PHARMACOTHERAPY OF OBESITY

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BMI = BODY MASS INDEX

- BMI = body mass in kg / square of the height in metres = kg/m2
- BMI < 18.5 kg/m2 – underweight
- 18.5 < BMI < 25 – normal or acceptable weight
- 25 < BMI < 30 – obesity grade 1
- 30 < BMI < 40 – obesity grade 2
- BMI > 40 – obesity grade 3 or morbidly obese
- Excessive central adiposity increases risk for development of type 2 diabetes, hypertension, and dyslipidemia

CONDITIONS MORE PREVALENT IN OBESE POPULATIONS

Cardiovascular

- Hypertension
- Left ventricular hypertrophy
- Congestive heart failure
- Coronary artery disease
- Stroke

Pulmonary

- Obstructive airway disease
- Sleep apnea
- Pulmonary hypertension

Metabolic

- Hypercholesterolemia
- Hypertriglyceridemia
- Low serum high-density lipoprotein
- Diabetes mellitus and glucose intolerance
- Hyperinsulinemia
- Polycystic ovary syndrome
- Increased serum urate

Musculoskeletal

- Degenerative joint disease

Skin

- Acanthosis nigricans
- Stretch marks
- Hirsutism
- Skin tags

Gastrointestinal

- Cholelithiasis
- Esophageal reflux
- Hiatus hernia

Psychological

- Eating disorders
- Depression
- Affective disorders
- Social stigma

Neoplasm

- Breast cancer
- Colon cancer

EFFECTS OF VARIOUS NEUROTRANSMITTERS, RECEPTORS, AND PEPTIDES ON FOOD INTAKE

Brain Site	Increased Eating	Decreased Eating
Arcuate Nucleus of Hypothalamus (ARC)	Ghrelin	Leptin Glucagon Like Peptide-1 (GLP-1) Peptide YY (PYY)
Paraventricular Nucleus of Hypothalamus (PVN)	Neuropeptide Y (NPY) Agouti Related Protein (AgRP) Opioids (especially mu) Galanin	Melanocyte Stimulating Hormone (MSH, Melanocortin) Corticotropin Releasing Hormone (CRH) Cholecystokinin (CCK)
Lateral Hypothalamus (LH)	Orexin Melanocyte Concentration Hormone (MCH)	
Hypothalamus	Norepinephrine $\alpha 2$ Serotonin 5-HT1A	Norepinephrine $\alpha 1$ and $\beta 2$ Serotonin 5-HT1B and 5-HT2C Histamine H1 and H3
Nucleus Accumbens	Dopamine	
Amygdala	Opioids (especially mu)	

EFFECTS OF VARIOUS NEUROTRANSMITTERS, RECEPTORS, AND PEPTIDES ON FOOD INTAKE

Brain Site	Increased Eating	Decreased Eating
Brainstem (Hindbrain)	Neuropeptide Y (NPY) Agouti Related Protein (AgRP) Opioids (especially mu)	Leptin Melanocyte Stimulating Hormone (MSH, Melanocortin)
Vagus Nerve	Ghrelin	Leptin Cholecystokinin (CCK) Glucagon Like Peptide-1 (GLP-1) Peptide YY (PYY)
Various or Undetermined	Cannabinoid CB1	Dopamine D1 and D2

FAT TISSUE – AN ENDOCRINE ORGAN !!!

Roles:

- storing excess energy as fat
- play pivotal roles in regulation of energy homeostasis
- **adipokines**
  - pro-inflammatory adipokines
    - TNFα, resistin, adipocyte fatty acid binding protein (A-FABP), retinol-binding protein 4, monocyte chemoattractant protein 1 (MCP1), interleukin 6 (upregulated in obesity)
  - Adiponectin (downregulated in obesity)
- leptin
  - secreted by fat cells into the bloodstream
  - acts on the brain to regulate food intake and energy expenditure

FAT TISSUE – AN ENDOCRINE ORGAN !!!

