EATING DISORDERS

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- Obesity
- Anorexia
- Bulimia
- Binge-eating
- Cachexia

Obesity

- Obesity is defined as a state of body mass index (BMI) bigger than 30 kg/m^2
- BMI = $\frac{\text{Body weight (kg)}}{\text{Height } (m^2)}$
- Normal BMI: 18.5 – 24.9
- BMI 25 – 29.9: Over weight
- Class I Obesity: BMI 30 – 34.9

  Class II 35 – 39.9

  Class III > 40

Obesity cont...

- Abdominal circumference:
  - Male: > 102 cm
  - Female: > 88 cm
- Waist-hip ratio:
  - Male: >1.0
  - Female: > 0.85

Obesity cont...

- Metabolic syndrome: 3+ of the following:
  - Increased abdominal circumference
  - Elevated BP
  - Elevated serum TgS
  - Elevated fasting blood glucose
  - Lowered HDL cholesterol

Etiology

- 40 – 70 % of obesity is genetic – 5 genes are involved in control of appetite. One gene codes leptin and another for leptin receptors in the brain
- Sedentary lifestyle plus chronic ingestion of excess calories
- Prevalence: USA: 2 – 5 yrs – 14 %
  6 – 9 yrs – 19 %
  12 – 19 yrs – 17 &
  20 – 74 yrs – 33 %

Etiology (cont…)

- Proportion of disease attributable to obesity:
  - 61 % - Diabetes
  - 34 % - Uterine cancer
  - 30 % - Gallbladder disease
  - 24 % - Osteoarthritis
  - 17 % - CHD & hypertension
  - 11 % - Breast & colon cancer
- Other conditions associated with obesity:
  - Ischaemic stroke, lower back pain, sleep apnoea

Medical examination of the obese patient

- Good historical info
- Degree & distribution of fat
- Overall nutritional status
- Signs of secondary causes of obesity
  - Hypothyroidism, Cushings
- Consequences of obesity: BP, waist circumference, fasting glucose, lipid profile

Mechanisms of weight gain:

- Drug-induced weight gain does not correlate with treatment outcomes, severity of depression, disease-induced weight loss, weight at the beginning of treatment or with sex or age
- Food craving: Drugs inducing weight gain might interfere with the function of specific CNS feedback systems regulating appetite
- Resting Metabolic Rate: 5 – 24 % reduction of basal energy turnover in patients taking TCA's.

  Under average conditions of motor activity: Basal energy turnover can account for as much as 70% of daily energy expenditure – much more than physical activity!

Mechanisms of weight gain (cont…)

- Monoaminergic Transmitters: Involved in appetite control – stimulation or functional antagonism of dopamine, NA, serotonin and histamine receptors
  - α-adrenergic neurotransmission stimulates appetite
  - β-adrenergic, histaminergic, dopaminergic & serotoninergic signal transduction confers satiety

Mechanisms of weight gain (cont...)

- Leptin: is a 167 amino acid peptide synthesized in fat cells, placenta, GIT and possibly the brain
  - A decrease in body fat mass → reduced leptin levels and vice versa.
  - In obese humans – leptin resistance, possibly caused by a limited capacity of the active transport system carrying leptin across the BBB which appears to be saturated at high leptin levels
  - Leptin is inhibited by testosterone, exercise & fasting
  - Leptin is increased by insulin, glucocorticoids and high energy input
  - Leptin orchestrates the complete network of orexigenic and anorexigenic transmitter systems
  - MOA: Inhibition of NPY, Orexin. Down reg.AgoutiRP

Mechanisms of weight gain (cont...)

The tumour necrosis factor system:

- TNF-α is involved in obesity – synthesized in fat cells
- TNF-α & soluble TNF receptor levels are increased in obese subjects
- All drugs which induce weight gain also activated the TNF-α system
- Is TNF-α system activation a predictor of drug-induced weight gain?

Neuromodulators

Appetite-regulating peptides and cytokines and their receptors	
Ligand	Receptor
Appetite stimulant (orexigenic)	
MCH	MC4R
Orexin A/B = hypocretin I/II	Orexin A/B receptor
Ghrelin	GHS-R
NPY	NPY Y_1 and Y_S
Galanin	Galanin receptor
Endocannabinoids	CB1-R
B-endorphin	μ-opiate receptor
Enkephalins, dynorphins	δ, κ-opiate receptors
Appetite suppressing (anorexigenic)	
Leptin	Leptin receptor
Insulin	Insulin receptor
CRH	CRH-1/2-R
CART	
TNF-α	TNF receptor
Melanocortin (α-MSH)	MC4R
Agouti-related protein	MC4R

AG, arachidonyl glycerol, CART, cocaine- and amphetamine-related transcript, CRH, corticotropin releasing hormone, GHS, growth hormone secretagogue, MSH, melanocyte-stimulating hormone, MCH, melanocyte-concentrating hormone, TNF-α, tumor necrosis factor.

