OBESITY

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Introduction

- 2 of 3 adults are overweight or obese in the US
- 1 of 3 adolescents are overweight or obese
- Overweight/obese associated with:
  - Increased risk for developing many diseases
  - Poorer outcomes of disease states
  - Increased healthcare costs

Introduction continued…

- 9.1% of total medical expenditures in the US
- Older patients: excess weight and adiposity increase risk of death

Conditions Prevalent in Obese Patients

- Cancer
  - Breast, colorectal, gallbladder, endometrial, esophageal, hepatic, kidney, ovarian, pancreatic, prostate, rectal
- Cardiovascular
  - Atrial fibrillation, CVA, CHF, CAD, hypertension, LVH, MI, PVD, PE, varicose veins, VTE
- Dermatologic
  - Cellulitis, carbuncles, lymphoedema, skin tags, stretch marks, psoriasis
- Endocrine and Reproductive
  - Amenorrhea, fetal abnormalities, hirsutism, hypogonadism (male), infertility, PCOS, sexual dysfunction

Conditions Prevalent in Obese Patients continued…

- Gastrointestinal
  - Cholelithiasis, GERD, hepatic cirrhosis, hernias, nonalcoholic fatty liver disease
- Genitourinary
  - Chronic kidney disease, increased serum urate, ESRD, glomerulopathy, urinary stress incontinence
- Metabolic
  - DM, hyperlipidemia, hyperinsulinemia, hypertriglyceridemia, high LDL, impaired glucose tolerance, metabolic syndrome
- Musculoskeletal
  - DJD, disc disease, gait disturbance, gout, fibromyalgia, immobility, LBP, osteoarthritis, plantar fasciitis

Conditions Prevalent in Obese Patients continued…

- Neurologic
  - Carpal tunnel syndrome, idiopathic intracranial hypertension, stroke
- Oral health
  - Dental caries, loss of teeth, periodontitis, xerostomia
- Psychological
  - Affective disorders, body image disturbance, depression, eating disorders, low self-esteem, social stigmatization
- Respiratory
  - Asthma, COPD, dyspnea, OSA, hypoventilation syndrome, pneumonia, pulmonary hypertension

Epidemiology

- Increasing prevalence
- Obese children=obese adults
- Race/sex differences
- Age
- Socioeconomic status
- Degree of education

Etiology

- Obesity occurs when increased energy storage results from imbalance between energy intake and energy expenditure over time
- Genetic influences
- Environmental factors
- Underlying medical condition or effect of a medication

Etiology—Genetic Influences

- Role of genetics in obesity and distribution of body fat
- Genetic influence in body mass index (BMI) and body fat distribution is up to 80%
- Single-gene mutations producing extreme obesity have been identified
  - Rare, small number of the cases of obesity

Etiology—Environmental Factors

- Easily accessible food supply
- Reduction in physical activity due to comforts of modern life
- More sedentary lifestyles due to technology
- Increase in portion size of high-fat foods, also more convenient, less expensive
- Obesity more frequent in individuals within close social networks (siblings, friends, spouses, etc.)

Etiology—Medical Conditions

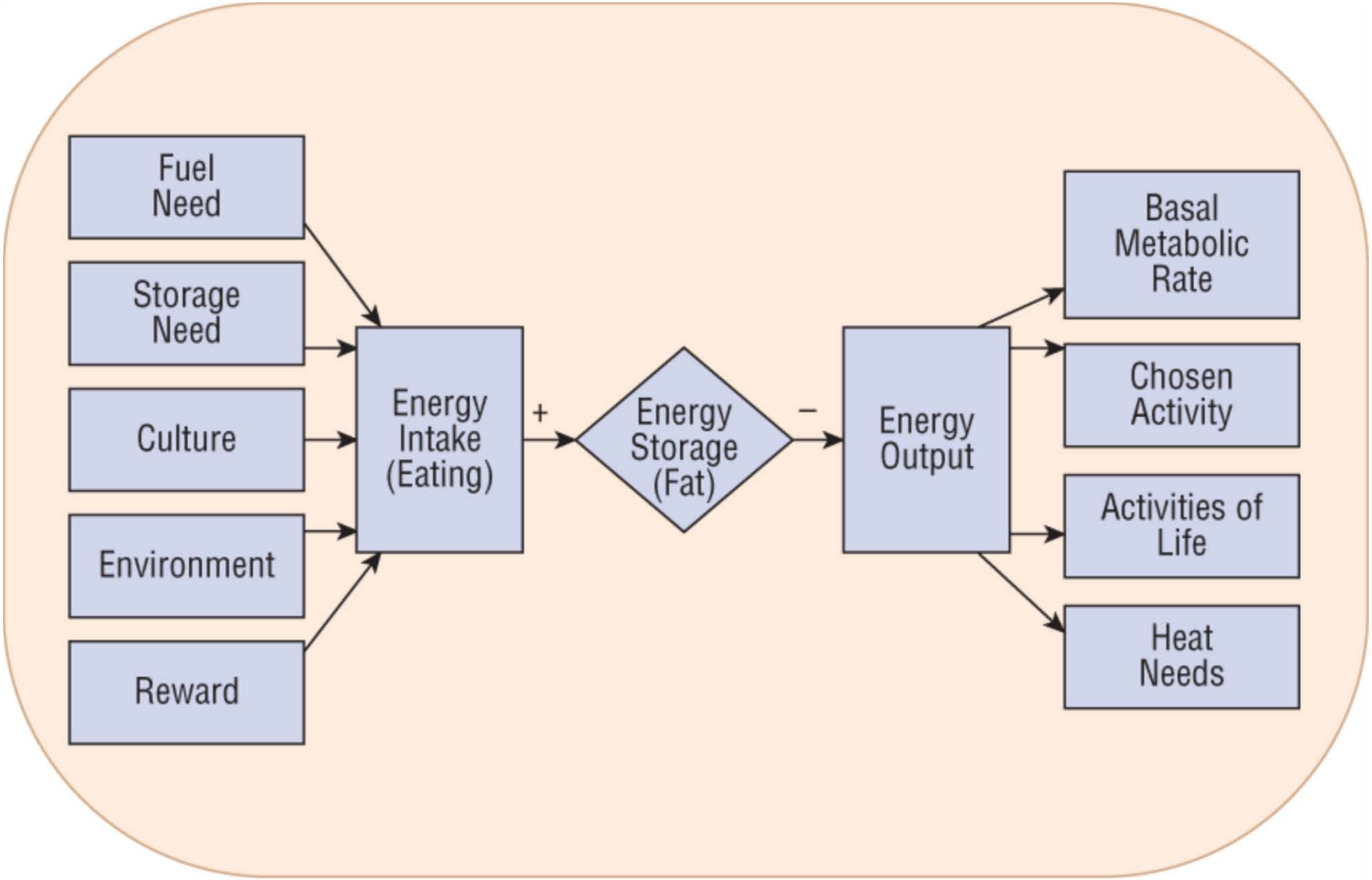
- Cushing's syndrome
- Growth hormone deficiency
- Insulinoma
- Leptin deficiency
- Psychiatric disorders
- Hypothyroidism
- Genetic syndromes

