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Pharmaceutical approaches to weight management: behavioural mechanisms of action

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Pharmacotherapy as an adjunct to behaviour modification, may provide an effective addition to individual weight management plans in specialised weight management services. There are four FDA approved centrally acting weight-loss drugs (liraglutide, bupropion/naltrexone, lorcaserin, phentermine/topiramate), and several additional candidate drugs yet to receive approval. Each drug has a distinct pharmacological mechanism of action, and presumably will support eating behaviour modification in different ways. Here, we assess to what extent behavioural mechanisms of action have been characterised. We recommend a methodological platform to be introduced pre-approval in order to achieve principal objectives of phase II and III trials (demonstrate efficacy), and afford stratification of responders to treatment, by behavioural and neurophysiological response.

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Introduction

Obesity has now reached pandemic status across the developed and developing world [1]. The escalating health, social, and economic impacts of this means that there is a pressing need for safe and effective treatments. Pharmacotherapy may be one method to provide much needed assistance for patients to make the necessary behaviour modification to achieve meaningful weight loss. There is potential for a variety of weight-loss drugs to be used in specialist weight management services, each to be tailored to patient's individual needs. However currently not enough is being done to characterise responders to drug treatment, or fully appreciate drug effects on the minutiae of appetite expression, indeed it is notable that there is a huge variation in clinical response to drug therapy. In this review, we discuss the mechanistic data available for the currently approved anti-obesity drugs, and the potential behavioural action of candidate drugs. We suggest that a behavioural and neuroimaging experimental platform should be utilised earlier in the drug approval process to assess how novel candidate weight-loss drugs will work on a behavioural level enabling accurate identification on who will benefit the most.

Behaviour change

Behaviour modification is the cornerstone of obesity management [2]. Changes in eating behaviour are necessary to reduce energy intake, and it is preferential for daily activity to be increased in order to expend more energy. However, making the necessary changes to eating behaviour is extremely difficult for many people. Individuals with obesity commonly have a biological vulnerability for overconsumption which is expressed in behaviours that comprise a susceptible behavioural phenotype for obesity [3]. Our (neuro)biological differences underpin our experienced differences in satiety (feelings of hunger, and fullness), food-reward (pleasure/enjoyment of eating, food craving, and ability of food to grab our attention), and ability to exert inhibitory control (stop ourselves from eating beyond our energetic needs) over our behaviour. In addition to this, behaviour is shaped by life-long learning, and change requires tackling habits that have become entrenched. Difficulties in adhering to behaviour change is further compounded by the fact that energy restriction causes increases in hunger, dysphoria, increased motivation to eat, and distraction by, and preoccupation with food. Taken together, this means that behaviour modification requires constant exertion in people who are already biologically predisposed to overeat.

Personalised approach

A biopsychosocial approach to personalised weight management strategies includes utility of psychological interventions, pharmacotherapy, and if necessary bariatric surgery [4]. Pharmacotherapy, as an adjunct to behaviour modification, may provide an effective addition to individual weight management plans in specialised weight management services if used correctly. Critically, if we wish to use weight-loss drugs as part of a personalised intervention, it is necessary to understand individual differences in patient experiences and their personal barriers to behaviour change, as well as how a drug therapy may impact the particular behaviours the patient exhibits. To achieve this, the behavioural mechanism of action of a drug needs to be characterised, and effectively

communicated to patients and practitioners before implementing as part of a suite of personalised weight-management strategies.

Currently approved drugs (EMA and or FDA approval)

There are currently 2 EMA, and a further 2 FDA approved centrally acting medications for weight loss. Each of these drugs has a different pharmacological mechanism of action (see Table 1 and Figure 1), meaning that they ostensibly have a distinct behavioural mechanism of action, and act differently at important neural networks associated with satiety, reward and inhibitory control.

