Navigating the new weight loss medications
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Objectives
- Discuss the evolution of obesity as a diagnosis and disease.
- Discuss the epidemiology and pathogenesis involved in obesity.
- Understand role of new medication in obesity treatment.
- Understand mechanism of action, side effects, and contraindications of obesity directed medications.
- Discuss the PA role in obesity care and use of pharmacotherapeutics in that care.

Definition of Obesity
- Condition characterized by the excessive accumulation and storage of fat in the body.
- Overweight → BMI of 25 - 29.9 kg/m²
- Obese → BMI ≥30 kg/m²

Evolution of Obesity

Forces at work:
- Major labour-saving technology changes of the 20th century
- Rise of an automobile-based way of life
- Introduction of radio and television broadcasting
- Increasing participation of women in the work force
- Industrial processing of food
- Spread of fast-food eateries
- Culture of consumption
- The IT revolution

Sources of data:
- BRFSS
- NHANES

http://www.voxeu.org/article/100-years-us-obesity
Obesity Trends* Among U.S. Adults
BRFSS, 1990, 2000, 2010
(*BMI ≥ 30, or about 30 lbs. overweight for 5'4" person)

Epidemiology of Obesity (Children)
- Overweight or obese (body mass index [BMI] ≥85th percentile)
  - 22.8 percent of preschool children (2 to 5 years)
  - 14.5 percent of school-aged children (6 to 11 years)
  - 14.5 percent of adolescents (12 to 19 years)
- Obese (BMI ≥95th percentile)
  - 8.4 percent of preschool children
  - 17.7 percent of school-aged children
  - 20.5 percent of adolescents
- Severe obesity (BMI that is either ≥120 percent of the 95th percentile or ≥35 kg/m²)
  - 2.2 percent of preschool children
  - 8.9 percent of school-aged children
  - 11.4 percent of adolescent girls and 9.2 percent of adolescent boys

Obesity as a chronic disease
- Historically debated
  - When recognized: 2013 by AMA; 2008 by The Obesity Society
  - Why?
    - 1 in 3 Americans
    - Global epidemic
    - To change the way the medical community tackles the issue
    - Aid the fight against other diseases (T2DM, heart disease)
    - Improve funding
    - Decrease stigma of obesity
    - Meets medical criteria for being a “disease” (ie: impairing body function)
- Reasons for opposition
  - Measurement for diagnosis (BMI) is flawed
  - Should be a condition or disorder, not a disease
  - Creates situation where 1/3 of Americans are “sick”
Screening for Obesity

- Rationale for screening:
  - Increasing prevalence
  - Risk of mortality
  - Risk for co-morbidities: DM, HTN, Dyslipidemia, Heart Disease, Stroke, Sleep apnea, Cancer
  - Increasing health care expenditures
  - Availability of weight loss interventions
  - Cost effective and available to nearly all clinicians


Screening for Obesity

- Screening Measures ANNUALLY:
  - Height, Weight, Calculate BMI
  - If BMI between 25 - 35 kg/m²: Obtain waist circumference
  - Risk factor assessment at least ANNUALLY but should be reviewed at any periodic visit

Calculating/Classification of BMI

\[ BMI = \frac{\text{weight (lb)} \times 703}{\text{height}^2 \text{ (in)}^2} \]

- Underweight: BMI < 18.5 kg/m²
- Normal weight: ≤ 18.5 to 24.9
- Overweight: ≤ 25.0 to 29.9
- Obesity: ≤ 30.0
- Obesity Class I: 30.0 - 34.9
- Obesity Class II: 35.0 - 39.9
- Obesity Class III: ≥ 40.0
Waist Circumference

- Measurement of abdominal obesity
- Technique: measurement taken on the horizontal plane at level of iliac crest
- PUT IN FIGURE 2 from UP TO DATE
- Elevated and indicative of increased cardiometabolic risk:
  - ≥ 40 inches (102 cm) for MEN
  - ≥ 35 inches (88 cm) for WOMEN

Evaluation of Obesity

- History and Physical
- Measurement of:
  - Fasting glucose (or HgbA1C)
  - TSH
  - Liver enzymes
  - Fasting lipids
  - In females, urine pregnancy
- Assessment of risk
  - Coexisting conditions including sleep apnea, osteoarthritis, T2DM, CHD, other atherosclerotic disease

