Medical Treatment of Obesity – The search for the magic pill

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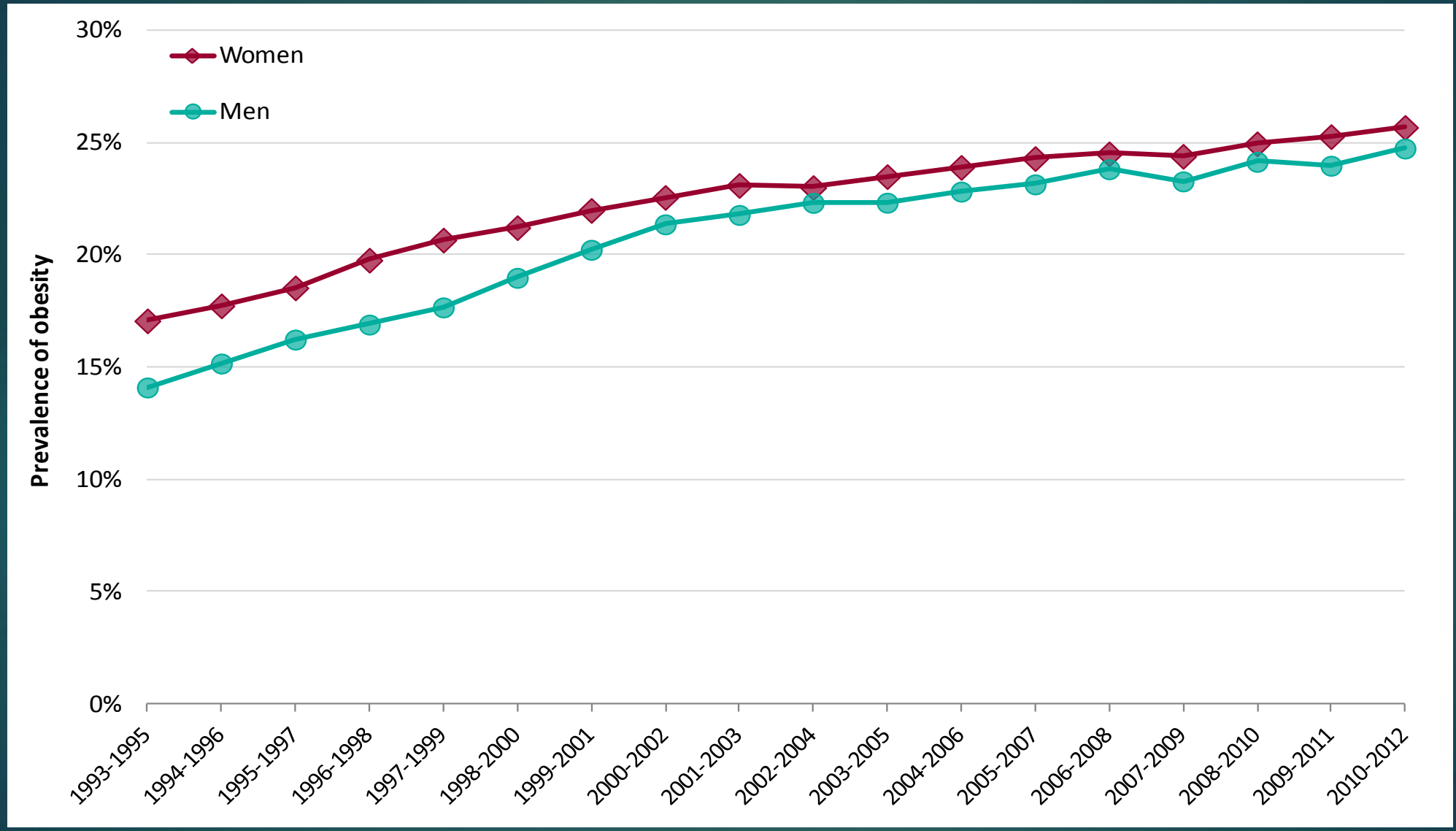
Objectives

- Discuss Obesity trend and its consequence in the UK
- Briefly discuss current concepts in regulation of body weight
- Obesity Pharmacotherapy and its limitations
- Obesity drugs for the future

Trend in obesity prevalence among adults

Health Survey for England 1993-2012 (3-year average)

