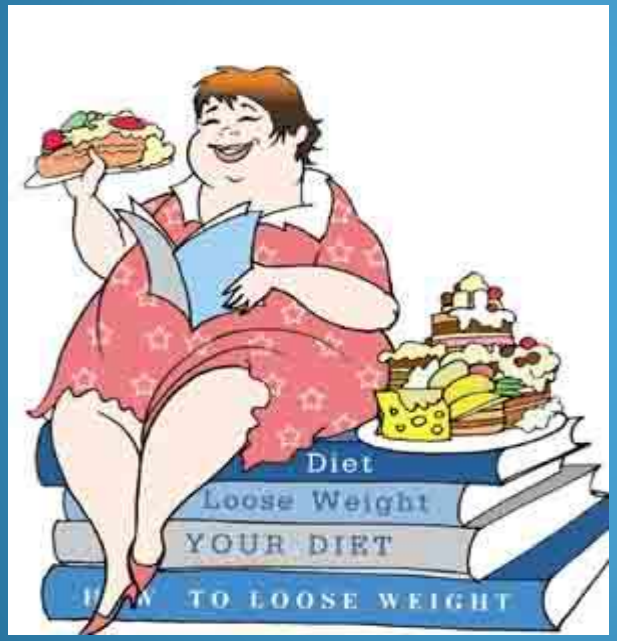
Farmakologi
OBAT ANTI OBESITAS



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Definisi Obesitas

- Obesitas : akumulasi lemak yang berlebihan dalam tubuh
- Sulit diobat dan sering menetap sepanjang hidup
- Diagnosa obesitas berdasarkan perhitungan dari :
  - Body mass index (BMI)
  - Rasio pinggang –panggul (waist-hip ratio)

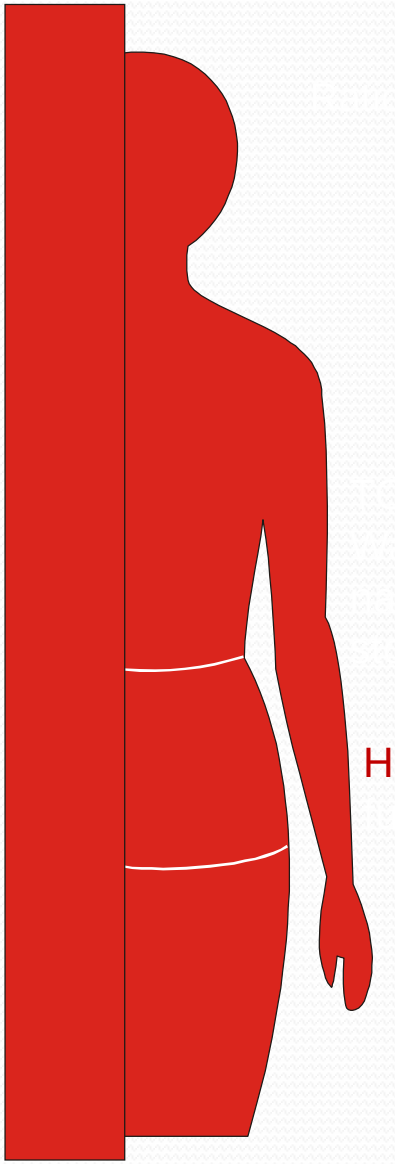
Classification of Overweight and Obese by Body Mass Index

$$BMI = \frac{\text{Weight (kg)}}{[\text{Height(m)}]^2}$$

	WHO guidelines	Proposed Asia Pacific guidelines
Underweight	< 18.5	< 18.5
Normal	18.5-24.9	18.5-22.9
Overweight	25.0-29.9	≥ 23
At risk	-	23-24.9
Obesity	30-34.9 (Class I)	25-29.9 (Class I)
	35-39.9 (Class II)	≥ 30 (Class II)
Extremely Obese	≥ 40 (Class III)	-