Liraglutide 3 mg (Saxenda)

The GLP-1 receptor agonist Liraglutide is approved for weight-loss by both the EMA and FDA at the 3.0 mg injectable dose, due to it demonstrating efficacy of achieving weight loss in the Satiety and Clinical Adiposity-Liraglutide Evidence (SCALE) studies [5–7]. However mechanistic data are limited to one study with the approved 3.0 mg dose [8], which showed liraglutide (3.0 and 1.8) reduced food intake at an *ad-libitum* lunch meal by 16% compared to placebo. Liraglutide increased post-meal satiety, and fullness ratings, and reduced prospective consumption. The proposed behavioural mechanism by which liraglutide 3.0 mg produces weight-loss is by boosting satiety. However no other mechanistic data exist at the approved dose. Drug effects on hedonic aspects of eating and inhibitory control have yet to be tested, nor are there neuroimaging data available at this dose. Responders to liraglutide 3.0 mg for weight-loss have yet to be properly characterised. Our mechanistic understanding of how this drug works primarily comes from data with the 1.8 mg dose in diabetic populations (see Ref. [9••] for review).

Lorcaserin

An FDA approved 5-HT_{2c} receptor agonist. Patients have been shown to have higher chance of achieving 5% weight loss with lorcaserin compared to placebo in a number of weight-loss trials in obese populations [10–12]; although the weight loss associated with lorcaserin is argued to be modest [13]. However, lorcaserin has demonstrable cardiovascular safety, as reported by Bohula *et al.* [14•] and patients can be maintained on lorcaserin for over 3 years without increased incidence of cardiovascular problems. Lorcaserin has affinity for the $5HT_{2C}$ receptor subtype, which belies the improved safety profile relative to previous (withdrawn) serotonergic drugs with affinities of the 2A and 2B receptor subtypes (sibutramine, fenfluramine).

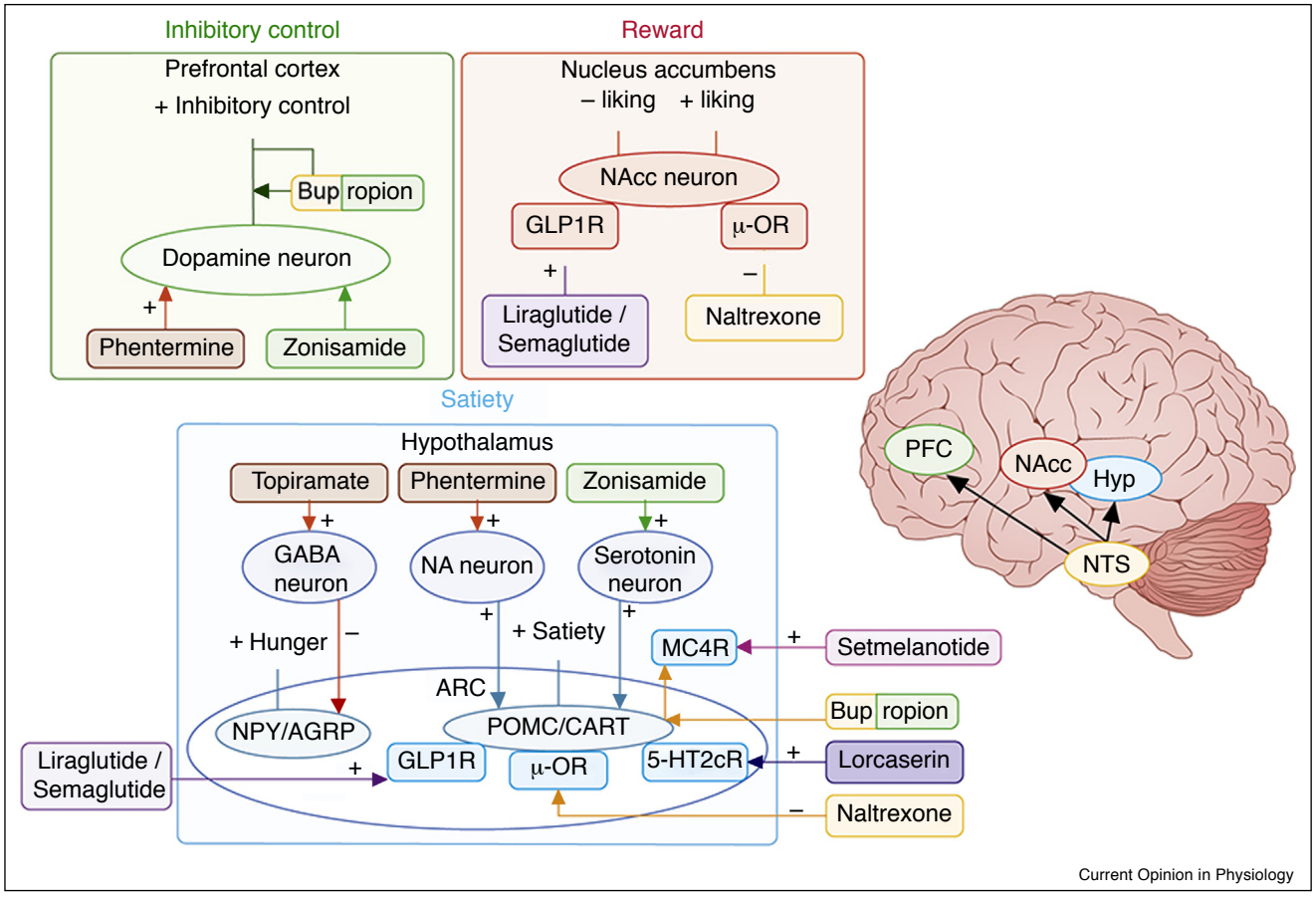
There are more mechanistic data for lorcaserin than other approved drugs, however complete behavioural and neurophysiological characterisation is elusive. Martin *et al.* [15] report reduced energy intake at lunch and

