise does not result in significant weight loss but may result in increased fat loss, increased FFM

ACSM physical activity guidelines -- Medicine and Science in Sports and Exercise, 2009

Behavior Modification

- **Self Monitoring**
 - recording intake and activities
- **Stimulus Control**
 - Avoiding triggers to eating
- **Social Support**
 - Recruiting friends and family
- **Cognitive Restructuring**
 - Thinking positively
- **Problem Solving**
 - Identifying barriers and finding solutions
- **Relapse Prevention**
 - Managing episodes of overeating/wt gain

Indications for Pharmacotherapy

- **BMI > 30 kg/m²**
- **BMI \geq 27 kg/m² with comorbidity**
- **Diet, exercise and behavioral modifications in place**

Rationale for Pharmacotherapy

- Weight loss medications reinforce behavioral changes, promote adherence to lifestyle, and increase physical activity potential
- Lifestyle changes are needed when using when using a weight loss medication
 - Medications will not work alone
 - Addition of a weight loss medication to lifestyle changes will likely result in greater weight loss

FDA Approval of Weight Loss Medications

- Phentermine, Diethylpropion -- 1959
 - Fenfluramine, Benzphetamine -- 1973
 - Phendimetrazine -- 1976
 - Dexfenfluramine (Redux™) – 1996
 - Sibutramine (Meridia™) -- 1997
 - Orlistat (Xenical™, Alli™)– 1999
-

- Phentermine/Topiramate ER (Qsymia™) – 2012
- Lorcaserin (Belviq™) – 2012
- Bupropion + Naltrexone (Contrave™) – 2014
- Liraglutide (Saxenda™) – 2014

Pharmacotherapy – Adrenergic Agents

- Phentermine, phendimetrazine, diethylpropion
- Approved for short-term, up to 12 weeks, treatment
- Adverse reactions: HTN, tachycardia, pulm HTN, cardiac ischemia, dizziness, HA, CVA, nervousness, insomnia
- Contraindications: uncontrolled HTN, CHF, CAD, CVA, glaucoma, hyperthyroidism, recent MAOI use

Pharmacotherapy: Lorcaserin (Belviq™)

- Selective serotonin 2c receptor agonist – increases satiety through activation of POMC neurons
- 10 mg BID, no titration
- Adverse effects: HA, dizziness, nausea, priapism, back pain, cbc abnormalities, URI
- Cautions/Contraindications: creatinine clearance <30, do not use with other serotonergic agents, CHF, pregnancy class X

Pharmacotherapy – Orlistat (Alli™, Xenical™)

- Pancreatic lipase inhibitor – reduces intestinal absorption of fat
- 120mg TID with meals
- Adverse reactions: cramps, borborygmi, oily spotting, frequent bowel movements; decreased absorption of fat-soluble vitamins; rare reports of liver injury; may contribute to nephrolithiasis
- Contraindications: Pregnancy, chronic malabsorption syndromes

Pharmacotherapy – Liraglutide(Saxenda)

- Human glucagon-like peptide 1 (GLP-1) analog
- Initial dose 0.6mg SC daily; can be increased by 0.6 mg daily at weekly intervals up to max dose of 3.0 mg daily
- Adverse reactions: N/V, diarrhea, constipation, HA, elevated HR, hypoglycemia; less common – renal insufficiency, pancreatitis, heart block, medullary thyroid carcinoma
- Contraindications: pregnancy, MEN2, personal or family history of MTC

Pharmacotherapy – Bupropion/Naltrexone (Contrave™)

- NE/DA reuptake inhibitor/opioid antagonist
- Exact mechanism of action w/r/t weight loss not fully understood
- Dose titration: 8/90 mg tablets
 - 1 tablet daily for 1 week, then 1 tablet BID for 1 week, then 2am/1pm for 1 week, then 2 tablets BID

Bupropion/Naltrexone – cont'd

- Adverse reactions: HA, sleep disorder, nausea, vomiting, constipation, dizziness, dry mouth; elevated BP, HR; suicidal ideation
- Contraindications: Chronic opioid use, recent MAOI use, uncontrolled HTN, seizure disorder, eating disorder

Pharmacotherapy – Phentermine/Topiramate (Qsymia™)

- Topiramate associated with weight loss when used to treat seizures, migraines; exact mechanism responsible for weight loss not known
- Adverse Reactions: elevated HR, paresthesia, HA, insomnia, xerostomia, constipation, decreased serum bicarb, URI, acute angle-closure glaucoma, suicidal ideation, confusion/memory problems
- Contraindications: Pregnancy, glaucoma, hyperthyroidism
(Due to risk for teratogenicity, pregnancy test recommended prior to starting Rx and monthly during treatment.)