Waist-to-hip ratio

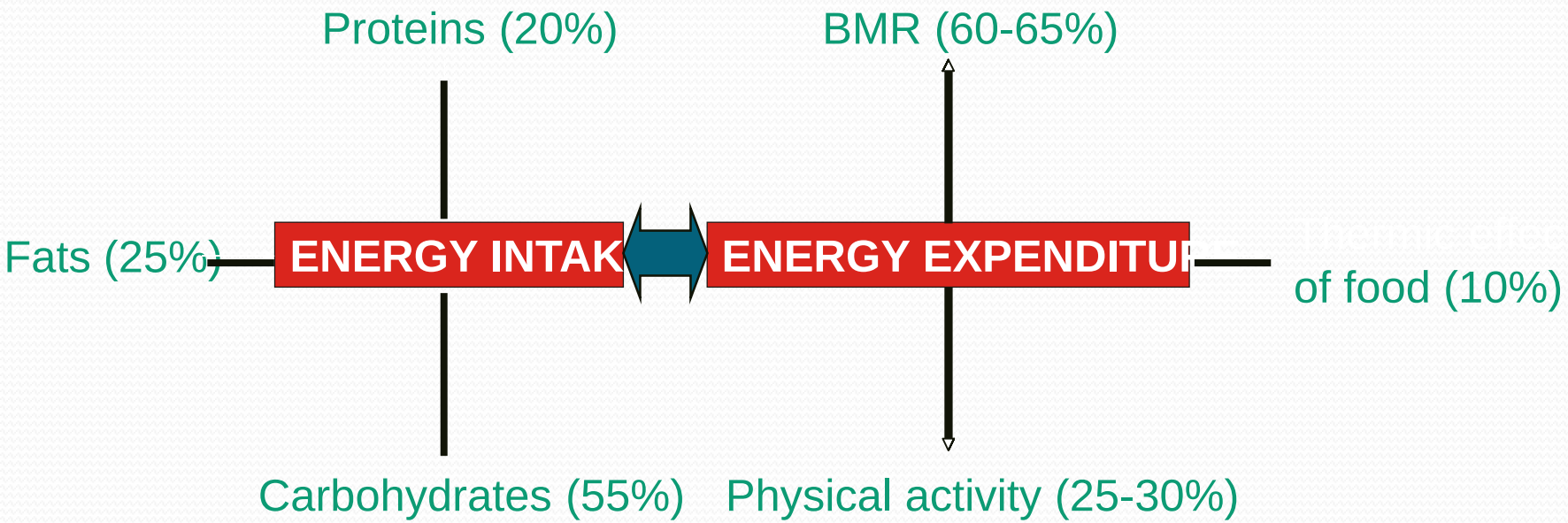
Risk increases if waist circumference is >94 cm in men and >80 cm in women



