Pharmacotherapy for obesity: Mechanisms of action

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Pharmacotherapy

- Pharmacotherapy provides an aid to behaviour modification in the management of weight-loss.

Drug	Mechanism of action
Liraglutide/ Semaglutide	GLP-1 receptor agonist
Bupropion/naltrexone	Dopamine and norepinephrine reuptake inhibitor+opioid (mu and k) receptor antagonist
Lorcaserin	Selective $5HT_{2C}$ receptor agonist
Phentermine/topiramate	TAAR1 agonist and norepinephrine releasing agent+sulphamate-substituted monosaccharide with action on GABA signalling

- 3 have EMA and FDA approval: Liraglutide, Semaglutide and Bupropion/Naltrexone
- 1 has FDA approval only: Phentermine/Topiramate (not approved by EMA due to safety concerns)
- Lorcaserin had FDA approval (subsequently withdrawn in 2020 due to increased risk of cancer – latest in long line of serotonergic drugs to be withdrawn)
- Each drug/combination acts differently. So can we assume they affect eating behaviour in different ways?

Personalised medicine

- Standardised personalised medicine approach is to target key genes

- Standardised PM approach not appropriate for weight-loss (too polygenic)

In order to personalise pharmacotherapy for weight-loss we need to target behaviour

Behavioural phenomena associated with obesity = susceptible behavioural phenotype

Individuals with obesity have a biological vulnerability for weight gain which is manifested in eating behaviours that lead to overconsumption.

Individuals with obesity tend to demonstrate weaker regulatory control of eating behaviour. Moreover, appetite regulation is more likely to be overwhelmed by environmental cues to over-consume

Inadequate impact of ingestants (Satiety)

- Often increases in eating rate and a failure to develop normal satiation during the course of a meal
- After consumption demonstrate weakened satiety responsiveness

Hedonic Eating (reward) – wanting/liking

- Greater responsiveness to food cues
- Craving
- Heightened hedonic responses to palatable food
- Eating for pleasure

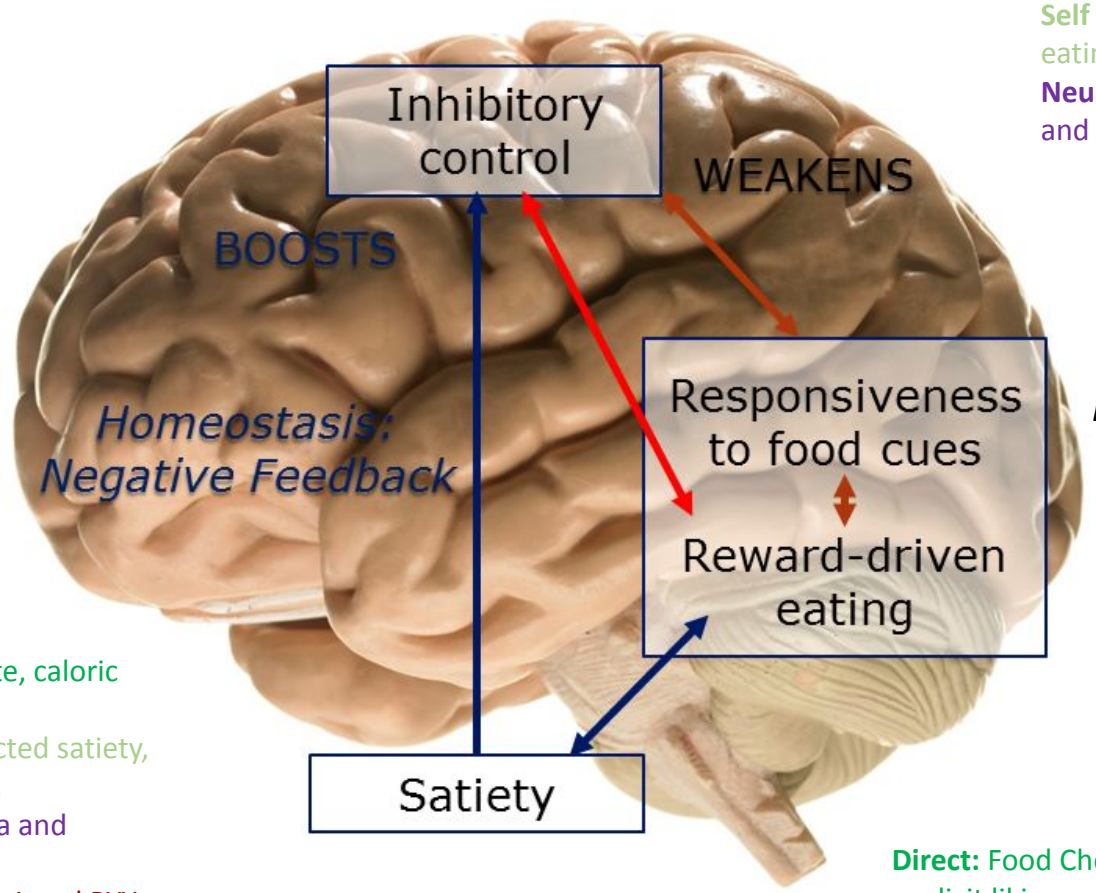
Less control of ingestion

- Experiences of uncontrolled hunger a
- Greater disinhibition of eating behaviour

