New Treatments / New Ideas in Obesity Management

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Anti-obesity therapeutic strategies

- **Reducing food intake**
  Either amplify effects of signals / factors that inhibit food intake or block signals / factors that augment food intake
- **Blocking nutrient absorption**
  (especially fat or carbohydrates) in the intestine
- **Increasing thermogenesis**
  Either increase metabolism and dissipate food energy as heat or increase energy expenditure through the enhancement of physical activity
- **Modulating fat metabolism / storage**
  Regulate fat synthesis/breakdown by making appropriate adjustments to food intake or energy expenditure
- **Modulating the central regulation of body weight**
  Either alter the internal set point or modulate the signals presented regarding fat stores

Obesity Regulatory Guidelines

- Both FDA (2007) and EMA (2006) guidelines require phase 3 studies to be designed as randomised, double-blind, placebo-controlled trials including patients with a BMI of ≥ 27 kg/m2 accompanied by co-morbidities and with a BMI of ≥ 30 kg/m2, without co-morbidities.
- The FDA recommends efficacy to be based on 12-month data showing statistical differences in
  - the mean placebo subtracted **weight loss ≥ 5%**;
  - or the proportion of subjects who **lose ≥ 5% of baseline body weight** in the active-product group **is at least 35%** and approximately **double the proportion** in the placebo treated group, with the difference between groups being **statistically significant**.

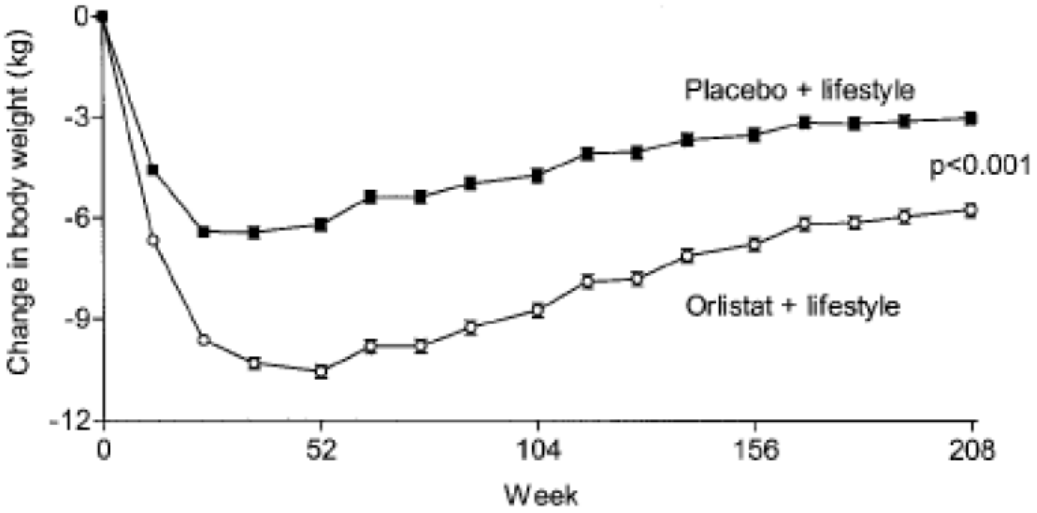
Obesity Regulatory Guidelines

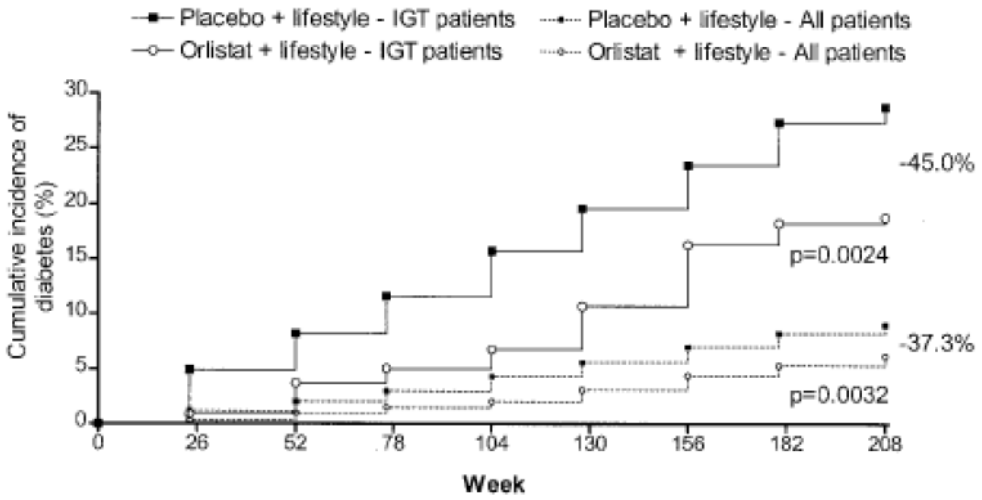
- The FDA requires the safety database to include at least **3,000 subjects** randomised to active doses of the product and no fewer than 1,500 subjects randomised to placebo **for one year** of treatment.
- The EMA recommends efficacy to be based on a significant weight loss at 12 months of 10% of the baseline weight that is also significantly different from the placebo change from baseline.