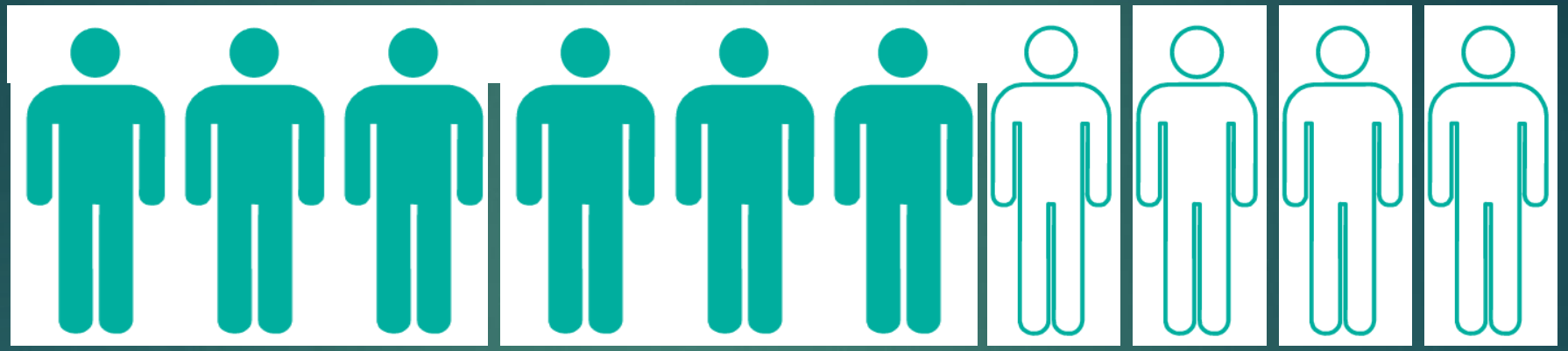


Adult (aged 16+) obesity: BMI ≥ 30kg/m^2

Overweight and obesity among adults

Health Survey for England 2010-2012

More than 6 out of 10 men are overweight or obese (66.5%)

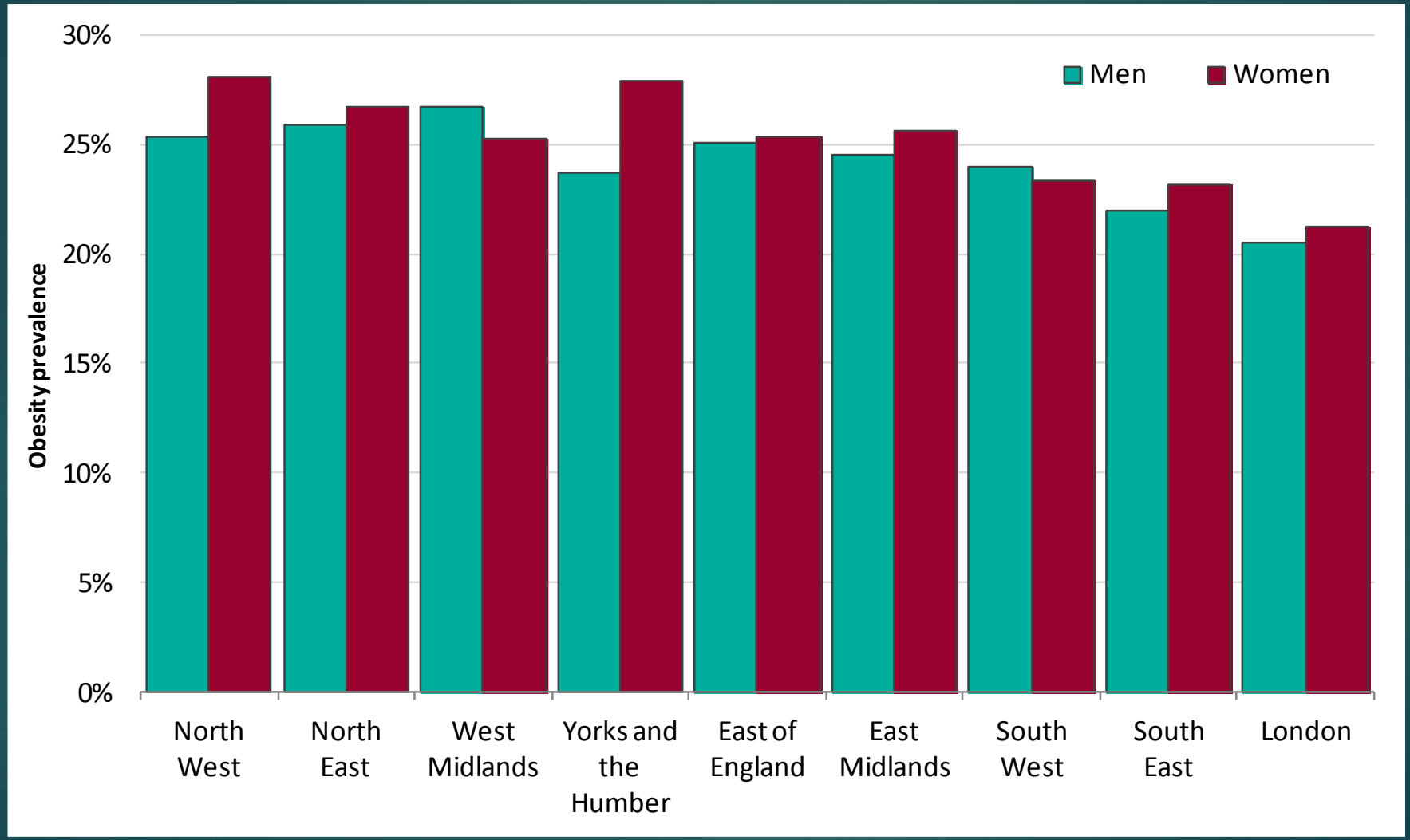


More than 5 out of 10 women are overweight or obese (57.8%)

Adult (aged 16+) overweight and obesity: BMI ≥ 25kg/m^2

Prevalence of adult obesity by region

Health Survey for England 2009-2011 (3-year average)