Increase Insulin resistance	**In obese people**	**Insulin sensitizers**	**In majority of obese people**
Resistin	↑	Leptin	↑ leptin receptorial resistance is common
TNF alpha	↑	Adiponectin	↓

ETIOLOGY

- GENETIC PREDISPOSITION
- ENVIRONMENTAL FACTORS
- NUTRITION
- APPETITE
- ACTIVITY
- WEIGHT GAIN SECONDARY TO MEDICAL CONDITIONS
  - Hypothyroidism
  - Cushing's syndrome (idiopathic/iatrogenic)
- Medications
- Antidiabetics: insulin, sulfonylureas, and thiazolidinediones
- Psychiatric medicines
- Anticonvulsants EXCEPT topiramate

PHARMACOTHERAPY OF OBESITY

- Patients with BMI >30
- Patients with BMI >28 with additional risk factors (hypertension, hyperlipidemia, T2D.
- First-line therapy : change diet and lifestyle
- 1. Drugs that affect appetite
  - Sympathomimetics, psychostimulants
  - Peptides
  - Drugs influencing behavior and moodness
- 2. Drugs that decrease absorption of fat, cholesterol or carbohydrates
- 3. Drugs that increase metabolic rate
- 4. Drugs for lowering risk of complications in obese people
  - e.g. insulin sensitizing, lipid lowering drugs,
  - antihypertensive therapy

GENERAL APPROACH TO TREATMENT

- Diet
- Exercise
- Behavior modification
  - with or without pharmacologic therapy
  - and/or surgical intervention

- Secondary obesity

RECENTLY USED WEIGHT REDUCING DRUGS

Group	WHO name	Brand name
Psychostimulant + antiepileptic anorexigen	Phentermine + topiramate	Qsymia
Psychostimulant, anorexigen	mazindol	Mazanor, Sanorex
Psychostimulant, anorexigen	lorcaserin	Belviq
Psychostimulant, anorexigen	bupropion+ naltrexon	Mysimba
Leptin analog, anorexigen	metreleptin	Myalept
Inhibitor of lipid absorption, Lipase inhibitor	orlistat	Xenical
Inhibitor of glucose absorption Alpha glucosidase inhibitor	acarbose	Glucobay
Inhibitor of glucose absorption Alpha glucosidase inhibitor	miglitol	Glyset
GLP-1 receptor agonist	exenatide	Byetta sc inj.

DRUGS AFFECTING APPETITE
1.A. SYMPATOMIMETIC DRUGS, PSYCHOSTIMULANTS

Phentermine

- structurally similar to amphetamine
- enhanced NE and dopamine neurotransmission
- effective adjunct to diet, exercise, and behavior modification
- Adverse effects:
  - Insomnia
  - Significant increases in blood pressure, palpitations, arrhythmias
  - + MAO inhibitors !!!!!
- Contraindications
  - in patients who are abusers of substances such as cocaine, phencyclidine, and methamphetamine
  - glaucoma
  - hypertensive patients, unstable cardiovascular function
  - pregnancy, during breast-feeding
  - psychosis
  - childhood and in elderly

Phentermine + topiramate (used today)

DRUGS AFFECTING APPETITE
1.A. SYMPATOMIMETIC DRUGS, PSYCHOSTIMULANTS

Mazindol

- tricyclic structure
- DA uptake inhibitor
- decreases appetite
- Whithdrawn in some countries

DRUGS AFFECTING APPETITE
1.A. SYMPATOMIMETIC DRUGS, PSYCHOSTIMULANTS

Fenfluramine and dexfenfluramine

- "fen-phen," combined fenfluramine and phentermine
- were withdrawn in the late 1990s
  - life-threatening heart valve disease
  - pulmonary hypertension

Lorcaserin

- selective agonist of 5HT2C receptors on anorexigenic proopiomelanocortin neurons in the arcuate nucleus of the hypothalamus
- decreases appetite
- Side effect:
  - Mitral regurgitation, valvulopathy in clinical trials (2014)