Treatment of obesity

Multidisciplinary approach = NB!

- Behaviour modification
- Exercise
- Social support
- Diet: very low calorie diets < 800 kcal/D for 4 – 6 months: loss of 1.2 kg/w
- Medications:
- Surgery: Bariatric surgery – gastric operations: Roux-en-Y-gastric bypass (GBP)

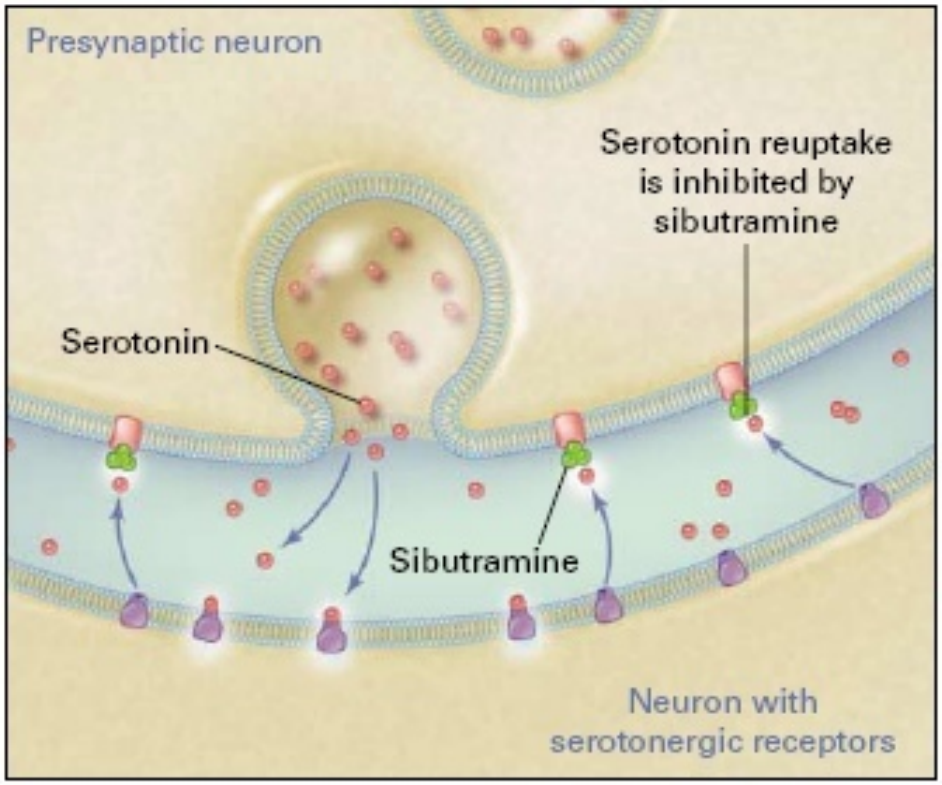
  Mortality is high – 2 % within 30 days!

MOA: Anti-obesity drugs

- Sympathomimetics:benzphentamine(Didrex), diethylpropion(Tenuate),phentermine(Duromine) & phendimetrizine(Obesan)
  - β-phentylamine derivatives
  - Structurally related to the biogenic amines NE, DA & amphetamine
  - Indicated for short term (12 w) treatment of obesity
  - Increase the synaptic concentration of NE, DA by promoting their release
  - Suppress appetite through effects on the satiety centre in the hypothalamus

Sibutramine

- Inhibits reuptake of NE, DA & 5HT – a $5HT_{2c}$ receptor agonist
- Suppresses appetite & increase thermogenesis
- ↑HDL; ↓waist-to-hip ratios
- Improves glycaemic control in type 2 DM
- Approved for long-term use
- Deregistered due to side-effects