Appetite regulation involves a complex interplay between satiety, reward and inhibitory control

Regulatory control (satiety) and reward:

Dual System Model of CNS integration



Direct: Cue specific inhibitory control task.
Self report: Power of food, external eating, mindful eating.
Neurophysiological markers: anterior cingulate and dorsolateral PFC

Hedonic Drive: Positive Feedback

Direct: ad libitum intake, eating rate, caloric compensation.
Self-report: Appetite ratings, expected satiety, perceived hunger, satiety quotient.
Neurophysiological markers: insula and hypothalamus.
Physiological makers: Ghrelin, GLP-1 and PYY, metabolic factors, energy balance.

Direct: Food Choice, macronutrient intake, implicit & explicit liking and wanting, visual probe, eye tracking.
Self-report: palatability, taste, pleasure, expected palatability, food preference, cravings,.
Neurophysiological markers: activation and connectivity mesolimbic DA system

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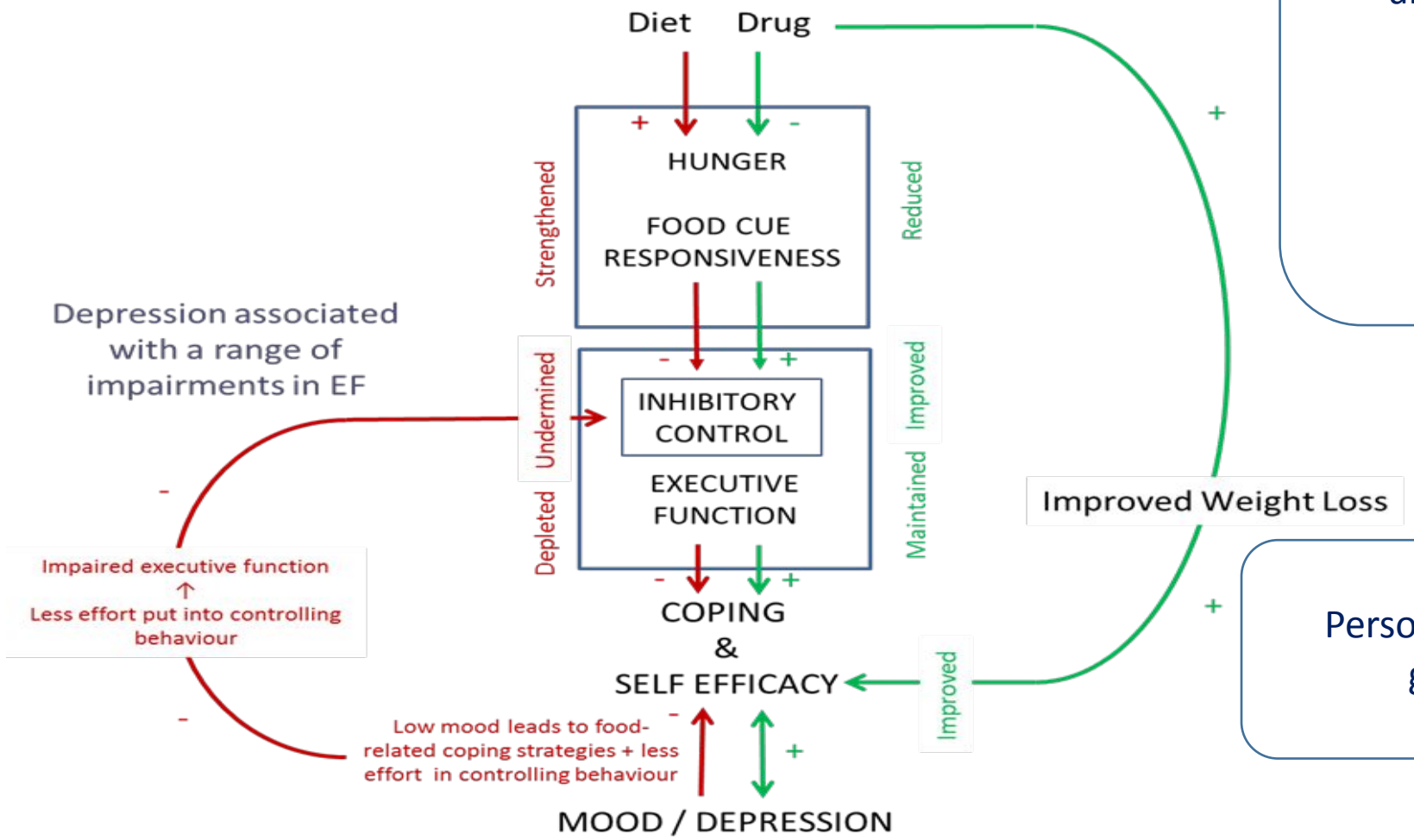
Drugs vs Diet

Pharmacotherapy could improve weight loss outcomes through reducing –ive psychological and biological consequences of dieting

Aiding behaviour change

Improving self-efficacy



Personalised approach not possible without guidance from patient experience

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REVIEW ARTICLE

Tailoring pharmacotherapy to specific eating behaviours in obesity: Can recommendations for personalised therapy be made from the current data?

