

# Anti-obesity Drugs

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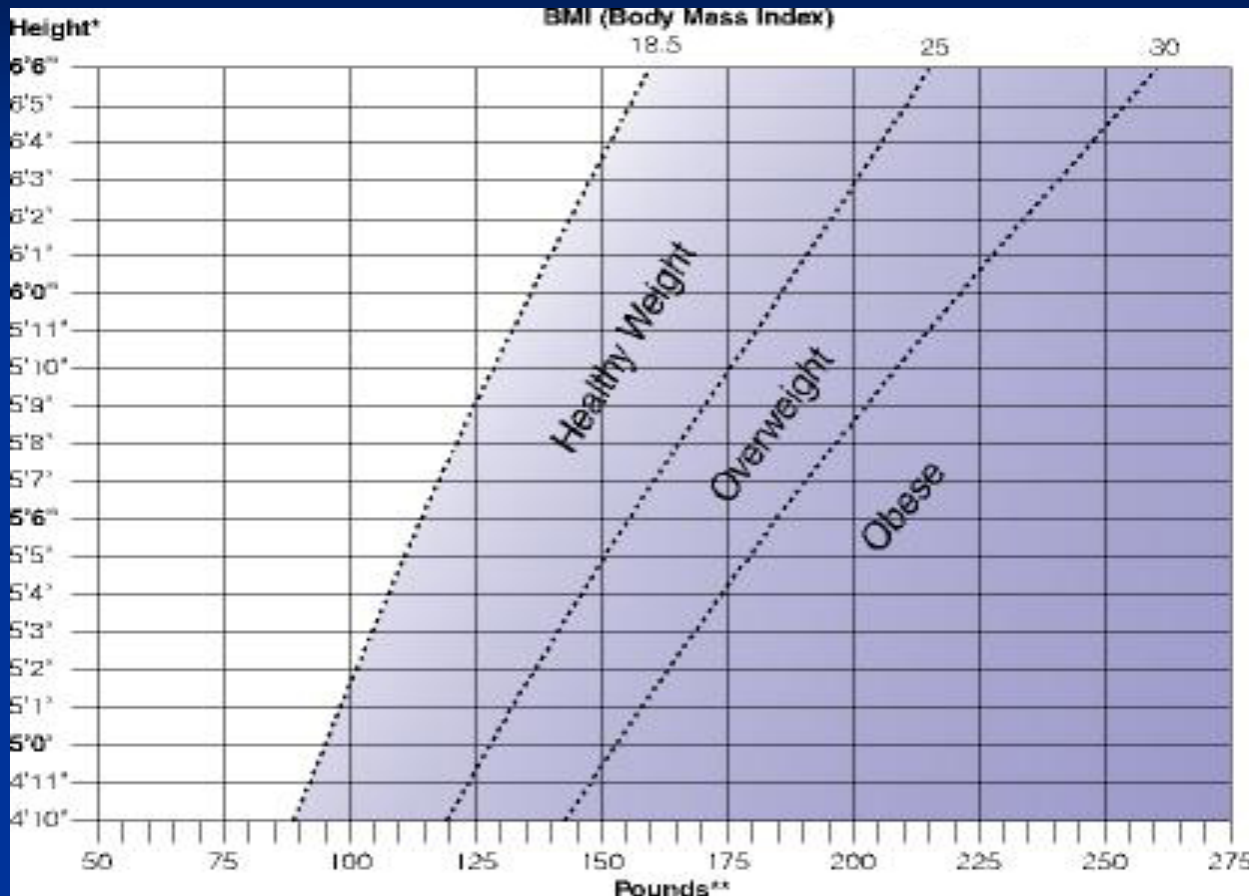
Cardiovascular Module