Orlistat (*Xenical®*)

- Pancreatic lipase inhibitor that blocks the absorption of up to one third of ingested fat.
- In addition to helping reduce weight, orlistat has been shown to also:
  - lower plasma low-density lipoprotein cholesterol (LDL) cholesterol levels.
  - The decline in LDL cholesterol is greater than that expected due to weight loss alone.
  - Lower HbA1C in diabetic patients

Orlistat


Change in body weight (kg)
0
-3
-6
-9
-12
0
52
104
156
208
Week
Placebo + lifestyle
p<0.001
Orlistat + lifestyle


Placebo + lifestyle - IGT patients
Placebo + lifestyle - All patients
Orlistat + lifestyle - IGT patients
Orlistat + lifestyle - All patients
Cumulative incidence of diabetes (%)
30
25
20
15
10
5
0
0
26
52
78
104
130
156
182
208
Week
-45.0%
p=0.0024
-37.3%
p=0.0032

Phentermine / Topiramate extended release (*Qsymia®*)

- Topiramate is an antiepileptic drug approved by the FDA as an anti-seizure medication in 1996.
- When reports surfaced that patients enrolled in initial trials of the drug and also in clinical practice were experiencing unexpected weight loss, the effects of the drug on weight began to be studied.
- Mechanism for weight loss is still poorly understood

Bupropion / Naltrexone (*Contrave® / Mysimba®*)

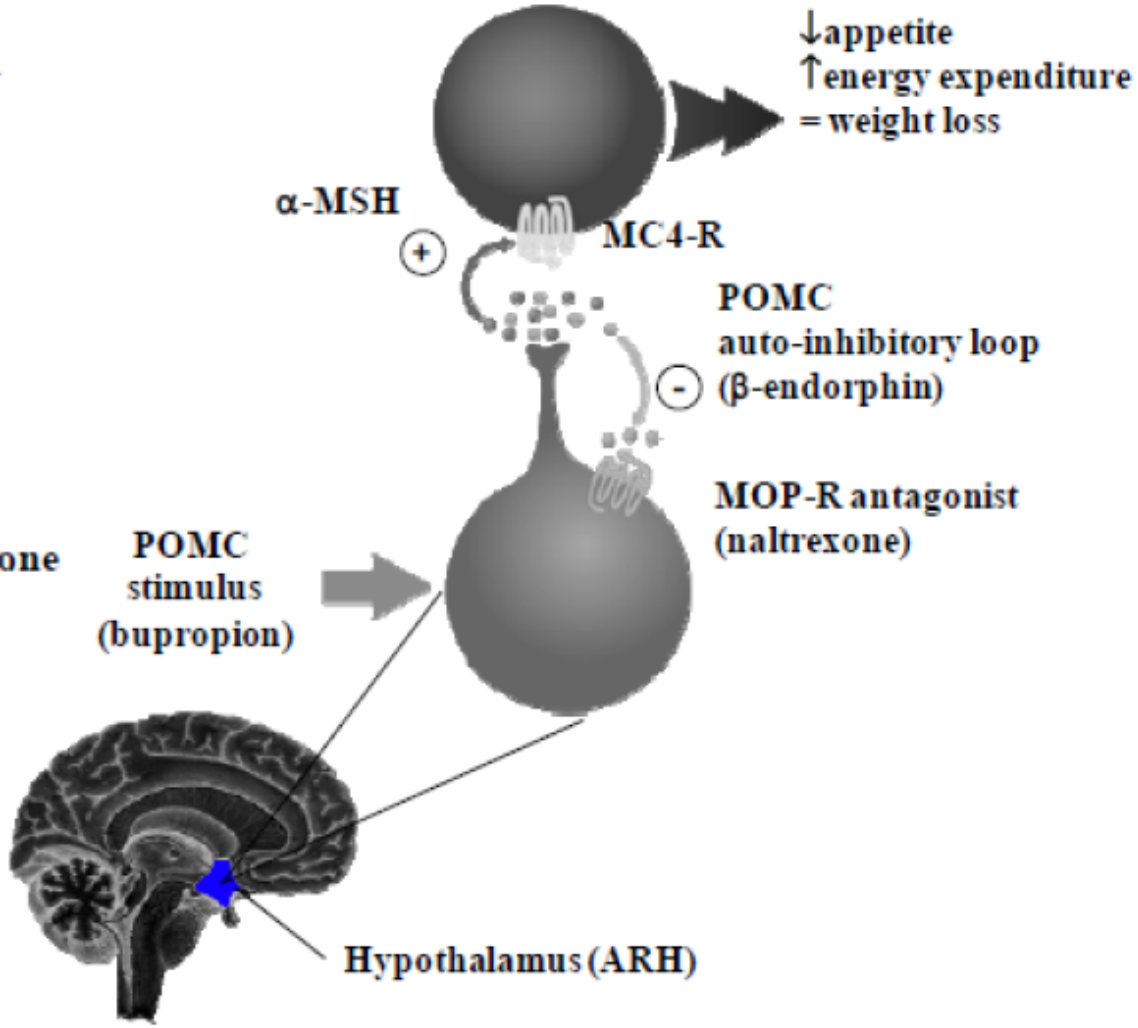
- **Contrave** (NB) is a combination of **bupropion**, a relatively weak inhibitor of the neuronal uptake of norepinephrine (NE) and dopamine (DA), combined with **naltrexone**, a mu-opioid receptor antagonist.
- Both naltrexone, an opioid antagonist, and bupropion, an inhibitor of neuronal uptake of norepinephrine and dopamine, are already FDA approved for other indications;
  - naltrexone for opioid and alcohol addiction and
  - bupropion for depression, smoking cessation, and seasonal affective disorder.

