NEW DRUGS FOR OBESITY

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Introduction
Options for treatment of Obesity
Anti obesity drugs – Past
Anti obesity drugs – Present
New anti obesity drugs
Summary
All Wales Obesity pathway
• Obesity is a largest and fastest growing public health problem in the developed and developing world

• As per the latest statistics, 27% of adults in England are obese (increase from 15% in 1993) Almost 60% of adults are overweight or obese in Wales, of which 24% are obese

• It is defined as a body mass index (BMI) of ≥30 kg/m² and caused by an imbalance between energy intake and expenditure

• Complex, multicomponent metabolic disease of energy homeostasis involving central and peripheral mechanisms

• It is associated with substantial increase in morbidity, premature mortality, impaired quality of life and large healthcare costs
TREATMENT OF OBESITY

• **Life style modification (Diet and exercise)**
  - Does not produce marked or sustainable weight loss

• **Psychological therapies**
  - Cognitive behavioural therapy

• **Weight loss surgery**
  - More effective in terms of weight loss, comorbidity reduction and enhanced survival
  - Concerns about perioperative mortality, surgical complications and the need for reoperation

• **Pharmacotherapeutics**
  - An alternative strategy to surgery to reduce body weight by decreasing the consumption or absorption of food and/or by increasing energy expenditure
<table>
<thead>
<tr>
<th>Decade</th>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td>1960s</td>
<td>Amphetamine derivatives, Desoxycorticosterone, Phentermine, Diethylpropion</td>
<td>Activates sympathetic nervous system, leading to reduced appetite, reduced resting energy expenditure, increases leptin levels</td>
<td>Withdrawn due to side effects like valvular insufficiency leading to pulmonary hypertension</td>
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<td>1970/1980s</td>
<td>Serotonin (5-HT)-releasing agents, Fenfluramine, Dexfenfluramine</td>
<td>Anorectic action is probably by an effect on the appetite control centres in the hypothalamus and enhances glucose uptake into skeletal muscle</td>
<td>Withdrawn due to cardiovascular side effects</td>
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<td>1990s/2000</td>
<td>Monoamine (Serotonin and norepinephrine) uptake inhibitor, Sibutramine</td>
<td>Serotonergic action enhances satiety leading to reduced appetite</td>
<td>withdrawn due to cardiovascular side effects</td>
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<td></td>
<td>Selective Serotonin receptor agonist, Lorcaserin</td>
<td>Stimulates 5-HT₂c receptors in the arcuate nucleus resulting in the release of alpha-melanocortin-stimulating hormone which acts on melanocortin-4 receptors in the paraventricular nucleus to suppress appetite</td>
<td>Withdrawn in 2015 due to increased cancer risk</td>
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<td>Cannabinoid CB1 receptor antagonist, Rimonabant</td>
<td>Endocannabinoid system plays a role in appetite drive and Rimonabant blocks endogenous CB1 receptor activation</td>
<td>Withdrawn due to psychiatric side effects</td>
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<td>Anti Obesity Drugs - Present</td>
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<tr>
<td><strong>Pancreatic lipase inhibitor</strong> <strong>Orlistat</strong></td>
<td>Reduces fat absorption from gut. Gastrointestinal side effects. Moderate weight loss</td>
<td>Approved by NICE</td>
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<tr>
<td>Dopamine &amp; Norepinephrine reuptake inhibitor <strong>Bupropion</strong> /Opioid antagonist <strong>Naltrexone</strong></td>
<td>Mechanism of action not fully understood. Thought to work synergistically in the hypothalamus and the mesolimbic dopamine circuit to promote satiety, reduce food intake, and enhance energy expenditure.</td>
<td>Not approved by NICE</td>
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<tr>
<td>Amphetamine derivative <strong>Phenteramine/Topiramate</strong></td>
<td>Phenteramine – Lower strength which doesn’t cause valvular insufficiency. Topiramate – Mechanism of action in obesity is unknown, may decrease food intake via effects of carbonic-anhydrase inhibition on taste or through its effects on GABA transmission as it mediate effects on appetite and metabolism. It may also affect energy expenditure.</td>
<td>Not approved by NICE</td>
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NEW ANTI OBESITY DRUGS – GLUCAGON LIKE PEPTIDE (GLP 1) ANALOGUES

- GLP 1 is an incretin hormone secreted by L cells of ileum and colon in response to eating
- Cleared by dipeptidyl peptidase 4 (DPP4) inactivation

GLP 1 actions
GLP 1 ANALOGUES

- Used in the treatment of Type 2 diabetes since 2005
- Exenatide was the first GLP 1 analogue introduced
- It is a synthetic version of Exendin-4, a peptide found in the venom of the Gila monster
- Exenatide bears a 50% amino acid homology to human GLP-1 and it has a longer half-life

- Number of human GLP 1 analogues were produced in the later years
HIGH DOSE LIRAGLUTIDE (SAXENDA)

- High dose GLP-1 analogue **Liraglutide (3 mg)**
- Liraglutide is an analogue which is structurally similar to human GLP-1 with 97% identical amino acid residues
- Made by adding C16 fatty acid which makes it resistant to DPP4 cleavage and has long circulatory half life
A 56-week, double-blind trial involving 3731 patients who did not have type 2 diabetes, had a body-mass index of at least 30 or at least 27 if they had treated or untreated dyslipidemia or hypertension.