Phentermine/Topiramate – cont'd

- Dose titration:
 - Initial dose 3.75/23 mg QD for 14 days, then, if tolerating, increase to 7.5/46 mg QD
 - If <3% weight loss after 12 weeks at this dose, discontinue or increase dose to 11.25/69 mg QD for 14 days, then 15mg/92 mg daily
 - If <5% loss of baseline body weight after 12 weeks at maximum dose, gradually discontinue (take every other day for at least 1 week prior to stopping)
- In moderate or severe renal insufficiency or moderate hepatic impairment, dose should not exceed 7.5/46 mg daily

Comparison of Weight Loss Medications

<u>Drug</u>	<u>Advantages</u>	<u>Disadvantages</u>
Phentermine	Inexpensive (\$) Greater weight loss ^a	Side effect profile No long-term data ^b
Topiramate/phentermine	Robust weight loss ^a Long-term data ^b	Expensive (\$\$\$) Teratogen
Lorcaserin	Side effect profile Long-term data ^b	Expensive (\$\$\$)
Orlistat, prescription	Nonsystemic Long term data ^b	Less weight loss ^a Side effect profile
Orlistat, over-the-counter	Inexpensive (\$)	
Natrexone/bupropion	Greater weight loss ^a Long-term data ^b	Side effect profile Mid-level price range (\$\$)
Liraglutide	Side effect profile Long-term data ^b	Expensive (\$\$\$) Injectable

a Less weight loss _ 2–3%; greater weight loss __ 3–5%; robust weight loss __ 5%.

b Long term is 1–2 years.

Pharmacotherapy: Medications not FDA-approved for weight loss

- Bupropion alone
- Topiramate alone
- Zonisamide
- Metformin
- Pramlintide
- SGLT-2 inhibitors – canaglifozin (InvokanaTM), empaglifozin (JardianceTM), Dapaglifozin (FarxigaTM)
- Other GLP-1 agonists – exenatide (ByettaTM, BydureonTM), dulaglutide (TrulicityTM)

Special Situations/Dual Benefit

- Diabetes Mellitus type 2
- Atypical-antipsychotic-induced weight gain, IFG, PCOS
- Depression, smoking cessation
- Binge-eating Disorder (BED)
- Migraine, seizure disorder