Etiology—Medications

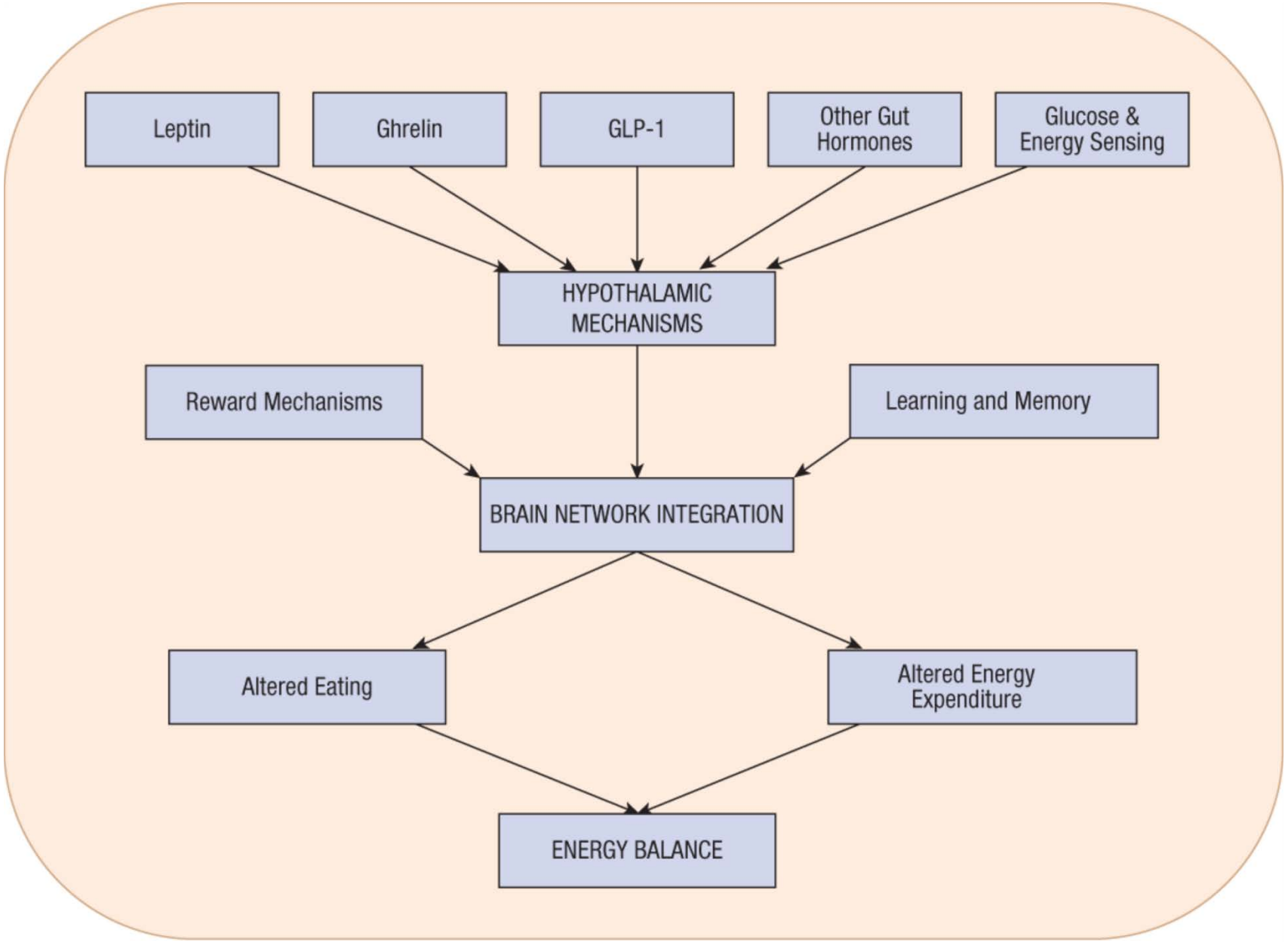
- Anticonvulsants
  - Carbamazepine, gabapentin, pregabalin, valproic acid
- Antidepressants
  - Mirtazapine, tricyclics
- Atypical antipsychotics
  - Clozapine, olanzapine, quetiapine, risperidone
- Conventional antipsychotics
  - Haloperidol
- Hormones
  - Corticosteroids, insulin, medroxyprogesterone

Pathophysiology

- Involve factors that regulate appetite, energy storage, and energy expenditure
- Appetite
- Biogenic amines—serotonin, histamine, and dopamine
- Neuropeptides
- Peripheral appetite signals—leptin
- Gut-hormones—glucagon-related peptide 1, oxyntomodulin, peptide YY



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, Ninth Edition:* www.accesspharmacy.com



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Energy Balance

- Obesity determined by net balance of energy ingested relative to energy expended over time
- Metabolic rate largest determination of energy expenditure
- REE (resting energy expenditure)—energy expended by someone at rest under conditions of thermal neutrality
- BMR (basal metabolic rate)—REE measured soon after awakening in the morning 12 hours after last meal

Peripheral Storage

- 2 types of adipose tissue
  - White—lipid manufacture, storage, and release
  - Brown—importance remains unclear

Clinical Presentation

- Apparent
- Seek healthcare when comorbidities become a problem
- Excess weight defined by BMI
  - Measure of total body weight relative to height
  - Normal: BMI 18.5-24.9
  - Overweight: BMI 25-29.9
  - Obese: BMI 30-39.9
  - Extreme obese: BMI $\geq$40

Clinical Presentation continued…

- Children 2-18 years
  - Overweight: BMI 85th-94th percentile
  - Obese: BMI 95th percentile or above
- BMI calculation: weight in kg/height in meters squared
- BMI can overestimate the amount of excess body fat in certain cases:
  - Edematous states, extreme muscularity, muscle wasting, short stature

Body Mass

- Can measure fat mass by:
  - Underwater body weight
  - Dual-energy X-ray absorptiometry
  - CT
  - MRI
- All fat not equal
- Central obesity—high levels of intraabdominal or visceral fat
  - WC→ >40 in. in men and 35 in. in women
  - CT
  - MRI

BMI vs. WC

- Each predicts disease risk
- Both should be assessed and monitored during therapy for obesity
- Increased WC=increased risk, even in “normal” weight patients

Comorbidities of Obesity

- Obese patients=increased mortality rates, especially BMI >35 kg/m^2
- BMI >35 kg/m^2 patients have reduced life expectancy, and even further reduction in obese patients that are smokers/history of smoking
- Associated with increased mortality: ↑body fat, ↑total body weight, central distribution of body fat

Comorbidities of Obesity

- Hypertension
- Hyperlipidemia
- Insulin resistance
- Glucose intolerance (then type 2 diabetes)
- ↑ Risk of stroke
- ↑ Risk of cardiovascular disease
- Sleep apnea
- Osteoarthritis
- Reproduction

Desired Outcomes

- Patient-specific goals (weight loss, improving chronic conditions)
- Per guidelines: weight loss goal 10% of initial weight gradually over 6 months of therapy
- Equates to 1-2 pounds lost per week
- Decreasing weight gain/maintaining weight-neutral
- Set realistic time course for weight loss plan

