

# Drug therapy of Obesity



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- Obesity
  - A condition of abnormal or excessive accumulation of adipose tissue to the extent that health may be impaired.

# Assessment of Obesity

- Body mass index
- Waist circumference
  - **Body mass index** (BMI = Body weight in kg/height in meter<sup>2</sup>)
  - **As per western countries**
    - Normal BMI = 18.5 to 24.9
    - Over weight BMI = 25 to 29.9
    - Obesity BMI = >30
    - Severe obesity BMI 35 or >35
  - **According to asian criteria obese is BMI >23**

## Cont...

- **Waist circumference** if  $>102$  cm in men &  $>88$ cm in women considered obese. (western countries)

For Asians – obese figures of waist circumference are 90cm in men & 80 cm in women.

# Reasons for Obesity

- Hereditary
- Endocrine disease
- Excessive eating and lack of adequate exercise
- Drug induced

# Diseases which can occur in obese individuals

- Heart disease
- Hypertension
- Diabetes
- Sleep apnoea
- Osteo arthritis
- Bowel cancer

# Treatment of Obesity

- Drug therapy
  - If BMI  $>27$  with complicated diseases
  - If BMI  $>30$  with out complications
- Surgical – bariatric surgery if BMI  $>40$

# Principles of treatment of Obesity

- Dietary treatment
  - Low calorie diet (1000 – 1500 calories per day) containing all essential nutrients.
  - Protein 1g/kg body weight daily
  - Fat intake below 25% of total calories
  - Diet rich in fruits, vegetables, pulses
  - Liberal use of fibre containing foods



# Principle of treatment of obesity Cont...

- Regular exercise (30-60 minutes/day)
  - Brisk walking
  - Cycling
  - Jogging
  - Swimming
  - Stair climbing
  - Changing life style (behavioral therapy)
- Restriction of alcohol
- Anorectic drugs as adjunctive therapy.

# Role of neuro transmitters and neuropeptides in food intake

- Which increase food intake
  - Neuropeptide – Y (abundantly present in hypothalamus and decrease sympathetic activity).
  - Ghrelin (28-amino acid peptide powerful appetite stimulant, produced by neuroendocrine cells in gastric fundus & acts on hypothalamus)
  - Opioids
  - Endogenous cannabinoids

# Cont...







- Which decrease food intake
  - 5hydroxy tryptamine (5-HT)
  - Noradrenaline
  - Dopamine
  - Cholecysto kinin (CCK), GLP (Glucagon Like Peptide)
  - Neurotensin,  $\alpha$ -MSH,
  - CRF (Corticotrophin Release Factor).
- Leptin (Synthesized in fat cells, acts on arcuate nucleus of hypothalamus and increase calorie expenditure through inhibition of neuropeptide-Y).

# Classification of drugs used in Obesity

- Centrally acting appetite suppressants (Anorexians)
  - **Adrenergic agents** – Amphetamine, methylamphetamine, mazindol.
  - **5-HT enhancers** – Fenfluramine, dexfenfluramine, fluoxetine, lorcaserin.
  - **Drug acting on both adrenergic and 5-HT systems** – Sibutramine
  - **Cannabinoid receptor antagonist** – Rimonabant
- Drugs acting in G.I tract
  - **Bulk anorexians** – dietary fibre, methyl cellulose, guar gum.
  - **non absorbable fat substitute** – olestra
  - **Lipase inhibitor** – Orlistat
- Miscellaneous - Metformin

# Individual drugs

- **Amphetamine & methyl amphetamine**
  - Sympathomimetic drugs
  - ↑ release of NA & DA from adrenergic neurons, also blocks uptake of NA & DA
  - Dose: 5 to 10mg/day
  - Rapid tolerance to anorectic effect
  - A/E: insomnia, tremors, hypertension, addiction (more with methyl amphetamine)

-  DA transporters
-  NA transporters
-  DA
-  NA
-  DA or NA receptors
-  Dexamfetamine