DRUGS AFFECTING APPETITE
1.A. SYMPATOMIMETIC DRUGS, PSYCHOSTIMULANTS

Sibutramine

- is a monoamine reuptake inhibitor (MRI
  - in humans, reduces the reuptake of norepinephrine (by ~73%), serotonin (by ~54%), and dopamine
- withdrawn (2010)
  - increased cardiovascular toxicity

DRUGS AFFECTING APPETITE
I.A. SYMPATOMIMETIC DRUGS, PSYCHOSTIMULANTS

Toxicity of amphetamine-like drugs and psychostimulants:

- too much stimulatory effects in sympathetic vegetative center of hypothalamus
- Synonym names of this syndrome:
- Sympathetic overflow, serotonine syndrome, disco fever, amfetamine intoxication

Disorder in control of body temperature

malignant hypertermia → DEATH

Hypertonia with high amplitudes

hypertonic crisis → stroke → DEATH

Overstimulation of cardiac muscle

ischaemia myocardial infarction → DEATH

DRUGS AFFECTING APPETITE
1.A. SYMPATOMIMETIC DRUGS, PSYCHOSTIMULANTS

Bupropion+ naltrexone

- Bupropion
  - a reuptake inhibitor and releasing agent of both norepinephrine and dopamine
  - a nicotinic acetylcholine receptor antagonist
  - activates proopiomelanocortin (POMC) neurons in the hypothalamus which give an effect downstream, resulting in loss of appetite and increased energy output
- Naltrexone
  - a pure opioid antagonist
- bupropion/naltrexone has an effect on the reward pathway that results in reduced food craving

DRUGS AFFECTING APPETITE
1.A. SYMPATOMIMETIC DRUGS, PSYCHOSTIMULANTS

Bupropion+ naltrexone

- bupropion inhibits CYP 2D6 – drug interactions !!
- CYP2B6 inductors enhance toxicity of bupropion e.g. carbamazepine, phenytoin
- Adverse effects:
  - Epileptiform convulsions
  - psychotic symptoms with suicid actions
  - anxiety,insomnia, tremor, head-ache, tinnitus, vertigo, fever
  - hypertension, palpitation, angina pectoris
  - arthralgia,myalgia
  - nausea, mild hepatotoxicity, colica abdominalis,
  - pruritus, sweating
- CONTRAINDICATIONS:
  - epilepsy
  - risk for suicid actions
  - MAO-I therapy
  - uncontrolled hypertension
  - addiction of opioids/etanol/benzodiazepines,
  - malignancies in CNS
  - hepatic and renal insufficiencies
  - pregnancy
  - childhood
- **Bupropion/zonisamide**
- **at phase II testing**

DRUGS AFFECTING APPETITE
1.A. SYMPATOMIMETIC DRUGS, PSYCHOSTIMULANTS

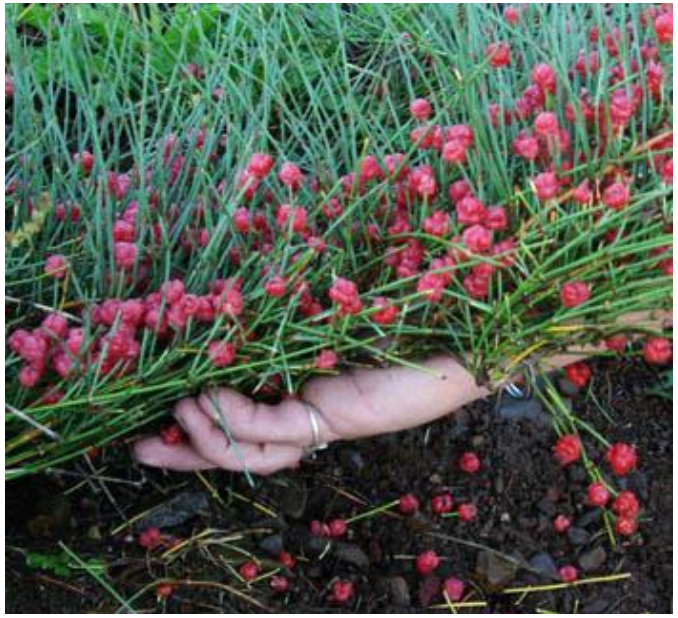
Rimonabant

- an inverse agonist of the CB1 receptor
- was developed for smoking cessation and to facilitate weight loss
- decreases neurotransmitter release at GABAergic and glutamatergic synapses