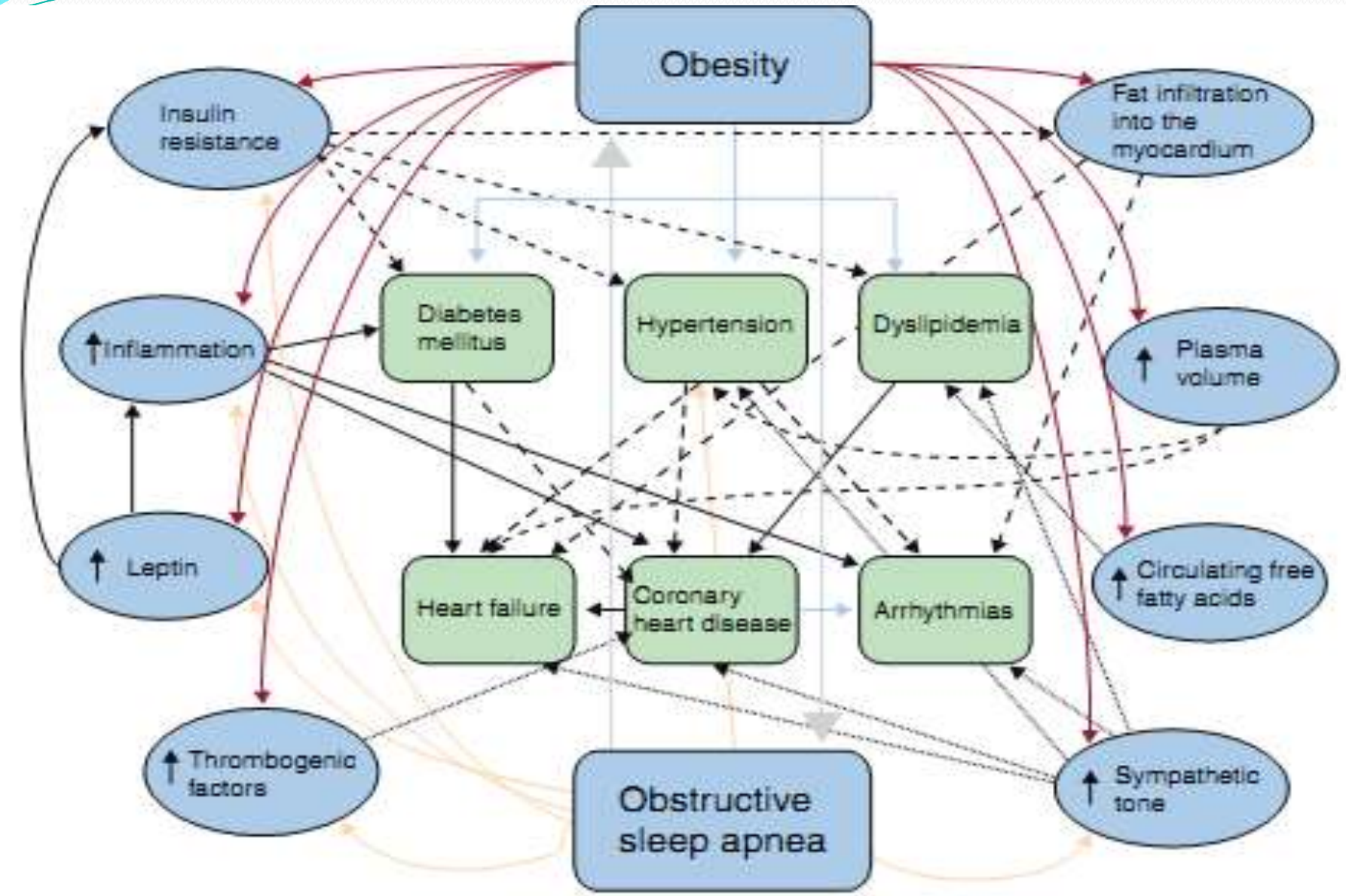
Hips: Measure at

Desired Ratio
Women : ≤0.8
Men : ≤ 1.0

Obesity – An imbalance in energy intake and energy expenditure



Obesitas sebagai Faktor resiko Penyakit lain



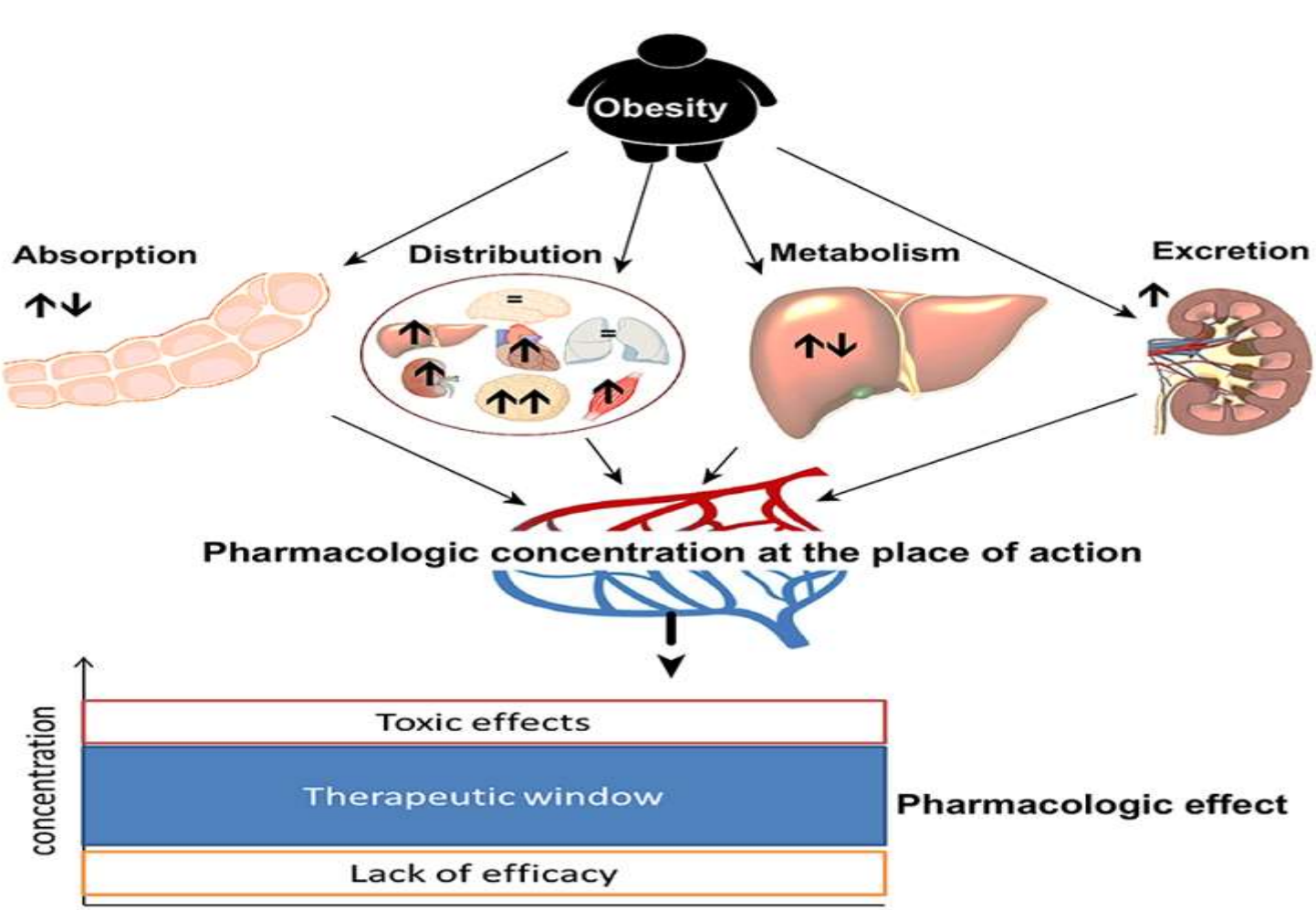
Diseases and conditions for which obesity is a risk factor