Table 1

Current approved drugs (EMA and/or FDA) for weight loss, pharmacological mechanism of action, effects on eating behaviour, and CNS activity

Drug	Approval	Pharmacological mechanism of action	Satiety	Reward	IC	Neuronal activity
Liraglutide 3 mg	EMA, FDA	GLP-1 receptor agonist	Reduced ad-lib meal intake. Increased post-meal satiety	No data	No data	No data
Lorcaserin	FDA	Selective 5HT2C receptor agonist	Reduced intake. Decreased hunger	No effects on cravings. No behavioural data	No effect on inhibitory control performance	Reduced activity in parietal cortex in response to food images
Bupropion/ naltrexone	EMA, FDA	Combination of a dopamine/noradrenalin reuptake inhibitor + opioid receptor antagonist	No behavioural data	No behavioural data	No behavioural data	Reduced anterior cingulate activity (passive viewing of food images). Reduced functional connectivity between parietal cortex, insula and anterior cingulate (resting state fMRI).
Phentermine/ topiramate	FDA	TAAR1 agonist and noradrenalin releasing agent + sulfamate-substituted monosaccharide with action on GABA signalling	No data	No data	No data	No data

Figure 1



Proposed mechanisms of action of approved and candidate weight loss drugs.
1) Lorcaserin stimulates 5-HT receptor subtype 2C in arcuate nucleus of hypothalamus which is proposed to boost satiety.
2) Bupropion/Naltrexone: Bupropion stimulates POMC neuron to produce MC4R agonist αMSH. Naltrexone antagonises opioid receptors on POMC to prevent auto-inhibition of POMC following bupropion stimulation. Naltrexone also antagonises opioid receptors in hedonic hotspots of nucleus accumbens, reducing reward (liking). Bupropion blocks reuptake of dopamine, which in the PFC may improve inhibitory control.
3) Liraglutide and Semaglutide both stimulate GLP1 receptors located in arcuate nucleus of hypothalamus which increases satiety. Moreover, GLP1 receptor agonism in the nucleus accumbens reduces liking.
4) Phentermine/Topiramate: Topiramate stimulates GABA release which has an inhibitory effect of NPY/AGRP, and so reduces feelings of hunger normally precipitated by stimulation here. Phentermine stimulates noradrenalin release from the hypothalamus, which increases satiety. Phentermine also has an effect on dopamine, which in the PFC may improve inhibitory control.
5) Setmelanotide is an agonist at the MC4R which increases satiety.
6) Zonisamide/Bupropion. Zonisimide stimulates serotonin, dopamine, and has effects at sodium channels. Bupropion action is outlined above.