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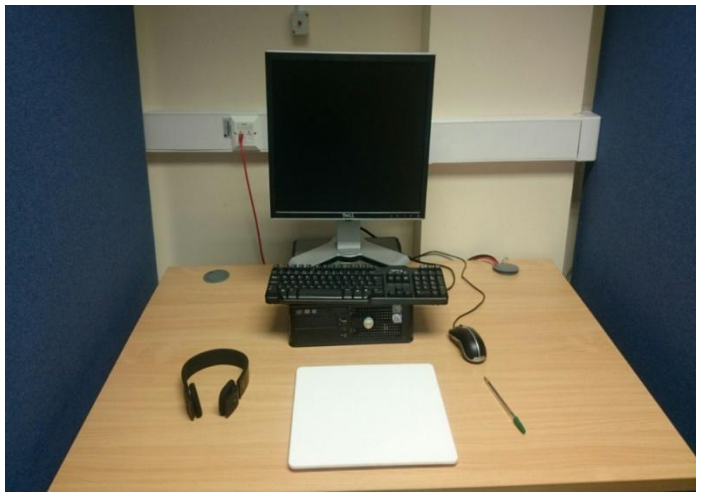
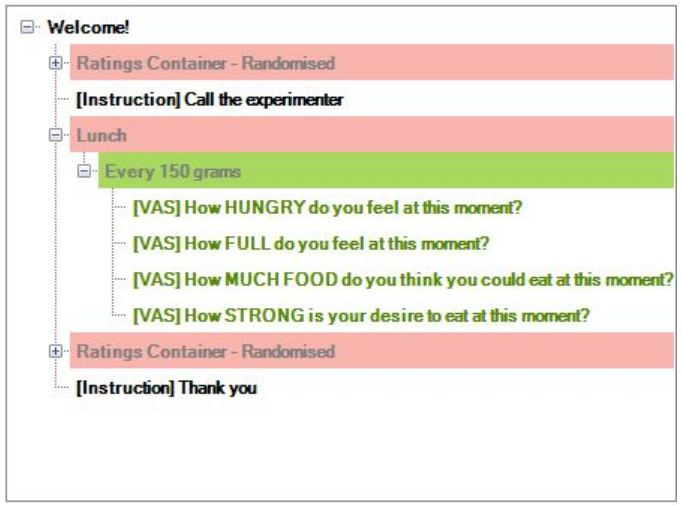
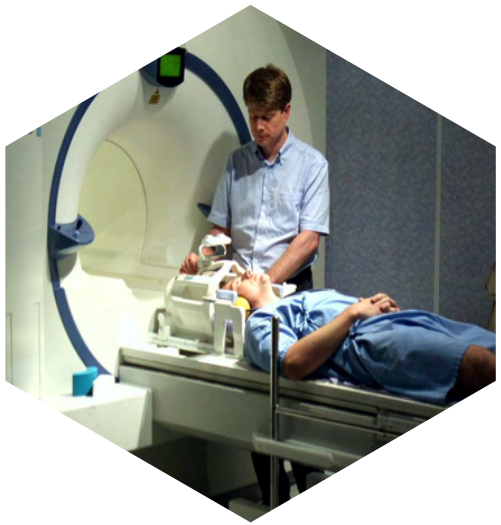
Measures to assess drug action on behaviour

- Experimental procedures do exist to answer how drugs can modify satiety, food reward (wanting and liking), and control over eating behaviour