5 December 2010

# Agenda

- Overview and Prevalence
- Mechanisms
- Gut peptides
- **Management**
- Summary

# Obesity-WHO Criteria



Male

Female

W/H Ratio

>1.0

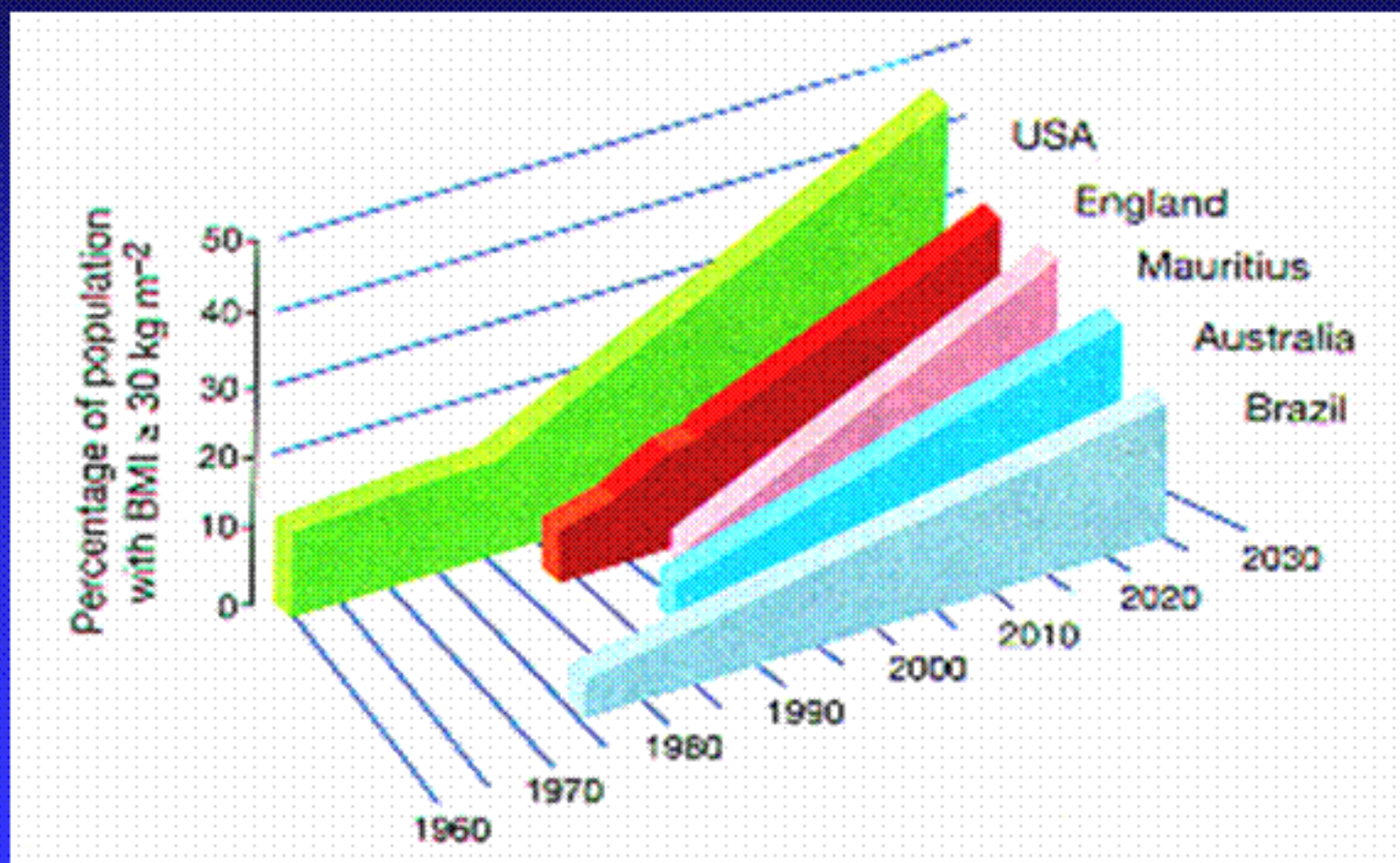
>0.9

% TBF

>25%

>35%

# Historic, Current and Prospective Obesity Prevalence Rates



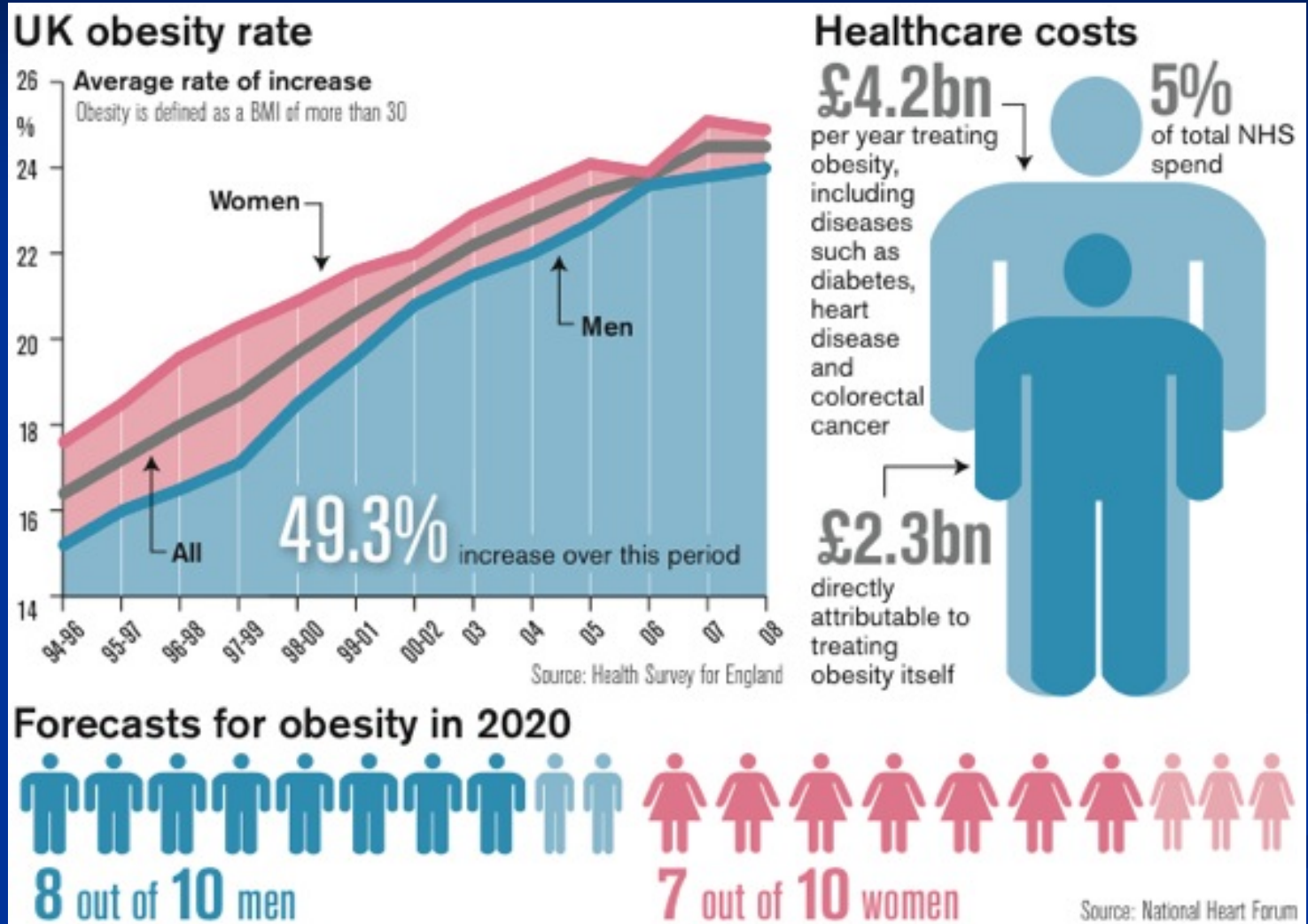
# Childhood Obesity



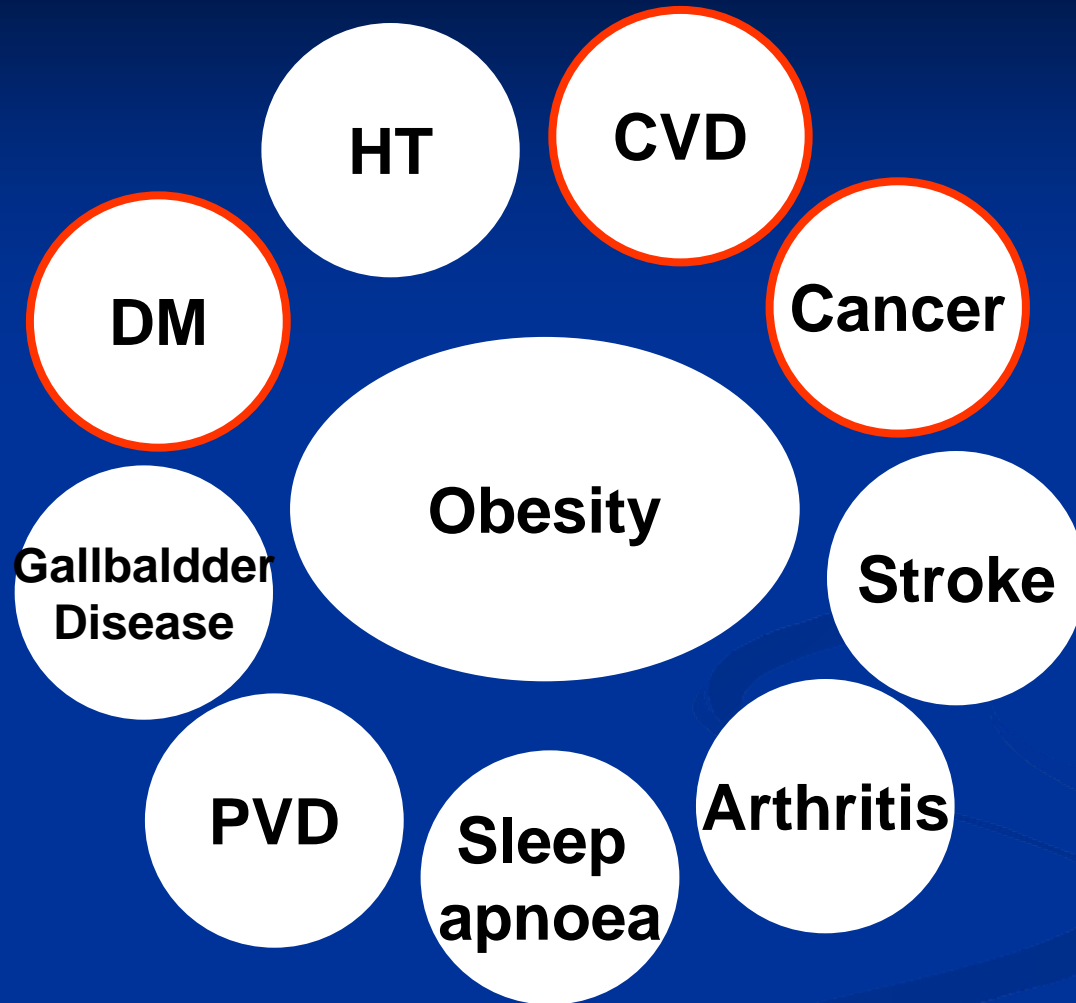
*“If the rapid acceleration in childhood obesity is taken into account, 50% of British children would be obese by 2020 unless the trend is reversed” (CHSC 2004)*