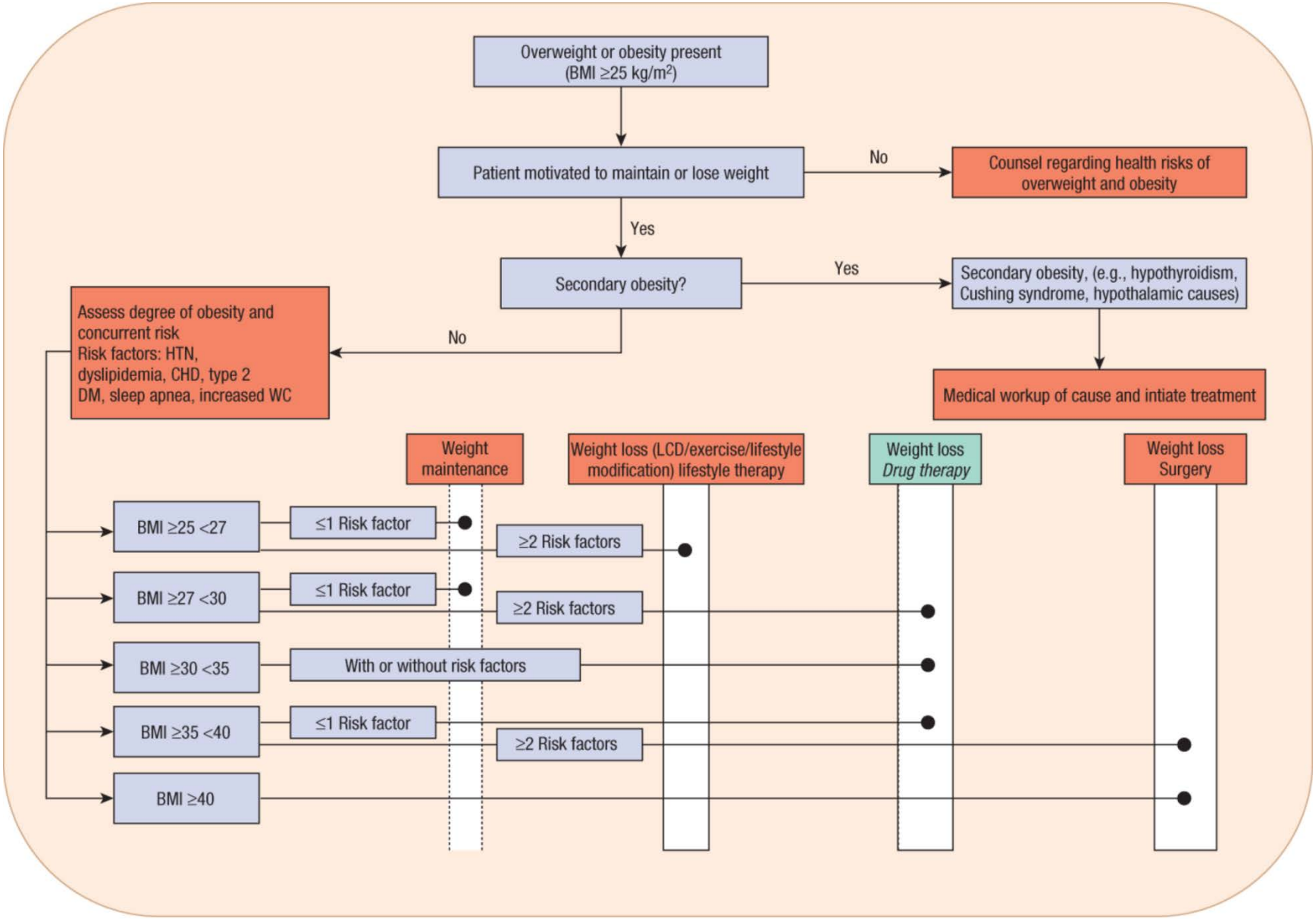
Treatment

General Approach

- Dietary intervention
- Exercise
- Behavior modification
- Surgical intervention

Look AHEAD trial

- Look AHEAD (action for health in diabetes)
- 11 year study
- Diabetes patients with lifestyle modifications for weight loss
  - No reduction in CV events
  - Reduced need for medications
  - Other positive health benefits



Nonpharmacologic Therapy

Nonpharmacologic Therapy—General

- Mainstay of obesity management
  - Reduced caloric intake
  - Increased physical activity
  - Behavioral modification
- First-line therapy according to evidence-based guidelines: NIH

Reduced Caloric Intake

- Adhere to low-calorie diet (LCD)
  - Calorie deficit of 500-1000 kcal
  - Total intake of 800-1200 kcal/day
- Severely obese may require more energy (higher calorie) at initiation of diet
- Results in 8% weight loss over 6 months

Low-Calorie Diet

Nutrient	**Recommended Intake**
Total fat	25%–35% or less of total calories
Saturated fat	<7% of total calories
Monounsaturated fat	≤20% of total calories
Polyunsaturated fat	≤10% of total calories
Cholesterol	<200 mg/day
Protein	~15% of total calories
Carbohydrate	50%–60% or more of total calories
Fiber	20–30 g
Calories	*Overall daily intake reduced by 500–1,000 kcal (2,093–4,186 kJ)*
Total caloric intake	*1,000–1,200 kcal/day (4,186–5,023 kJ/day) for most women; 1,200–1,600 kcal/day (5,023–6,697 kJ/day) for most men*

Adapted from Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106(25):3143–3421.

Popular Diets

- Moderate energy-deficient plans
  - Weight Watchers, LEARN, Jenny Craig
- Vegetarian-based plans
  - Ornish
- Low-carbohydrate plans
  - Zone, Atkins
- Short-term vs. long-term weight loss
  - Low-carb>low-fat for 1st 6 months, similar after 1 year

Very-Low Calorie Diet

- Less than 800 kcal/day
- Not recommended in general
- Early weight loss ≠ long-term weight loss due to compliance
- Require intensive medical monitoring

Increased Physical Activity

- Important in equation of greater energy expenditure than energy intake
- Monotherapy: modest results
- Combined with reduced calories and behavior modification, augments weight loss and improves comorbidities and CV risk factors
- Adults: ≥150 minutes moderate physical activity per week
- Start low, go slow

Behavioral Modification

- Self-monitoring of diet
- Self-monitoring of exercise
- Behavioral contracts
- Social support (friends, relatives, etc.)
- Most effective = combination of modifications