- Type II Diabetes Mellitus***
- Hypertension**
- Dyslipidemia***
- Respiratory disease***
- Gout**
- Reflux disease
- Coronary artery disease**
- Psychological problems
- Gallbladder disease***
- Osteoarthritis**
- Infertility*
- Venous circulatory disease
- Increased anaesthetic risk*
- Low back pain*
- Polycystic ovary disease*
- Cancer* (ovarian, breast, endometrial, gallbladder, prostate, colon)

Advantages of weight loss

- Weight loss of 0.5-9 kg (n=43,457) associated with 53% reduction in cancer-deaths, 44% reduction in diabetes-associated mortality and 20% reduction in total mortality
- Survival increased 3-4 months for every kilogram of weight loss
- Improvement in severity of diseases
- Person feels ‘fit’ and mentally more active
- Decreased risk for cardiovascular disease (hyperlipidemia, hypertension and insulin resistance)
- Decrease in severity of sleep apnea.
- Reduced symptoms of degenerative joint disease.

Obesitas mempengaruhi farmakokinetik obat



Penurunan BB

Tujuan :

- Mencegah penambahan BB
- Menurunkan BB serealistis mungkin (target BMI)
- Memelihara BB yang sudah turun jangka panjang

Target : penurunan 5-10% BB dlm 6 bulan

Cara :

1. Non Farmakologi = *life style modification (diet & olah raga)*
2. Farmakologi
3. VLCD, Surgery

Approaches to obesity management

	Diet	Activity	Drugs	VLCD	Surgery
BMI 23-25 *No risk factors* *DM/CHD/HT/HL*	 √ √	 √ √	 - √		
BMI 25 – 30 No risk factors DM/CHD/HT/HL	 √ √	 √ √	 √ (consider) √		
BMI > 30 No risk factors DM/CHD/HT/HL	 √ √	 √ √	 √ √	 √(in √ severe)	 √(consider √ in severe)