# The Estimated Obesity Healthcare Cost

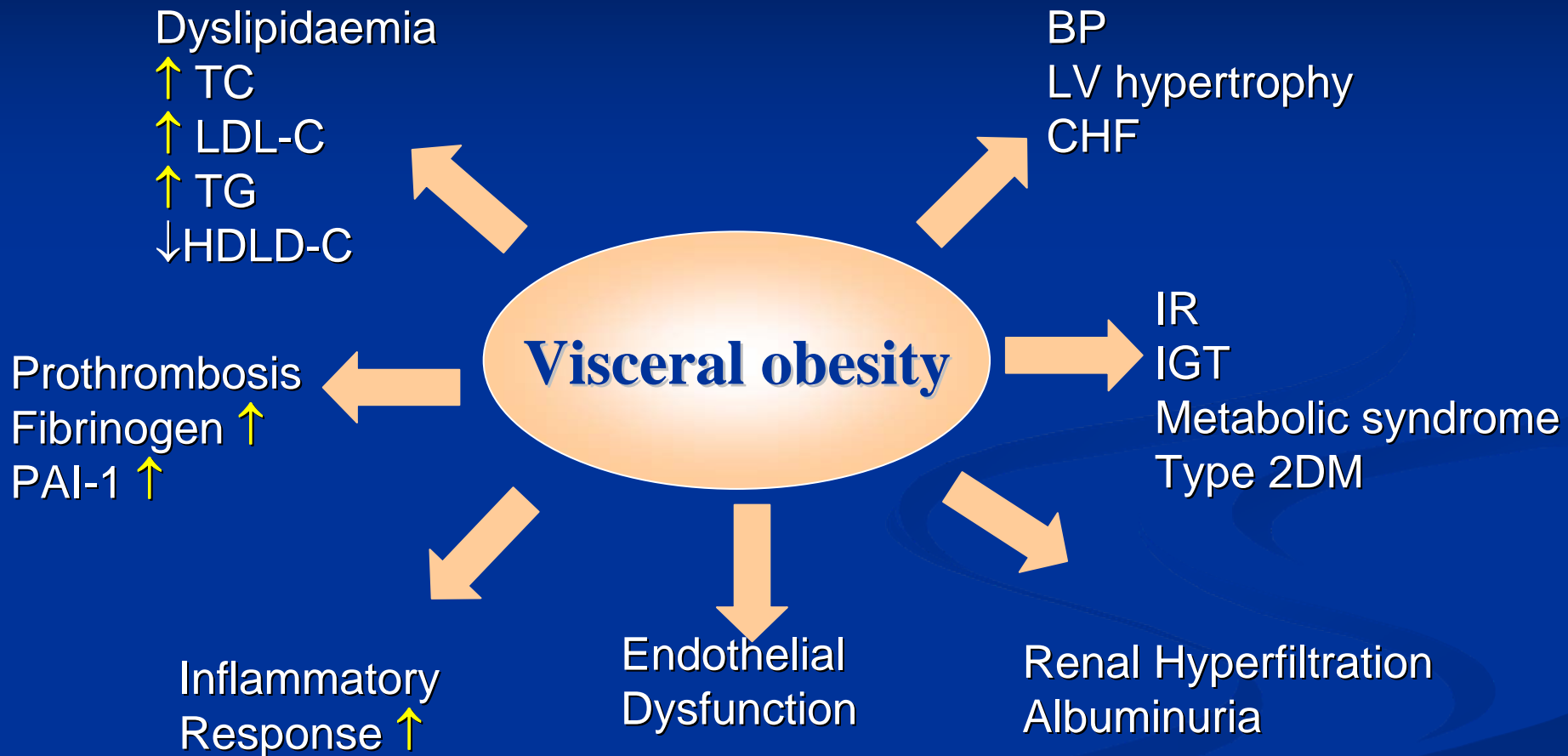


# Obesity Health related Risks



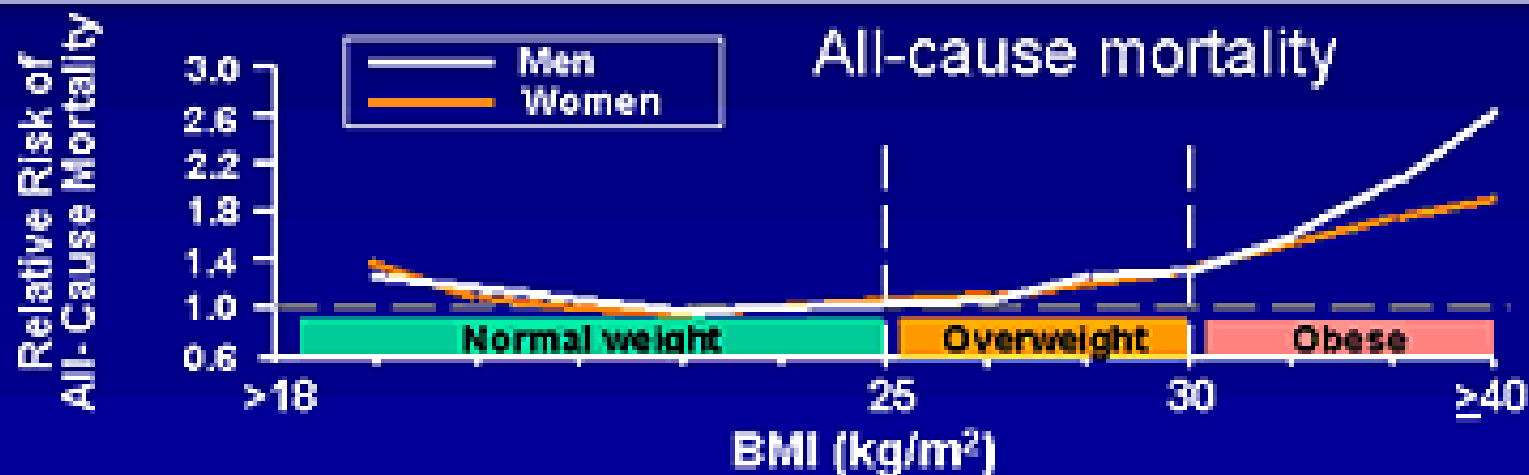
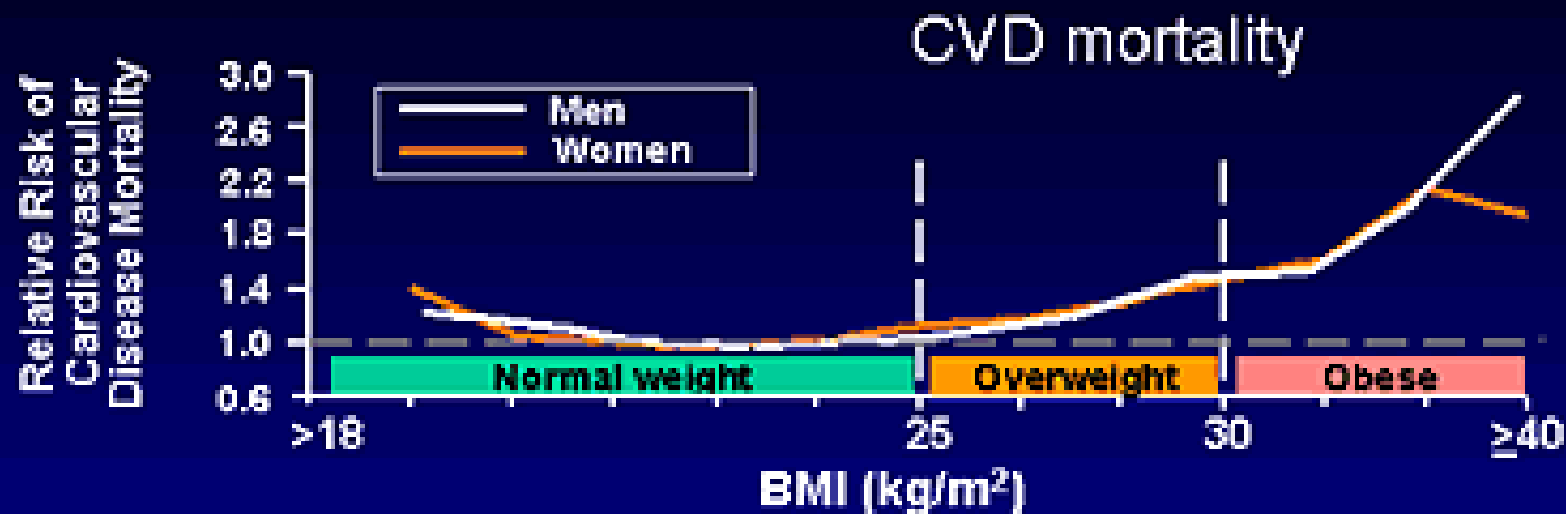
↑ Risk of Mortality- 2.5 million/yr worldwide  
0.25 million/ yr in EU