Bupropion / Naltrexone (*Contrave® / Mysimba®*)

- Bupropion has been shown to stimulate hypothalamic pro-opiomelanocortin (POMC) neurons that release alpha-melanocyte stimulating hormone (α-MSH) which, in turn, binds to MC4 receptors.
- The binding of α-MSH to MC4 receptors initiates a cascade of actions that results in reduced energy intake and increased energy expenditure.
- When α-MSH is released, POMCs simultaneously release β-endorphin, that mediates a negative feedback loop on POMC neurons leading to a decrease in the release of α-MSH.
- Blocking this inhibitory feedback loop with naltrexone is thought to facilitate a more potent and longer-lasting activation of POMC neurons, thereby amplifying effects on energy balance.

Bupropion / Naltrexone

- **POMC**
  - Integrate multiple energy balance signals
  - Increased firing leads to weight loss
  - Activated by bupropion
- **β-Endorphin**
  - Released with α-MSH
  - Inhibits POMC firing
  - Effect blocked by naltrexone



Body Weight

DPP-4 inhibitors do not have major effects on weight.

Sitagliptin has been associated with changes in body weight of between 0.0 and −1.5 kg.

Clinical studies examining **saxagliptin** have shown either dose-independent, numerical decreases (−0.11 to −1.8 kg) or increases (+0.5 to +0.8 kg) in body weight

Vildagliptin treatment has been associated with minimal weight gain of 0.2–1.3 kg

Body Weight

In randomized controlled trials, use of the GLP-1 receptor agonists exenatide, liraglutide, or lixisenatide has been associated with body weight reductions.

Exenatide BID treatment has been associated with average weight losses of up to 2.8 kg and **exenatide LAR** with mean weight losses of up to 3.7 kg.

Similarly, in the GetGoal phase 3 development programme, **lixisenatide** was associated with mean body weight reductions of up to 3.0 kg, although not all observed weight changes were statistically different from comparators (placebo, exenatide).