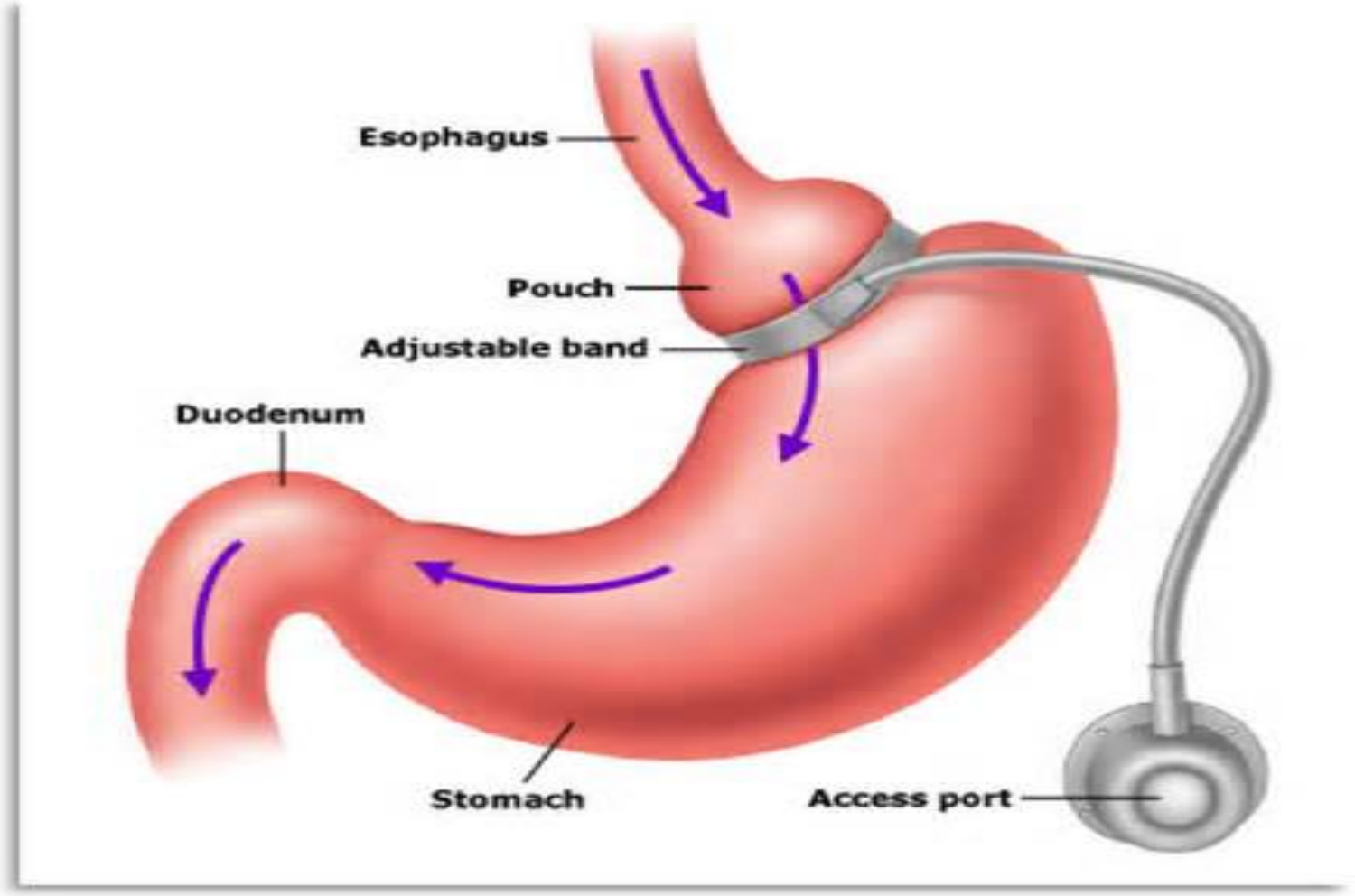
Bariatric Surgery

- Most effective intervention for obesity
- Downside: morbidity and mortality occurs
  - Only for patients with BMI $\geq$40 kg/m^2 or $\geq$35 kg/m^2 with comorbidities
- Must meet eligibility criteria
- 2 mechanisms:
  - Restriction/reduction of food intake by reducing stomach volume
  - Malabsorption by decreasing absorption surface of GI tract

4 Types of Bariatric Surgery

- Adjustable gastric banding
  - Reduce volume of stomach
- Vertical banded gastroplasty
  - Reduce volume of stomach
- Biliopancreatic diversion with duodenal switch
  - Malabsorption
- Roux-en-Y gastric bypass
  - Combines reduced volume of stomach and malabsorption

Adjustable Gastric Banding



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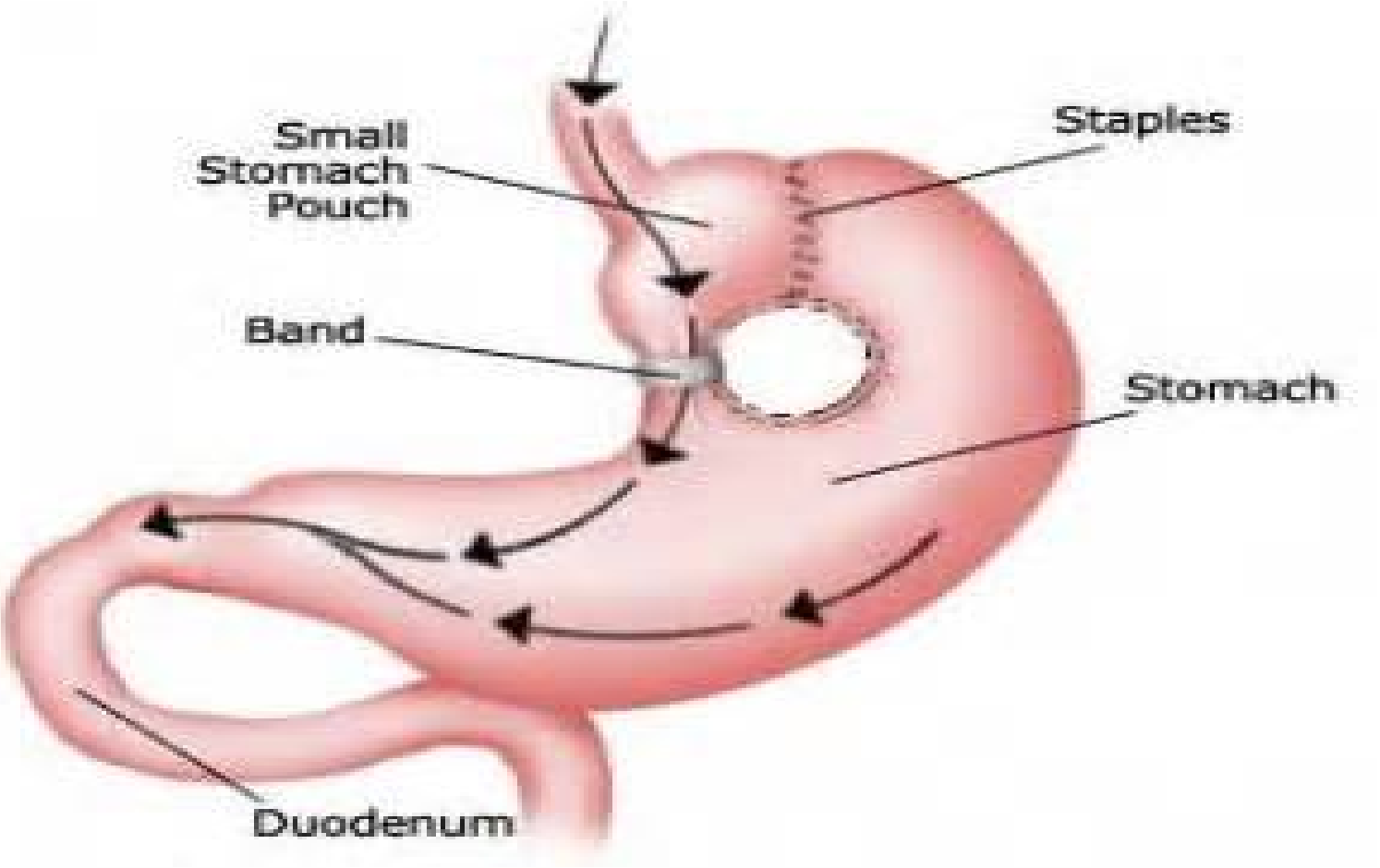
Vertical Banded Gastroplasty