Both groups received counselling on lifestyle modification.

A total of 63.2% of the participants in the liraglutide group as compared with 27.1% in the placebo group lost at least 5% of their body weight (P<0.001), and 33.1% and 10.6%, respectively, lost more than 10% of their body weight (P<0.001).

Reduction in cardiometabolic risk factors noted in Liraglutide group.

Common adverse events were nausea, diarrhoea, constipation, vomiting and 9.9% of participants withdrew due to side effects in Liraglutide group.

>0.2% had acute pancreatitis and gall bladder related events.

A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. N Engl J Med 2015; 373:11-22
The odds ratios and 95% credible intervals (CrI) for achieving at least 5% weight loss at one year in phase III clinical trials for liraglutide as compared with placebo and other FDA approved long-term weight loss agents.

• NICE approved Liraglutide 3 mg (Saxenda) in December 2020 with following recommendations

  • Liraglutide is recommended as an option for managing overweight and obesity alongside a reduced-calorie diet and increased physical activity in adults, only if:

    • They have a body mass index (BMI) of at least 35 kg/m² (or at least 32.5 kg/m² for members of minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population) and

    • They have non-diabetic hyperglycaemia (defined as a haemoglobin A1c level of 42 mmol/mol to 47 mmol/mol [6.0% to 6.4%] or a fasting plasma glucose level of 5.5 mmol/litre to 6.9 mmol/litre) and

    • They have a high risk of cardiovascular disease based on risk factors such as hypertension and dyslipidaemia and

    • It is prescribed in secondary care by a specialist multidisciplinary tier 3 weight management service

    • Should be used for maximum of two years
SWANSEA BAY DATA – HIGH DOSE LIRAGLUTIDE

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<th>Pre treatment</th>
<th>Post treatment</th>
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<td><strong>Series1</strong></td>
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<tr>
<td><strong>Series2</strong></td>
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- **Total number of patients**: 10
- **Duration of follow up**: 14 months (3 to 14 months)
- **Average weight reduction**: 19 Kg (10 to 31)
- **Percentage of weight loss**: 11% (6 to 20)
- **Average BMI reduction**: 6 kg/m² (3 to 10)
- **Average reduction in HbA1c**: 7 mmol/mol (3 to 11)
- **Average reduction of total Cholesterol**: 0.12 mmol/L (-2 to 2.6)
- **Average reduction in systolic BP**: 17 mmHg (-9 to 31)
- **Average reduction of diastolic BP**: 16 mmHg (2 to 56)
HIGH DOSE SEMAGLUTIDE (2.4 MG WEEKLY) – PHASE 3 TRIAL

The mean change in body weight from baseline to week 68 was −14.9% in the semaglutide group as compared with −2.4% with placebo.

Gastrointestinal side effects were common and 2.4% had gall bladder related events in Semaglutide group.

SEMAGLUTIDE

- Not approved by the NICE yet.
- Draft of NICE recommendation for the prescribing of Semaglutide:
  - Semaglutide is recommended as an option for weight management, including weight loss and weight maintenance, alongside a reduced calorie diet and increasing physical activity in adults, only if:
    - They have at least 1 weight related co-morbidity and:
      - A body mass index at least 35kg/m$^2$ (BMI) or
      - Exceptionally, a BMI of 30kg/m2 if they are referred to tier 3 services
    - Prescribe Semaglutide as part of a specialist weight management service with multidisciplinary input (such as a tier 3 or 4 service)
    - Only use Semaglutide for a maximum of 2 years
GLP 1 AND GLUCOSE DEPENDENT INSULINOTROPIC POLYPEPTIDE (GIP) ANALOGUE TIRZAPATIDE

• GIP is an incretin produced by K cells of jejunum and duodenum in response to oral intake

• Functions of GIP
  • Stimulates glucose-dependent insulin release
  • Delays gastric emptying
  • Enhances β cell proliferation and survival in islet cell lines
  • Cleared by dipeptidyl peptidase 4 inactivation and renal elimination
DUAL GIP AND GLP-1 RECEPTOR AGONIST MAIN COMBINED EFFECTS

DUODENOJEJUNAL K CELLS

GIP

INCREASE

Beta cell proliferation
Insulin sensitivity
Insulin secretion
Triglyceride clearance
Satiety
Lipolysis
Natriuresis
Ventricular contractility

ILEOCOLONIC L CELLS

GLP-1

DECREASE

Glucagon secretion
Gastric secretion
Gastric emptying
Apetite
Ectopic fat deposition
Hepatic glucose production
Gastrointestinal motility
Beta cell apoptosis
TIRZAPATIDE – PHASE 3 TRIAL