Site of action:

- CNS:
  - hypothalamus, limbic system
  - u opioid receptor antagonists potentiate its effect (eg. naltrexon)
- Periphery:
  - Liver: inhibits lipogenesis
  - Visceral fat:inhibits lipogenesis, adiponectin production, increases beta-oxidation of fats
  - Skeletal muscles: increases glucose uptake and thermogenesis
- withdrawn (2008)
  - major depression
  - increased suicidality

DRUGS AFFECTING APPETITE
1.A. SYMPATOMIMETIC DRUGS, PSYCHOSTIMULANTS



Ephedra sinica

- about 0,5 m in height, Northeast-China
- Active ingredient:
  - ephedrin and pseudoephedrin alkaloids.
- Mode of action of ephedrin :
- Indirect + direct mixed type sympatomimetics
- Effects in CNS + periferally.
- Indirect : neurotransmitter release from adrenerg neurons – amfetamin-like effect

  ⇓

  CNS sympathetic overflow sy – stimulatory amfetamine-like effect – euphoria
- Direct effect:

	alfa 1	beta 1	beta 2
norepinephrine	+++	++++	+++
ephedrine	+	+++	++

DRUGS AFFECTING APPETITE
1.A. SYMPATOMIMETIC DRUGS, PSYCHOSTIMULANTS

Ephedra sinica

- ephedra is one of the most infamous dietary supplement
- Use:
- body building, sportsmen
- obesity, for weight reducing, enhancement of performance
- Effects:
- weight reducing effect within 1-12 months
- synergistic effect in combination with caffeine
- Acute sympathomimetic effects in CNS + periferally
- Reduced sensation of fatigue
- enhance breath volume + cardiac output
- Adrenergic effects , e.g. enhanced blood sugar → energy

↓

Enhancement of performance

DRUGS AFFECTING APPETITE
1.A. SYMPATOMIMETIC DRUGS, PSYCHOSTIMULANTS

Ephedra sinica

- Ephedrin-containing dietary supplements: are PROHIBITED to sell
- 2004.U . S . Food and Drug Administration (FDA) banned dietary supplements, herbs containing ephedra sinica
- Serious adverse events
- seizures, stroke, death
- cardiovascular symptoms

DRUGS AFFECTING APPETITE
PEPTIDES UNDER INVESTIGATION

Leptin

- Leptin circulates at levels proportional to body fat and BMI
- It enters the CNS in proportion to its plasma concentration
- Its receptors are found in brain neurons involved in regulating energy intake and expenditure
- It controls food intake and energy expenditure by acting on receptors in the mediobasal hypothalamus
- periferally it increases insulin sensitivity, influences maturation of hemopoietic cells
- glucocorticoids and oestrogenes decrease leptin blood level
- beta3 receptor agonists decrease insulin-induced leptin release
- **Metreleptin**
- The form of leptin that is currently available for human therapy is known as recombinant methionyl human leptin (metreleptin, Myalept®)
- is the only pharmaceutical form of leptin
- has been recently approved by the FDA for the treatment of congenital or acquired generalized lipodystrophy
- has a very limited role in the treatment of patients with common obesity

DRUGS AFFECTING APPETITE
PEPTIDES UNDER INVESTIGATION

- Leptin sensitizers
  - celastrol
  - a very potent leptin sensitizer that reduces food intake and body weight in diet-induced obese (DIO) mice
  - leptin with amylin
  - Pramlintide acetate, a synthetic analog of amylin and metreleptin, a recombinant methionyl form of human leptin
  - the development of a pramlintide/metreleptin combination therapy has been stopped due to potential safety concern
  - co-administration of leptin and exendin-4, a natural agonist of GLP-1 receptor, restored leptin responsiveness in DIO mice switched to normal diet
- Leptin receptor agonists
- leptin mimics
  - ciliary neurotrophic factor (CNTF) – a pluripotent neurocytokine that mimics the biological actions of leptin while overcoming "leptin resistance"
  - Axokine® - small positive effect. The drug was not commercialized.