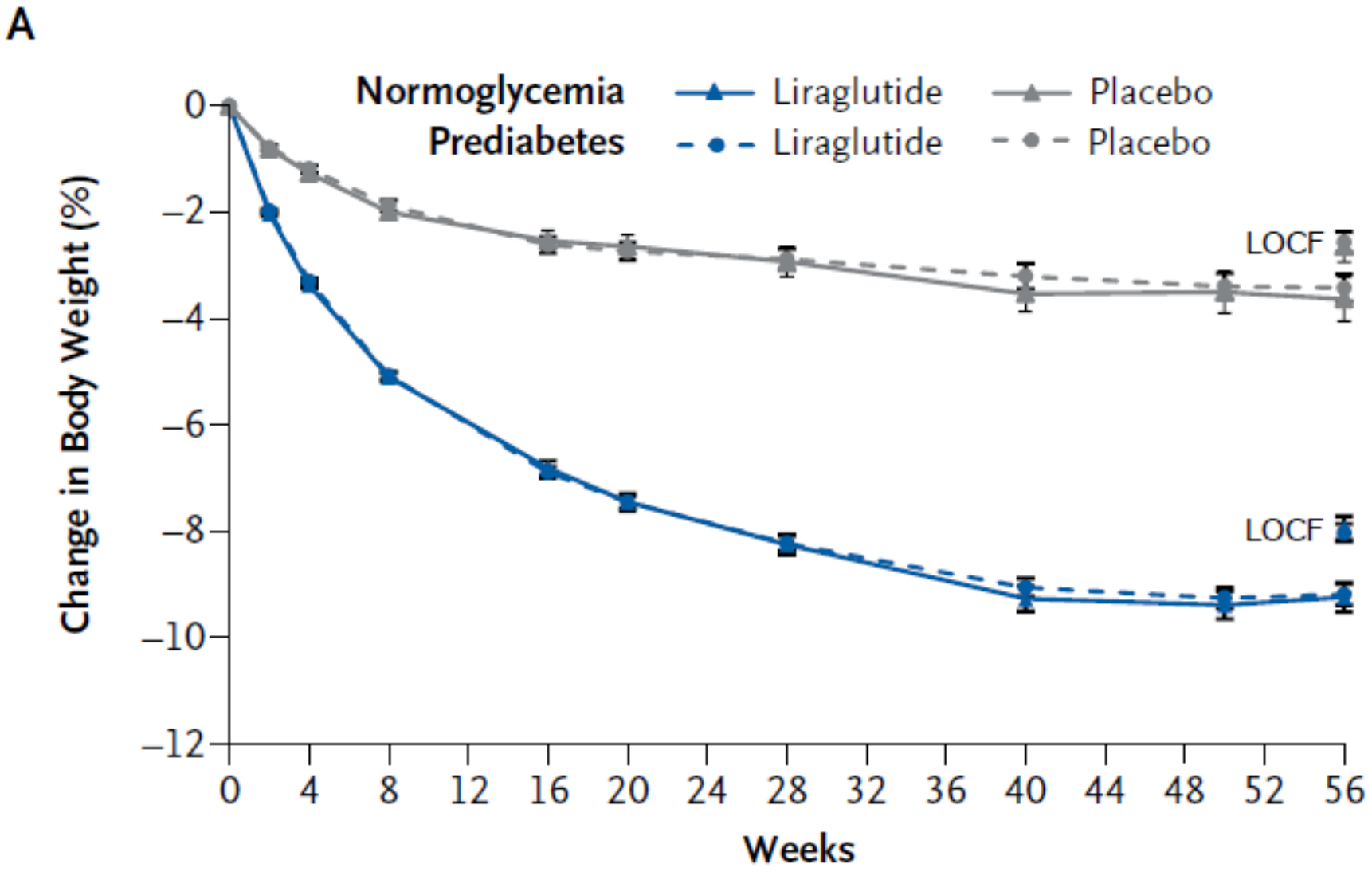
In the **Liraglutide** Effect and Action in Diabetes (LEAD) phase 3 clinical trials, consistent, significant improvements in body weight were observed with liraglutide use versus comparator arms, with average weight losses of up to 3.2 kg.

Head-to-head trials comparing exenatide LAR or liraglutide with sitagliptin have confirmed significantly greater changes in weight with the GLP-1 receptor agonists.