- so we should know how these drugs affect behaviour

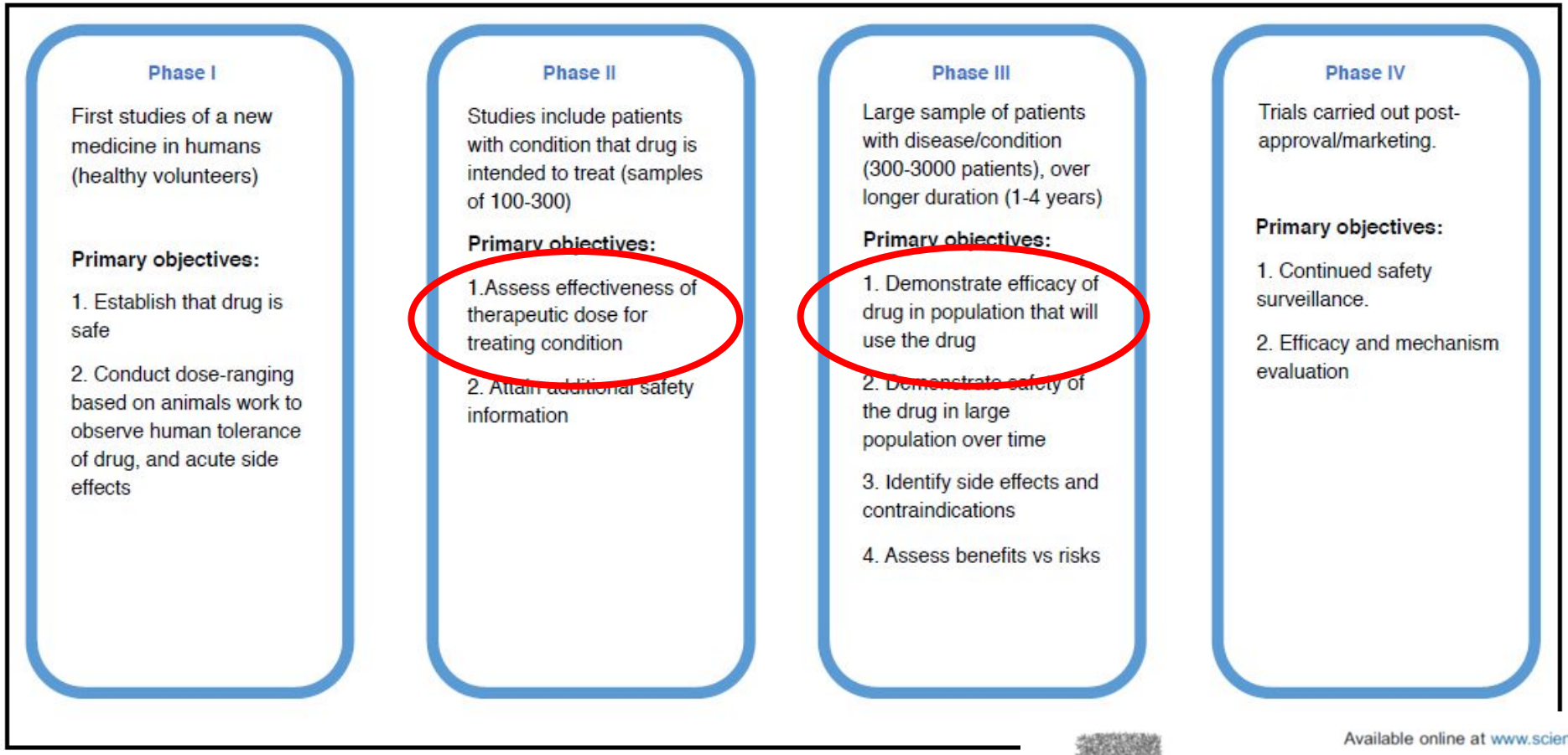






Arguably drug action on behaviour should be assessed prior to regulatory approval

Figure 2



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Pharmaceutical approaches to weight management: behavioural mechanisms of action

Carl A Roberts, Paul Christiansen and Jason CG Halford

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So what do we know?

- Proposed mechanisms of action 
- Efficacy for producing 5% weight loss in phase III clinical trials 
- *How* the drugs produce weight loss – effects on the brain and behaviour?
- Can successful responders be characterised from these data?

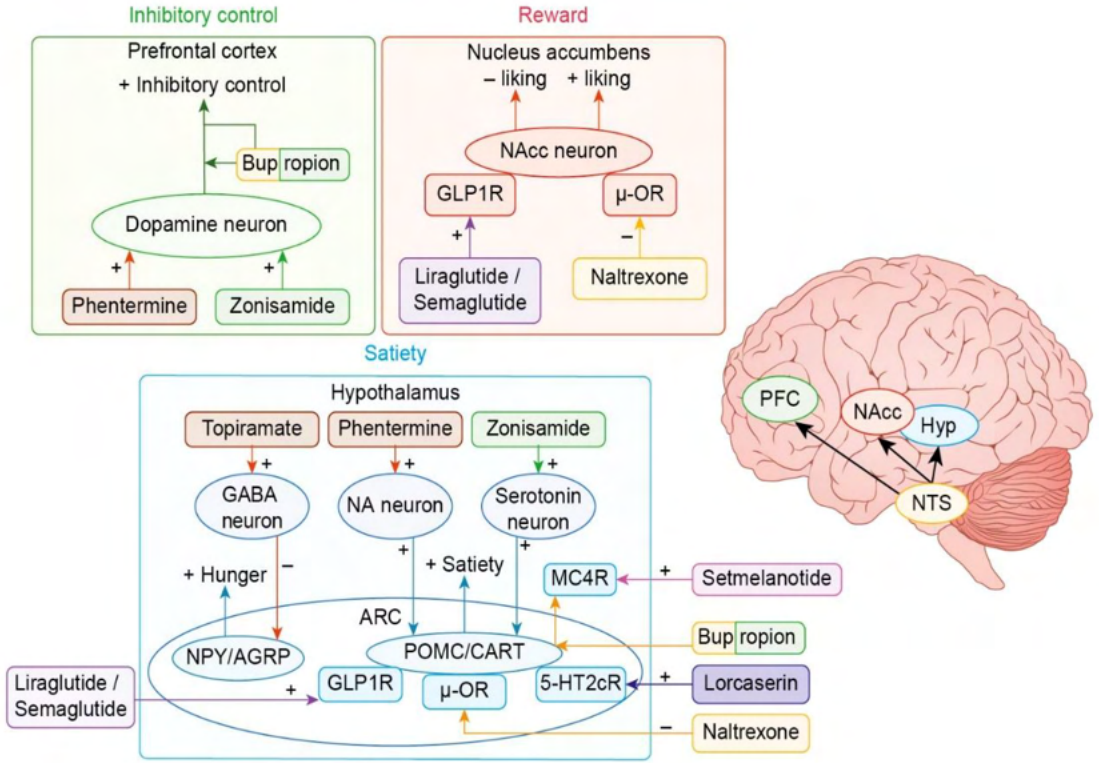
Proposed mechanisms of action

Bupropion-naltrexone: boost satiety, reduce “liking”, improve control

Phentermine-Topiramate: boost satiety, improve control

Liraglutide: boost satiety, reduce “liking”