	Drugs leading to weight gain	Weight gain in kg	Possible alternative	Weight loss in kg
Antiepileptics/mood stabilizer	Valproate	1.2–5.8[a]	Zonisamide	–7.7
	Gabapentin	2.2	Topiramate	–3.8
	Lithium	4.0[a]	Lamotrigine	±0
	Carbamazepine	1.0[a]		
Neuroleptics	Olanzapine	2.4	Ziprasidone	–3.2 to –2.7[a]
	Quetiapine	1.1		
	Risperidone	0.8		
	Clozapine	4.2 to 9.9[a]		
	Aripiprazole	0.6[a]		
Glucocorticoids	Class effect with approximately 4–8% increase in body weight			
Antidiabetics	Insulin	1.8–6.5[a]		
	Glimepiride	2.1	Metformin	–1.1
	Glibenclamide	2.6	Acarbose	–0.4
	Pioglitazone	2.6	GLP1-agonists	–1.2 to –5.6
	Tolbutamide	2.8	SGLT2-Inhibitors	–2.2 to –4.7
	Sitagliptin	0.55		
	Nateglinide	0.3		

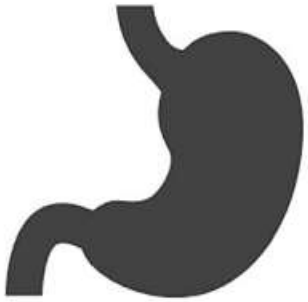
Antidepressives	Nortriptyline	3.7[a]	Bupropion	−1.3
	Doxepine	2.7[a]	Fluoxetine	−1.3
	Amitriptyline	1.8	Sertraline	(unknown)
	Mirtazapine	1.5	Venlafaxine	(unknown)
			Duloxetine	(unknown)
Betablockers	Atenolol	1[a]	(ACE-Inhibitors)[b]	+/−0
	Metoprolol	0.5–1.5[a]	(AT1-Blockers)[b]	+/−0
	Propranolol	−0.6 to 2.3[a]	(Thiazides)[b]	+/−0

Adapted from Pilitsi and colleagues,[8] Domecq and colleagues,[37] and Leslie and colleagues.[48]
[a]Limited or no data available from randomized placebo controlled trials and measured weight change.
[b]No effect on body weight but with metabolically favorable or at least neutral (thiazides) profile.
ACE, angiotensin-converting enzyme; AT1-Blockers, angiotensin II receptor antagonists; GLP1, glucagon-like peptide-1 receptor; SGLT2, sodium-glucose transport protein 2.

Potential Strategies for Anti-Obesity Drug Action

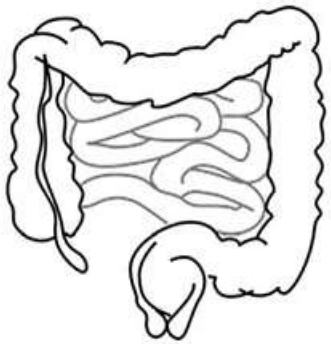
- **Reducing food intake.** Either amplify effects of signals/factors that inhibit food intake or block signals/factors that augment food intake
- **Blocking nutrient absorption** (especially fat or carbohydrates) in the intestine.
- **Increasing thermogenesis.** Either increase metabolism and dissipate food energy as heat or increase energy expenditure through the enhancement of physical activity.
- **Modulating fat metabolism/storage.** Regulate fat synthesis/breakdown by making appropriate adjustments to food intake or energy expenditure.
- **Modulating the central regulation of body weight.** Either alter the internal set point or modulate the signals presented regarding fat stores.

Target Tx antiobesitas



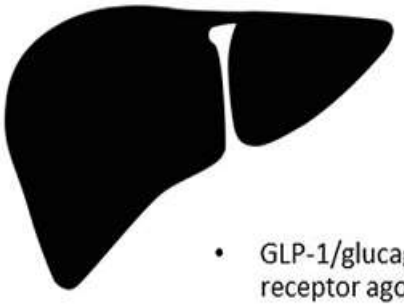
- GLP-1 analogues
- GLP-1 dual or triple agonists

- Phentermine/topiramate
- Lorcaserin
- Naltrexone/bupropion
- GLP-1 analogues
- Amylin mimetics
- Leptin analogues
- Ghrelin antagonists
- NPY antagonists
- MC4R antagonists
- Cannabinoid type-1 antagonists



- Orlistat

- SGLT-2 inhibitors



- GLP-1/glucagon receptor agonists
- GLP-1/GIP receptor agonists

ANTI OBESITY

Sebelum 1999

- Phentermine
- Dietylpropion
- Phendimetrazine
- Benzphetamine
- Orlistat

Setelah 2012

- Lorcaserin
- Phentermine HCL/topiramate extended release
- Naltrexone HCL/bupropion HCL extended release
- Liraglutide