Exenatide

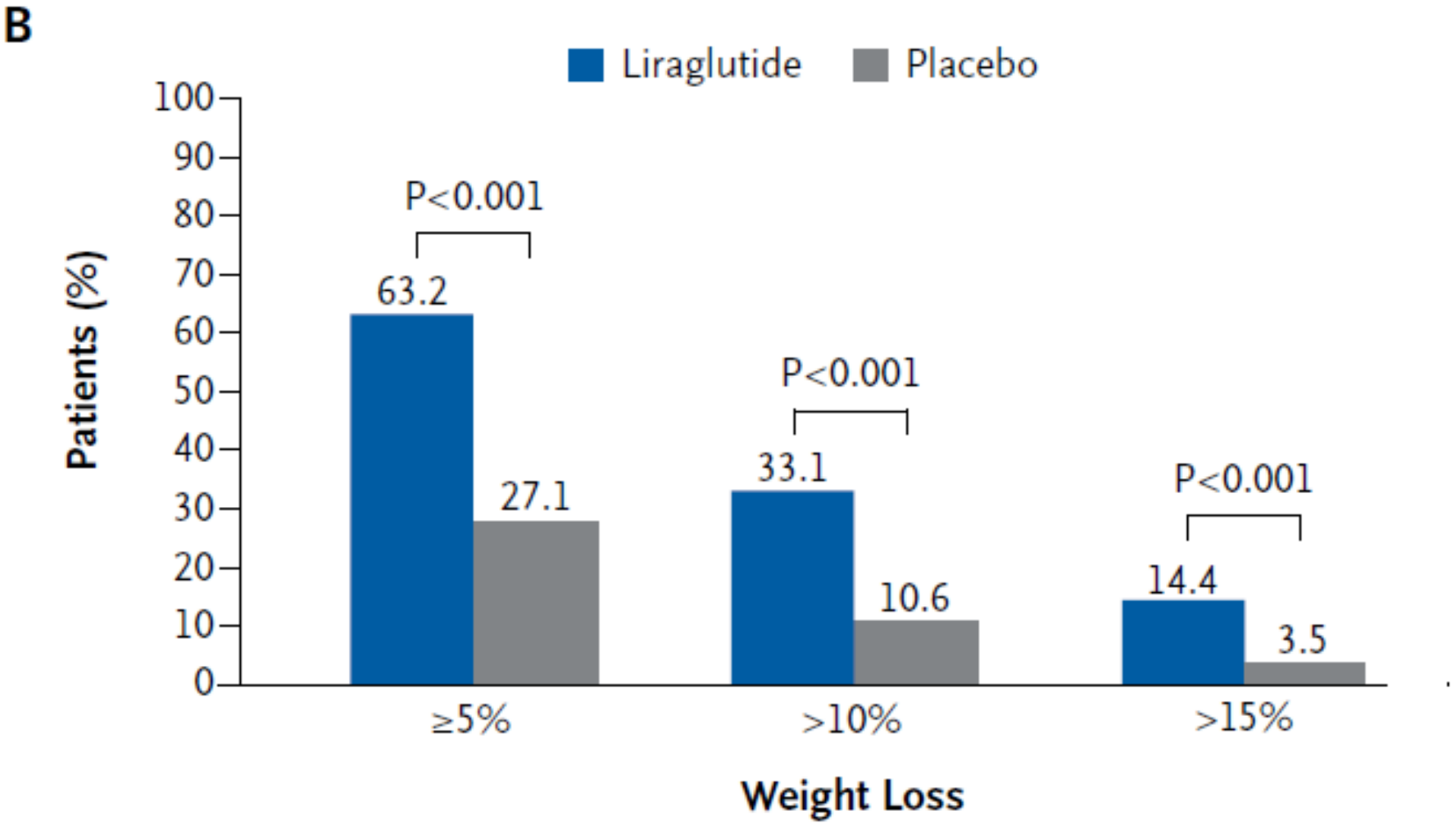
- Exenatide (Byetta) is a long-acting analogue of the hormone GLP-1, which the intestines secrete in response to the presence of food.
- Among other effects, GLP-1 delays gastric emptying and promotes a feeling of satiety.
- Some obese people are deficient in GLP-1.
- Byetta is currently available as a treatment for type 2 diabetes.
- Some, but not all, patients find that they lose substantial weight when taking Byetta.
- Drawbacks of Byetta include that it must be injected subcutaneously twice daily, and that it causes severe nausea in some patients.
- Byetta is recommended only for patients with Type 2 Diabetes.