Semaglutide: boost satiety, reduce “liking”



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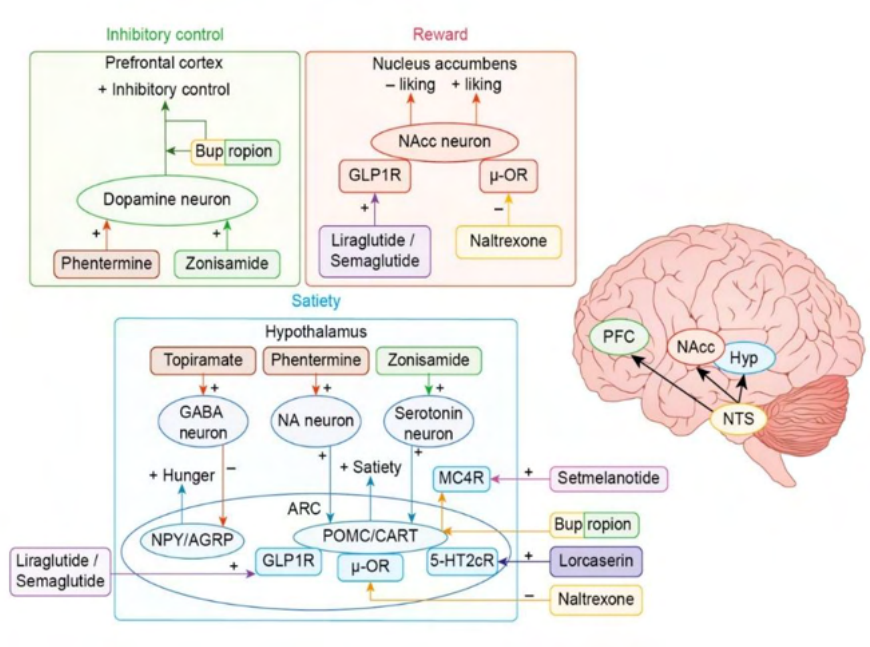
Phentermine/Topiramate (Qsymia)

- FDA approved only
- Phentermine = amphetamine derivative
- Topiramate = anticonvulsant with weight loss properties

- Combination of lower doses of each drug to reduce undesired cardiovascular effects whilst having a synergistic effect on weigh loss.

- Proposed mechanism of action: 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 ar effect on dopamine, which in the PFC may improve inhibitory control.



Efficacy: Phentermine/topiramate

- 75% of people achieved 5% weight loss (OR = 9.22, over 2 studies) - (Khera et al., 2016)

- No mechanistic/behavioural or neuroimaging data

- Behavioural specificity of phentermine/topiramate remains unknown

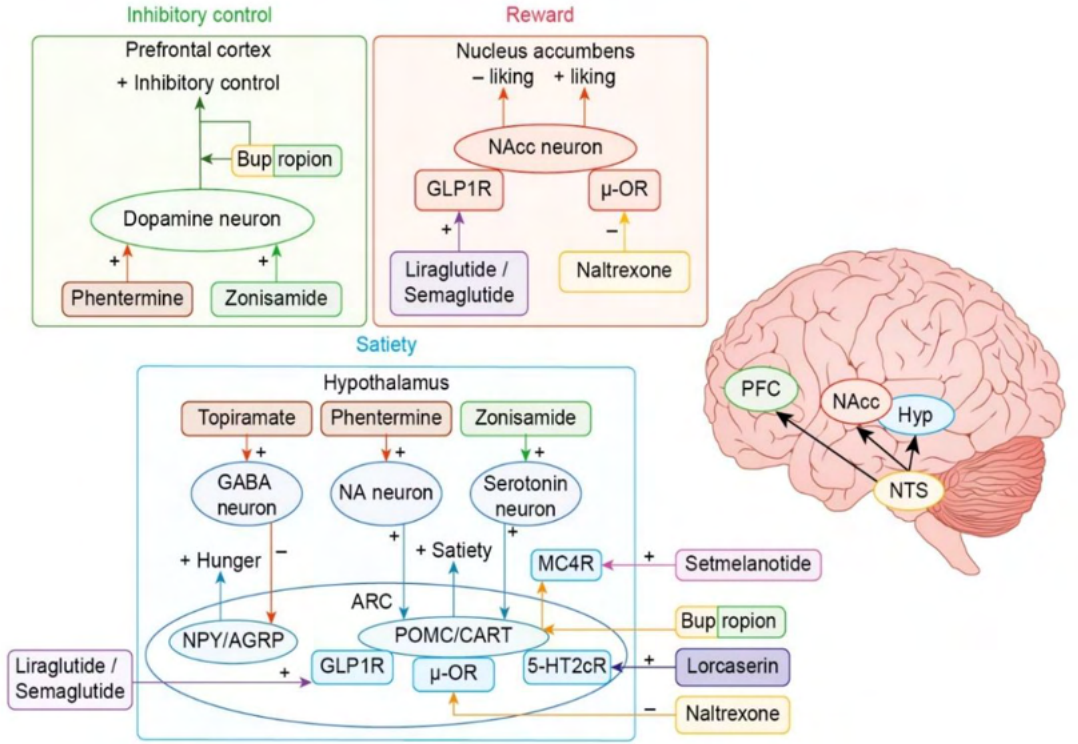
- Without clear data on how the drug effects eating behaviour it is difficult to suggest which individuals may benefit from taking this drug and to assess its tailoring potential.