DA- or  
NA-containing  
vesicles

Presynaptic axon terminal

Synaptic cleft

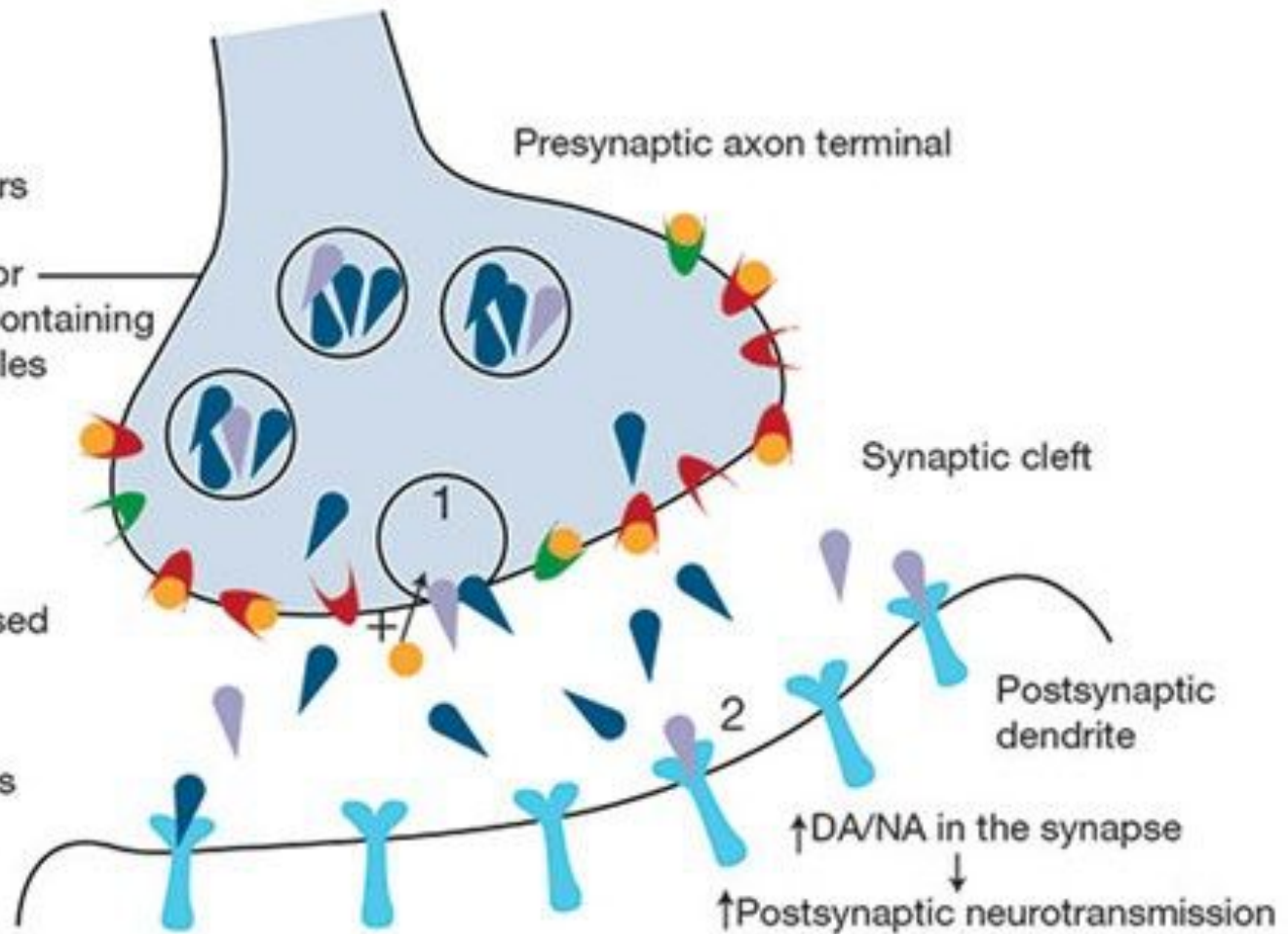
1 DA or NA is released  
into the synapse

2 DA or NA  
reversibly attaches  
to receptors

Postsynaptic  
dendrite

↑DA/NA in the synapse

↑Postsynaptic neurotransmission



- **Mazindol**

- Unrelated to amphetamine
- Acts through DA mediation
- Dose: 2mg /day

**Side effects**

An allergic reaction (difficulty breathing; closing of throat; swelling of lips, tongue, or face)  
an irregular heartbeat or very high blood pressure (severe headache, blurred vision); or  
hallucinations, abnormal behavior, or confusion.

# Fenfluramine and dexfenflurame

- Enhance 5-HT activity in brain by ↑5-HT release & ↓ its reuptake
- Dose: 20 to 40mg
- A/E: cardiac valvular injury, pulmonary hypertension hence withdrawn form market.

## **Fluoxetine**

- 5-HT reuptake blocker antidepressant (SSRI)
- Weight loss with 60mg/day
- A/E: Anxiety, agitation, ↓libido, serotonergic syndrome.