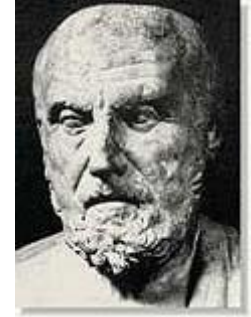
Health risk categories

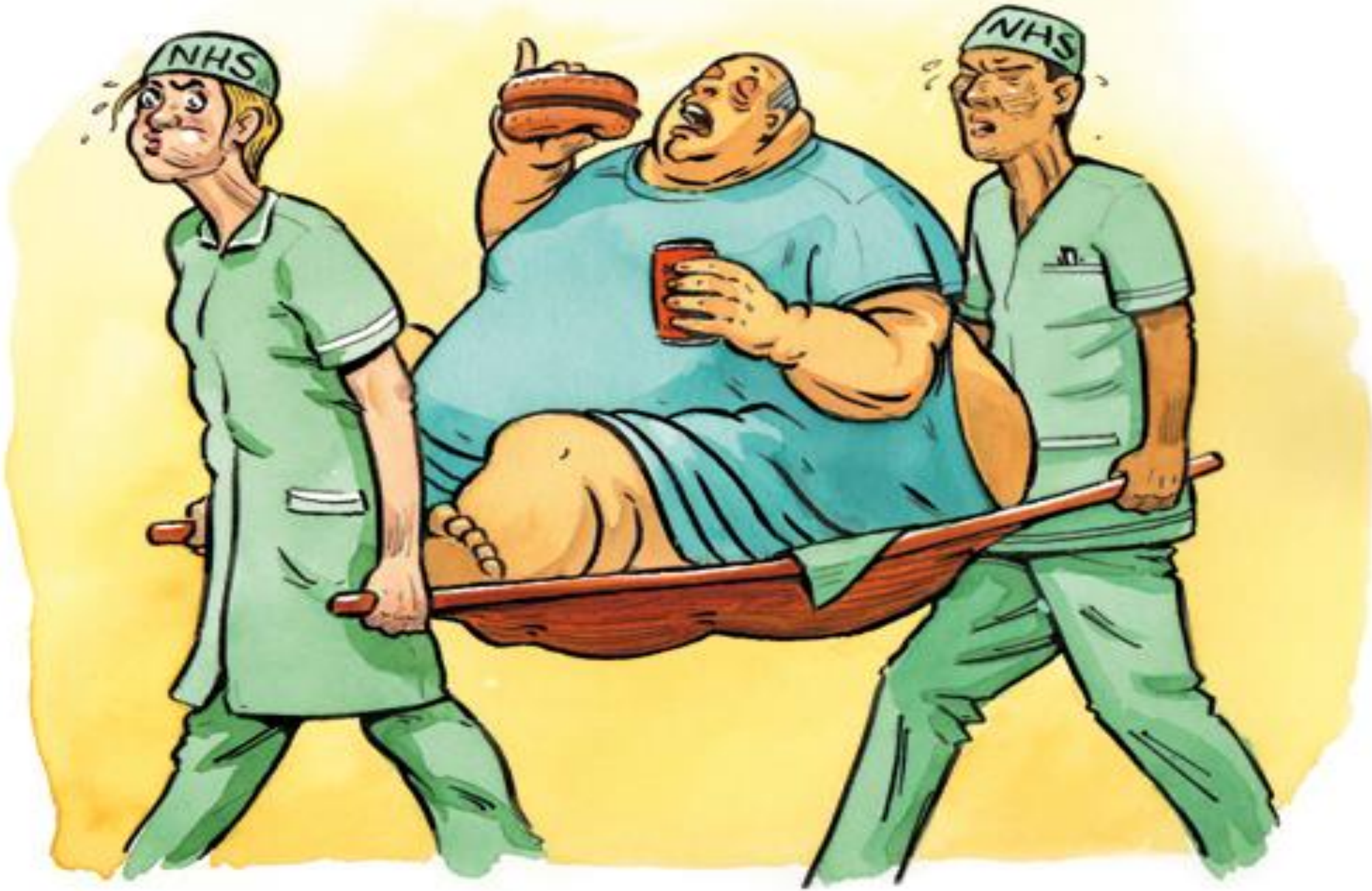
Health Survey for England/ NICE

BMI	Waist circumference		
	Low	High	Very high
	Men: <94cm Women: <80cm	Men: 94-102cm Women: 80-88cm	Men: >102cm Women: >88cm
Underweight ($<18.5 kg/m^2$)	Underweight (Not Applicable)	Underweight (Not Applicable)	Underweight (Not Applicable)
Healthy weight ($18.5\text{-}24.9 kg/m^2$)	No increased risk	No increased risk	Increased risk
Overweight ($25\text{-}29.9 kg/m^2$)	No increased risk	Increased risk	High risk
Obese ($30\text{-}34.9 kg/m^2$)	Increased risk	High risk	Very high risk
Very obese ($\geq 40 kg/m^2$)	Very high risk	Very high risk	Very high risk

Patterns and trends in adult obesity

"Corpulence is not only a disease itself but the harbinger of others"- Hippocrates





Medical Complications of Obesity

CNS
- Cerebrovascular disease/stroke
- Idiopathic Intracranial hypertension
-Cataracts