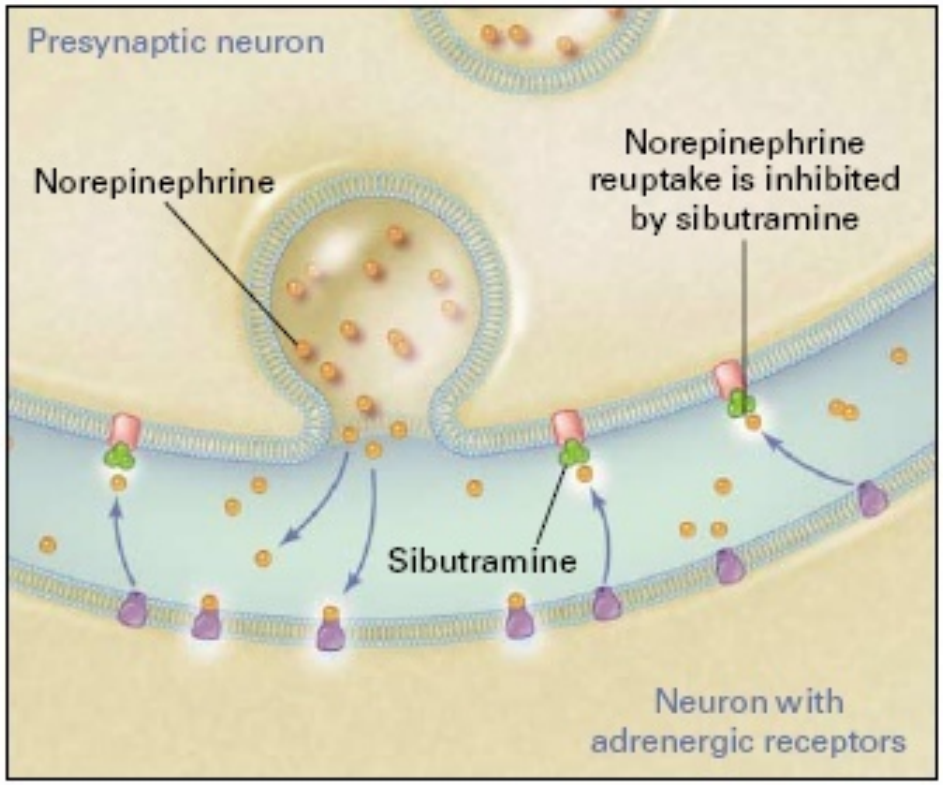


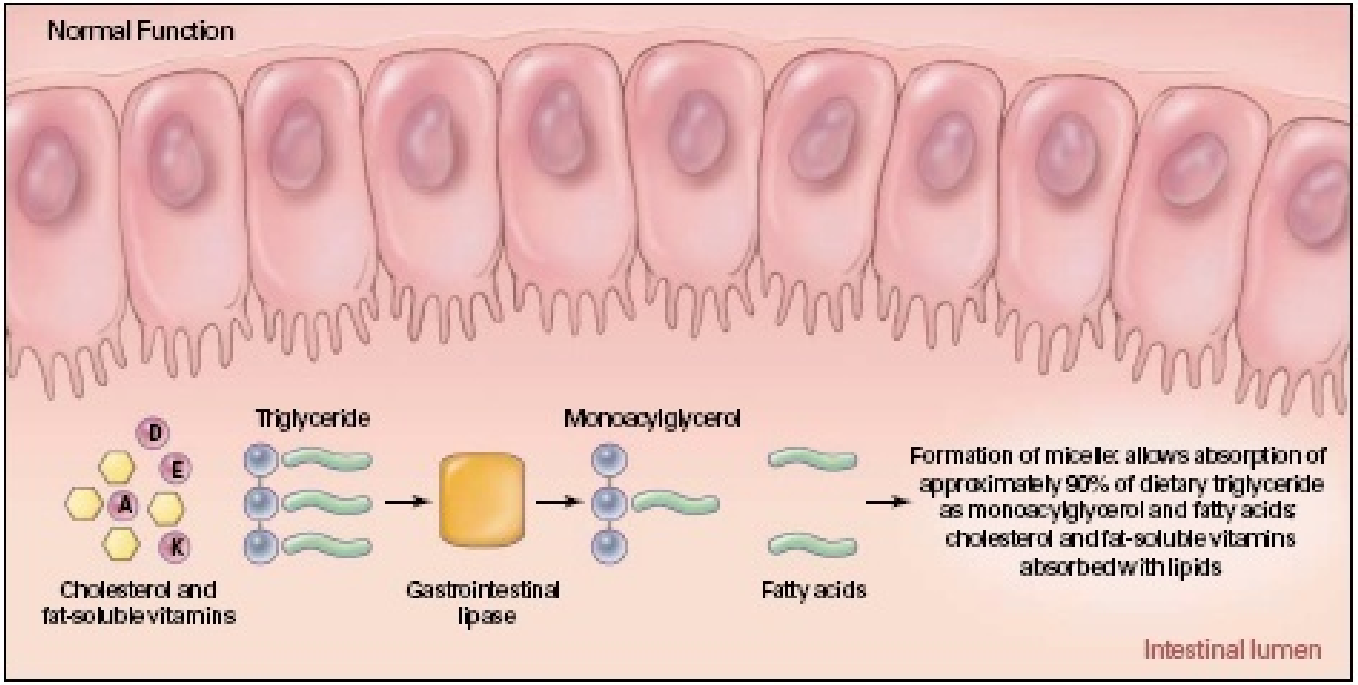
Figure 1. Mechanisms of Action of Sibutramine.