Bupropion-Naltrexone (Mysimba)

- FDA and EMA approval
- Bupropion = catecholamine reuptake inhibitor - anti-depressant used to reduce craving in smoking cessation.
- Naltrexone = opioid antagonist, reduces reward sensitivity to palatable food
- Proposed to boost satiety, dampen reward,

and improve control of eating

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.



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Efficacy: Bupropion/naltrexone

- 55% of people achieved 5% weight loss (OR = 3.96, n=2044, over 4 studies) - (Khera et al., 2016)

- Some self report data on fullness/hunger (satiety effects), desire for sweet foods (reward effects), ability to control eating and resist food cravings (craving control).

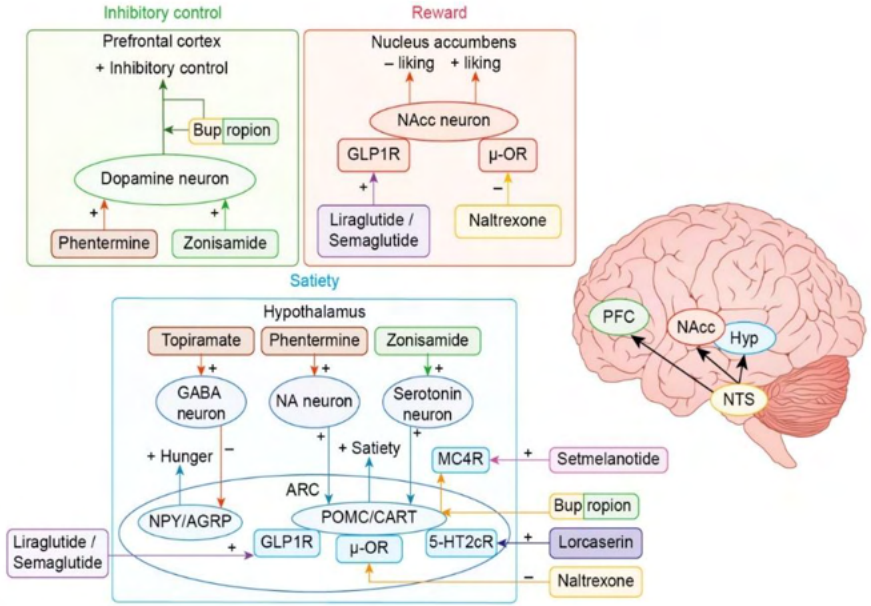
- Wang et al. (2014): increased activation in brain areas associated with control over eating

No clinical experimental data available for effects on eating behaviour

Without behavioural data, the suggestion of improved control from fMRI remains speculative

Liraglutide (Saxenda)

- FDA and EMA approved GLP-1 receptor agonist (A satiety hormone)
- Approved for weight loss at 3.0mg daily injectable dose
- Stimulate GLP1 receptors located in arcuate nucleus of hypothalamus which increases satiety. Moreover GLP1 receptor agonism in the nucleus accumbens may reduce 'liking'.
- May influence reward motivated eating, and reduce intake through effects on central appetite and reward neural pathways, as well as peripheral gastrointestinal sites.