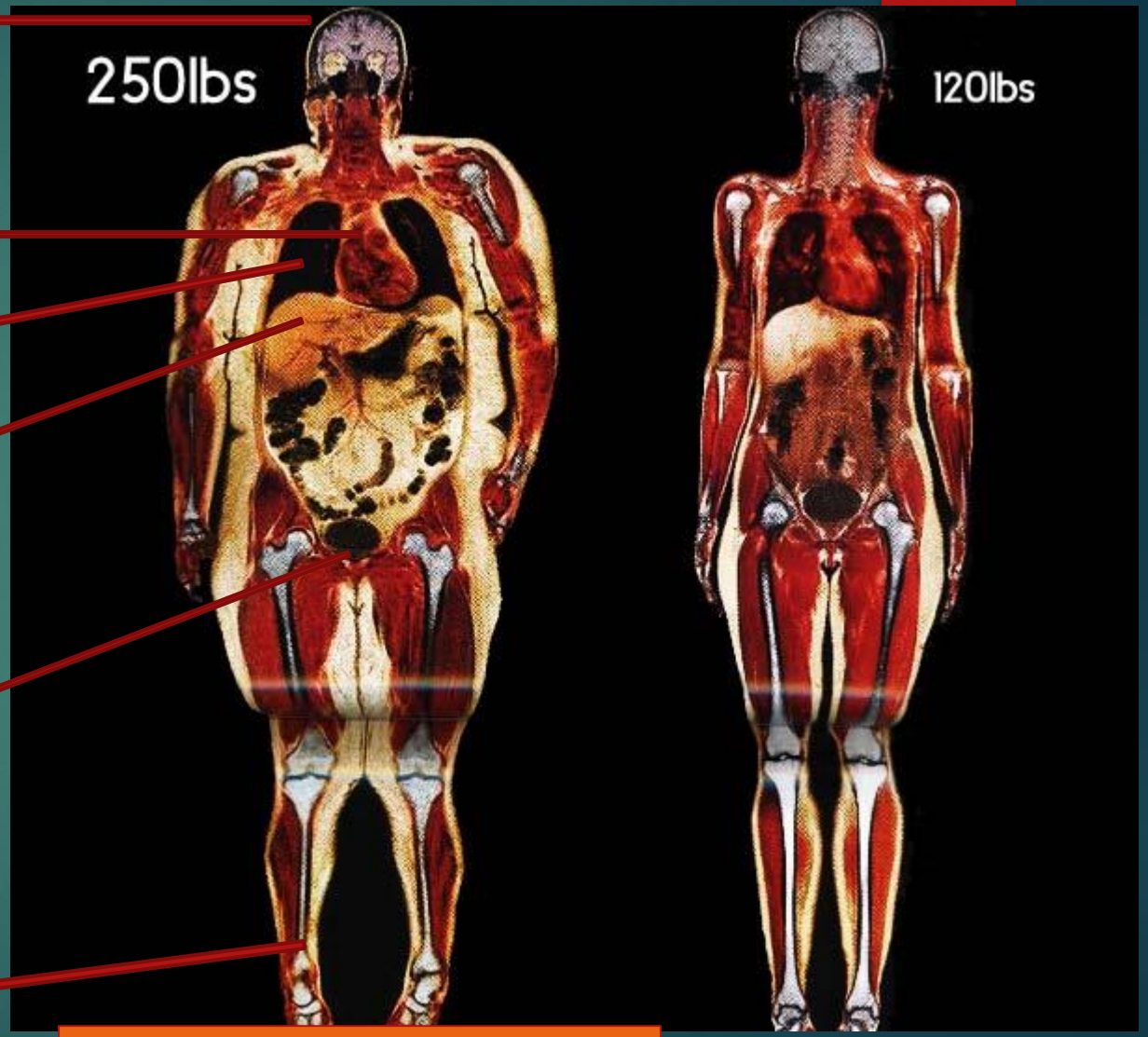
Cardiovascular
- T2DM
- Coronary heart disease
- Dyslipidaemia
- Hypertension

Pulmonary Disease
- Obstructive sleep apnoea
- Hypoventilation Syndrome

Gastrointestinal
- Pancreatitis
- Non-alcoholic fatty liver disease
- Gallbladder disease

Reproductive system
Hypogonadim, Infertility
Abnormal menses, PCOS

Musculoskeletal
lymphoedema, Gout, Phlebitis, Osteoarthitis



Cancer
Breast, uterus, cervix, prostate,kidney, colon, oesophagus, pancreas,liver

Hotspots for weight-related hospitalisations per 100,000 people

1. Bassetlaw 2,878
2. Doncaster 2,713
3. Plymouth 1,869
4. Wolverhampton 1,483
5. Northumberland 1,312
6. North Tyneside 1,242
7. Derby City 1,152
8. Harrow 1,027
9. Bradford & Airedale 970
10. Sandwell 953

Natural History of Obesity

- **Progressive weight gain**
- **Decrease of basal calorie requirement with age**
- **0.5kg to 1.0kg weight gain/ year on average in adult life**
- **obesity can develop with advancing age while exercise remains constant**
- **Normal physiologic studies did not demonstrate any difference between lean and obese individuals in the utilization of energy ie is not due to sluggish metabolism**