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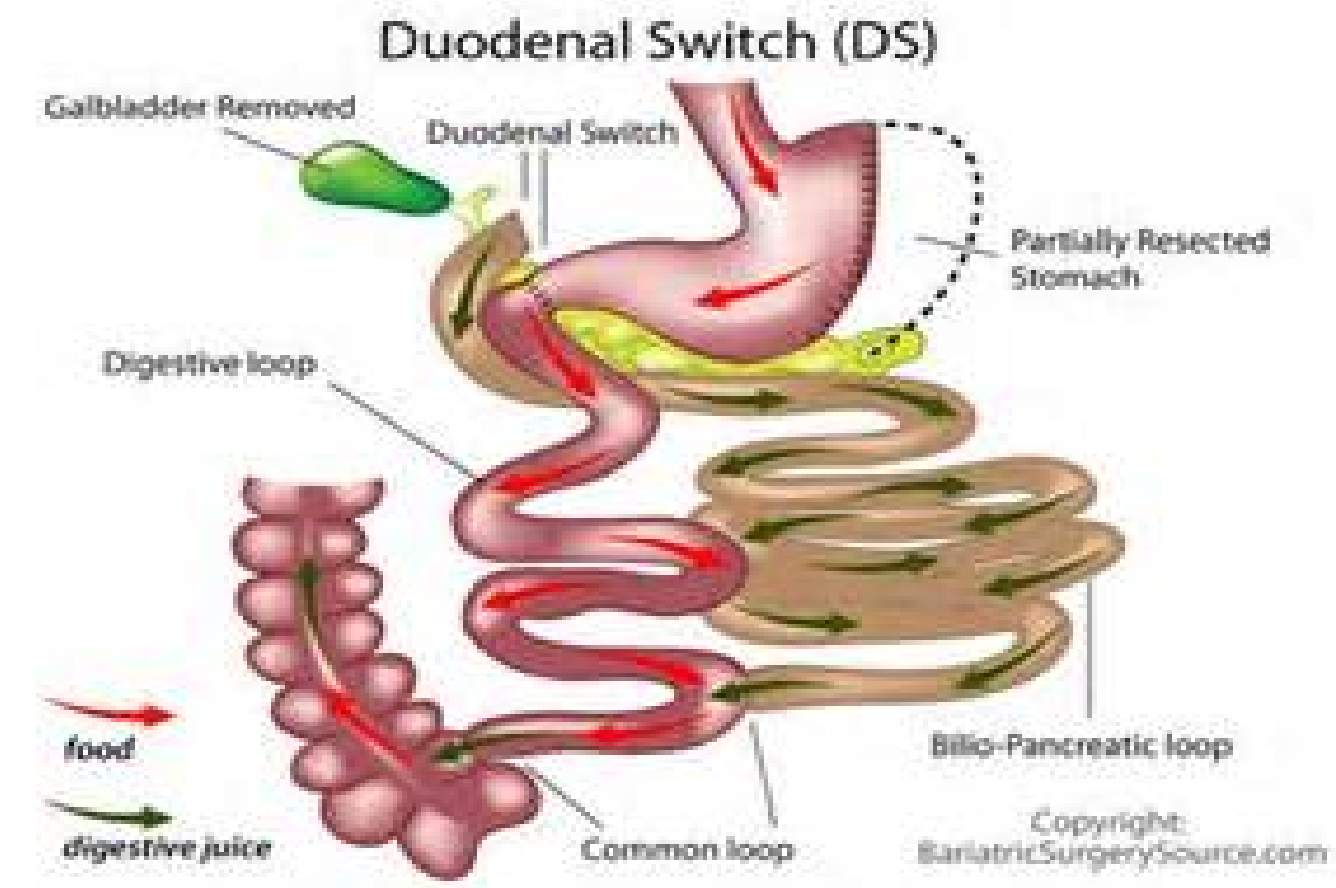
Biliopancreatic Diversion with Duodenal Switch



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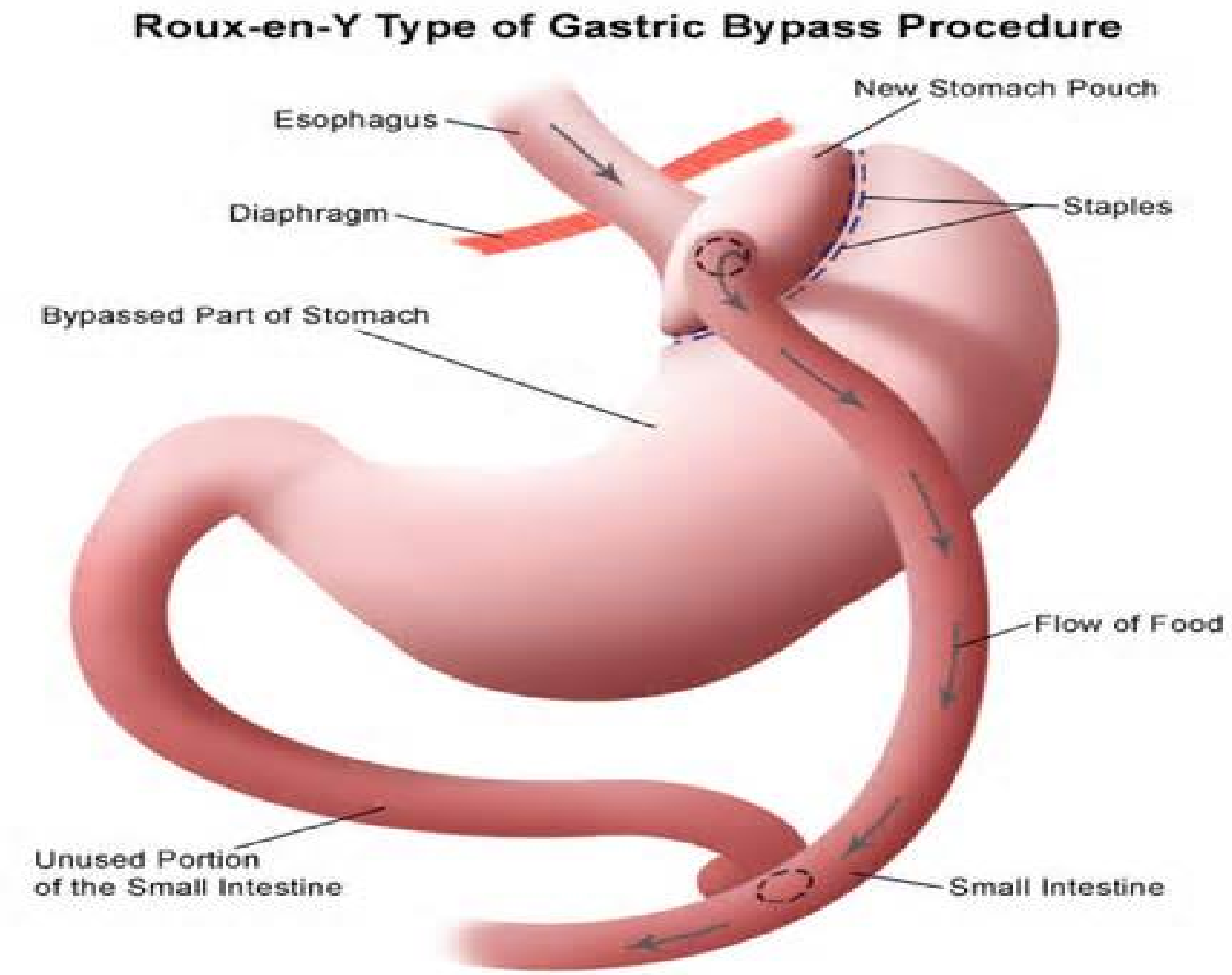
Roux-en-Y Gastric Bypass

- Most common procedure for weight loss
- Excludes 90-95% of stomach, entire duodenum, portion of proximal jejunum from the GI tract
- Greater weight loss, longer lasting than other procedures
- Decreased body weight of 48-85% can be seen within 1-2 years, maintenance of 25-68% pre-surgery weight after 7-10 years



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Post-Surgery

- Improvements in post-op care reducing morbidity/mortality
- 30 days post-op mortality rate = 0.3% with bypass or banding and 1.1% with malabsorptive surgery