DRUGS AFFECTING APPETITE
PEPTIDES UNDER INVESTIGATION

Cholecystokinin (CCK)

- a postprandial gut hormone
- Stimulates the activity of the exocrine pancreas
- inhibits gastric emptying
- promotes short-term satiety by acting on CCK1 receptor

- CCK analogues
- CCK1-receptor agonists
- CCk2-receptor agonists

DRUGS AFFECTING APPETITE
DRUGS INFLUENCING BEHAVIOUR AND MOODNESS

- Antidepressants
- especially serotonin reuptake inhibitors have good effect on weight loss

- Some antiepileptics (e.g. topiramate, zonisamide)
- may decrease attacks in food intake

DRUGS AFFECTING APPETITE
DRUGS THAT DECREASE ABSORPTION OF FAT, CHOLESTEROL OR CARBOHYDRATES

Orlistat (Xenical)

- GI lipase inhibitor
- reduces absorption of fats since triglicerides not split
- Side effects:
  - flatulance, steatorrhea, fecal incontinence
- Clinical use:
  - obesity for weight reducing and education of obese people for the proper diete!
  - In education it has similar role than disulfiram therapy in alcoholism
- OTC drug

DRUGS AFFECTING APPETITE
DRUGS THAT DECREASE ABSORPTION OF FAT, CHOLESTEROL OR CARBOHYDRATES

Bile acid binding resins

- Plant fibers

Ezetimibe

- Cholesterol absorption inhibitor

Alpha glucosidase inhibitors:

- acarbose, miglitol
- Side effects:
  - flatulence, diarrhoae, colica abdominalis
  - Hepatotoxicity
- Contraindication:
  - ulcus pepticum
  - inflammatory bowel diseases

DRUGS AFFECTING APPETITE
DRUGS THAT INCREASE METABOLIC RATE

Beta 3 agonists

- have remarkable antiobesity and antidiabetic effects in rodents
- Mirabegron
- stimulates brown adipose tissue in humans
- nebivolol (beta l antagonist) effective in metabolic sy

UCP (uncoupling protein) analogues

- Uncoupling from ATP production a good theoretical mechanism but that compounds which have been investigated with this mechanism of action have a great toxicity
- One of the pollutants of fat-burning dietary supplements
  - DNF = dinitrophenol is very toxic !!!

Adipose tissue specific Thyroid hormone analogues

DRUGS AFFECTING APPETITE
DRUGS FOR LOWERING RISK OF COMPLICATIONS IN OBESE PEOPLE

Insulin sensitizing drugs

- Metformin (biguanide derivative)
  - Side effect: lactic acidosis
  - Contraindicated in renal, hepatic, hypoxic pulmonary diseases, heart failure or shock
- PPAR (peroxisome proliferator-activated receptor) gamma agonists :
- troglitazone was withdrawn because of hepatotoxicity
- rosiglitazone was withdrawn (2010) because of increased blood volume and its consequences
- pioglitazone
- OBESITY
- suppress resistin production and increase insulin sensitivity in muscle cells

Lipid lowering drugs

Antihypertensive drugs

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- **Chromium**
- **St. John's wort (Hypericum perforatum)**
  - Hypericin
  - Serotonergic/monoamine oxidase inhibition
- **Pyruvate**
- **Hoodia (Kalahari cactus)**
  - is a desert cactus
  - stems and roots of this plant – appetite suppressant effects
- **Guarana Extract and Various Tea Extracts**
  - sources of caffeine
  - have inherent adrenergic properties
  - increase the effects of stimulant substances such as ephedrine or ephedra alkaloids
- **Chitosan**
  - a cationic polysaccharide
  - may be effective in blocking absorption of fat from the gut