Nelson R A et al JAMA. 1973;223(6):627-630

Etiologic classification of obesity

Iatrogenic causes
Drugs that cause weight gain
Hypothalamic surgery
Dietary obesity
Infant feeding practices
Progressive hyperplastic obesity
Frequency of eating
High fat diets
Overeating
Neuroendocrine obesities
Hypothalamic obesity
Seasonal affective disorder
Cushing's syndrome
Polycystic ovary syndrome
Hypogonadism
Growth hormone deficiency
Pseudohypoparathyroidism
Social and behavioral factors
Socioeconomic status
Ethnicity
Psychological factors
Restrained eaters
Night eating syndrome
Binge-eating
Sedentary lifestyle
Enforced inactivity (post-operative)
Aging
Genetic (dysmorphic) obesities
Autosomal recessive traits
Autosomal dominant traits
X-linked traits
Chromosomal abnormalities
Other
Low birth weight

Energy in

- Short term regulation – preventing over eating at each meal
- Long term regulation – maintenance of normal quantites of energy stores in the body
- Drivers – Hunger – internal drive to eat – Physiological
  - Appetite – External drive to eat- Psychological
- Satiety – hunger is suppressed
- Hypothalamus – both hunger and satiety centre
- Mediated by hormones and peptides

Energy Out

Metabolism: Age, gender, body composition, diet, exercise, stress, disease, drugs

Physical Activity

Daily Activity: Sedentary daily life activities vs busy or active life

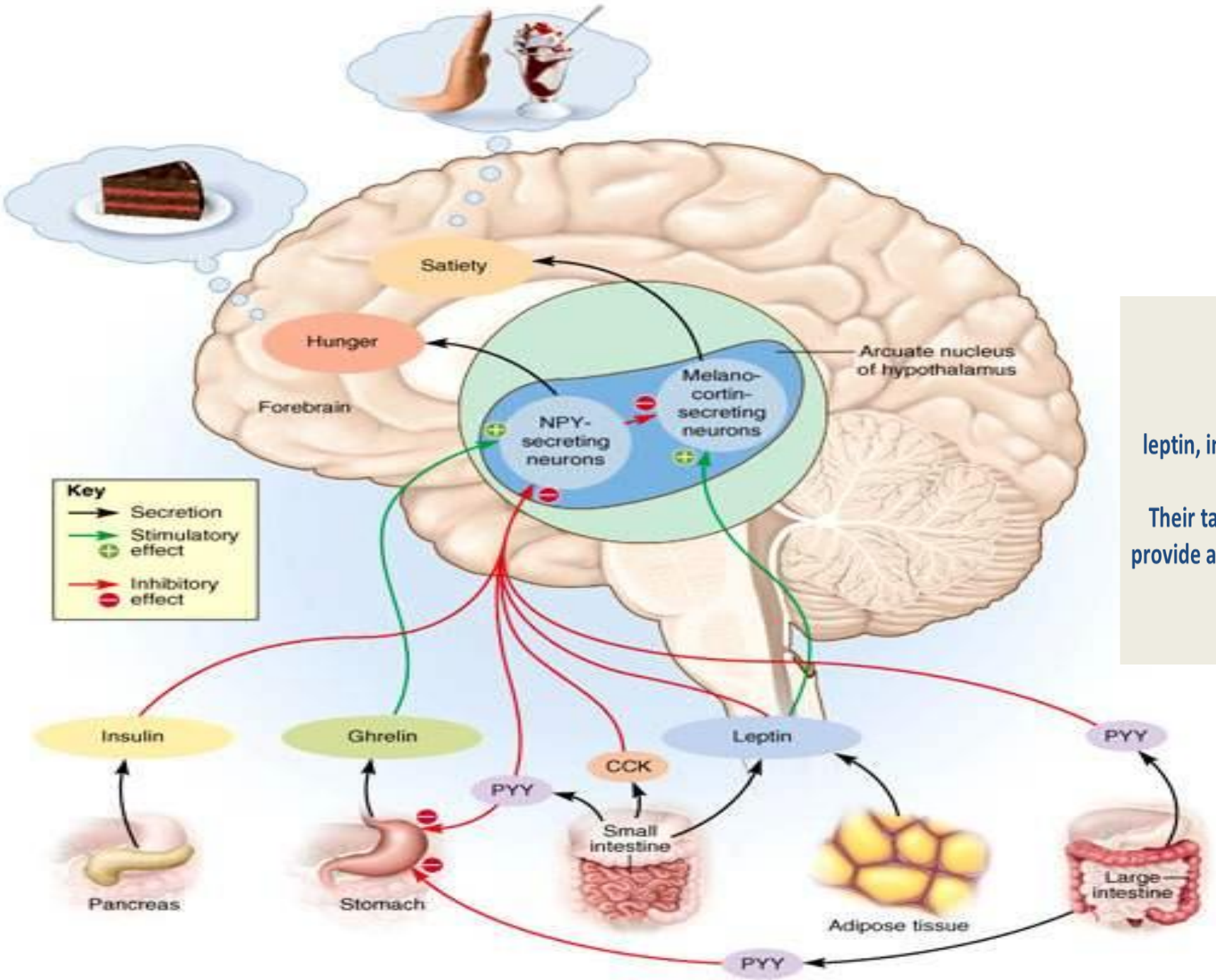
Exercise: Aerobic vs Resistant training, Duration and intensity

Thermal Effect of Meals: Type and Number of Meals

Peripheral signals involved in the regulation of food intake

- Gastrointestinal hormones
- Pancreatic hormones
- Adipose tissue hormones

- Orexigenic (e.g., ghrelin)
- Anorexigenic (e.g., insulin, peptide YY, CCK, leptin)



Ghrelin signals hunger (orexigen, stimulates food intake), leptin, insulin, CCK and PYY signal satiety (anorexigen, inhibit food intake).