- Improvements in cardiometabolic measures observed with tirzepatide.
- Most common adverse events with tirzepatide were gastrointestinal, and most were mild to moderate in severity, occurring primarily during dose escalation.
- Adverse events caused treatment discontinuation in 4.3%, 7.1%, 6.2%, and 2.6% of participants receiving 5-mg, 10-mg, and 15-mg tirzepatide doses and placebo, respectively

**N Engl J Med July 2022; 387:205-216**
## INCRETINS VS BARIATRIC SURGERY

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Average weight loss</th>
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<tr>
<td>Liraglutide 3 mg daily</td>
<td>5 to 10%</td>
</tr>
<tr>
<td>Semaglutide 2.4 mg weekly</td>
<td>15%</td>
</tr>
<tr>
<td>Tirzepatide 15 mg weekly</td>
<td>≥20%</td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>30 to 35%</td>
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<td><strong>NEW OBESITY DRUGS FOR GENETIC CONDITIONS</strong></td>
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<td><strong>Melanocortin 4 receptor agonist Setmelanotide</strong></td>
<td>MC4 receptors in the brain are involved in regulation of hunger, satiety, and energy expenditure. Setmelanotide restores impaired MC4 receptor pathway activity arising due to genetic deficits upstream of the MC4 receptor. Used in the treatment of genetic obesity.</td>
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<td><strong>Recombinant analogue of leptin Metreleptin</strong></td>
<td>Leptin is a satiety hormone. Metreleptin binds to and activates human leptin receptor to increase fat breakdown in the blood, muscles and liver, thereby correcting some abnormalities in patients with lipodystrophy.</td>
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NEW ANTI-OBESITY DRUGS ON THE HORIZON

- GLP 1 and Glucagon receptor analogue **Pemvidutide**
- Amylin mimetics **Davalintide/Cagrilintide**
- Cannabinoid type-1 receptor blockers **Zonisamide-Bupropion**
- Leptin analogues combination **Pramlintide-Metreleptin**
- Methionine aminopeptidase 2 inhibitor **Beloranib**
- Lipase inhibitor **Cetilistat**
- Triple monoamine reuptake inhibitor **Tesofensine**
- Anti-obesity vaccines **Ghrelin, Somatostatin, Adenovirus36**
SUMMARY

• Recent advances in anti-obesity drugs (incretins) have enabled the potential of achieving clinically meaningful weight loss with concurrent improvement in metabolic parameters as well as health-related quality of life.

• Understanding of the physiology of energy balance has opened new targets for pharmacological agents that can produce weight loss.

• Anti-obesity therapeutics have potential to personalized approach to obesity care.

• Early use of new pharmacotherapeutics along with life style measures prevents obesity associated co-morbidities, premature mortality and they might reduce the likelihood of requiring bariatric surgery.
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<th>Level</th>
<th>Description</th>
<th>Criteria</th>
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| 1     | Brief Advice and Self-Directed support Self-directed support for achieving or maintaining a healthy weight                                                                                                                                                                                                                                                  | BMI 25-30 kg/m² without co-morbidities  
Lower criteria by 2.5 kg/m² for people from black African, African-Caribbean and Asian groups.                                                                                                                                                                                                 |
| 2     | Multi-component weight management support Multi-component weight management interventions; addressing diet, physical activity and behaviour change skills, underpinned by behavioural science. Sessions offered over a minimum period of 12 weeks.                                                                                                                  | BMI ≥30 kg/m² without co-morbidities  
BMI ≥25 kg/m² with co-morbidities  
Lower criteria by 2.5 kg/m² for people from black African, African-Caribbean and Asian groups.                                                                                                                                                     |
| 3     | Specialist multi-disciplinary weight management services Specialist multi-disciplinary assessment and specialist interventions delivered by the multi-disciplinary team (MDT), including: medical, dietary, psychological, pharmacological and physical activity/mobility interventions.                                                                                       | BMI ≥40 kg/m²  
BMI ≥35 kg/m² with co-morbidities / significant additional considerations/both  
Lower criteria by 2.5 kg/m² for people from black African, African-Caribbean and Asian groups.                                                                                                                                                  |
| 4     | Specialist surgical services Specialist pre-surgical assessment is conducted by the level 4 bariatric multi-disciplinary team (MDT) to identify person suitability and treatment needs. If suitability is confirmed, a range of surgical options will be considered and an appropriate procedure performed. Pre and post-operative education and support is provided. Long-term follow-up, post-surgery, is provided by the bariatric MDT for a minimum of 2 years | BMI > 35 kg/m² and recently diagnosed diabetes (in last 10 years)  
BMI of >40 kg/m²  
Lower criteria by 2.5 kg/m² for people from black African, African-Caribbean and Asian groups.                                                                                                                                        |
Thank you