DRUG THERAPY OF OBESITY

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Drug therapy of Obesity

- 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 circumstance
  - **Body mass index** (BMI = Body weight in kg/height in meter\(^2\))
  - 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
Waist circumference if >102 cm in men & >88 cm in women considered obese. (western countries)

For Asians – obese figures of waist circumference are 90 cm in men & 80 cm in women.
Types of obesity
Reasons for Obesity

- Hereditary
- Endocrine disease
- Excessive eating and lack of adequate exercise
- Drug induced
Drugs that increase body weight

- Olanzepine (Antipsychotic)
- Glucocorticoids, insulin, O.C pills (Hormones)
- Glitazones (Antidiabetics)
- Beta blockers
- Antiepileptics like sodium valproate, phenytoin.
- First generation anti histamines.
Diseases which can occur in obese individuals

- Heart disease
- Hypertension
- Diabetes
- Sleep apnoea
- Osteoarthritis
- 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
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
- 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
● Which decrease food intake
  - 5-hydroxy tryptamine (5-HT)
  - Noradrenaline
  - Dopamine
  - Cholecystokinin (CCK), GLP (Glucagon Like Peptide)
  - Neurotensin, α-MSH,
  - CRF (Corticotrophin Releasing 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 (Anorexiens)
  - **Adrenergic agents** – Amphetamine, methyl amphetamine, 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 anorexients** – dietary fibre, methyl cellulose, guar gum.
  - **non absorbable fat substitute** – olestra
  - **Lipase inhibitor** – Orlistat

- Miscellaneous – Metformin
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)
1 DA or NA is released into the synapse
2 DA or NA reversibly attaches to receptors

Presynaptic axon terminal

DA transporters
NA transporters
DA
NA
DA or NA receptors
Dexamfetamine
DA- or NA-containing vesicles

Synaptic cleft

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)
- Irregular heartbeat or very high blood pressure (severe headache, blurred vision);
- Hallucinations, abnormal behavior or confusion.
- 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 from market.

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

**Lorcaserin**
- Central 5-HT2C agonist suppress appetite.
- A/E: Dizziness & euphoria (>40 mg/day)
Mechanism of action contd...

Lorcaserin

5-HT$_{2c}$ receptors on Pro-opiomelanocortin neurons

α-MSH

MC4R in paraventricular nucleus in the hypothalamus

Decrease in appetite
Lorcaserin

* **Dosage:** 10 mg, BD, orally with or without food for 12 weeks.

* If weight is not decreased by 5% or more, treatment should be discontinued.
Adverse effects

Nausea & Vomiting

Dizziness

Constipation

Headache
Serotonin syndrome

- Hyperreflexia (greater in lower extremities)
- Tremor (greater in lower extremities)
- Clonus (greater in lower extremities)
- Mydriasis
- Increased bowel sounds; may have diarrhea
- Autonomic instability; often hypertensive
- Agitation
- Diaphoresis
- Tachycardia

Hypoglycemia

Valvular heart defects

- Mitral Valve
- Coronary Sinus
- Tricuspid Valve
- Right Coronary Artery
- Left Coronary Artery
- Pulmonary Artery with Valve
- Aortic Valve
Sibutramine

- Prodrug
- Metabolised by cyp3A4 to active metabolite which inhibit transporters of 5-HT & NA.
- ↑ satiety, also stimulate thermogenesis by activating β3 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 polysaccharide
    - 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)
Olestra

- Mixture of sucrose fatty acid ester
- Neither digested nor absorbed from GIT. Advised 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.
Metformin
- Biguanide type of oral antidiabetic drug.
- Weight loss in nondiabetic obese people.

Mechanism of action
- Reduces appetite
- Slows glucose absorption
- Decrease Hepatic glucogenesis

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).
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.
Newer drugs for obesity

* Phentermine + topiramate –ER
  FDA approved in 2012
* Naltrexone + bupropion
  FDA approved in 2014
* Liraglutide (GLP-1 agonist)
  FDA approved in 2014
Bariatric surgery

- Laparoscopic Gastric Bypass
- Laparoscopic Sleeve Gastrectomy
- Adjustable Gastric Band
*Liposuction by expert surgeons*
Thank You