Their targets are neurons in the arcuate nucleus, of which POMPC/CART provide an orexic signal and AgRP/NPY neurons drive the anorexic response

Impact of Weight Loss on CV Risk Factors

1. Wing RR et al. *Arch Intern Med*. 1987;147:1749-1753.
2. Mertens IL, Van Gaal LF. *Obes Res*. 2000;8:270-278.
3. Blackburn G. *Obes Res*. 1995;3 (Suppl 2):211S-216S.
4. Ditschunheit HH et al. *Eur J Clin Nutr*. 2002;56:264-270.

Need for pharmacotherapy for weight loss

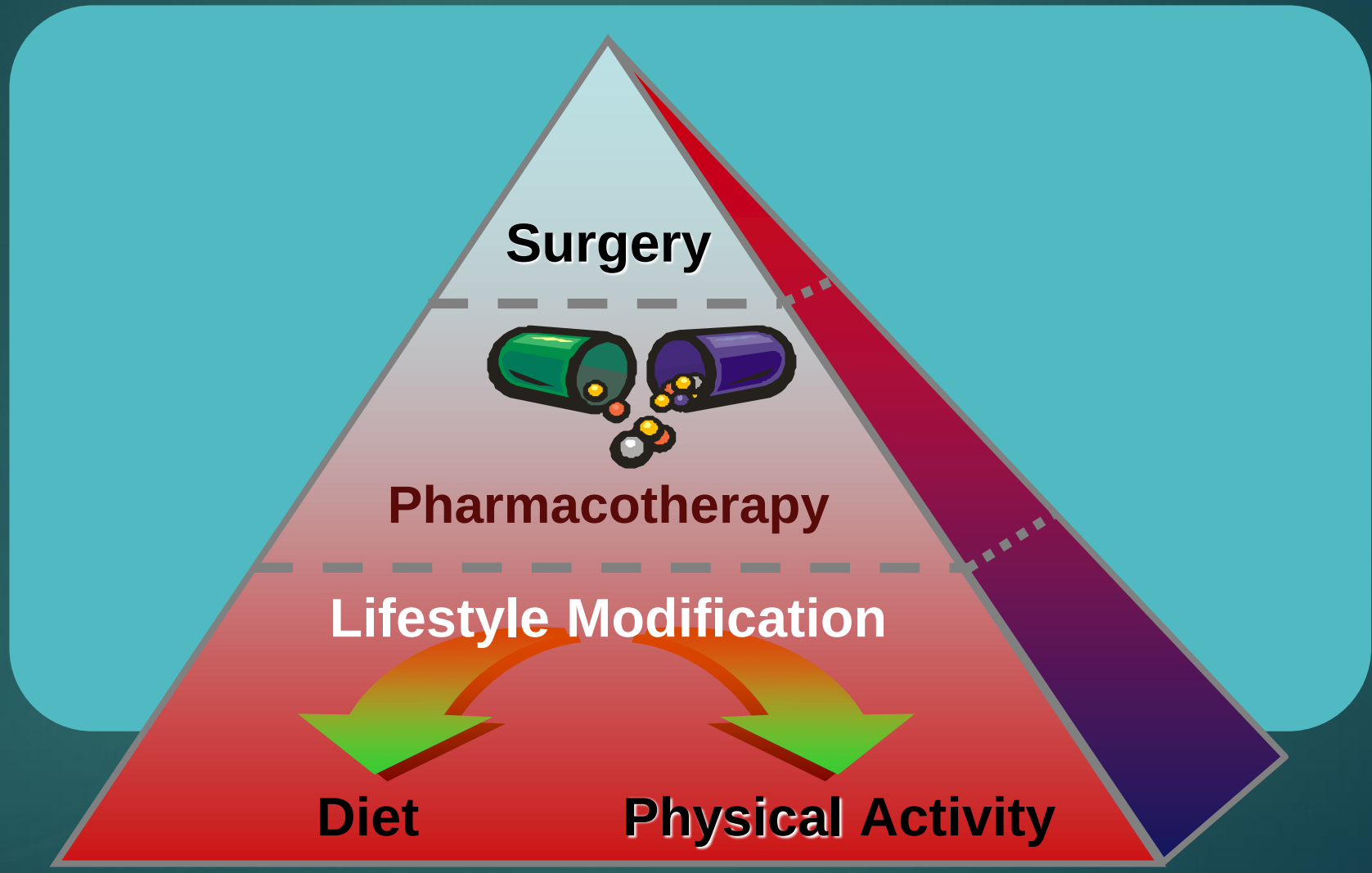
- Reality – extremely difficult to lose AND sustain weight loss
- Very hard to lose weight by physical activity and behavioural therapy alone

WHY?