dinner *ad-libitum* buffet meals compared to placebo, and decreased hunger ratings, but no effects on food cravings, or dietary restraint or disinhibition. Farr *et al.* [16••] measured neuronal activity in response to viewing food images in patients receiving lorcaserin and placebo. Lorcaserin reduced parietal cortex activity in response to food images relative to non-food images, which the authors suggest may reflect reduced motivational responses to foods. Although, Inhibitory control (measured outside of the scanner) was unaffected by lorcaserin. This study is of particular interest due to its novel use of baseline fMRI activity to predict responders to lorcaserin treatment. The authors report that amygdala and occipital activation in response to highly palatable food predicted reduced BMI at four weeks of treatment.

Chao *et al.* [17] included subjective measures of food craving, emotion, and stress related eating, binge eating, cognitive restraint, disinhibition, preoccupation with eating and fullness, in patients given either lorcaserin or placebo during a weight maintenance period immediately following successful 5% weight-loss. During this period lorcaserin treated patients had improved emotion and reductions in stress related eating, but no effects were observed in any other subjective measures relating to eating behaviour.

The totality of the data suggests that lorcaserin has modest effects on satiety, but may be useful for patients with cardiovascular problems, emotional eaters, or those who are highly responsive to palatable foods. However, confirmatory subjective and behavioural data are needed to elucidate this.

Bupropion/naltrexone

This is a combination drug of a catecholamine reuptake inhibitor (bupropion) and opioid receptor antagonist (naltrexone) which is both FDA and EMA approved. Several phase III trials have demonstrated improved odds of achieving 5% weight loss with bupropion/naltrexone compared to placebo [18,19]. However, there are no clinical experimental data showing how bupropion/naltrexone modifies eating behaviour. There is a narrative that this drug improves inhibitory control (an effect we suggest could be mediated by drug action on dopaminergic activity in prefrontal cortex — see Figure 1), and patient's ability to resist cravings which is based on an fMRI study suggesting bupropion/naltrexone increases anterior cingulate activity [20]. The anterior cingulate is an important brain region involved in inhibitory control, however the observed activity was not in relation to an inhibitory control task, so there are no corollary behavioural data. A more recent resting state fMRI study [21] suggests bupropion/naltrexone increases functional connectivity between areas of the parietal cortex, insula and anterior cingulate, which may underpin improved inhibitory control. This study also observed reduced functional connectivity in the medial prefrontal cortex — an area implicated in craving. Overall, we have some very interesting fMRI data with this drug; however, we are still some distance from properly characterising how drug treatment manifests behaviourally.

Phentermine/topiramate

This combination of the noradrenaline (and dopamine) releasing agent phentermine and GABAergic topiramate has FDA approval only. There are several studies demonstrating its efficacy for achieving at least 5% weight loss [22–24]. Despite meta-analysis of phase III weight loss trials suggesting this drug combination produces the greatest odds of achieving 5% weight-loss of all the approved weight-loss drugs, there are no mechanistic data available to demonstrate proof of concept for behaviour modification (potential behavioural mechanism of action outlined in Figure 1).

A comprehensive Bayesian network meta-analysis [25•] has been performed on pooled data from all of the phase III weight-loss studies with each of the FDA/EMA approved anti-obesity medications. A median of 75% participants achieved 5% weight loss with phentermine/topiramate. This number was 63% with liraglutide 3.0 mg, 55% with bupropion/naltrexone, and 49% with lorcaserin. Results from these meta-analyses suggest that there is clearly a large portion of the wider population that may not respond each treatment option [13]. It is increasingly clear that weight-loss trials alone are no longer adequate to address efficacy of these drugs. Rather, complete characterisation of the behavioural and neurophysiological manifestation of taking these drugs is necessary to improve efficacy of drug treatment, and optimise their tailored intervention potential.