# Obesity and Cardiovascular Risk





# Overweight and Obesity Increase the Risk of Cardiovascular Disease Mortality and All-Cause Mortality

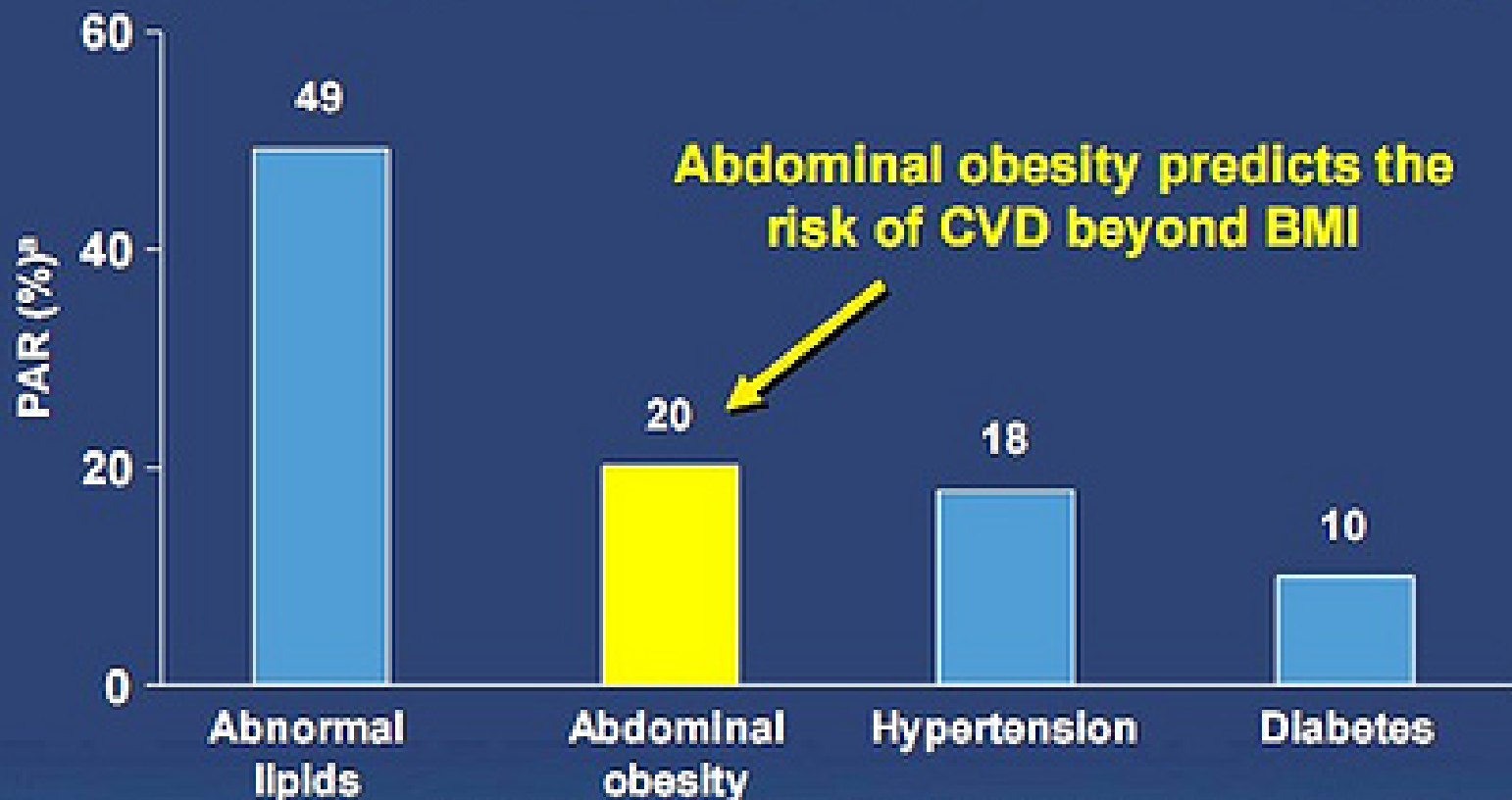


Data are from 1 million men and women followed for 16 years with an average age of 57 who never smoked and had no history of disease at enrollment.

Calle EE, et al. *N Engl J Med*. 1999;341:1097-1105.

# Abdominal obesity: a major underlying cause of acute myocardial infarction

Cardiometabolic risk factors in the INTERHEART Study



<sup>a</sup>Proportion of MI in the total population attributable to a specific risk factor; CVD: cardiovascular disease; BMI: body mass index; PAR: population attributable risk;

# Obesity

## A world health Problem

Why are some individuals lean & others obese?

Why is it so hard to lose weight?

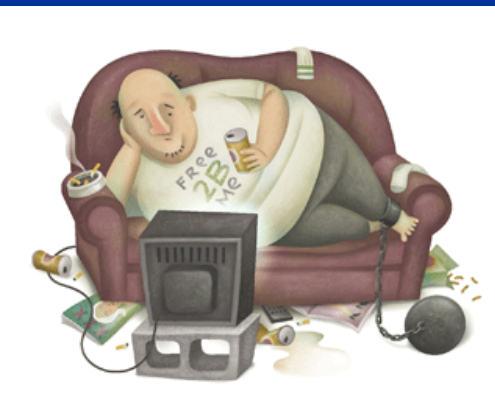
# Causative factors



Genetic

Environmental

Neuroendocrine/  
Hypothalamic system



# A simplified Model of Weight regulating Mechanisms

Energy Intake = Energy Expenditure

Food intake

Thermogenesis

Hypothalamus/Higher CNS

5-HT  
β3-A  
CNTF  
DDPIV  
PYY  
NPY

CB1  
MCH  
MC4R  
Amph

NPY POMC

Endocrine glands

Thyroxine  
Estrogen  
Androgen  
Glucocorticoids  
Progesterone

Leptin/Adiponectin

Adipose Tissue

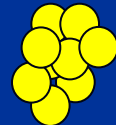
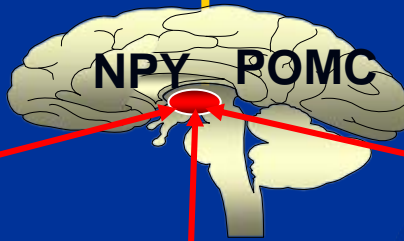
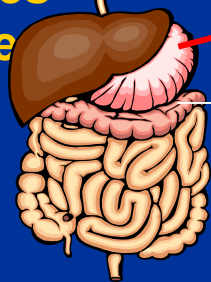
Gut peptides & meal size