Systematic reviews - SIGN

- **Dietary and lifestyle up to 5kg (2-4 yrs)**
- **Drugs 5-10kg (1-2 yrs)**
- **Surgery ~25-75kg (2-4 years)**
- **Surgery -21kg vs wt gain conventional at 8 years***
  - Cochrane collaboration*

Obesity Treatment Pyramid



Anti-Obesity Drug Potential Modes of Action

- Energy intake
  - Hunger ↓
  - Appetite ↓
  - Satiety ↑
- Energy metabolism
  - Digestion/Absorption ↓
  - Metabolism ↓↑
  - Partitioning ↓↑
- Energy expenditure
  - Metabolic thermogenesis ↑
  - Non-exercise activity thermogenesis (NEAT) ↑
  - Exercise thermogenesis ↑

Characteristics of the ideal Anti-Obesity Drug
The Magic pill

- Reduce body weight
- Maintain weight loss
- Well tolerated
- Long-term efficacy
- No rebound effect
- Reduce morbidity
- Reduce mortality

Historical perspective of Obesity Pharmacotherapy

- Unregulated until the 1990s, all withdrawn
- 1880's Thyroid extract (hyperthyroidism),in some cases mixed pituitary extract
- Predorminatly centralling acting anorexics
- 1930's Dinitrophenol (cataracts, neuropathy) – still on sale illegally on the internet – Leeds Medical Student death in 2012
- 1940's Amphetamine based (addiction, CNS/cardiac toxic)
  ex Stimplete Elixir (Dexamphetamine and Phenobarbitone),
  Dexten (Dexamphetamine Sulphate)
- 1960's Rainbow pills -digitalis/diuretics (sudden death) Not recommended
- 1956 – Phenmetrazine (Preludin) WD
- 1959 - Phentermine (Fastin, Ionamin) – W/D EU/UK 2000
- 1959 - Diethylpropion (Apisate,Tenuate) WD
- 1960 - Benzphetamine (Didrex) WD
- 1972 - Fenfluramine (Pondimin) – W/D 1997
- 1977- Fen-Phen – Fenfluramine and Phentermine WD 1997
- 1973 - Mazindol (Teronac)[2] WD
- 1995 – Dexfenfluramine (Redux) – W/D 1997
- 1999 – Sibutramine – (Reductil) WD 2010
- 2006 – Rimonanban –(Accomplia) WD 2008

- 1. All for short-term use except Sibutramine and Rimonanbant
- 2. All save Mazindol, Sibutramin and Rimonanban amphetamine related

Currently approved drug in the UK

ORLISTAT

Indications for Drug Therapy in Obesity

- As an adjunct to behavioural therapy including diet and physical activity

- "Consider drug treatment for patients who have not reached their target weight loss or have reached a plateau on dietary, activity and behavioural changes alone" - NICE Obesity (CG43)

Prescribe in accordance with the drug's summary of product characteristics.

Two important questions

- ***Who to treat?***
- ***For how long?***

Focus on co-morbidities
"Metabolic fitness"

Pharmacological Obesity Treatments

- Weight loss of about 1 lb/week can be expected
- Most weight loss will occur within the first 6 months of therapy
- Significant weight maintenance as long as the drug treatment is continued
- Most patients regain weight if medication is stopped

Cochrane Review 2009

- XENDOS(Orlistat) - Largest and longest trial, 60%of patients dropped out over the four year follow-up period
- Most common reasons for premature withdrawal - treatment refusal, loss to follow up and adverse effects.
- Orlistat reduced the incidence of type 2 diabetes from 9.0% to 6.2% (XENDOS).
- This benefit was primarily observed in the patients with impaired glucose tolerance at baseline.

Audit of weight management clinic Diabetes Centre BHNFT June 2009

- Medication used Sibutramine 12
- Rimonobant 4(not included)
- Orlistat 81
- Mean weight loss 12.2kg(1.8-34kg)
- Total reduction in insulin dose 767units daily
- High drop out rate 97-70-40(mainly orlistat)
- Reduction in HbA1c range 0.1-6.4%

Fat Soluble Vitamins

- Levels of fat-soluble vitamins (A,D, E) and beta-carotene were lowered by orlistat therapy
- vitamin D most frequently affected*
- No study reported the occurrence of clinically significant vitamin deficiency, although patients were routinely advised to take a multivitamin pill daily.

*(Finer 2000;Hauptman 2000;Hollander 1998; Sjostrom1998).