Novel candidate drugs on the horizon

There are currently several novel candidate drugs for weight-loss which may modify behaviour. These are at different stages the approval process, as well as their pharmacological and putative behavioural mechanism of action is summarised below (see also Figure 1).

Setmelanotide

This is a synthetic MC4R-agonist, which increases energy expenditure in preclinical studies [26]. Phase I studies in humans also suggest increased resting energy expenditure [27]. As setmelanotide acts on MC4 receptors, this may have an effect on satiety, which could be expressed as reduced meal intake and rate of eating. This drug is being investigated for treatment of rare genetic disorders of obesity, such as Prader–Willi syndrome [28].

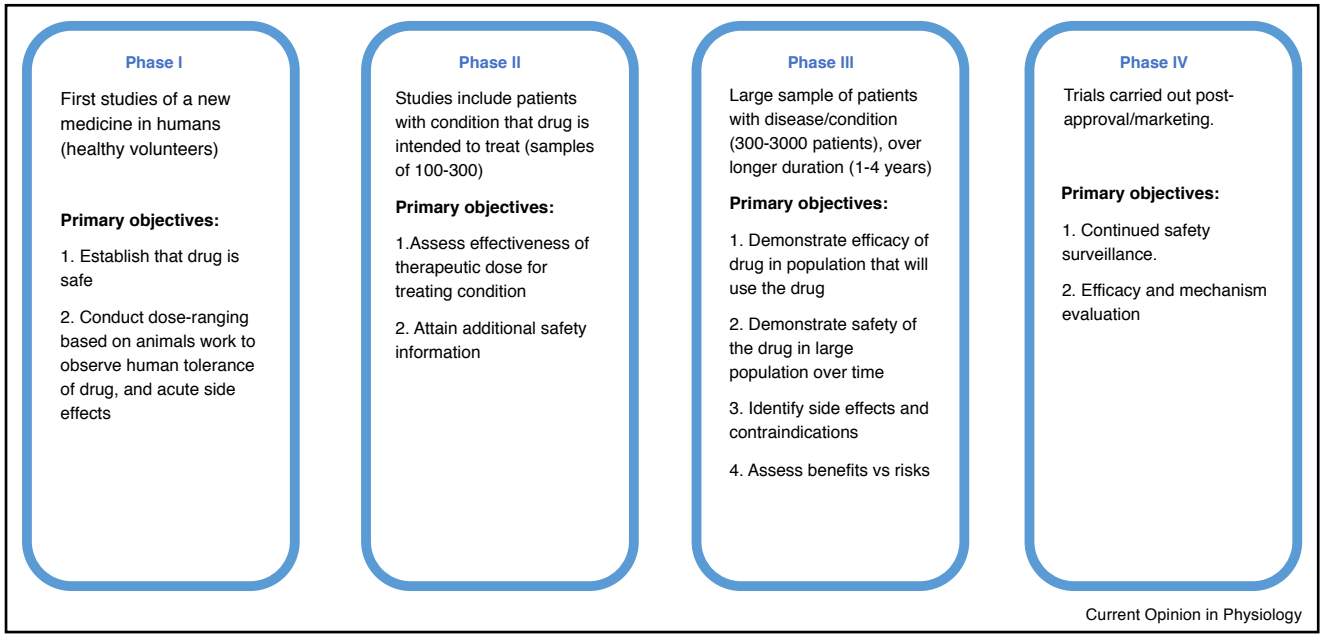
Zonisamide-bupropion

This combination therapy combines Zonisamide which is pharmacologically complex antiepileptic drug with action at sodium channels, as well as dopamine and serotonin activity. It is combined with the atypical anti-depressant bupropion. Combined, this drug targets three major neurotransmitters in regulation of appetite (serotonin, dopamine, and norepinipherine), so may modify regulatory components of eating behaviour [31]. Zonasimide-bupropion have completed phase II clinical trials with 60.4% of patients achieving 5% weight loss in 24 weeks [28].