GLP-1 agonists, lorcaserin, metformin, pramlintide, SGLT-2 inhibitors

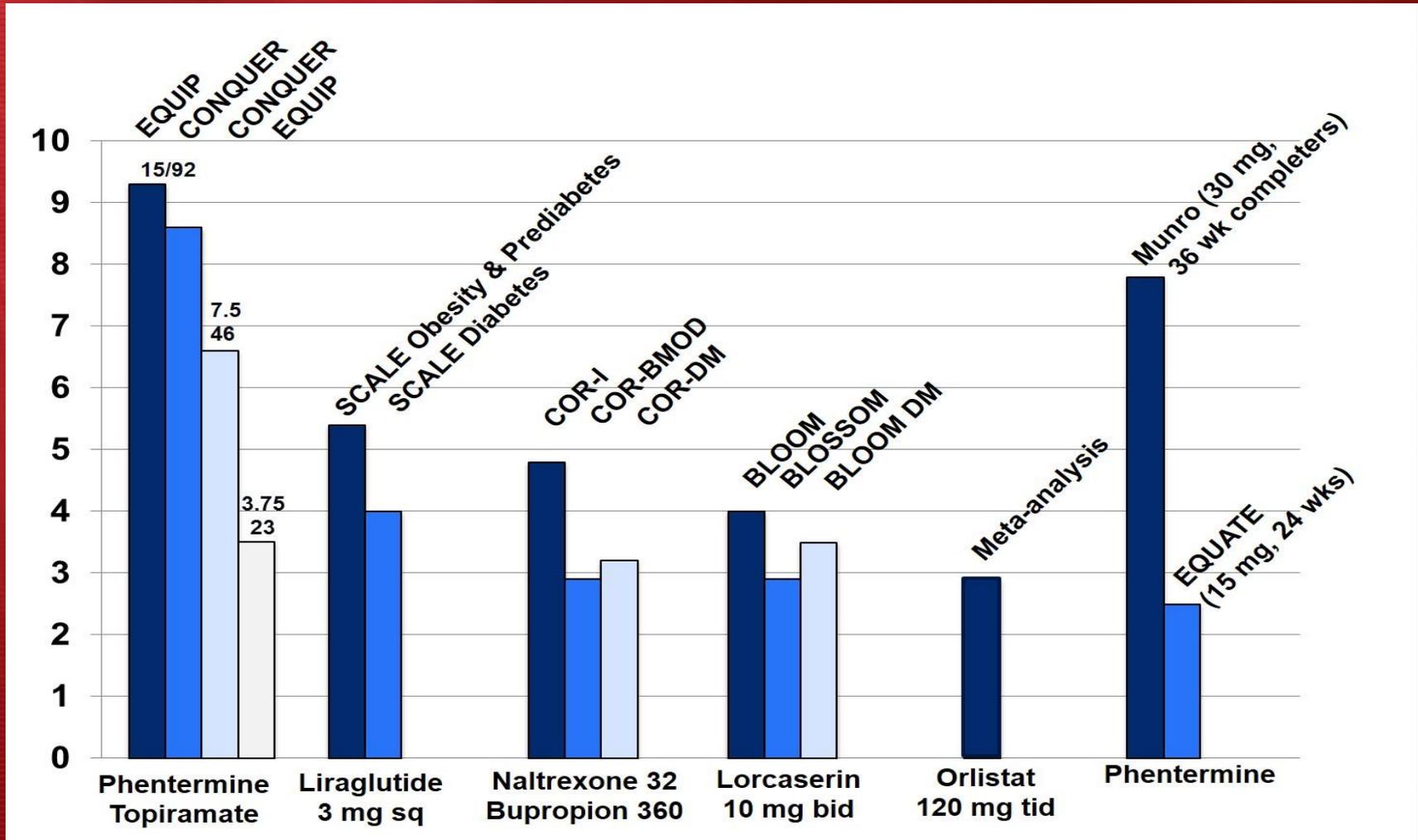
Metformin

Bupropion

Topiramate, Lisdexamphetamine, Contrave

Topiramate, Zonisamide

Placebo-subtracted Weight Loss of Obesity Medications (% weight loss at 1 year, ITT-LOCF)



General Guidelines for Pharmacotherapy

- When medication is initiated evaluate patient monthly for at least 3 months, then every 3 months
- If inadequate (<5%) weight loss at 3 months on maximum recommended/tolerated dose, discontinue medication
- If effective and well-tolerated, generally treat long-term (with approved agents)

Surgical and Endoscopic Procedures for Weight Loss

- Available Procedures:
 - Gastric bypass (RYGB)
 - Gastric sleeve
 - Laparoscopic adjustable gastric banding (LapBand™)
 - Biliopancreatic diversion
 - Intragastric balloon

Bariatric Surgery Indications

- BMI > 40 kg/m² or
- BMI 35-35.99 with significant comorbidity*
- Failure to achieve adequate weight loss with nonsurgical treatment including intensive lifestyle modification

*For LapBand™ ≥ 35, or 30-34.9 w/ comorbidity

Maintaining Weight Loss

- National Weight Control Registry
 - 75% weigh themselves at least once a week
 - 62% watch <10 hours of TV per week
 - 90% exercise, on average, about 1 hour per day
 - 78% eat breakfast every day

The National Weight Control Registry
Brown Medical School/The Miriam Hospital
Weight Control and Diabetes Research Center

Maintaining Weight Loss – Look AHEAD

Year 8 Behaviors	Maintained \geq 10% Loss	Regained Above Baseline
Physical Activity, Kcal/week	1471 \pm 121.2	799.9 \pm 100.9
Reduced Kcal (no. wk/yr.)	20.4 \pm 1.4	11.9 \pm 2.1
Reduced fat (no. wk/yr.)	24.2 \pm 1.5	15.6 \pm 2.2
Meal Replacements (no. wk/yr.)	22.8 \pm 2.0	17.3 \pm 2.9
Increased exercise (no. wk/yr.)	12.9 \pm 1.3	8.2 \pm 1.8
Monitored wt. \geq weekly N (%)	262 (82.4)	81 (69.8)
Monitored wt. \geq daily N (%)	152 (47.8)	33 (28.4)

Weight control behaviors at Year 8 for Intensive Lifestyle Intervention participants who maintained (N=234) versus regained (N=117) their \geq 10% weight loss, achieved at Year 1.