Sympathomimetic Amines

- Examples: Phentermine, diethylpropion, phendimetrazine, benzphetamine
- MoA=Increases satiety
- Potential adverse experiences include:
  - Palpitation
  - Tachycardia
  - Increased blood pressure
  - Overstimulation
  - Tremor
  - Dizziness
  - Insomnia
  - Dysphoria
  - Headache
  - Dryness of mouth
  - Dysgeusia
  - Diarrhea
  - Constipation
  - Pregnancy category X

Drug	Product name	Application	Mechanism of action	Main adverse effect	Contraindication	FDA approval
Orlistat	Xenical®, Alli®	60 or 120 mg TID during or within 1 hour of a fat-containing meal	Gastrointestinal and pancreatic lipase inhibitor; decrease lipid absorption	Oily stools, oily spotting, fecal urgency, fecal incontinence, hyperdefecation, flatus with discharge, deficiency in vitamins A, D, E, and K	Pregnancy, cholestasis, malabsorption	Yes 1999
Phentermine/ topiramate	Qsymia®	3.75/23 mg QD for 14 days and then 7.5/46 mg QD; If <3% weight loss is achieved at 12 weeks, increase to 11.25/69 mg QD for 14 days, followed by 15/92 mg QD; discontinue gradually if <5% weight loss is achieved at 12 weeks with the highest dose	NE agonist/GABA agonist, glutamate antagonist; suppress appetite	Paresthesia, dry mouth, constipation, insomnia, dysgeusia, anxiety, depression	Pregnancy, uncontrolled HTN, CVD, CKD, glaucoma, hyperthyroidism patients on MAOIs	Yes 2012
Naltrexon/ bupropion	Contrave®, Mysimba®	8/90 mg for 7 days; BID for 7 days; 2 tablets in the morning and 1 tablet in the evening for 7 days; and 2 tablets BID thereafter	Opioid receptor antagonist/dopamine agonist and NE reuptake inhibitor; increase satiety, suppress appetite	Nausea, headache, constipation, dizziness, vomiting, dry mouth	Pregnancy, uncontrolled HTN, seizure, anorexia or bulimia nervosa, abrupt discontinuation of alcohol, benzodiazepines, barbiturates or antiepileptic drugs, other bupropion-containing drugs, opioids or opiate agonists, MAOIs	Yes 2014
Liraglutide	Saxenda®	0.6 mg subcutaneous injection QD, increase by 0.6 mg weekly to a daily target dose of 3 mg	Glucagon-like peptide-1 agonist; slow gastric emptying, increase satiety, decrease food reward	Nausea, diarrhea, constipation, vomiting, dyspepsia	Pregnancy, personal or family history of medullary thyroid carcinoma or type 2 MEN	Yes 2014
Lorcaserin	Belviq®, Belviq XR®	10 mg BID 20 mg extended release QD	Serotonin 2C receptor agonist; reduce food intake	Headache, dizziness, fatigue, nausea, constipation, dry mouth	Pregnancy, severe renal disease	Yes 2012 Withdrawn from the market in February 2020

FDA: Food and Drug Administration, EMA: European Medicines Agency, XR: extended release, TID, three times per day, QD: once daily, BID: twice daily, NE: norepineph butyric acid, HTN: hypertension, CVD: cardiovascular disease, CKD: chronic kidney disease, MAOIs: monoamine oxidase inhibitors, MEN: multiple endocrine neoplasia.

Orlistat

- the longest licensed antiobesity drug for long-term use
- MoA= inhibition of gastric and pancreatic lipases, which leads to a ~30% decrease in the absorption of intestinal triglycerides and thus calories
- co-prescribing a fibercontaining supplement—psyllium, its gastrointestinal
side effects can be reduced.

- Potential adverse experiences include:
  – Oily discharge from the rectum
  – Flatus with discharge
  – Increased defecation
  – Fecal incontinence
  – May increase risk of cholelithiasis
  – May increase risk of urinary oxalate
  – Rare post-marketing reports of severe liver injury
  – May decrease fast-soluble vitamin absorption (e.g., vitamins A, D, E, K, and beta carotene)
  – Pregnancy category X

Lorcaserin

- MoA=a selective agonist of the 5-hydroxytryptamine (5-HT) 2C receptors
- decreases food intake by increasing satiety through its serotonin anorectic effect by stimulating the proopiomelanocortin (POMC) receptors in the arcuate nucleus of the hypothalamus

- **Most Common Adverse Reactions***
  - Headache
  - Dizziness
  - Fatigue
  - Nausea
  - Constipation
  - Cough
  - Dry Mouth

  *May increase prolactin levels
- Contraindication : Pregnacy (X)

Phentermine HCL/Topiramate Extended Release

the first combination agent
for the long-term management of obesity.