Liraglutide in non-diabetic individuals



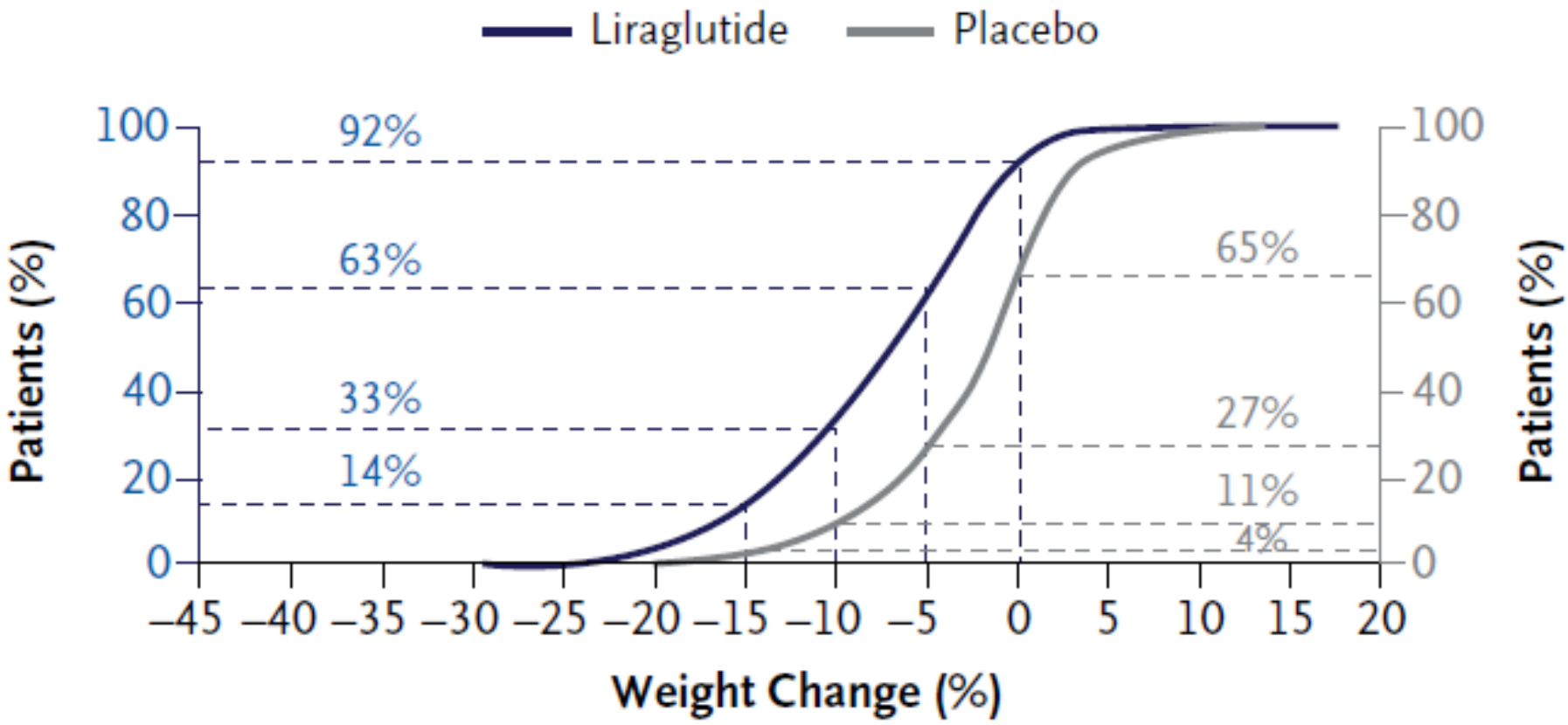
Pi-Sunier X *et al*, NEJM 2015

Liraglutide in non-diabetic individuals



Liraglutide in non-diabetic individuals

C



Body weight loss of currently licensed medicines

Table 1 | Weight loss after 56 weeks of anti-obesity drug treatment*

Drug	Weight loss with drug‡	Weight loss with placebo‡
Orlistat	6.10 kg	2.64 kg
Lorcaserin	5.8%	2.5%
Topiramate/phentermine	9.8%	1.2%
Naltrexone/bupropion	5.4%	1.3%
Liraglutide	8.0%	2.6%

*Drugs that have been approved by the FDA for long-term treatment of obesity. ‡Plus lifestyle modification. All data obtained from the FDA approved package inserts except liraglutide, which is from Pi-Sunyer *et al.*[1] For comparison, weight loss at 1 year in the lifestyle group in the Diabetes Prevention Program[5] was 7.6% and in the Look AHEAD Study[7] 8.6%.

Key molecules on the pipeline

Drug	Mechanism of action	Status	Comments
Cetilistat	Gastrointestinal and pancreatic lipase inhibitor	Phase III completed	Orally active; recently approved in Japan for the treatment of obesity with complications
Velneperit	Neuropeptide Y5 receptor inhibitor, appetite suppression	Phase II	Orally active
Tesofensine	Inhibition of serotonin, dopamine, and noradrenaline reuptake	Phase III	Orally active; originally investigated for the treatment of Alzheimer's disease and Parkinson's disease.
Metreleptin	Leptin receptor agonist	Phase III	Injectable formulation; FDA approved orphan drug indicated as an adjunct to diet as replacement therapy for treating the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.
Bupropion SR + zonisamide SR (*Empatic*)	Dopamine and norepinephrine reuptake inhibitor + antiepileptic causing enhancement of dopamine and serotonin neurotransmission	Phase II completed	Orally active
Obinepitide	Dual neuropeptide Y2/Y4 receptor agonist	Phase II	Injectable formulation

Investigational medicinal products in obesity

Atomoxetine

Atomoxetine is a potent central norepinephrine uptake inhibitor, currently marketed for the treatment of attention-deficit/hyperactivity disorder.