Semaglutide

Semaglutide is an extended release formulation of liraglutide which is currently undergoing phase II weight-loss trials for obesity management. Interestingly some behavioural characterisation has begun in phase II. Blundell *et al.* [29] has assessed energy intake at *ad-libitum* meals across the day, subjective fluctuations in satiety, fullness, hunger and prospective consumption across the day, palatability (food reward), and food preference, energy expenditure and subjective measures of control of eating. Semaglutide reduced energy intake across the day (24% total reduction relative to placebo), reduced hunger, food cravings and increased subjective feelings of control of eating, with lower preference for high-fat foods.

Figure 2



The four clinical trial phases for a new medicinal product. We argue that behavioural and neurophysiological assessments are required at phase II and phase III trials with weight-loss drugs to properly achieve the primary objectives. Meaning, to assess/demonstrate efficacy of drug for treating the condition.

The case for a methodological platform for assessing drug action to be implemented pre-approval

Currently, if any mechanistic data are conducted to observe how drugs produce weight loss, this is conducted in phase IV, post-approval, clinical trials. Moreover, as demonstrated in this review mechanistic data are being conducted piece-meal, in an uncoordinated manner, often on subjective rather than objective measures, meaning that our understanding of drug effects has to be reconstructed from datasets across studies. In our 2017 paper [9••], we proposed a novel methodological platform to investigate the interplay between satiety, reward, and inhibitory control using a comprehensive test battery of validated measures for assessing eating behaviour, subjective experiences of appetite regulation, and neurophysiological effects. Using this platform across studies would allow 1) characterisation of drug effects on the interaction of the full range of mechanisms which control eating behaviour, 2) proof-of-concept data linking pharmacological mechanism of action to human appetite expression, 3) stratification of responders to treatment, by behavioural and neurophysiological response, 4) allow effective communication to patients and practitioners of real world benefits of tailored pharmacotherapy, and 5) effective testing of novel candidate drugs at an earlier stage than phase IV clinical trials.

Principal objectives of phase II and phase III clinical trials are to demonstrate effectiveness of a new medicine to treating a condition (Figure 2). Given the importance of behaviour, and neurocognition in the aetiology of obesity, it is our opinion that weight-loss studies are inadequate in fulfilling the basic objectives of phase II and phase III studies. Our experimental medicine approach can be used in phase II and III clinical trials with novel compounds to demonstrate effectiveness of new medicines to modify eating behaviour in order to produce meaningful weight-loss, and to enable predictions of responders. Using this platform would not only provide consistency for interpretation of effects across drugs, but it would also add value to phase III clinical trial data, enabling pharmaceutical companies to demonstrate cost-effectiveness of their drug for specific treatment populations.

In addition to the measures outlined in our methodological platform, the Accumulating Data to Optimally Predict Obesity Treatment (ADOPT) project [30••] have also proposed several core measures that should be considered for use in obesity trials. Beyond eating behaviour ADOPT propose core measures in other behavioural, biological, environmental, and psychosocial domains with a view to accumulate data on individual variability in response to various obesity treatment options, in order to inform personalisation of obesity treatment.

In conclusion, it is clear that response to any weight-loss treatment will have large individual variability. Therefore, conducting the necessary mechanistic assessments,

in a consistent and coordinated manner will increase the likelihood of effective use of anti-obesity drugs in our attempts to reduce current pandemic levels of obesity.

Conflict of interest statement

C.A.R. declares an association with Unilever.

P.C. declares associations with American Beverage Association.

J.C.G.H. declares associations with Astra Zeneca, American Beverage Association, Bristol Meyers Squibb, Novo Nordisk and Orexigen.

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- • of special interest
- •• of outstanding interest

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