Lorcaserin

- MOA:
  - Selective 5-HT_{2c} receptor agonist
  - Activation of 5-HT_{2c} receptors in the hypothalamus → promote weight loss through satiety
- Adverse events:
  - Headache, dizziness, nausea
- Restrictions
  - Patients with BMI > 30 OR
  - Patients with BMI > 27 with comorbidity (high blood pressure, type 2 DM)

Orlistat

- Binds to & inhibit lipase in lumen of stomach & small intestine ≡ lipase inhibitor
- Causes ↓ production of absorbable monoglycerides & free fatty acids from TgS
- Reduces fat absorption up to 30 %
- Facilitates gastric emptying & secretion of pancreatic & biliary substances



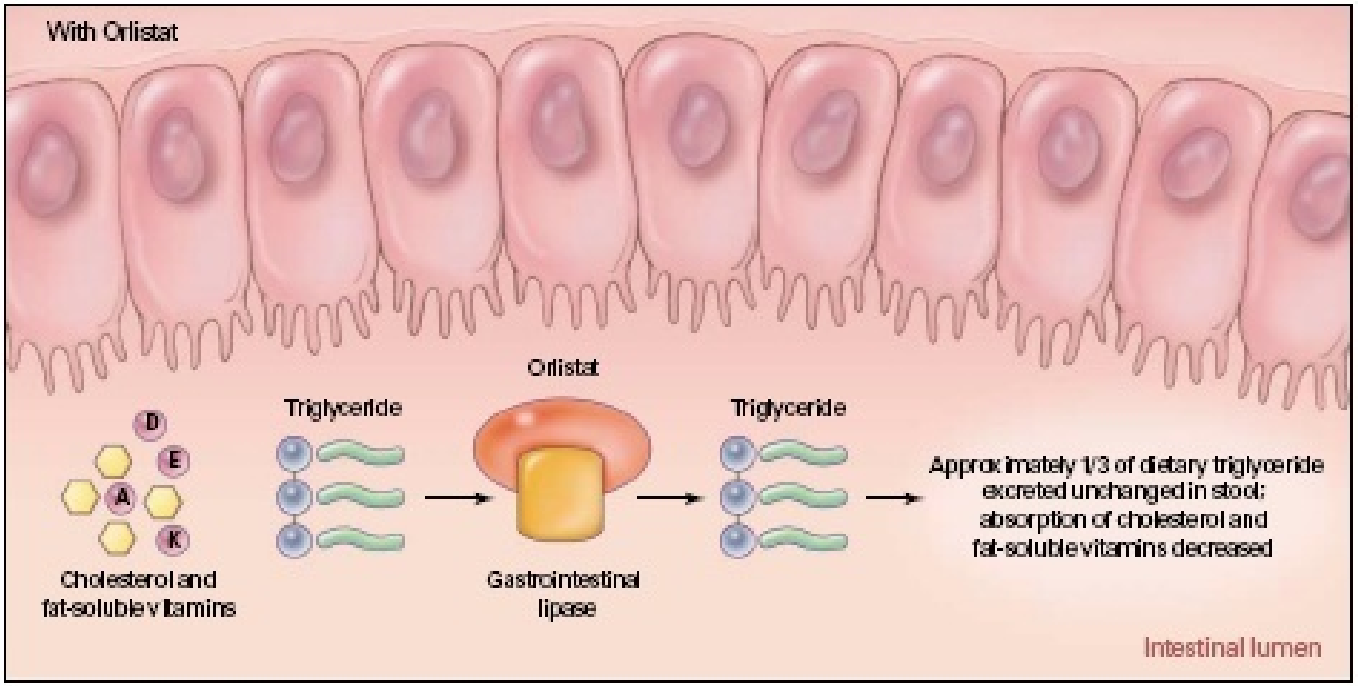


Figure 2. Inhibition of Fat Absorption by Orlistat.