In a 12-week randomised, double blind, placebo-controlled study to evaluate the short-term efficacy and safety of atomoxetine in obese adults, participants were randomly assigned to receive atomoxetine (n = 15) or placebo (n = 15). All participants followed a balanced hypocaloric diet (500 kcal/day deficit).

Atomoxetine therapy was started at 25 mg/day orally, with gradual increase to 100 mg/day over 1 week.

Last-observation-carried-forward analysis of the available data for participants who had completed at least one post-randomisation assessment demonstrated that the atomoxetine group (n = 12) lost more body weight over the 12-week period than the placebo (n = 14) group [mean (SE) -3.6 (1.0) kg (-3.7% loss) vs. 0.1 (0.4) kg (0.2% gain); $p < 0.0001$].

Three participants in the atomoxetine group and none in the placebo group lost more than 5% weight.

Atomoxetine was well tolerated with minimal side effects.

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Subtype-selective Serotonin Receptor Agonists

Some of the medicines that were used to treat obesity, such as sibutramine, increase signalling by the neurotransmitter serotonin 5-HT. A detailed analysis of the mechanism of action of these drug revealed that it directly activates hypothalamic POMC neurons through 5-HT2C receptors, expressed on a majority of these cells. Further studies identified a complementary role for the 5-HT1B receptor in feeding regulation.

The clinical implication of these findings is that a combined 5-HT2C/1B receptor agonist should powerfully stimulate catabolic melanocortin pathways in the hypothalamus.

Clinical studies examining the use of isoform-selective 5-HT receptor agonists as anorectic agents appear to confirm that stimulation of 5-HT2C, and possibly 5-HT1B, reduces hunger, food intake and body weight in humans.

A small double-blind, placebo-controlled trial, the combined 5-HT2C/1B-receptor agonist **m-chlorophenylpiperazine**, reduced subjective hunger ratings and caused a small (0.75 kg) but significant weight loss over 2 weeks in obese individuals. 5-HT2C selective agonists are also under development (BVT-933, Org-12962). One such agonist (APD356) tested in a 12-week phase IIb randomised, double-blind, placebo-controlled, multicentre trial on 469 obese subjects caused 3.6 kg of weight loss, compared with placebo individuals.

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Neuropeptide Y

Chronic NPY administration powerfully increases food intake and body weight, hence blockade of NPY signalling is a potential anti-obesity strategy.

Although NPY might not be necessary to maintain normal body weight, it is required for the full response to leptin deficiency.

NPY is the most abundant central neuropeptide, and its pleiotropic functions make global blockade of NPY signalling challenging.

This peptide acts through at least five G protein-coupled receptor (GPCR) subtypes (Y1-Y6). Y1 is widely expressed in the brain and periphery, and its importance in NPY-related feeding is well established.

Selective Y1 agonists increase food intake and body weight, whereas **Y1 antagonists** block NPY-induced feeding as well as re-feeding hyperphagia.

However, there are no definite data regarding which Y receptor subtype is the most important for NPY-induced feeding and studies on NPY blockade are very limited.

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Melanin-concentrating Hormone

Melanin-concentrating hormone is expressed in magnocellular neurons of the lateral hypothalamic area.

MCH acts downstream of at least some levels of leptin resistance, this makes it another potential anti-obesity agent.

MCH administration or transgenic over expression increases body weight by stimulating food intake and adipogenesis, at the same time decreases energy expenditure. MCH knockout mice have reduced food intake and elevated metabolic rate, with consequently lowered body weight and adiposity.

The feeding effects of MCH are mediated by a GPCR, the MCH1 receptor (MCHR1)

Human trials on **MCHR1 antagonism** are currently underway.