Gastric Bypass

- Complications—early
  - DVT, pulmonary emboli, anastomotic leaks, bleeding, wound infections
- Need for vitamin supplementation
  - No vitamin supplementation = vitamin B_{12} and iron deficiency, microcytic anemia
- Vitamins recommended:
  - 1-2 tablets multivitamin daily
  - 1200-2000 mg calcium citrate daily
  - 400-800 IU vitamin D daily
  - 400 mcg folic acid daily
  - 40-65 mg elemental iron daily
  - 350 mcg oral vitamin B_{12} daily

Gastric Bypass continued…

- Dumping syndrome
  - Abdominal pain, abdominal cramping, nausea, diarrhea, bloating, tachycardia, syncope
- Diet changes help dumping syndrome
  - Small frequent meals, avoid refined sugar, increase intake of fiber/complex carbohydrates/protein
- Weight loss = improvements of obesity complications
  - Remission of type 2 diabetes up to 80%
  - Improve other comorbidities
  - Discontinue pharmacotherapy for complications of obesity

Bariatric Surgery Effects on Medications

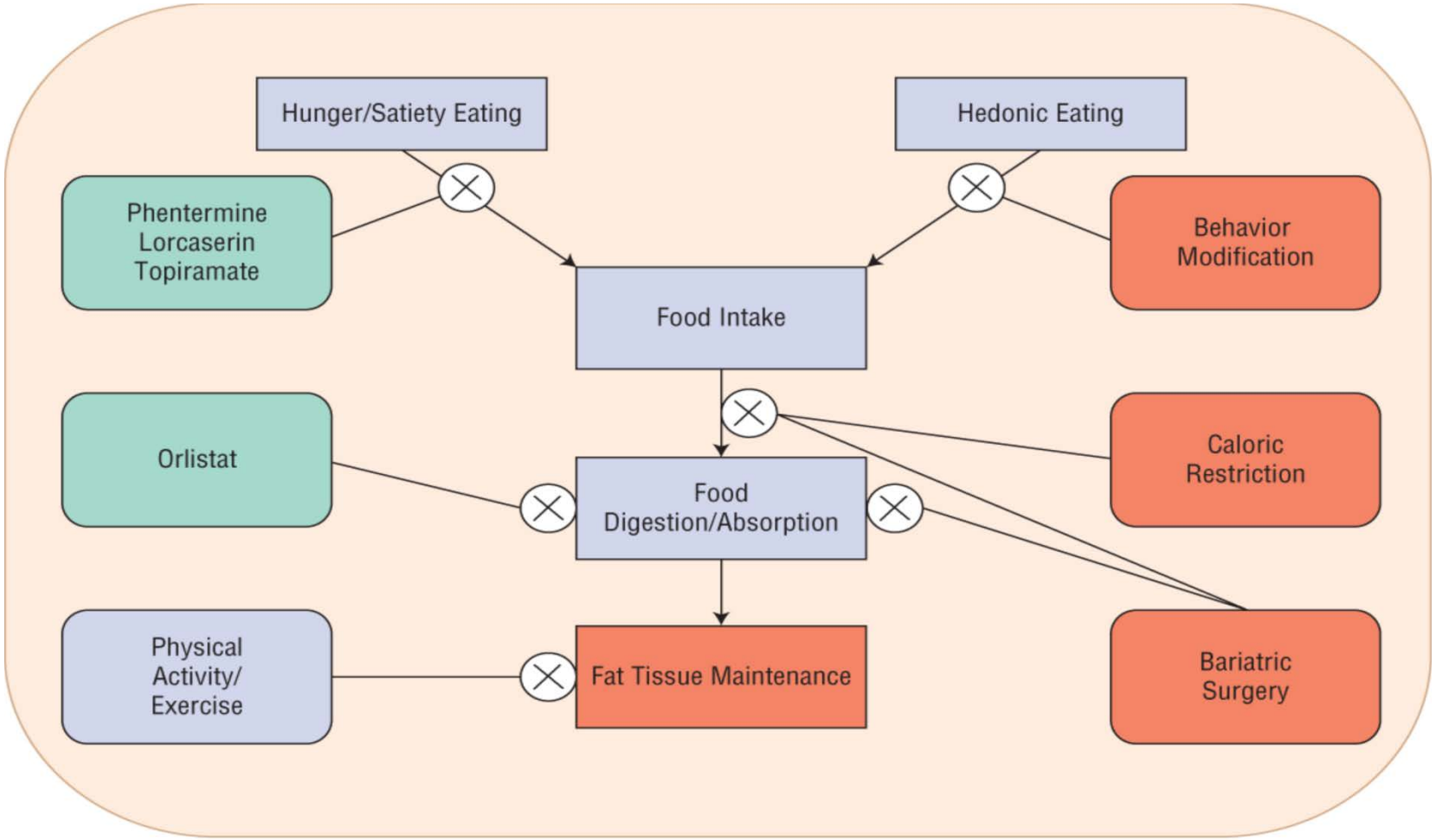
- Impede drug absorption
- Alter dissolution of pH-dependent medications
- Narrow therapeutic window medications
- May need to alter medication therapy

Pharmacologic Therapy

General Information

- Debate on use is ongoing
- Short-term use has predictable weight regain after therapy discontinued
- Long-term therapy may be more appropriate if no contraindications to therapy
- NIH: consider medication use in adults with BMI $\geq$30 kg/m^2 or WC of $\geq$40 in. for men and $\geq$35 in. for women, or BMI 27-30 kg/m^2 with $\geq$2 risk factors if 6 months of diet, exercise, and behavioral modification does not achieve desired weight loss

Sites of Action for Pharmacotherapy



General Information continued…

- Not monotherapy, combo of diet, exercise, and behavior modification, sometimes complementary and alternative therapies
- Use patient-specific factors and characteristics to determine if pharmacologic therapy is appropriate and which one to use

Available Therapies

- Approved for long-term use
  - Orlistat (Xenical, Alli)
  - Lorcaserin (Belviq)
  - Phentermine/topiramate (Qsymia)
  - Naltrexone/bupropion (Contrave)
  - Liraglutide (Saxenda)
- Approved for short-term use
  - Phentermine
  - Diethylpropion
  - Amphetamines

Available Therapies continued…

- Other agents
  - Off-label use of serotonergic agents
  - Noradrenergic-serotonergic agents
- Complementary and alternative agents
  - Bitter orange
  - Chromium
  - Chitosan
  - Ephedra alkaloids
  - Guarana extract/tea extracts
  - Hoodia
  - Pyruvate

Long-Term Agents

- Obesity chronic disease
- Agents approved by FDA show limited data on morbidity and mortality outcomes
- Not known optimal length of therapy
- Discontinuation leads to weight regain, so continuing effective and tolerated regimen is common practice

Orlistat: Lipase Inhibitor

- GI lipases essential in absorption of long-chain triglycerides
- Orlistat synthetic derivative of lipstatin→natural lipase inhibitor
- Minimally absorbed, weight loss result of persistent lowering of dietary fat absorption through selective inhibition of GI lipase
- 30% reduction in fat absorption in prescription doses

Orlistat continued…

- Available as prescription and nonprescription
- Take within 1 hour of consuming foods that contain fat to have effect
- If skip meal, do not take
- If no fat in meal, do not take

