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Utility of an experimental medicine model to evaluate efficacy, side-effects and mechanism of action of novel treatments for obesity and Binge-Eating Disorder

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Abstract

Obesity and Binge Eating Disorder (BED) are prevalent conditions that are associated with increased risk of morbidity and mortality. There is evidence that the use of pharmacotherapy alongside behavioural treatments can improve quality of life and reduce disease risk for patients with these disorders. However, there are few approved drug therapies for obesity, and these are limited by poor efficacy and/or side effects and only one drug has been approved for the treatment of BED. There is considerable potential to use experimental medicine models to identify new drug treatments for obesity and BED, with greater efficacy and an improved side effect profile, at an early stage of development. Here, we present a model developed in our laboratory that incorporates both behavioural and neuroimaging measures which can be used to facilitate drug development for obesity and BED. The results from validation studies conducted to date using our model suggest that it is sensitive to the effects of agents with behavioural, neurophysiological and neuropharmacological mechanisms of action known to be associated with weight loss and reductions in binge eating. Future studies using the model will be valuable to evaluate the potential efficacy and side-effects of new candidate drugs at an early stage in the development pipeline for both obesity and BED.

PROVIDE MIN SIX KEYWORDS

Keywords: Obesity, Binge-eating disorder, Eating disorder, Pharmacotherapy, Medication, Drug, Experimental medicine, Translational medicine, Behaviour, fMRI, Neuroimaging

1. Introduction

Obesity is characterised by a body mass index (BMI) equal to or exceeding 30 kg/m^2 and is associated with increased prevalence of hypertension, type 2 diabetes, heart disease, cancer and stroke and diminished quality of life (Agha & Agha, 2017). Individuals with obesity have increased prevalence of anxiety and depression, (Jagielski, Brown, Hosseini-Araghi, Thomas, & Taheri, 2014), and these mood disorders are more common in women than men (Tronieri et al., 2017). Obesity is often co-morbid with binge-eating disorder (BED) (Cossrow et al., 2016). BED is characterised by eating, in a discrete time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances and the sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating) (American Psychiatric Association, 2013). BED is the most common eating disorder and diagnoses for women outnumber those for men by a ratio of 3:1 (Erskine & Whiteford, 2018). Patients with BED can present as underweight (1.3%), healthy weight (31.7%), overweight (30.7%) or having obesity (36.2%) and the disorder is associated with diabetes, hypertension, and chronic pain including headache and neck/back pain (Kessler et al., 2013). BED is often co-morbid with depression, anxiety, self-harm, substance abuse, and Attention-Deficit Hyperactivity Disorder (ADHD) (Kaisari, Dourish, & Higgs, 2017; Kessler et al., 2013).

Behavioural modifications including diet, exercise and psychotherapy are the initial treatment options for obesity and BED (Hay et al., 2009; Jensen et al., 2014; Palavras et al., 2017; Wilfley et al., 2018; Wilson et al., 2010), but high incidences of non-responders and weight regain suggest some individuals may benefit from drug therapy (Foster, 2006; Linardon, 2018). Given the medical and psychological burdens associated with obesity and BED, it is

essential that a wide range of treatment options, including drug therapies, are available to the patient.

There are few approved drug therapies for obesity, and these are limited by poor efficacy and/or side effects (Tak & Lee, 2021) and only one drug has been approved for the treatment of BED (McElroy et al., 2015). Hence, there is a need for novel drugs with greater efficacy and an improved side effect profile to treat both obesity and BED. There are drugs in the development pipeline but the process of clinical development is expensive and slow. In Phase 1 clinical trials, safety, bioavailability, metabolism and pharmacokinetics of a novel compound are assessed in 20-100 healthy participants over a period of several months. Approximately 70% of compounds move to the next phase. In Phase 2 clinical trials, compound efficacy and side-effects are assessed in up to several hundred participants with the target disorder over a period of up to two years. Approximately 33% of compounds move to the next phase. In Phase 3 clinical trials, compound efficacy, side-effects and adverse reactions are assessed in 300-3000 participants with the target disorder over a period of one to four years. Approximately 25-30% of compounds move to the next phase of assessment for regulatory approval (FDA, 2018). Although not yet widely employed to date in the development of drugs for obesity and BED, experimental medicine models in Phase 1 can be a useful proof-of-concept approach to determine whether a compound should proceed to large scale Phase 2 and Phase 3 clinical trials as well as providing insight into mechanisms that may be targeted for future drug development. The aims of this review are first to briefly summarise current and potential future drug therapies for obesity and BED. Second, and more specifically, we explore the utility of an experimental medicine approach in drug development and present a model developed and validated in our laboratory that can be used to facilitate drug development for obesity and BED.