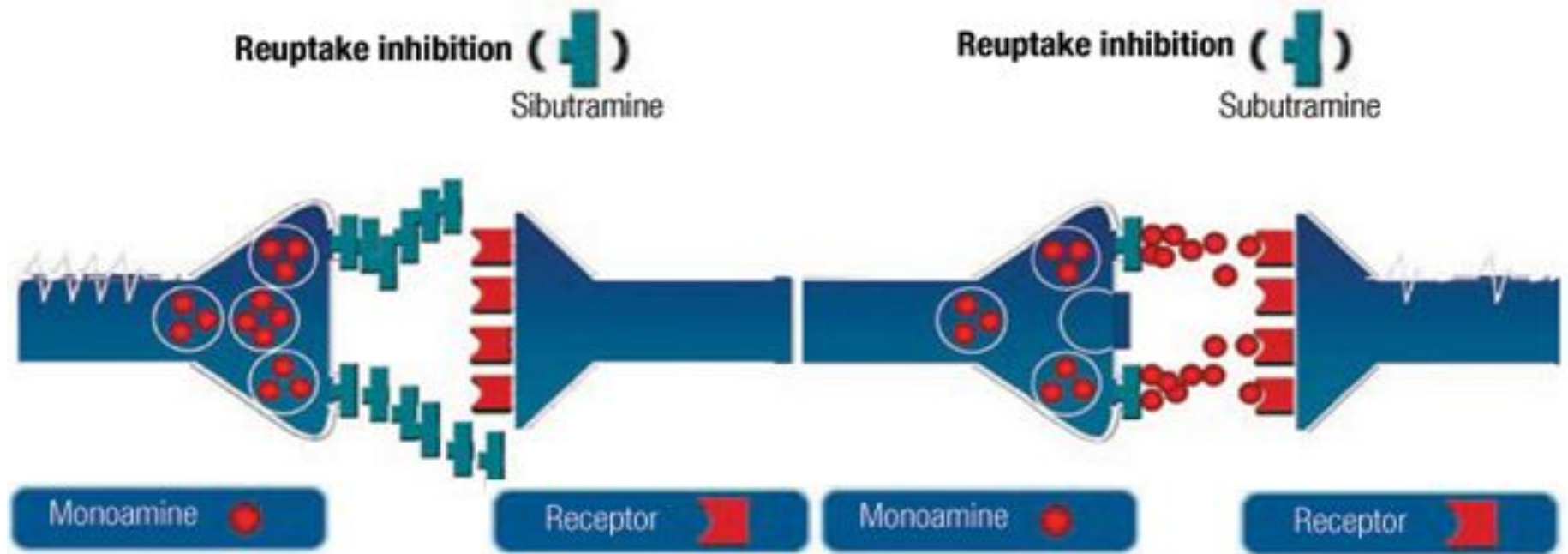
## **Lorcaserin**

- Central 5-HT<sub>2C</sub> agonist suppress appetite (under evaluation)
- A/E: Dizziness & euphoria (>40 mg/day)



# Sibutramine

- Prodrug
- Metabolised by cyp3A4 to active metabolite which inhibit transporters of 5-HT & NA.
- ↑satiety, also stimulate thermogenesis by activating  $\beta$ 3 receptors in adipose tissue.
- Weight loss of 4-5%/year (low efficacy) also ↓plasma VLDL, LDL, & triglycerides.
- Dose: 10 to 15mg orally OD.
- A/E: ↑HR & BP, occasionally cardiac arrhythmias, insomnia, drymouth.



**Figure 1.** Sibutramine: mechanism of action.

# Rimonabant

- Cannabinoid receptor antagonist (CB1) in brain.
- Also neurokinin antagonist in brain.
- ↑ CCK induced satiety
- ↓ food intake
- Peripheral action also – inhibit lipogenesis & increase thermogenesis.
- ↑HDL
- Dose: 20mg OD
- A/E: CNS- depression (6-7% of patients) hence withdrawn from Indian market recently.

# Drugs acting in G. I Tract

- **Bulk anorexients**
- Methyl cellulose
  - Non digestive polysacharide
  - When ingested swells, adds bulk to diet.
  - Important cheap constituent of many commercial anti obesity preparations.
  - Dose: 1 to 4 g/day with 30 to 40ml water.
- Guar gum (carbotard)
- Glucomannan (Dietmann)

# Digestion inhibitors

- Olestra
  - Mixture of sucrose fattyacid ester
  - Neither digested nor abosrbed from GIT. Adviced as fat substitute in cooking.
  - A/E: ↑stool bulk, Expensive.

- Orlistat
  - Synthetic ester
  - inhibits pancreatic & other lipases.
  - Not absorbed from GIT.
  - Prevents breakdown of fats into fatty acids  
Reduces  $\frac{1}{3}$  of diet fat absorption.
  - Also ↓ plasma LDL & total cholesterol.
  - Dose: 120mg TDS for maximum of two years.
  - A/E: Oily spotting & faecal urgency, deficiency of vitamin A,D,E,K, Flatulence, Abdominal pain.

# Miscellaneous drug

- Metformin
  - Biguanide type of oral antidiabetic drug.
  - Weight loss in nondiabetic obese people.
- Mechanism of action
  - Reduces appetite
  - Slows glucose absorption
  - Decrease Hepatic gluconeogenesis
- Dose: 500 mg twice a day with food
- A/E: anorexia, flatulence, diarrhoea (3-5% cases), ↓B12 absorption (long term use), lactic acidosis (Renal/hepatic disease, CHF, alcohol ingestion).

# Duration of drug therapy & assessment of drug response

- As obesity is a chronic disease and relapse common after cessation of drug therapy, prolonged life long drug therapy may be desirable with planned diet (reorientation of eating habits).
- Weekly loss of 0.5kg adequate which result in annual loss of 25kg.
- If significant weight loss does not occur within 4-6 months of drug therapy, drug may be discontinued.
- Combined drug therapy no better than monotherapy.



# Drugs that increase body weight

- Olanzapine (Antipsychotic)
- Glucocorticoids, insulin, O.C pills (Hormones)
- Glitazones (Antidiabetics)
- Beta blockers
- Antiepileptics like sodium valproate, phenytoin.
- First generation anti histamines.

**Thank You**