- Phentermine is a shorter-acting sympathomimetic amine approved as monotherapy as a weight-management drug
- a noradrenergic agonist, is to enhance the release of norepinephrine, dopamine, and serotonin
- Topiramate is a longer-acting neurostabilizer approved as monotherapy for seizure disorders and migraine headache prevention.
- a gammaaminobutyric acid agonist, glutamate antagonist, and carbonic anhydrase inhibito
-

Potential Drug Interactions

• May alter the exposure to oral contraceptives, causing irregular menstrual bleeding but not an increased risk of pregnancy
– Oral contraceptives should not be discontinued if spotting occurs
• May potentiate central nervous system depressants such as alcohol
– Patients should avoid concomitant alcohol
• May potentiate hypokalemia of non-potassium-sparing diuretics

Most Common Adverse Reactions

- In clinical trials, adverse reactions occurring more than or equal to 5 percent of the time include:
  – Paresthesia
  – Dizziness
  – Dysgeusia (taste distortion/perversion)
  – Insomnia
  – Constipation
  – Dry mouth

- **Laboratory Abnormalities May Include**
  – Metabolic acidosis
  – Elevated creatinine
  – Lowering of glucose levels

Contra-indicated:

- – Glaucoma
  – Hyperthyroidism
  – During or within 14 days of taking monoamine oxidase inhibitors
  – Women of reproductive potential should have a negative pregnancy test before treatment and monthly thereafter and should use effective contraception while on phentermine HCL/topiramate extended release
  – Pregnancy or nursing (Pregnancy category X)

Should be discontinued in patients with:

- – Unacceptable increases in adrenergic responses, such as increase in heart rate, especially in those with cardiac and/or cerebrovascular disease
  – Suicidal behavior and ideation
  – Acute myopia and secondary angle-closure glaucoma
  – Unacceptable mood and sleep disorders
  – Cognitive impairment
  – Pregnancy or nursing

Naltrexone HCL/Bupropion HCL Extended Release

- Bupropion is an aminoketone antidepressant with relatively weak inhibition of neuronal reuptake of norepinephrine and dopamine. bupropion is used as a smoking cessation aide

- Naltrexone is an opioid antagonist. approved for the treatment of opioid and alcohol addiction and antagonizes an opioid-dependent feedback loop that limits the effects of bupropion on the POMC neurons; hence, this drug combination works synergistically

-

Liraglutide

- an injectable glucagon-like peptide 1 (GLP-1) derivative that was approved by the FDA in 2014 for weight management (dose, 3.0 mg subcutaneous [SC] daily)
- After meals, GLP-1 is secreted from the distal ileum, proximal colon, and the vagal nucleus of the solitary tract and exhibits multiple effects as an incretin hormone.
- GLP-1 :
  - mainly regulates blood glucose by enhancing insulin secretion from the pancreatic beta-cells
  - inhibits glucagon secretion in a glucose-dependent manner.
  - induces postprandial satiety and fullness, slows gastric emptying, and decreases appetite and food consumption by acting on the hypothalamus, limbic/reward system, and cortex
- liraglutide is more stable in plasma and binds strongly to plasma proteins, thereby enabling a much longer half-life (13 hours) than the human endogenous GLP-1 (a few minutes)