Rimonabant

- CB1 receptor antagonist – actions opposite to that of dronabinol
- CB1 receptors – brain, fat cells & GIT
- Dual action:

  i) Decreases food intake

  ii) Increases energy expenditure - ↑adiponectin ≡ insulin sensitivity
- ↑ HDL, ↓TgS, fasting insulin & CRP
- S/E: depression, anxiety & insomnia

Interesting points

- Weight loss of < 0.45 kg/month = unsatisfactory when on treatment/diet
- Pharmacotherapy recommended only in pts with a BMI of at least 30 in the absence of obesity-related medical conditions or a BMI of at least 27 in the presence of such conditions (NIH)
- Weight loss of 2 kg + during first 4 weeks is a good indicator of possible success
- Pharmacotherapy for the prevention of weight regain

Interesting points

- Intermittent use: 12 w on, 12 w placebo
- Drug combinations:
  - Qnexa: phentermine + topiramate
  - Contrave: bupropion + naltrexone
- Children & adolescents: treat if BMI in the 95th percentile or higher for age & sex and obesity-related condition. No studies in children. Current CT's: orlistat, sibutramine, ephedrine, caffeine & metformin

Drug induced weight gain

- Not all changes in weight observed in depressed patients are induced by drug treatment
- Weight gain in patients treated for depression is an important reason for non-compliance with treatment
- Epidemiological data on obesity in depressed patients is inadequate
- In the USA: 97 million people (half the adult population) is overweight
- Obesity causes 280,000 – 350,000 deaths/annum

AD, lithium & glucose metabolism

- The impact of TCA and lithium on insulin action and glucose metabolism yielded ambiguous results!
- Lithium – ? Insulin-like effect
- Fluoxetine – increased insulin action in patients with NIDDM

Management of Drug-induced weight gain

- The benefit of ongoing drug treatment must be weighed up against accepting weight gain!
- Practice the clinical guidelines on the identification, evaluation and treatment of overweight and obesity in patients!
- Look for relevant risk factors
  - Management:
    1. Adaptation of Pharmacotherapy
    2. Patient counselling, dietary programs and behaviour therapy
    3. Add-on pharmacotherapy to achieve weight loss

Effect of antidepressant drugs on body weight

Drug	Effect on weight
Monoamine oxidase inhibitors (irreversible type)	Weight gain likely in short term (< 6 months) and long term (≥ 1 year)
Tricyclic compounds	Weight gain likely in short term and long term
Selective serotonin reuptake inhibitors (SSRIs) other than paroxetine eg. Prozac	Weight gain in short term less likely Weight gain in long term possible, but evidence is varied
Paroxetine(Aropax)	Weight gain in short and long term more likely than for other SSRIs
Nefazodone(Serzone)	Likely to have no effect on weight
Bupropion(Welbutron)	Likely to cause weight loss
Mirtazapine(Remeron)	More likely than placebo to cause weight gain in short term, but less likely than tricyclics
Venlafaxine(Efexor)	Likely to have no effect on weight

Add-on pharmacotherapy

- Ephedrine-sympathomimetics
- Sibutramine-SSNRI
- Orlistat-lipase inhibitor
- Topiramate(Topamax) -GABAergic & glutamate antagonist
- H_2-antagonists eg. nizatidine,famotidine
- Naltrexone-opioid antagonist
- Serotoninergic drugs-SSRI's - fenfluramine
- Metformin-biguanide
- Amantadine-dopaminergic effect
- Surgery

A practical hint:

- Add low-dose bupropion (100 – 150 mg/D) or
- Topiramate (25 – 50 mg/D)
- + diet control
- + exercise!

Pre-requisites for new anti-obesity drugs

- Has it got substantial beneficial effects on glucose tolerance?
- Does it have lipid-lowering effects?
- Does it protect against vascular complications?

New drug development

- Appetite control mechanisms
- Nutrient absorption & lipid metabolism control
- Nutrient sensing & regulations
- Energy expenditure
- Adiposity control

Drugs for other eating disorders

Anorexia & Bulimia

- Antidepressants in all classes: TAD's, MAOI's & SSRI's. Latter = first line
- Antidepressants reduce binge eating, vomiting & depression and improve eating habits in Bulimia: Imipramine, desimipramine, phenelzine & trazodone
- Fluoxetine – only AD approved for bulimia

Cachexia

Orexigenics:

- Progestational agents e.g. megestrol
- Corticosteroids: dexamethazone
- Anabolic steroids: oxandrolone & nandrolone
- Dronabinol: Cannabinoid type 1 receptor agonist (CB1) – hypothalamus, limbic forebrain & GI Tract → appetite stimulation
  - Used to prevent N & V - chemotherapy

End

Thank you