Orlistat continued…

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comment
Gastrointestinal Lipase Inhibitor					
Orlistat	Xenical	120 mg three times daily with each main meal containing fat	120 mg three times daily with each main meal containing fat		•Approved for long-term use •Take during or up to 1 hour after the meal. •Omit dose if meal is occasionally missed or contains no fat
Orlistat	Alli[a]	60 mg three times daily with each main meal containing fat	60 mg three times daily with each main meal containing fat		Same as Xenical

Orlistat continued…

- Clinical studies show modest increase in weight lost and decrease in amount regained during supervised programs
- XENDOS (Xenical in the prevention of diabetes in obese subjects)
  - Longest trial of orlistat (4 years)
  - Double-blind, placebo-controlled prospective trial
  - Moderate weight loss sustained after 4 years compared to placebo
  - Orlistat use decreased development of T2DM by 37.3% in patients with impaired glucose tolerance

Orlistat continued…

- Improvement in lipids (TC and LDL), glucose control, other markers of metabolism with diet and orlistat
- Approved for chronic treatment of obesity in adults and adolescents aged 12-16 years
- Dose is 120 mg TID

Orlistat Side Effects

- GI—up to 80% of patients on prescription dose
  - Soft stools, abdominal pain or colic, flatulence, fecal urgency, incontinence
- GI SE most common in first 1-2 months of therapy
- SE mild to moderate, improved with length of use
- Helpful to limit dietary fat prior to starting orlistat

Orlistat Side Effects continued…

- Severe diarrhea affects the absorption of oral medications
  - Oral contraceptives, fat-soluble vitamins, β-carotene
- MVI should be taken along with orlistat therapy
- Reduced fat absorption can affect absorption of lipophilic drugs
- May interfere with absorption of narrow therapeutic range drugs
- Separation of administration times can minimize drug interactions

Orlistat—Liver

- 2009-2010: FDA did safety review for risk of rare liver damage
- Small amount of cases of liver damage between 1999-2009
- Causality not found
- Recommend to monitor for signs/symptoms of liver injury
  - Itching, yellow eyes/skin, dark urine, loss of appetite, light-colored stools

Orlistat—Monitoring

- BMI
- Calorie and fat intake
- BG in DM patients
- Thyroid function in thyroid patients
- Liver function test if showing symptoms of hepatic dysfunction

Lorcaserin: Serotonin Receptor Agonist

- Selective serotonin 5-HT_{2c} receptor agonist
- FDA approved for BMI ≥30 or ≥27 with comorbidity
- Results in appetite suppression so reduced energy intake, enhanced satiety
- BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management)
  - 2 years, randomized, placebo-controlled, double-blind, prospective
  - Decreased weight, improved fasting glucose, insulin, TC, LDL, and TG at 1 year
  - Some weight regain seen after 2 years, but some able to maintain weight loss

Lorcaserin continued…

- Effective in type 2 diabetes—weight loss of 4.5% and improved hemoglobin A1c and fasting glucose at 1 year
- Discontinue therapy if 5% weight loss not achieved by week 12

Lorcaserin continued…

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comment
Serotonin 2C Receptor Agonist					
Lorcaserin	Belviq	10 mg twice daily	10 mg twice daily	Use with caution in moderate renal impairment and severe hepatic impairment; not recommended in patients with end stage renal disease	Approved for long-term use Controlled substance: C–IV

Lorcaserin—Side Effects

- Headache
- Dizziness
- Constipation
- Fatigue
- Nausea
- Dry mouth
- Contact PCP if symptoms of cardiac valve disease (dyspnea, edema)

Lorcaserin—Side Effects/Interactions

- Do not use with other serotonergic and dopaminergic medications
  - Increased risk of serotonin syndrome
  - Increased risk of neuroleptic malignant syndrome-like reaction
- Use with caution in patients with CHF, increased risk of valvulopathy
- Rare SE: psychiatric disorders, priapism, elevated serum prolactin concentrations
- Listed as controlled substance IV due to potential for abuse

Phentermine-Topiramate ER

- Approved by FDA for chronic weight management in patients with BMI ≥30 or BMI >27 with at least one weight-related comorbidity
- MOA: phentermine: enhances norepinephrine and dopamine neurotransmission which leads to appetite suppression effects; topiramate: antiepileptic drug with effects on weight management not known

Phentermine-Topiramate ER

- Doses lower than doses of each separate product as monotherapy
- Gradually titrate dose
- Increase dose after 14 days; after 12 weeks of therapy, dose may be increased again to maximum dose
- When discontinuing therapy, dose should be gradually tapered by taking a dose every other day for at least 1 week to decrease risk of possible seizures

Phentermine-Topiramate ER

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comment
Phentermine–Topiramate Combination					
Phentermine and topiramate extended release	Qsymia	3.75 mg of phentermine and 23 mg of topiramate once daily for 14 days; then increase to 7.5 mg of phentermine and 46 mg of topiramate once daily	7.5 mg of phentermine and 46 mg of topiramate once daily to a maximum dose of phentermine 15 mg and topiramate 92 mg	Maximum dose for patients with moderate or severe renal impairment or patients with moderate hepatic impairment is 7.5 mg of phentermine and 46 mg of topiramate	•Approved for long-term use •Take dose in the morning to avoid insomnia •Controlled substance: C–IV

Phentermine-Topiramate ER

- Trials have shown weight loss when used along with diet and lifestyle changes, also beneficial effects on blood pressure, TC, LDL, TG, fasting glucose, and A1c
- CONQUER trial:
  - Randomized, placebo-controlled, double-blind, prospective trial with 2487 patients
  - 4-week titration phase at 2 doses, weight loss at 1 year greater than placebo for both doses

Phentermine-Topiramate ER

- Side effects
  - Constipation
  - Dry mouth
  - Paraesthesia
  - Dysgeusia
  - insomnia
- Contraindications
  - Pregnancy
  - Glaucoma
  - Concomitant use with MAOI
  - Untreated hyperthyroidism

Phentermine-Topiramate ER

- Monitoring
  - Heart rate
  - Serum bicarbonate, potassium, electrolytes
  - Scr
- Drug interactions
  - Breakthrough bleeding with concomitant use of oral contraceptives
  - Non-potassium sparing diuretics

Phentermine-Topiramate ER

- Classified controlled substance schedule IV due to abuse potential of phentermine
- Discontinue therapy if 5% weight loss not achieved after 12 weeks

Naltrexone-Bupropion

- Approved by FDA in 2014 for adults with BMI of ≥30 or ≥27 with obesity-related comorbidities
- MOA not entirely understood, effect is to reduce hunger (no effect on energy metabolism)
- Naltrexone: non-selective opioid receptor antagonist, bupropion: selective reuptake inhibitor of dopamine and noradrenaline

Naltrexone-Bupropion Dosing

- Initiate with 8 mg natrexone-90 mg bupropion daily for 1 week, then escalate to maintenance 2 tablets BID (32 mg naltrexone-360 mg bupropion)
- Discontinue therapy if 5% weight loss not achieved by week 12

Naltrexone-Bupropion Trials

- COR-I (Contrave Obesity Research)
  - Multi-center, double-blind, placebo-controlled, phase 3
  - 1742 participants
  - Mean weight loss greatest in patients who took naltrexone-bupropion combination (vs. placebo)
- COR-II
  - 1496 obese/overweight patients with dyslipidemia or hypertension
  - 24-hour systolic and diastolic blood pressure and heart rate patterns similar across both groups
  - Those treated with naltrexone-bupropion: improved cardiometabolic risk factors, QOL, control of eating