Consider the possible etiologies

- Diet
- Lifestyle
- Drugs
- Endocrine disorders
- Genetics
  - FTO variants
  - MC4R variants
  - Agouti gene
  - Leptin gene
- Genetic disorders
  - Prader-Willi syndrome
  - Bardet-Biedl syndrome
Management of Obesity

- Approach to weight management
  - Diet
  - Exercise
  - Behavioral Modification
  - Surgery
  - DRUG THERAPY
  - Vagal blockade
  - Complementary therapies

Goals of Treatment

- Prevent further weight gain
- Increase energy expenditure
- Realistic amount of weight loss (5-15%)
  - 5-7% \(\rightarrow\) GOOD
  - 8-10% \(\rightarrow\) VERY GOOD
  - 10-15% \(\rightarrow\) EXCELLENT
- Body Mass Index
  - Below 25
    - 20-25 shows lowest risk category
- Maintain weight loss

Body Mass Index

- Below 25
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Goals of Treatment

- In setting of drug therapy, successful program is:
  - 2 kg during first month (1 pound per week)
  - Fall more than 5% below baseline between 3-6 months
  - Do not exceed recommend maximal duration of use for drug
  - Avoid weight gain when drug therapy discontinued
  - Select drugs that will not worsen or counter other underlying conditions

Drug Therapy in Treatment and Management of Obesity

Agents available

- Orlistat
- Lorcaserin
- Phentermine-topiramate
- Bupropion-naltrexone
- Liraglutide (Injection)
- HCG Hormone
- Dietary supplements
- Experimental agents
Orlistat

- Best for initial therapy
- MOA: Alters fat digestion by inhibiting pancreatic lipases
- To work most effectively diet contains no more than 30% fat
- Dose: 120mg capsules TID (OTC version at 60mg)

- Benefits:
  - Weight loss
  - Reduction in conversion from IGT (impaired glucose tolerance) to DM
  - Decreased HgbA1c
  - Improved blood pressure (vs placebo)
  - Improved serum lip values by
  - Equally effective in Caucasians and minority groups

- Side effects:
  - May decrease the absorption of fat-soluble vitamins
  - GI: cramps, flatus, fecal incontinence, oily spotting and stools, excessive bowel sounds
  - Liver injury (rare)
  - Oxalate-induced acute kidney injury or stones

Lorcaserin

- Used in combination with reduced calorie diet and exercise
- MOA: Activates central serotonin 2C receptor which reduces appetite and food intake
- Similar efficacy as orlistat with few adverse side effects
- Dose: 10mg twice daily
Lorcaserin

Benefits:
- Significantly higher percentage of weight loss vs placebo
- Increase in weight maintenance
- Improved markers of cardiovascular and diabetes risk
- Decreased blood pressure, heart rate

Side effects:
- Headaches
- URI, nasopharyngitis
- Dizziness
- Nausea
- Back pain

Phentermine-Topiramate

This combination preparation FDA approved in 2012.
- Not recommended in patients with HTN or coronary heart disease, hyperthyroidism, history of drug abuse, and if pregnant
- Contraindicated in patients with glaucoma and who take MAOI
- Caution in patients with history of renal stones
- Best used in obese postmenopausal women and men w/o CVD and who do not tolerate orlistat or lorcaserin

MOA Phentermine: noradrenergic sympathomimetic drug which stimulates the release of norepinephrine and/or inhibits its reuptake into nerve terminals; also reduces food intake by causing early satiety


Phentermine-Topiramate

Dose: initial 3.75/23mg QD x 14 days then 7.5/46mg QD thereafter
- After 12 weeks...option to bump dose to 11.25/69mg x 14 days then 15/92mg thereafter
- If 5% loss not achieved after 24 weeks, gradually taper and discontinue
- Do NOT abruptly stop due to risk of seizures
Phentermine-Topiramate

**Benefits:**
- Significantly higher percentage of weight loss vs placebo
- Improved markers of cardiovascular and diabetes risk
- Decreased blood pressure, heart rate

**Side effects:**
- Increased blood pressure and heart rate
- Insomnia
- Dry mouth
- Constipation
- Nervousness
- Potential for abuse
- Renal stones (primarily due to topiramate)
- Increased incidence of psychiatric and cognitive disturbances (topiramate)
- Paresthesias (topiramate)

Bupropion - Naltrexone

**This combination preparation was approved in 2014 as an adjunct to diet and exercise**

**NOT recommended as a first line pharmacologic therapy**

**Contraindicated in patients with HTN, seizure disorder, eating disorder, chronic opioid use**

**Caution in patients with history of suicidal ideations**

**Best used in obese smoker who did not tolerate orlistat or lorcaserin and also seeking smoking cessation**

**MOA Bupropion:** antidepressant and used in prevention of weight gain during smoking cessation. Acts through modulating the action of norepinephrine.