Ghrelin

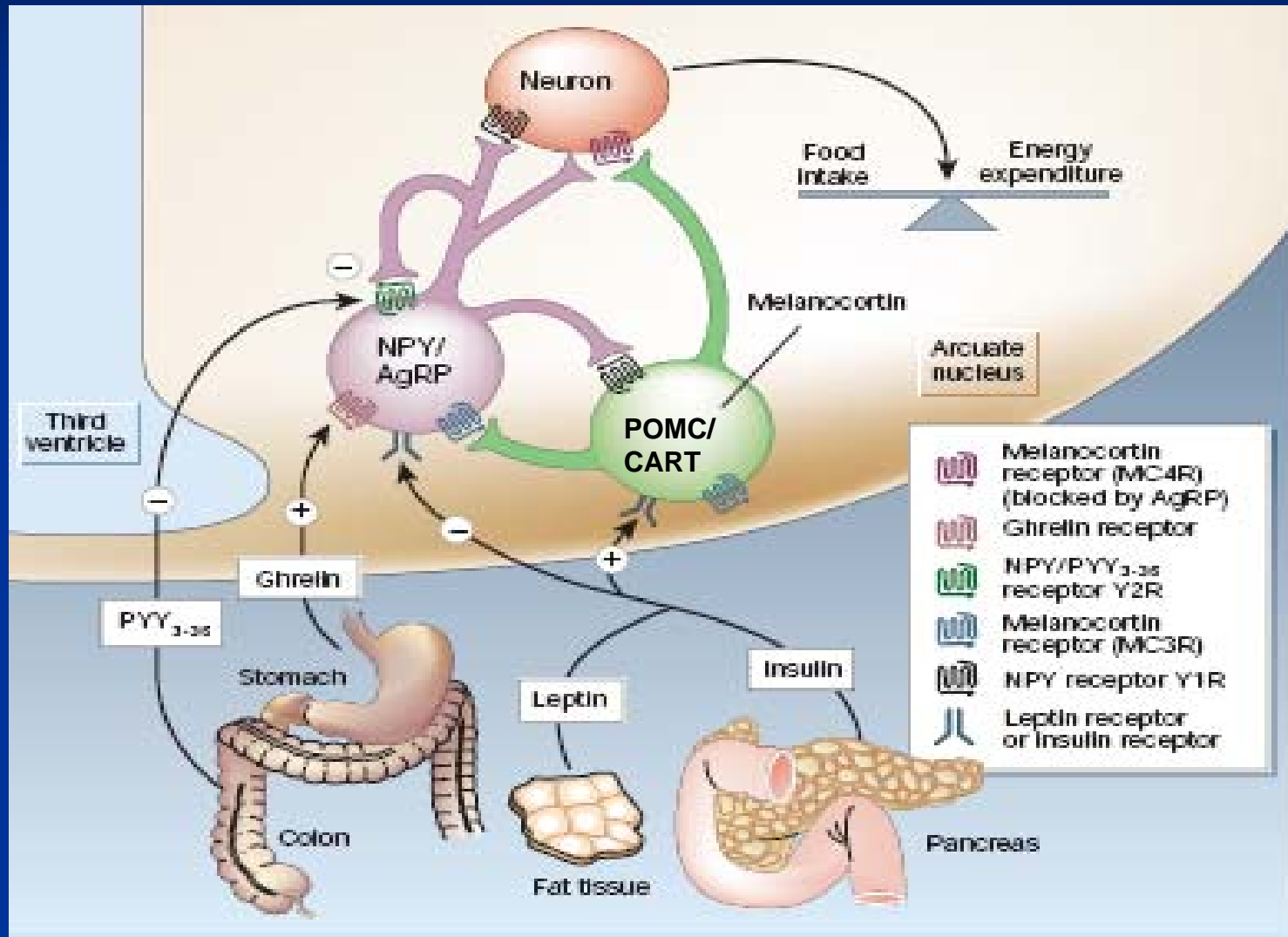
Insulin  
PP  
Amylin

PYY  
OXM  
GLP-1

GI Tract



# Neuroendocrine Hypothalamic System





# Management

# NICE Guidelines 2010

<http://www.nice.org.uk/guidance/cg43>

- Life style modification

- Diet
- Exercise
- Behavioural
- Psychosocial

- **Pharmacotherapy**

- Bariatric Surgery

- Gastric banding
- Roux -en Y gastric bypass
- Duodenal Switch gastric bypass

# Pharmacotherapy

- Drugs in use as anti-obesity treatment
- In use but not licensed as anti-obesity Tx
- OTC
- Drugs in development

# Historical Background

- 2<sup>nd</sup> Century AD- Laxatives and Purgatives
  - - 1st described by Soranus Ephesus (Greek Physician)
- 1920-1930- Thyroid hormone
- 1933- Dinitrophenol (DNP)- thermogenesis
- 1930s- Amphetamines
- 1967- Phentermine
- 1973- Fenfluramine
- 1990s- Dexfenfluramine
  
- **2000s?**

# Anti-obesity Drugs in use

Short Term

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Long Term

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Central

Local

Sympathomimetics

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SNRI

ECB

Lipase inhibitor

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Phentermine  
Mazindol  
Diethylpropion

Sibutramine

Rimonabant

Orlistat

↓  
US only

Withdrawn  
2010

Withdrawn  
2010

# Orlistat (Lipstatin)- Xenical

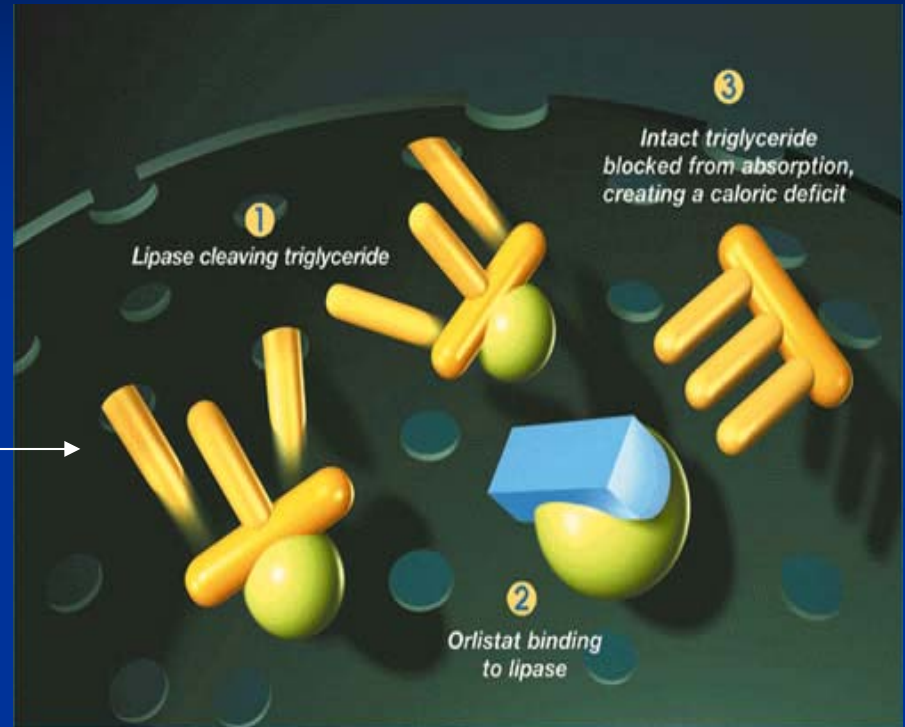
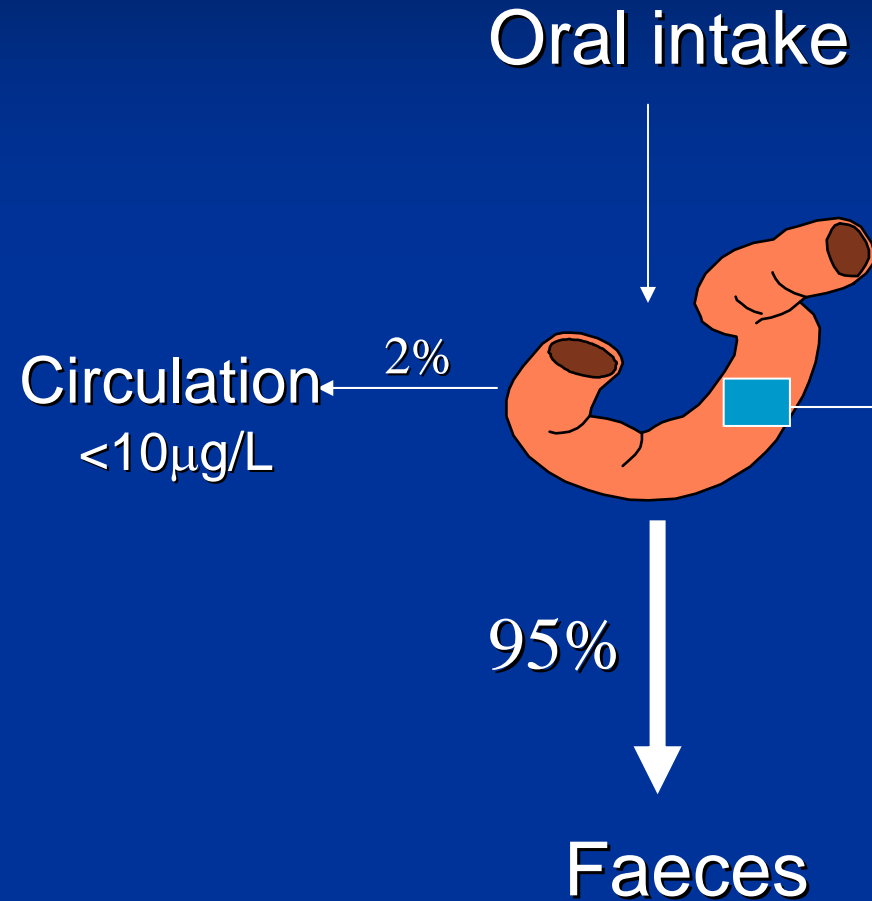
Pancreatic Lipase Inhibitor