Emerging Concepts in Medical Therapy

- **Chronic therapy (continuous or intermittent)**
- **Individualized therapy (one-drug-for-all not realistic)**
- **Combination therapy**

New Drugs in Development

- Liraglutide (Victoza) Novo-Nordisk – Approved by FDA 0n 11th September 2014 3.0mg sc od for Obesity Vs 1.2mg to 1.8mg for T2DM
- Injectible GLP-1 receptor agonist
- 3 Phase III trials (SCALE)
- 1- Overweight and Obese patients
- 2 -Overweight & Obese T2DM patients
- 3 – Obesity patients with moderate to severe obstructive sleep apnoea

New Drugs

- **Qsiva(EU)** - Phentermine / Topiramate (Oral Tablet) Vivus
- Rejected by EMA in Oct 2012
- US licence **(Qsymia) July 2012**
- EU and UK –not recommended for approval - issues relating to cardiac safety.
- Awaiting further safety studies for resubmission
- ? 2015 earliest

New Drugs

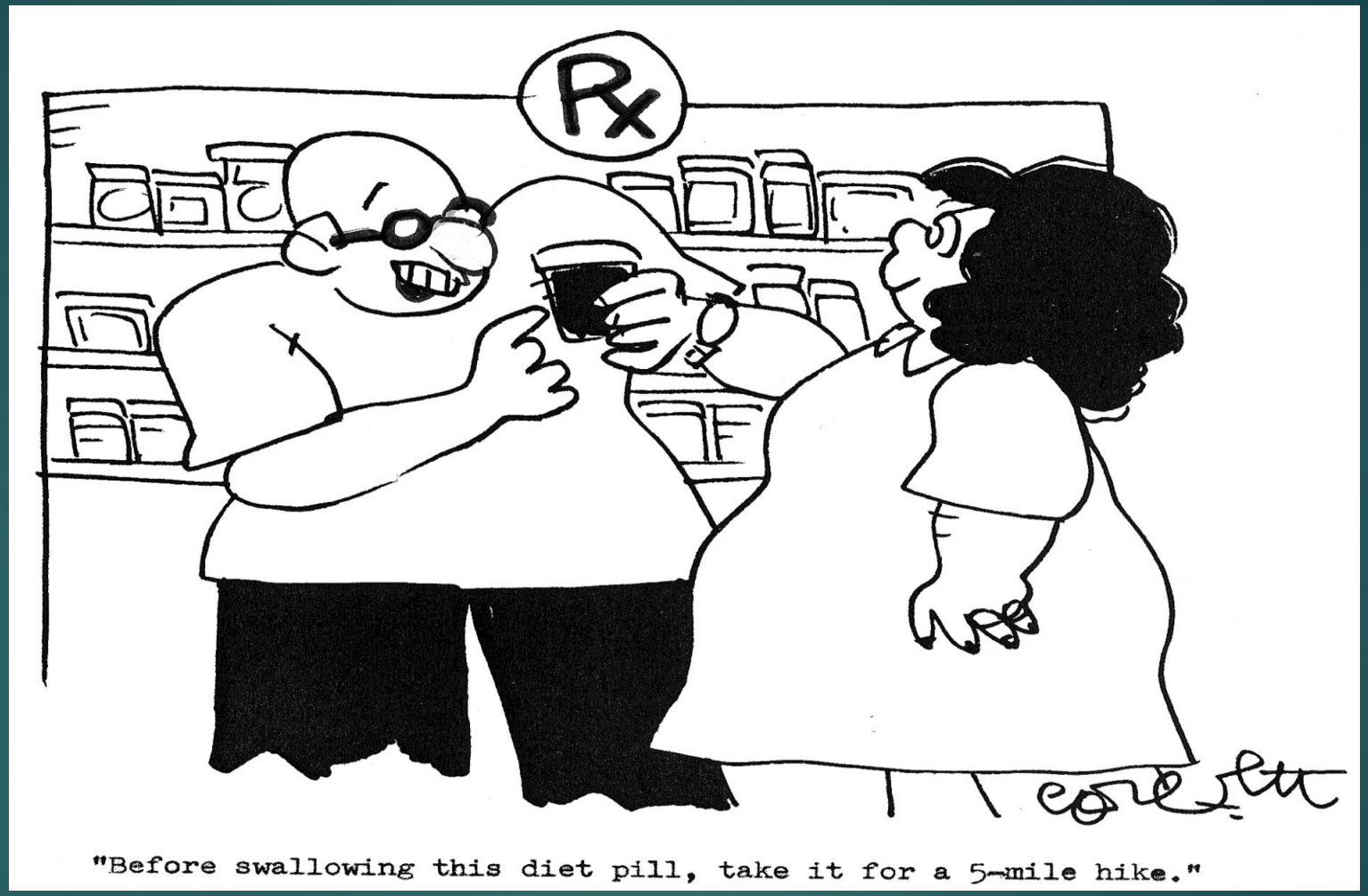
- Bupropion and Naltrexone Combo(Contrave)
- FDA Approval on 10th September 2014
- Opiod receptor antagonist and inhibitor of neuronal re-uptake of NA and Dopamine
- Application with EMA
- Favourable outcome expected
- ? End of 2014

New Drugs

- Lorcaserin (Belviq) – Selective Serotonin 2C Receptor Agonist. (5-HT2C)
- Appetite suppressant (Oral tablet)
- US licence (Schedule IV controlled substance) in 2012
- EU and UK – company withdrew submission for marketing approval
- Concerns about depression and valvulopathy
- Unlikely to be available in the UK

CONCLUSIONS

- Treatment of obesity should be directed at achieving metabolic fitness.
- Diet, exercise, behavior modification are rarely effective for long-term.
- Combo pill promising
- No magic pill exists so far



Thank you