**MOA Naltrexone:** opioid receptor antagonist used to treat alcohol and opioid dependence. It is still unclear but suspect it boosts the effect of bupropion.

**Dosing:**
- Initial one 8mg/90mg (nalt/bupr) tablet QD x 1 week; increase to BID x 3 weeks; increase to 2 tabs BID

**Benefits:**
- Studies reveal typically 4-6% weight loss below baseline
- Can have as much as 10% weight loss below baseline
- Extension studies reveal weight loss is maintained (over 6 months)

**Side Effects:**
- Insomnia
- Vomiting
- Dizziness
- Dry mouth
- Seizure
- Increased blood pressure
- Suicide risk during initial weeks of treatment
- Neuropsychiatric events
Liraglutide (Exenatide?)
- Indicated for use in overweight or obese patients with type 2 diabetes
- Although can be used in individuals seeking weight loss without T2DM
- MOA: inhibits glucagon release and gastric emptying; stimulates glucose-dependent insulin secretion
- Contraindicated in patients with personal or family history of medullary thyroid cancer or MEN 2A/2B.
- Dose: initial 0.6mg SQ in abdomen, thigh, upper arm QD
- At one week intervals can increase 1.2, 1.8, 2.4mg to max dose of 3mg
- If after 16 weeks a 4% or greater loss from baseline weight should be discontinued
- Side Effects:
  - Nausea
  - Vomiting
  - Diarrhea
  - Pancreatitis (rare)
  - Hypoglycemia
  - Renal impairment
  - Increased risk of benign and malignant thyroid C-cell tumors

HCG Hormone
- MOA: still not clear, but believe that HCG will "reset" the hypothalamus improving metabolism and allowing the body to release abnormal fat stores and use them for fuel
- Dose: 250-300iu green lutein once daily x 40 days
- Benefits:
  - Quicker weight loss (1 pound per day)
  - Patient learns diet discipline and portion size
  - Absence of hunger
  - Fat metabolism with maintenance of muscle tone
  - Reset of hypothalamic gain control of metabolism
- Side Effects:
  - Adherence to very low calorie diet 500-750 calories daily
  - Strict food choices
  - Fatigue
  - Headaches
  - Irritability
  - Rebound weight gain (not seen if follows stabilization and maintenance recommendations)

Dietary supplements
- Ephedra
- Green tea
- Chromium
- Chitosan
- Garcinia
- Hoodia
- Other
- Calcium
Experimental drugs

- Peptides
  - Leptin
    - Peptide produced in adipose tissue
    - Absence or resistance to leptin leads to increases in appetite, food intake, and weight gain
    - Some evidence that leptin supplementation after weight loss may prevent regaining weight
  - Peptide YY
    - Gut hormone peptide that suppresses appetite and decreases food intake
    - Intranasal and IV formulations
    - Studies reveal only minimal weight loss at low doses; no studies at high doses due to SE's and drop-out rate
  - Oxyntomodulin
    - Peptide produced in L-cells of GI tract
    - Administered TID, 30 min before meals
    - Promising studies show significantly more weight loss vs placebo groups when administered TID
  - Melanocortin-4 receptor agonists
    - Effects hypothalamic melanocortin system
    - Intranasal formula
    - Varying results from current studies

Summary

- Intensive lifestyle modification should be implemented in BMI ≥ 25 kg/m² in all patients
- Pharmacotherapy is indicated in BMI ≥ 30 kg/m² or in BMI 27-29.9 kg/m² with comorbidities or if failed to meet weight loss goals with lifestyle change alone
- Orlistat is suggested as first line pharmacologic therapy
- 2 year treatment duration recommended
- Discontinue or change pharmacologic approach if patient does NOT achieve at least 5% loss in 12 weeks
- Sympathomimetic drugs should NOT be prescribed for LONG TERM weight loss or in patients with abuse history due to potential for abuse
- Metformin is suggest initial therapy in patients with T2DM, Liraglutide is best alternative
- Patients with BMI ≥ 40 kg/m² who have failed lifestyle, pharmacologic approaches, should be referred for bariatric surgery approach

Questions?