2. Marketed drugs and the drug development pipeline for obesity and BED

2.1. Marketed drugs for obesity

Currently, there are five medications approved by the United States Food and Drug Administration (FDA) for long-term weight loss: orlistat (Xenical®, Alli®), phentermine/topiramate (Qsymia®), bupropion/naltrexone (Contrave®), liraglutide (Saxenda®), and semaglutide (Wegovy®). A sixth drug, setmelanotide (Imcivree™), is approved only for patients diagnosed with one of three rare genetic disorders: proopiomelanocortin, proprotein convertase subtilisn/kexin type 1 or leptin receptor deficiency. The European Medicines Agency (EMA) has currently approved only three drug therapies for obesity (orlistat, bupropion/naltrexone (Mysimba®) and liraglutide) but has recently recommended the granting of a marketing authorisation for semaglutide. This recommendation is also applicable in the UK after BREXIT where for a period of 2 years, from 1 January 2021, the UK will continue to adopt decisions taken by the EMA on the approval of new marketing authorisations. Orlistat inhibits the action of gastrointestinal and pancreatic lipases, which reduces the absorption of fatty acids. It has modest efficacy but the presence of the non-absorbed fats in the intestine often causes severe gastrointestinal side-effects for patients (Torgerson et al., 2004). Phentermine/topiramate is an appetite suppressant and effective weight loss agent but the mechanisms underlying its efficacy are unclear and the drug has many potential side effects including insomnia, dizziness, paresthesia, dry mouth, dysgeusia, constipation, anxiety and depression (Allison et al., 2012). Bupropion/naltrexone is a combination of the μ-opioid receptor antagonist naltrexone and the dopamine and noradrenaline reuptake inhibitor bupropion (Sherman et al., 2016). Bupropion/naltrexone is an effective weight loss agent but side effects include nausea, headache

and dizziness. Liraglutide and semaglutide are Glucagon-like Peptide-1 (GLP-1) receptor agonists that are self-administered by subcutaneous (SC) injection either daily or weekly respectively to treat obesity and diabetes. Greater weight loss may be achieved with a GLP-1 receptor agonist compared with other approved medications (Tak & Lee, 2021) but the SC route of administration is problematic for some patients and common side effects include nausea and vomiting. Therefore, there is a need to identify new and improved drug treatment options for obesity.

2.2. Drug development pipeline for obesity

There is a broad range of potential new mechanisms and drugs in the pipeline to treat obesity and we provide a brief overview of these below (see Table 1). Tesomet is a combination of the β_1 adrenoceptor antagonist metoprolol and the dopamine, serotonin and noradrenaline (triple) reuptake inhibitor tesofensine which is in Phase 2 clinical trials (https://saniona.com/pipeline/). Tesofensine has also been submitted for regulatory approval for the treatment of obesity in Mexico (https://news.saniona.com/news-releases/news-release-details/saniona-provides-update-ongoing-review-tesofensine-mexico). Dual acting GLP-1/ Gastric Inhibitory Polypeptide [also known as Glucose-dependent Insulinotropic Polypeptide] (GIP) receptor agonists are being developed for obesity. GIP is a peptide hormone released by K-cells of the small intestine in response to food that increases insulin release and enhances the effects of GLP-1 (Bergmann et al., 2019). For example, tirzepatide is a long-acting GIP/GLP-1 receptor agonist that is in Phase 3 clinical trials (https://www.lilly.com/discovery/clinical-development-pipeline). There is also interest in analogues of amylin (a peptide co-secreted with insulin that has satiety-enhancing effects) such as cagrilintide and combinations of amylin analogues with other weight loss agents

126 e.g. cagrilintide and semaglutide (Sonne et al., 2021;
127 https://clinicaltrials.gov/ct2/show/NCT04940078). Similarly, peptide tyrosine tyrosine (PYY)
128 fragments are being developed for the treatment of obesity. (PYY) 3-36 is a preferential Y2
129 neuropeptide Y (NPY) receptor agonist and is one of two main endogenous fragments of PYY
130 which is released in endocrine cells of the small intestine after a meal. Intravenous infusion of
131 PYY 3-36 reduces hunger and food intake in patients with obesity (Batterham et al., 2003) but
132 also causes severe gastrointestinal adverse effects (nausea and vomiting) limiting its therapeutic
133 utility (Greenhill, 2019). However, recent evidence suggests that topical-lingual (on the tongue)
134 administration of PYY does not induce nausea (https://www.gilatherapeutics.com/technology/)
135 and initial studies to assess the efficacy in obesity of this route of PYY delivery are underway
136 (https://clinicaltrials.gov/ct2/show/NCT05110664). NPY increases food intake and body weight
137 by activating Y5 receptors in the hypothalamus (Parker et al., 2002). On the basis of these
138 results, NPY5 receptor antagonists such as S-237648 are being developed as potential therapies
139 for obesity (https://www.shionogi.com/global/en/innovation/pipeline.html).
140
141 2.3. Marketed drugs for BED
142 Pharmacological therapy for BED is restricted to one medication, lisdexamfetamine
143 dimesylate (LDX; Vyvanse®), which is only approved in the United States and in a limited
144 number of other countries including Canada and Australia. LDX was initially approved by the
145 FDA in 2007 for the treatment of ADHD and subsequently in 2015 the drug received approval
146 for the treatment of BED. FDA approval was based on a Shire (now Takeda) clinical
147 development program that included an 11-week Phase 2 randomised placebo controlled clinical
148 trial assessing doses of 30, 50, and 70mg/day LDX (McElroy et al., 2015) and two 12-week