- Manufacturer

- Roche- POM
- GSK (Alli) OTC

- Licensed 1998

# Orlistat- Pharmacokinetics



- Blocks absorption of 30% fat
- Protein and CHO absorption unaffected
- $t_{1/2}$  = 1-2 h
- 99% bound to protein
- Bioavailability- Negligible



# Orlistat- Indications

- Management of obesity + reduced calorie diet
- Reduction of risk of wt regain after initial wt loss
  - In patients with BMI > 30 kg/m<sup>2</sup>
  - In patients with BMI > 27 kg/m<sup>2</sup> + other risk factors (DM, HT, Dyslipidaemia)
- Dose
- 120\* mg x3 daily (before/during/ 1H after meals)

\*60 mg dose is available as OTC

# Orlistat- Contraindications/Warnings

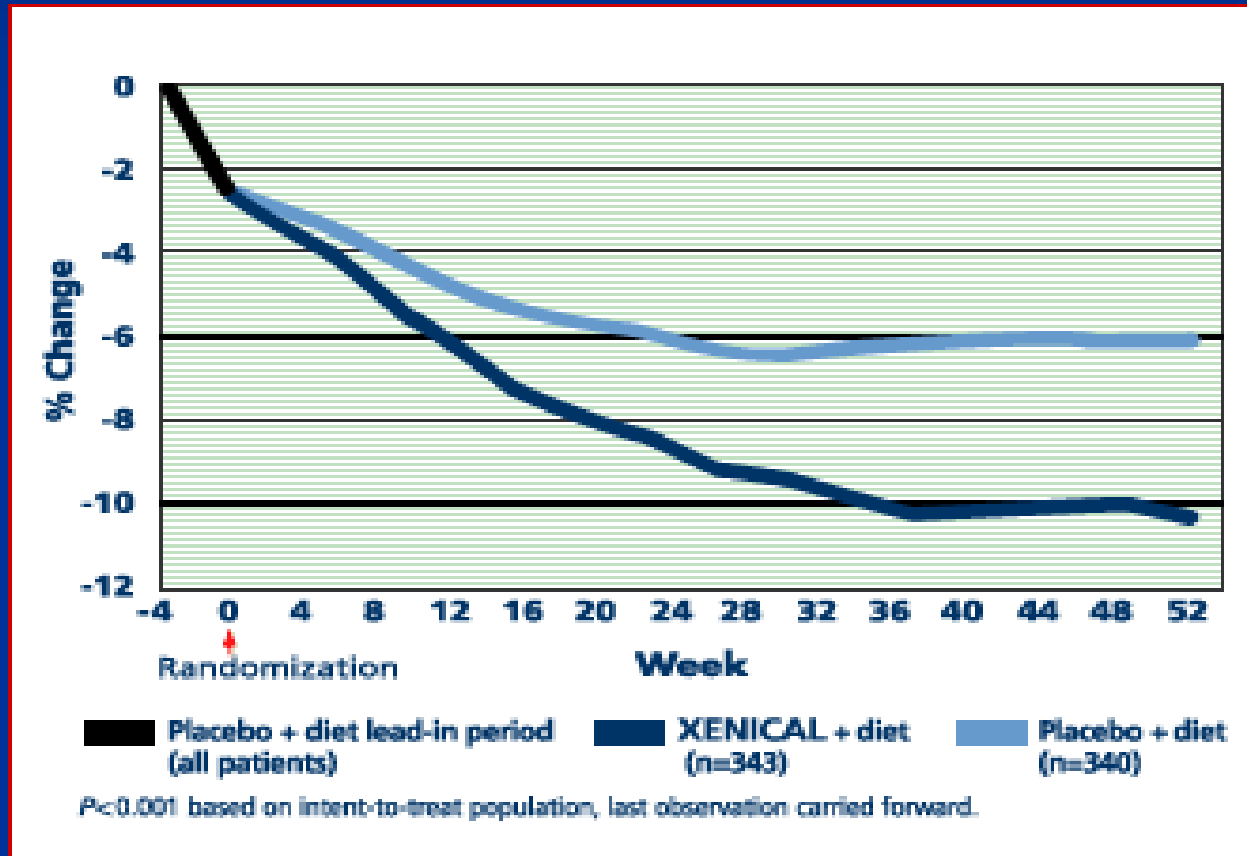
- Patients with Chronic malabsorption syndrome
- Cholestasis
- Patients with known hypersensitivity to Orlistat

## Warnings

- Pregnancy/breast feeding
- Use with caution in pancreatic, liver and bile duct disease