INDICATIONS FOR USE OF OBESITY DRUGS

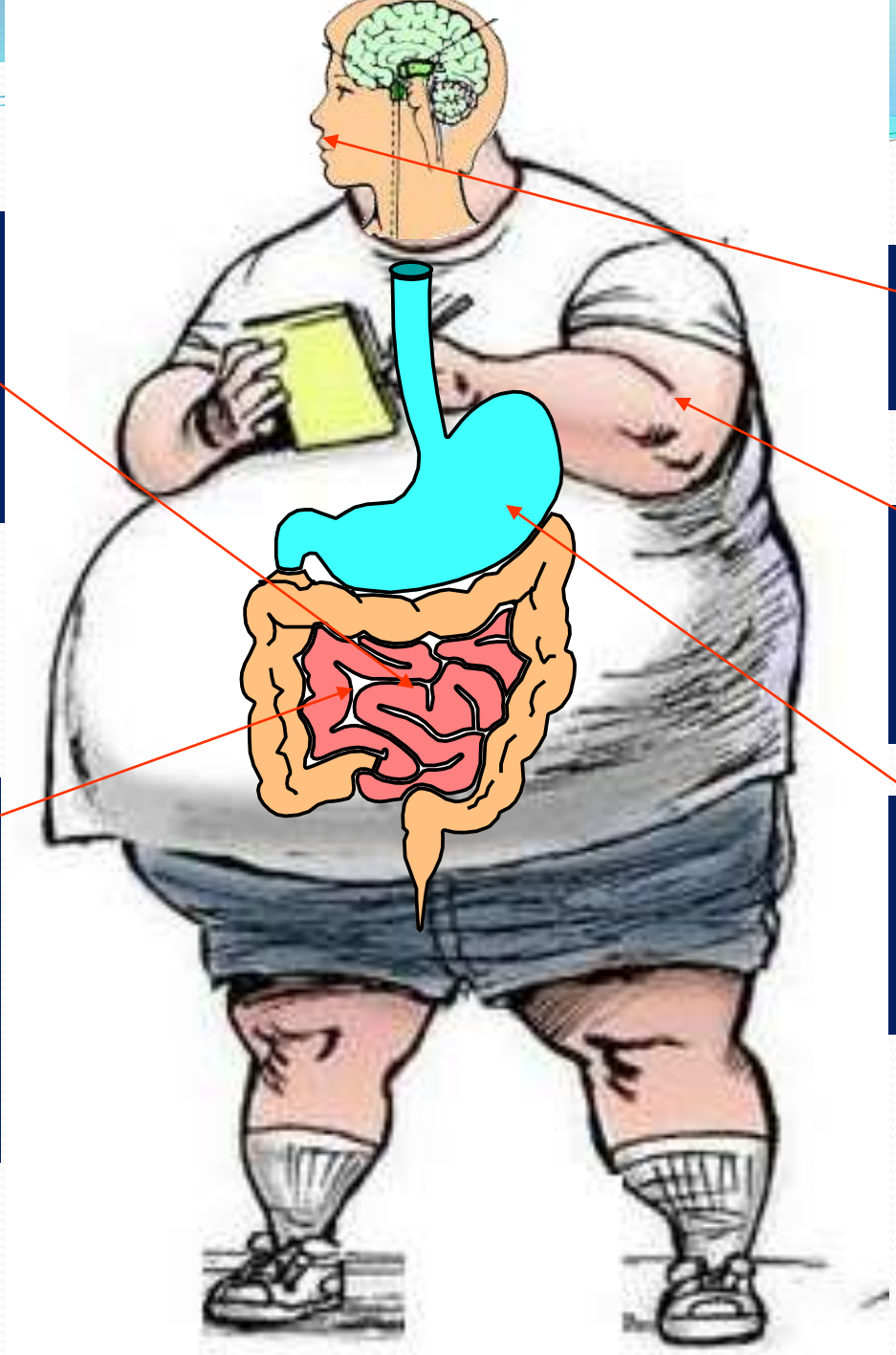
- A combined intervention of behavior therapy, dietary changes and increased physical activity should be maintained for at least 6 months before considering pharmacotherapy.

NHLBI Obesity Education Initiative, Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults

INDICATIONS FOR USE OF OBESITY DRUGS

- BMI of 30 kg/m^2 or more or a BMI of 27 kg/m^2 or more with comorbid condition
- Understand that drug therapy is adjunctive to lifestyle intervention
- Have realistic expectations about weight loss goals and outcomes
- Demonstrate readiness for change
- Are unable to lose/maintain weight with lifestyle change alone
- Comply with medication use
- Have no medical or psychiatric contraindications

↓ absorption of fat "Orlistat" "Chitosan"



Anorexic drugs "Sibutramine"

energy expenditure by "Sibutramine"

↓ absorption of CHO "Acarbose" "Gymenemic acid"

↓ gastric emptying by "Acarbose"

Terima Kasih
Atas
Perhatiannya