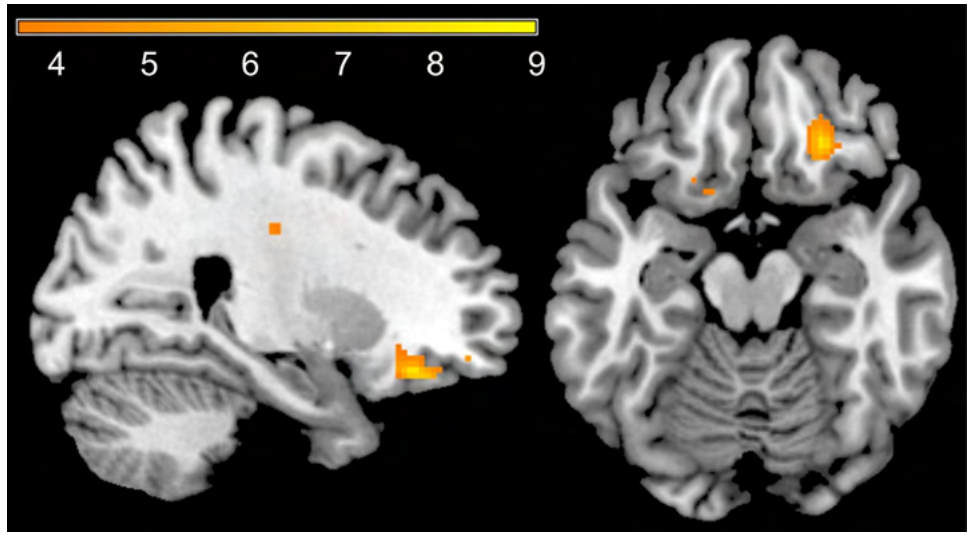
Efficacy: Liraglutide

- 63% of participants achieved 5% weight-loss (OR = 5.54) in phase 3 trials (Khera et al., 2016) 2921 participants (3 studies)

- Only 1 study on behaviour with the 3.0mg dose: Decreased ad lib food intake (lasagne), increased satiety and fullness (post-meal), reduced prospective consumption (post-breakfast). No increase in Energy expenditure

Liraglutide - fMRI

- Farr et al. (2019) - Brain activation in response to food images as compared to non-food images in right orbitofrontal cortex increases with 3.0 mg liraglutide treatment in a whole-brain paired samples t-test when BMI is controlled ($P < .05$, FWE-corrected for peak).

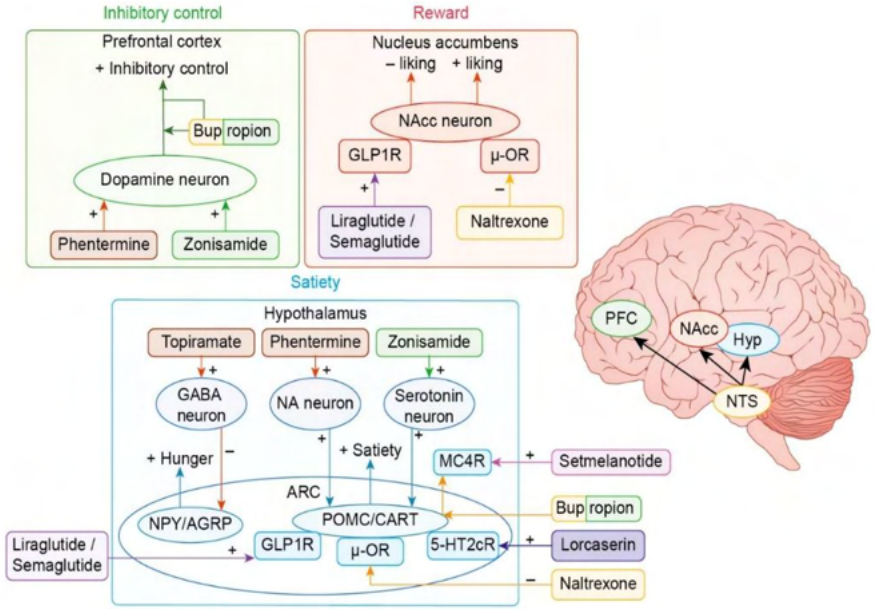


Conclusion?

- Produces weight loss through homeostatic mechanisms that boost satiety, leading to reduced intake.
- More data is needed with the 3.0mg dose in non-T2DM samples to characterise effects on the interplay between satiety, reward and IC.
- Potential counter-regulatory increase in reward activity – could explain later plateaus in weight-loss

Semaglutide (Wegovy)

- FDA and EMA approved GLP-1 receptor agonist (A satiety hormone)
- Approved for weight loss at 2.4mg ***weekly*** injectable dose
- Mechanism of action: stimulate GLP1 receptors located in arcuate nucleus of hypothalamus which increases satiety. Same mechanism as Liraglutide, but change in formulation meaning longer half-life i.e. once weekly dosing rather than daily – reduced patient burden, so should improve adherence



Semaglutide (efficacy) – Impressive weight loss data

- Wilding et al. (2021) – 84% (n= 1047/1306) in Semaglutide group achieved 5% weight loss at 68 week assessment

- Rubino et al. (2021) - The observed proportions of participants achieving 5% or more, 10% or more, 15% or more, and 20% or more body weight loss from week 0 to week 68 with continued semaglutide vs placebo were 88.7% vs 47.6%, 79.0% vs 20.4%, 63.7% vs 9.2%, and 39.6% vs 4.8%, respectively

- Wadden et al. (2021) - Of 611 randomized participants 567 (92.8%) completed the trial, and 505 (82.7%) were receiving treatment at trial end. At week 68 more participants treated with semaglutide vs placebo lost at least 5% of baseline body weight (86.6% vs 47.6%, respectively; $P < .001$)