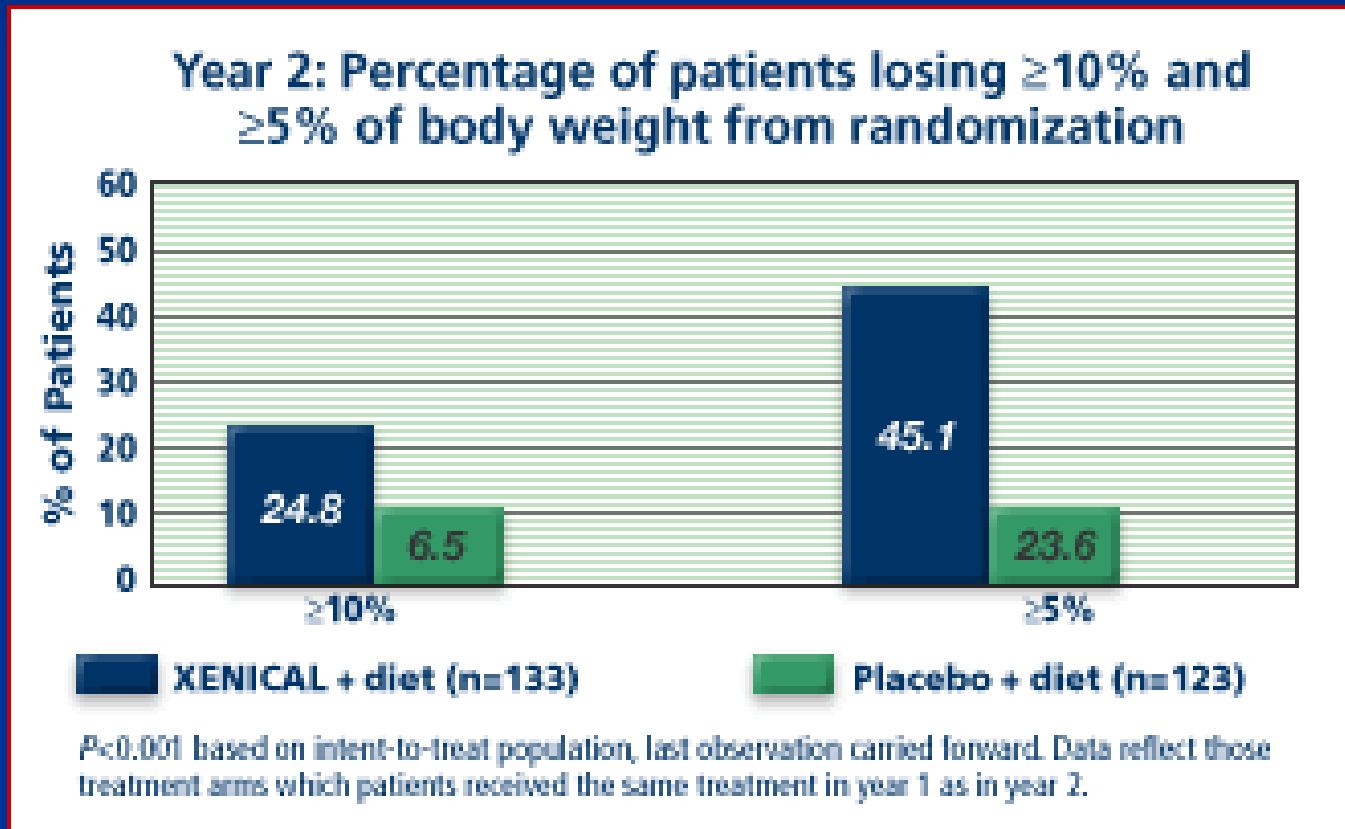
# Orlistat- Efficacy

Year 1: Faster and greater weight loss



# Orlistat- Efficacy

## Year 2: Significant weight loss maintained



# Orlistat- Drug interactions

- Orlistat and cyclosporine
  - should not be taken within 2 hours of each other
  - More-frequent monitoring of cyclosporine levels should be considered in patients taking both drugs
  
- Impaired fat soluble Vit. levels (A, D, E & K)
  - Supplements should be taken at bed time

# Orlistat- Side Effects

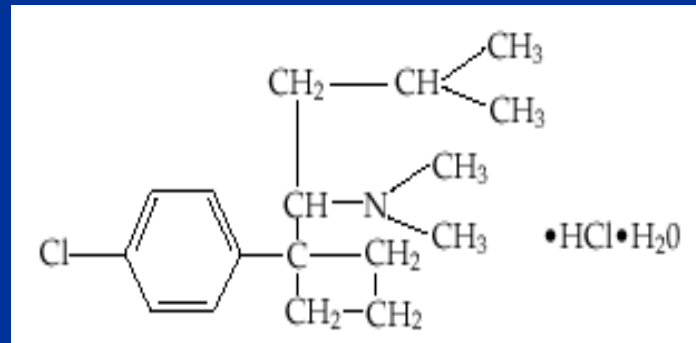
- GI (affect tolerability)
  - Steatorrhea (Oily stool)
  - Urgency
  - Flatulence
- Low systemic effects
  - However, recent rare cases of liver toxicity & Kidney injury reported ( FDA 2009)



Q?

# Long-Term CAAS- Withdrawn 2010

Sibutramine (Abbot)- Meridia (US)/Reductil (UK)

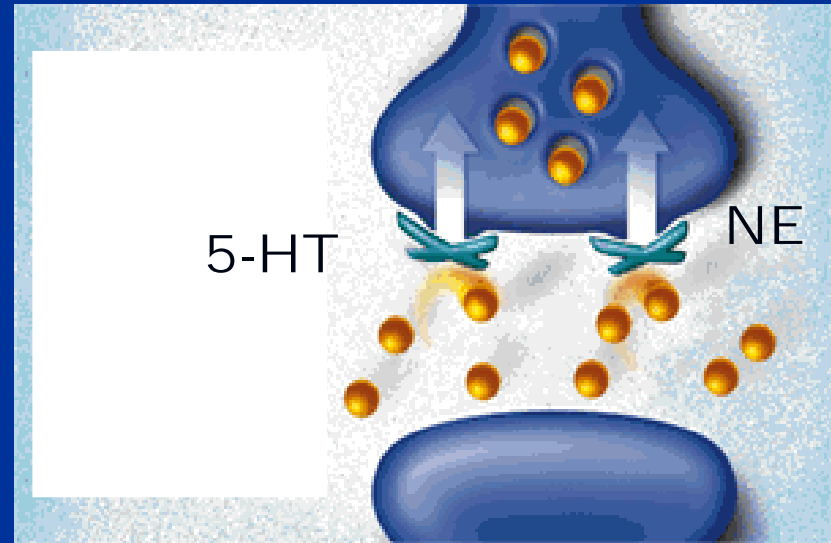


Sibutramine hydrochloride monohydrate

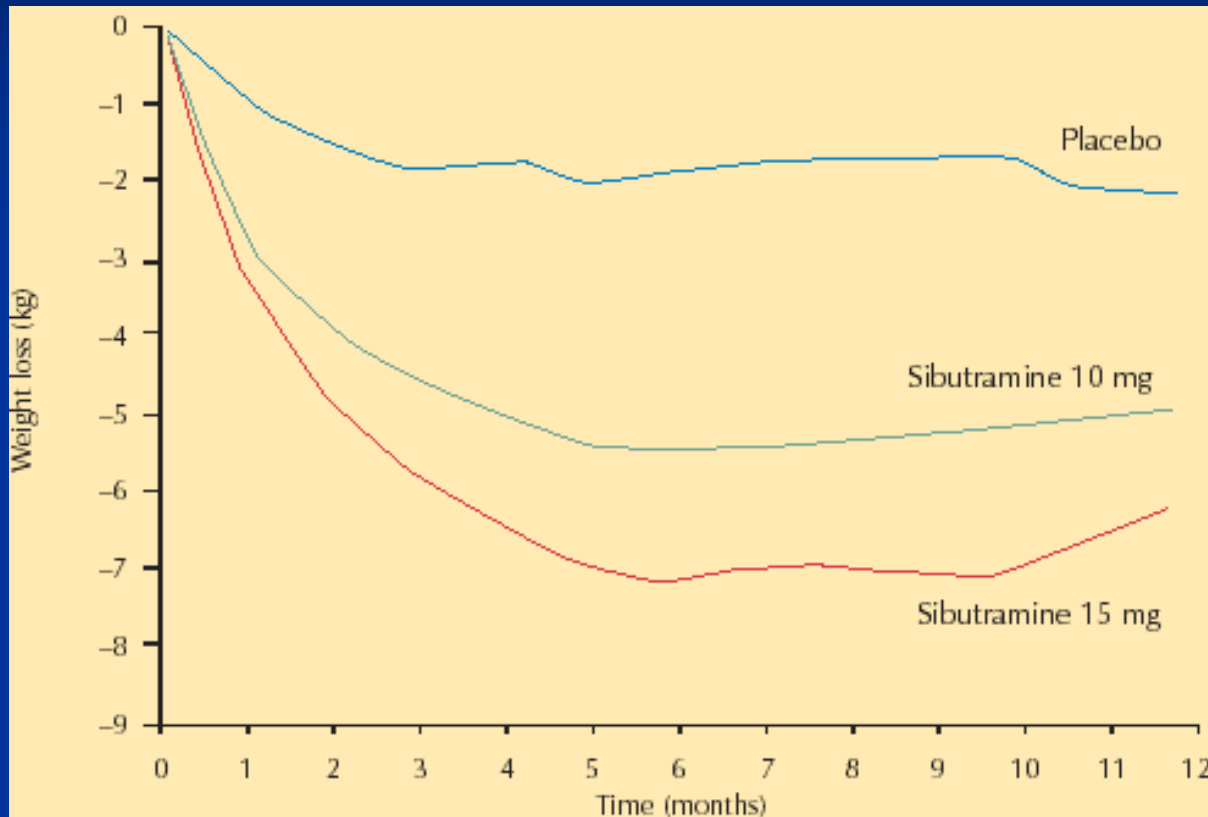
# Sibutramine- Pharmacodynamics

## Mechanism of action

1. Noradrenergic, inhibits amine reuptake
2. Blocks reuptake of serotonin and nor-adrenaline in the CNS (NE>5-HT>DA)
3. Suppresses appetite and promotes satiety
4. Increases resting energy expenditure (thermogenesis)



