Obesity, present and future therapies

Prof. Sir Stephen Bloom – Imperial College London, UK

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Obesity, Present and Future Therapies

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Why do we over eat?

Summer all the time

• Natural to conserve energy, maximise food intake
  − In evolution, populations expand to starvation
  − Only the very hungry, who conserve energy, survive

• New obesogenic environment
  − Delicious high calorie food available 24 hourly
  − No need for exercise

• Consequence
  − Inevitably we become obese
  − But we haven’t evolved with obesity
  − Resulting metabolic disequilibrium causes early death

Please press on link below

https://www.youtube.com/watch?v=52CvF5oxTGQ
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Epidemic sweeping the world

- 800 deaths per week UK
- 800 deaths per day in USA
- And rising - no action in sight!

Fact

3,000,000,000 obese people
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**Age-adjusted prevalence of obesity and diabetes among U.S. adults aged 18 years or older**

- Obesity (BMI ≥30 kg/m²)
  - 1994: 14.0%
  - 2000: 18.2%
  - 2010: 22.6%

- Diabetes
  - 1994: 4.5%
  - 2000: 6.4%
  - 2010: 8.0%


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**Change in county life expectancy (women)**

- Life expectancy improving a lot
- Life expectancy improving mean
- Life expectancy improving
- Life expectancy not changed
- Life expectancy on or less than zero
- Life expectancy worsening

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**Advice to the obese**

Eat less food, take more exercise

To help, the British Dietetic Association (BDA) looks at the pros and cons and gives its verdict on the some of the most popular diets.

- 5:2 diet
- Dukan diet
- Paleolithic diet
- Atkins diet
- Atkins diet
- Cambridge diet
- South Beach diet
- Slimming World diet
- Slim Fast diet
- Weight Watchers diet
- Roxanne Carbs diet

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Past obesity drugs

1) Thyroxine
2) Dinitrophenol
3) Amphetamines (Benzedrine)
4) Ephedra (traditional Chinese)
5) Phentermine
6) Dextefluoramine (Redux) & Fenfluramine
7) Fen-phen
8) Sibutramine (Meridia, Reductil)
9) Rimonabant (Acomplia)
10) Dopamine
11) Hoodia
12) Boxers use diuretics & laxatives!

Present obesity drugs in EU

1) Orlistat (Xenical, Ali)
2) Liraglutide 3mg
3) Metformin

Marketed GLP1 mimetics

From "Diabetes in Control"
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**Drugs approved for obesity in USA Sept 2014**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Components</th>
<th>Mechanisms</th>
<th>Weight loss</th>
<th>Side effects</th>
<th>Annual cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xenical</td>
<td>Orlistat</td>
<td>Lipase inhb</td>
<td>3%</td>
<td>Abdo pain, Anal leak, Safe</td>
<td>$2K</td>
</tr>
<tr>
<td>Qsymia</td>
<td>Topiramate + phentermine</td>
<td>Unknown + amine mimetic</td>
<td>10%</td>
<td>Cleft palate, Loss of concentration, Numerous CNS</td>
<td>$2.4K</td>
</tr>
<tr>
<td>Belviq</td>
<td>Lorcaserin</td>
<td>5HT 2c agonist</td>
<td>5%</td>
<td>CNS, Cardiac</td>
<td>$1.3K</td>
</tr>
<tr>
<td>Saxenda</td>
<td>Linagliptin</td>
<td>GLP1 3mg daily</td>
<td>5%</td>
<td>Nausea, Diarrhea</td>
<td>$10K</td>
</tr>
<tr>
<td>Contrave</td>
<td>Naltrexone + topiramate</td>
<td>Opiate antag + amine uptake inhb</td>
<td>5%</td>
<td>Nausea, Headache, CVS/CNS</td>
<td>$2K</td>
</tr>
</tbody>
</table>

**Qsymia**
10% Wt loss 1 year
- Phentermine + Topiramate (Vivus)
- Licenced in USA (slow sales), but not in Europe
- Effect on cardiovascular mortality not established
- Females of reproductive capacity should have a negative pregnancy test
- Increases pulse rate – regularly check
- Glaucoma, Cleft Palate, Mood disorders (depression, anxiety), Impaired concentration (speech disorders), Hyperchloraemia (metabolic acidosis), also over 5%: paraesthesia, dizziness, dysgeusia, insomnia, constipation and dry mouth
- Recommended dose (7.5 mg/46 mg) - $135.62, Top dose (15 mg/92 mg) - $183.90, both per month

**Medical failure**
- 3 billion obese people need treatment
- For example, 800+ obesity deaths every week in UK
- No satisfactory medication
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What does “cure” obesity?

- Roux-en-Y gastric bypass
- Excellent long-term weight loss (25%)

Bariatric surgeries
- Gastric balloon
- Gastric band
- EndoBarrier
- Sleeve gastrectomy
- Gastric plication
- Gastric bypass

Bariatric bypass surgery: only successful therapy
- Sjostrom et al., Sweden, NEJM 2007
  - Prospective controlled study, 4000 subjects
  - Gastric Bypass group 10 year wt. loss 25%
- Adams et al., USA, NEJM 2007
  - Retrospective cohort study
  - Gastric bypass, 7 years, 15000 subjects
- Myocardial infarct & cancer rates halved

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**Bariatric bypass surgery**

*Excellent life long weight loss but:*

- Expensive
- Significant death rate
- 50% morbidity
- Can’t be adjusted
- Works by sending satiety gut hormone signals, fooling the brain that the gut is full
- Note: good effects seem entirely proportional to the degree of weight loss

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**Future obesity drugs**

- Bypass surgery works
- So develop medical bypass
- We do know what drugs are going to be available in the future
- And… there is nothing promising

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**The gut hormones**

[Diagram showing various gut hormones including CCK, Pancreatic Polypeptide, GIP, Melanin, GLP1, GLP2, Oxyntomodulin, and PYY]
Functional MRI analysis of brain regions after satiety gut hormone infusion

Co-administration of PYY & GLP-1 produce changes closely similar to eating in brain reward regions

Amalgamated functional MRI data

% BOLD change (food vs non food)


"Curing" diabetes

Zhipps' combination of oxy and y late stage analogues have superior glycaemic control compared to GLP-1 and result in substantially weight loss, despite similar food intake