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Ciliary Neurotrophic Factor

Ciliary neurotrophic factor is a glial cell-produced cytokine that exhibits neuro-protective effects. It has been explored as an agent to treat neurodegenerative diseases.
Recently there is an increased interest in CNTF as a treatment for obesity as individuals who received CNTF in clinical trials for neurodegenerative diseases showed a 10-15% weight loss. The exact mechanisms mediating these catabolic effects are unclear, although it is known that they do not result from cachexia or muscle wasting.

Unlike leptin, CNTF causes weight loss independent of melanocortins and is effective in mice lacking either POMC or Mc4r. It also reduces body weight in animals with leptin resistance resulting from diet-induced obesity and the catabolic effects of CNTF persist long after its administration is discontinued. In hypothalamic feeding centres,

Investigational medicinal products in obesity

Ciliary Neurotrophic Factor

CNTF induces proliferation of neurons that contain leptin-responsive elements, and chemical inhibition of cell division abrogates the long-term, but not the short-term, effects of CNTF on body weight.

CNTF signalling has been targeted in clinical anti-obesity studies using **axokine**, a recombinant human variant of CNTF, modified to increase potency.

In a 12-week, randomised, double-blind, placebo-controlled, multimember, dose-ranging trial involving 173 obese and non-diabetic participants,[75] optimal dose produced a 4.1-kg weight loss, compared with a 0.1-kg gain in the placebo group.

However, many subjects developed antibodies to CNTF and stopped responding, hence the trial was discontinued.

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Obesity-related Leptin Resistance

Obesity results in impaired transports of leptin across the blood-brain barrier by a saturable system resulting in leptin insensitivity. There is recent evidence that intra-nasal delivery of leptin can bypass the system and lead to weight loss.

In one study leptin delivered intra-nasally to rats resulted in supraphysiological levels in the brain, especially in the hypothalamus. This effect was not diminished when circulating leptin levels were raised by concomitant intravenous administration.

The leptin receptor is a single membrane spanning class I cytokine receptor with tyrosine kinase activity. Development of synthetic leptin receptor agonists remains in preclinical stages.

Leptin receptor activation engages two intracellular proteins that terminate receptor signalling, the suppressor of cytokine signaling-3 (SOCS3) and protein tyrosine phosphatase-1B (PTP1B). Inhibition of either of these auto inhibitory factors could theoretically increase leptin sensitivity. SOCS3 activity is increased in obesity, suggesting an aetiological role in leptin resistance. Reduction in SOCS3 activity by either neuron-specific conditional knockout or heterozygous global knockout increases leptin-induced activation of intracellular signalling events and catabolic neuropeptide expression, with accompanying enhancement of leptin's weight-reducing effects and resistance to diet-induced obesity.

Investigational medicinal products in obesity

Leptin and Leptin Receptor Agonists

The obesity phenotype that results from leptin deficiency distinguishes leptin as probably the single most important molecule in mammalian energy homeostasis.

Among rare individuals who are obese due to lack of leptin, physiological replacement can be curative.

Common obesity, however, is a state of leptin resistance and even exogenous administration of extremely high doses of leptin has proved relatively ineffective at reducing body weight.

Hence leptin might help maintain the weight loss once lifestyle modifications and anorectic medications restore leptin sensitivity.

Reductions in food intake and body weight caused by sibutramine treatment in rats are synergistically enhanced by administration of leptin at low doses, but only to restore circulating leptin to pre-weight loss levels.

Investigational medicinal products in obesity

Melanocortins

Genetic evidence proves that melanocortin 4 and 3 receptors (Mc3r, Mc4r) are critical components of the body weight regulation system. Null mutations in Mc4r cause marked, dominantly inherited monogenic obesity in rodents and humans, associated with increased food intake and decreased energy expenditure.

These mutations may account for up to 5% of severe human obesity. Because of the very strong genetic proof that Mc4r signalling is indispensable for normal energy homeostasis, pharmaceutical companies are working to develop small-molecule agonists to the GPCR, with or without combined Mc3r agonist activity.

It was first shown, almost 10 years ago, that food intake in rodents decreases markedly after administration of the melanocortin receptor agonist melanotan II, whereas it is increased by the **melanocortin receptor antagonist** SHU9119. Recent evidence has identified single-minded 1 (SIM1), which is a transcription factor involved in embryological development of the paraventricular nucleus, as a proximal mediator for the anorectic, but not thermogenic, effects of melanocortins. As with many other components in the leptin-melanocortin pathway, genetic evidence in rodents and humans demonstrates that haploinsufficiency or loss of SIM1 causes hyperphagic obesity, as well as resistance to the anorectic effects of melanocortins. At present SIM 1 stimulation remains a potential anti-obesity agent which needs further studies.