# Weight changes observed during a 12-month trial of sibutramine



sibutramine 10 mg (n = 81) or 15 mg (n = 94), and placebo (n = 80)

# Sibutramine

## Adverse Effects

Headache  
Tachycardia  
Increase in BP  
Dry mouth, constipation  
Insomnia  
Serotonin syndrome  
**Increase risk of non-fatal MI**  
**Increased risk of stroke**

## Drug interactions

- Inhibitors of CYP3A4
  - Erythromycin
  - Cimetidine
  - Ketoconazole
  - NSAID
  - Antidepressants
  - Antipsychotic

# Sibutramine Summary

Marketing Authorisation Withdrawn Jan 2010

**NICE clinical guideline 43 recommended sibutramine for the treatment of obesity in certain circumstances. These recommendations have now been withdrawn and healthcare professionals should follow the MHRA advice.**

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# ECB

## Physiological functions (through CB1)

- Energy balance
- Body weight
- Affect glucose/lipid metabolism
- Modulates intake of highly palatable sweets/fatty food



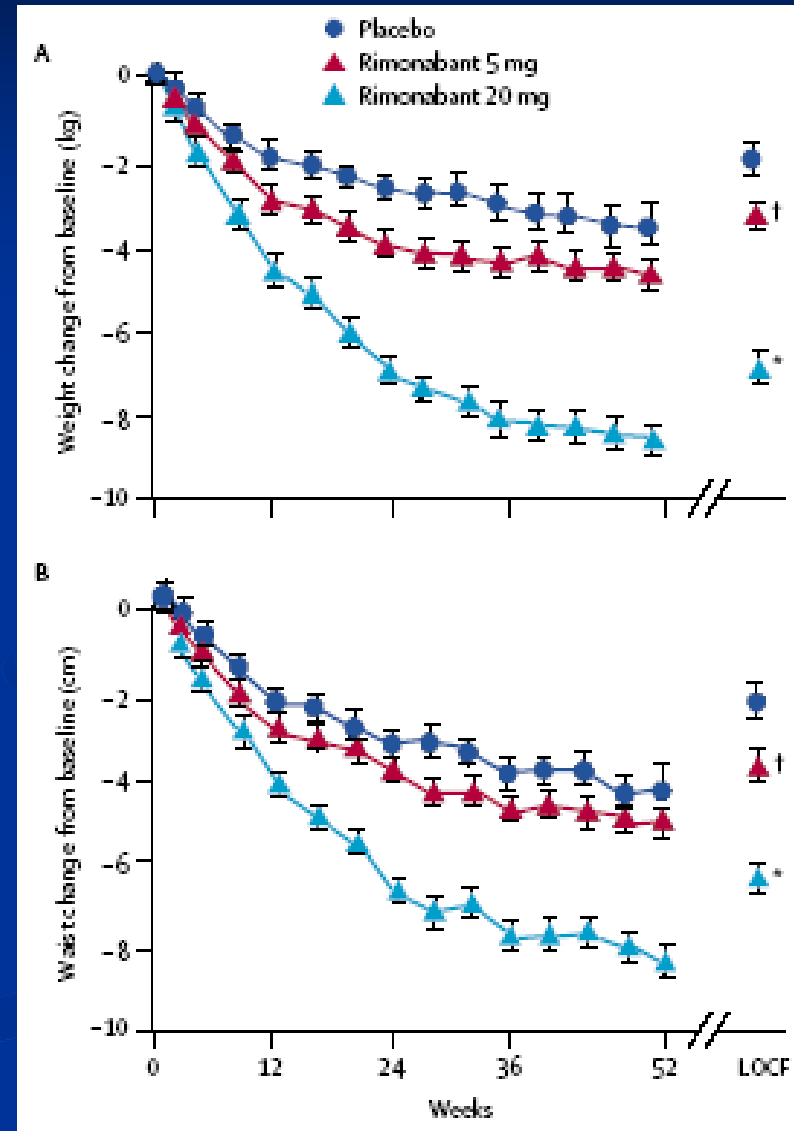


# Rimonabant- Efficacy

RIO- Europe study

Double blind randomised-  
placebo controlled

- Subjects n= 1507
- BMI > 30 Kg/m<sup>2</sup>  
>27 Kg/m<sup>2</sup> + HT/dyslipidaemia
- Endpoint- wt change at 1Y



# Rimonabant

## Side effects (Can occur 15.7%)

- Nausea/GI disorders
- **Mood alteration, Depressive symptoms, Depressive disorders- Suicidal ideation**
- Anorexia
- insomnia
- Anxiety
- dizziness

Where are we now?

# Drugs in use but not licensed as anti-obesity

Drug	Indications	1 action	2 action
Metformin	Type 2 DM	Glucose sensitisation	↓ wt
Exenatide/Liraglutide	Type 2 DM	GLP-1 agonist	↓ Wt
Diazoxide	Insulinoma	↓ Insulin ↑ $\beta_3$ adrenergic R	↓ %body fat
Bupropion	Depression Smoking cessation	Noradrenergic/ Dopaminergic	↓ appetite
Topiramate	Epilepsy	GABA-A R blocker	↓ Appetite ↓ wt
Thyroxine	Hypothyroid	↑ thermogenesis	↓ Wt

# Drugs withdrawn

## Centrally acting appetite suppressants

- Amphetamine- *Stimulant, dependence*
- Fenfluramine
- Dexfenfluramine *Associated with valvular heart disease*
- Phentermine
  
- Sibtramine  $\uparrow$  nonfatal MI and stroke
- Rimonabant Suicidal tendency

# Drugs in development

Compound	Action	Company	Phase
Contrave Bupropion+ Naltrexone	Dopamine and NA reuptake inhibitor (bupropion) Opioid recp antagonist (naltrexone)	Orexigen	III
CNTF (Axokine)	Receptor stimulant in the leptin Pathway	Regeneron/Emisphere Technologies/Shearwater	III
AOD 9604	Human GH Fragment promote fat burn	Metabolic pharmaceuticals	IIc
ATL-962	Lipase inhibitor	Alizyme	III to begin 2007
Qnexa Toperamide+phentermine	Anticonvulsant + Amphetamine derived	Vivus	IIb
Pramlintide	Delays gastric emptying	Amylin	III
PYY3-36	Inhibit food intake	Nashtech	II

# Other targeted mechanisms as antiobesity therapeutics

- MCR agonists
- MCH antagonists
- Ghrelin antagonists
- B<sub>3</sub>-adrenoceptor agonists



# Bariatric Surgery-NICE Guidelines

- Bariatric surgery is recommended as a treatment option for people with obesity if all of the following criteria are fulfilled:
  - • they have a BMI of 40 kg/m<sup>2</sup> or more, or between 35 kg/m<sup>2</sup> and 40 kg/m<sup>2</sup> and other significant disease (for example, type 2 diabetes or high blood pressure) that could be improved if they lost weight
  - • all appropriate non-surgical measures have been tried but have failed to achieve or maintain adequate, clinically beneficial weight loss for at least 6 months
  - • the person has been receiving or will receive intensive management in a specialist obesity service
  - • the person is generally fit for anaesthesia and surgery
  - • the person commits to the need for long-term follow-up.

# Summary

- Prevalence of obesity is increasing world wide
- Public health problem and high economic burden- ↑ Co-morbidities
- Is an IR, pro-inflammatory and prothrombotic state that interacts with risk factors to accelerate atherosclerosis and CHD
- 5-10% Wt loss→ significant ↓ risk
- Management proves very challenging
- Orlistat is the only licensed drug (UK) in use but more in the pipeline....?
- Better understanding of targets and counter regulatory mechanisms
- Continued drug surveillance and long term safety measures