Naltrexone-Bupropion Side Effects

- Nausea
- Headache
- Constipation
- Dizziness
- Vomiting
- Dry mouth

Naltrexone-Bupropion Place in Therapy

- Larger degree of weight loss than orlistat
- Small side-effect profile
- Good choice for patients who smoke and have mild to moderate level of depression

Liraglutide

- Only currently available FDA-approved injectable weight loss medication
- Glucagon-like peptide-1 receptor agonist
- Indicated as adjunct to low-calorie diet and increased physical activity for chronic management in adults with BMI $\geq$27 in presence of at least one weight-related comorbidity

Liraglutide Trial

- SCALE (Satiety and Clinical Adiposity-Liraglutide Evidence in Non-diabetic and Diabetic Individuals)
  - 56 weeks, randomized, placebo-controlled
  - Overweight/obese adults without diabetes
  - Participants treated with liraglutide: greater body weight loss, reduced cardiometabolic risk factors, improved fasting and postprandial glycemic variables, β-cell function and insulin sensitivity, delayed onset of T2DM

Liraglutide Side Effects

- Nausea
- Hypoglycemia
- Diarrhea
- Constipation
- Vomiting
- Headache
- Decreased appetite
- Dyspepsia
- Fatigue
- Dizziness
- Abdominal pain
- Increased lipase activity

Liraglutide Place in Therapy

- Particularly attractive for patients with hyperglycemia or overt diabetes
- Avoid in patients at risk for hypoglycemia
- Discontinue in those with sustained increase in resting heart rate (can raise heart rate)

Short-Term Agents

- Not consistent with current national guidelines for chronic obesity management
- Use have limited clinical use in practice

Phentermine

- IR and SR forms
- Effective when used with diet, exercise, and behavior modification
- Intermittent use shows same results as continuous use
- Most patients show weight regain after discontinuing use, some during use
- Suppresses appetite
- Most widely prescribed weight management medication by obesity specialists

Phentermine

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comment
Noradrenergic Agents					
Phentermine	Adipex-P, Suprenza	• Orally disintegrating tablet: 15 or 30 mg once every morning • Phentermine hydrochloride: 15–37.5 mg/day given in one or two divided doses; administer before breakfast or 1–2 hours after breakfast	• Orally disintegrating tablet: 15 or 30 mg once every morning • Phentermine hydrochloride: 15–37.5 mg/day given in one or two divided doses; administer before breakfast or 1–2 hours after breakfast	Use with caution in patients with renal impairment	• Approved for short-term monotherapy • Controlled substance: C–IV • Prescriptions should be written for the smallest quantity to minimize possibility of overdose • Individualize to achieve adequate response with lowest effective dose

Phentermine

- Do not use at night due to insomnia
- Due not use in patients with hypertension or cardiac abnormalities
- Monitoring:
  - Baseline cardiac evaluation, ECHO, weight, WC, BP
- Drug interactions
  - MAOI
- Contraindications
  - Hyperthyroidism or agitated states
  - Abuse substances : cocaine, methamphetamine
  - Glaucoma

Phentermine—Side Effects

- Insomnia if dosed late afternoon
- Increased blood pressure
- Ischemic events
- Palpitations
- Tachycardia
- Valvular disease
- Agitation
- Dizziness
- Headache
- Insomnia
- Psychosis
- Restlessness
- Dry mouth
- Constipation
- Thirst
- diarrhea

Diethylpropion

- Stimulated NE release from presynaptic storage granules
- Results in decreased appetite and food intake
- First-pass hepatic metabolism
- Elimination T½ life is 8 hours
- No dosing adjustments for renal or hepatic insufficiency
- Divided daily doses, usually TID before meals, or ER daily
  - Both are effective in short-term weight loss

Diethylpropion

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comment
Noradrenergic Agents					
Diethylpropion	Tenuate, Tenuate Dospan	• Immediate release: 25 mg three times daily administered 1 hour before meals • Controlled release: 75 mg once daily administered at midmorning	75 mg/day	Use with caution in patients with renal impairment	• Approved for short-term monotherapy • Dose should not be administered in the evening or at bedtime • Controlled substance: C–IV

Diethylpropion—Side effects

- Insomnia if dosed late afternoon
- Increased blood pressure
- Ischemic events
- Palpitations
- Tachycardia
- valvular disease
- Agitation
- Dizziness
- Headache
- Insomnia
- Psychosis
- Restlessness
- Dry mouth
- Constipation
- Thirst
- diarrhea

Diethylpropion

- Contraindications
  - Severe hypertension
  - Significant cardiovascular disease
- Monitoring parameters
  - Baseline cardiac evaluation
  - ECHO during therapy
  - Weight
  - WC
  - BP

Amphetamines

- Increase BP
- Show mild bronchodilation
- Have powerful stimulant effects and have addictive potential so no longer used anymore

Off-Label Use of Serotonergic Agents

- By increasing central serotonin levels, you decrease the amount of food eaten and increase the time between food intake
- Not approved by FDA as weight loss agents
- Not recommended for treatment of obesity
- Fluoxetine has been given as appetite suppression: higher doses (60 mg) used
- Weight regain occurs with cessation of therapy

Noradrenergic-Serotonergic Agents

- Sibutramine was used for long-term weight loss
- Showed an increased cardiovascular risk
- Voluntarily withdrawn from US market

Complementary and Alternative Therapies

- 34% of US adults have used alternative therapies for weight loss
- Recently, some products have been found to have undeclared prescription drugs in them

Bitter Orange

- Structural similarities to ephedrine
- Used more since ephedrine banned
- SE:
  - Increased heart rate
  - Increased BP

Chromium

- Essential nutrient
- Cofactor for carbohydrate, protein, and lipid metabolism
- Food sources:
  - Brewer's yeast
  - Calves' liver
  - American cheese
  - Wheat germ
- Trials have not shown efficacy in weight loss

Chitosan

- May block absorption of fat from the gut
- In many weight loss supplements
- Short-term investigations show more effective than placebo, but not clinically significant weight loss

Ephedra Alkaloids

- Plant source of ephedrine
- 1994-1997 FDA received reports of SE such as seizures, stroke, and death
- 2004 FDA removed from use due to health risk

Hoodia

- Appetite suppressant effect
- Short-term trial (15 days) did not have decreased food intake
- Purified Hoodia extract associated with nausea, vomiting, changes in skin sensation

Pyruvate

- Common ingredient in weight loss products
- Advertised to increase metabolism
- No evidence to support efficacy
- Very large doses can cause GI side effects
  - Bloating
  - Diarrhea

Agents Under Investigation

- Tesofensine: reduction in appetite
- Cetilistat: lipase inhibitor
  - Compared to orlistat: similar weight loss, more GI affects with orlistat
- Bupropion and naltrexone
- Bupropion and zonisamide
- Pramlintide and metreleptin

Personalized Pharmacotherapy

- Genetic influences contribute to variance in body weight, up to 80%
- Research focusing on identifying specific genes involved
- No therapy as of yet

Evaluation of Outcomes

- Assess patient progress 1-2 times per month for a few months, then monthly
- Each evaluation should include weight measurement, WC, BMI, BP, medical history, and assessment of medication tolerability
- Discontinue therapy after 3-4 months if not weight loss or maintenance of prior weight
- Patients with DM on weight loss medication require more intensive monitoring and monitoring of BG

Summary

- Obesity is chronic disease
- Nonpharmacologic therapy is mainstay of therapy
- Drug therapy considered as adjunct for patients who fail nonpharmacologic therapy alone after 6 months
- Individualize treatment for obesity
- Management is a lifelong process