Semaglutide (efficacy) – brain and behaviour

- Currently no brain imaging data – no fMRI studies investigating brain activity in satiety / reward / control brain regions
- Gibbons et al. (2020) – Lower ad lib energy intake across day (homogenous lunch meal, and self-served evening meal). After a fat-rich breakfast, there were significant differences in favour of oral semaglutide versus placebo for measures of satiety, hunger and for overall appetite score, with no significant differences following a standard breakfast. Fewer food cravings and better eating control were seen with oral semaglutide versus placebo. – No data on reward, small sample (n=15), daily oral semaglutide (not approved dose, regimen, or route of admin), in T2DM patients
- Blundell et al. (2017) – Reduced energy intake at homogenous meals and across day (satiety), lower intake of high fat foods, increased satiety ratings across day, greater control of eating (driven by less hunger), liking and wanting lower for high fat foods, but wanting higher for sweet foods – mechanism seems largely satiety related. – Small sample (n=30), not approved dose (1mg)

Semaglutide (efficacy) – brain and behaviour

- Only 1 study with approved dose / licensed use
- Friedrichsen (2020) – Reduced intake at lunchtime meal, and increased satiety ratings up to 5 hours later, control of eating generally improved on COEQ – reduced cravings for savoury foods, but not sweet. Limited reward data

- Conclusion - Produces weight loss through homeostatic mechanisms that boost satiety, leading to reduced intake. More data on reward driven eating needed and patient reported outcomes

Drugs for weight-loss – what we know

- What we do know: Drugs can be effective in achieving 5% weight loss
- Each drug will have a portion of non-responders
- Developing tailored weight management plans to meet individual needs is the gold standard in specialist weight management services
- Pharmacotherapy as an aid to reduced calorie diets and behaviour modification may provide additional benefit for achieving and maintaining clinically meaningful weight loss.

Drugs for obesity – what we don't know

- Which drugs will benefit which patients (more data needed to enable the link between pharmacology and real world therapeutic benefits i.e. proof of concept) – although this is aspect is definitely improving – next steps = greater characterisation and predictors of responders based on patient barriers/behaviours, and brain activity
- Why people don't respond to drug treatment
- Mechanisms that underpin plateauing of weight-loss in responders
- There are not enough data for clinicians to make fully informed decisions about the pharmacotherapeutic tools at their disposal. (but again this is improving all the time
- Without appropriately designed, well-powered mechanistic studies detailing drug effects on the substrates of eating behaviour, the tailoring potential of these drugs remains speculative – but we are getting there

What needs to be done?

- In order to deliver personalised treatment it is necessary to characterise drug effects on behaviors associated with increased energy intake.
- Clinical response to pharmacotherapy can vary greatly, sub-populations of people who respond to drug treatment successfully need characterising
- Understand mechanisms that underpin plateauing weight-loss
- Ultimately patients understand their own needs and behaviour better than anyone. Personalised treatment requires input from the patient.- Use of Patient Reported Outcomes (PROs) and linking these to mechanisms of action will help. Personalised approach requires patient to be at the centre
- If we know more about how the drugs work on behaviour, then clinicians and patients together will be able to make informed decisions about the most appropriate drugs to target specific barriers to weight-loss goals

Thank you for listening

- Questions?

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A methodological platform to assess drug effects on satiety, reward and inhibitory control

Regulatory control (satiety) and reward:

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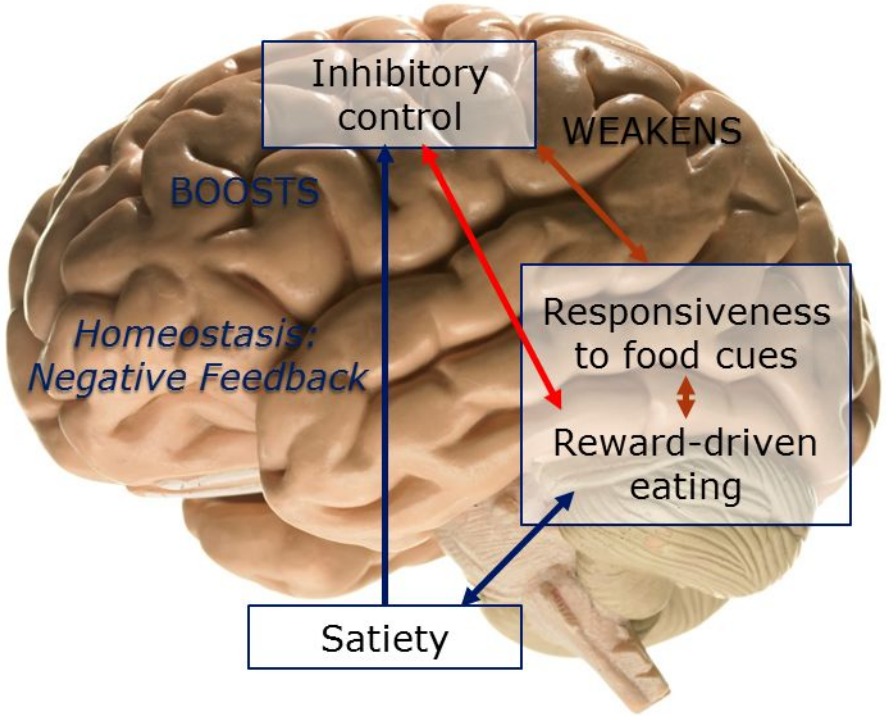

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