149 Phase 3 randomised placebo controlled clinical trials investigating 50 and 70mg/day doses
150 (McElroy et al., 2016). The results of these trials showed that LDX at 50 and 70mg /day reduced
151 binge-eating episodes and BED-related symptoms and subsequent studies have confirmed the
152 efficacy of LDX in the treatment of BED (for review see Schneider, Higgs, & Dourish, 2021).
153 Though the pharmacological effects of LDX are known, in that the drug increases central
154 noradrenergic, dopaminergic and serotonergic neurotransmission, the neuropharmacological and
155 neurobehavioural mechanisms that mediate the clinical efficacy of LDX in treating BED remain
156 unclear (Schneider et al. 2021). In addition, qualitative analysis of treatment-emergent adverse
157 events reported by participants in three clinical trials found that ~ 24% - 85% of participants
158 experienced at least one treatment-emergent adverse event (Schneider et al. 2021). Further, LDX
159 is a stimulant drug and thus is classified as a Schedule II controlled substance by the US Drug
160 Enforcement Administration (DEA) due the potential risk of abuse and dependence. Therefore,
161 as for obesity, there is a need to identify new and improved drug treatment options for BED.
162
163 2.4. Drug development pipeline for BED
164 In contrast to obesity, there are few potential new mechanisms and drugs in the pipeline for
165 treating BED. Several other stimulant drugs marketed and/or developed for the treatment of
166 ADHD have been studied in BED. For example, methylphenidate has been reported to decrease
167 binge eating in a small, randomised trial in which it was compared to cognitive behavioural
168 therapy (Quilty et al., 2019). Dasotraline was in development for both ADHD and BED and
169 showed efficacy in Phase 3 trials for BED but in May 2020 it was announced that the New Drug
170 Application (NDA) submitted for approval to the FDA had been withdrawn and development
171 discontinued as further clinical studies would be needed to support regulatory approval for both

indications (https://news.sunovion.com/press-releases/press-releases-details/2020/Sunovion-Discontinues-Dasotraline-Program/default.aspx). The hypothalamic neuropeptide orexin increases eating which is thought to be mediated by OX_1 receptors (Tsujino & Sakurai, 2013) and the OX_1 receptor antagonist ACT 539313 is in Phase 2 clinical development for the treatment of BED (https://www.idorsia.com/about-idorsia/idorsia-today/our-pipeline). Drugs marketed for obesity such as liraglutide, phentermine/topiramate and naltrexone/bupropion are also being investigated for their potential efficacy in treating BED (Appolinario et al., 2019) but as noted above a third of BED patients are not overweight or obese and therefore a drug that causes weight loss would be contraindicated for these patients. See Table 1 for a summary of approved drugs and drugs in the pipeline for treatment of obesity and BED.

Table 1. An overview of currently approved drugs and drugs in development for treatment of obesity and BED.

Obesity		BED	
Mechanism	**Example compound**	**Mechanism**	**Example compound**
Approved		**Approved**	
Lipase Inhibition	Orlistat	Dopamine, serotonin and noradrenaline reuptake inhibitor	Lisdexamfetamine dimesylate
Indirect noradrenaline agonist/GABA-A agonist, glutamate antagonist	Phentermine/ topiramate		
Dopamine and noradrenaline reuptake inhibitor/μ-opioid receptor antagonist	Bupropion/ naltrexone		
GLP-1 receptor agonist	Liraglutide		

In development		In development	
β_1 adrenoceptor antagonist/ dopamine, serotonin and noradrenaline reuptake inhibitor	Tesofensine	OX_1 receptor antagonist	ACT 539313
Dual acting GLP-1 receptor agonist/GIP receptor agonist	Tirzepatide		
Amylin analogues	Cagrilintide		
Y2 receptor agonist	PYY 3-36		
Y5 receptor antagonist	S-237648		

185

186 3. Drug Development Process

187 The journey from identifying a new drug candidate to its launch as a marketed treatment is long
188 and on average in the US it takes 12 years for a novel compound to pass through the phases of
189 development from the laboratory to regulatory approval for use in patients (Van Norman 2016).
190 The long duration of the process contributes to the high costs of drug development (which on
191 average are $985.3 million in the US, Wouters et al., 2020) but costs are also increased by the
192 fact that many drugs that are tested in the early phases of development fail to make it to market,
193 largely due to lack of efficacy in late stage clinical trials or failure during the regulatory approval
194 process (Kola & Landis, 2004). For example, the cannabinoid receptor antagonist rimonabant
195 was initially approved for use as a weight management therapy by the EMA but due to a higher
196 incidence of psychiatric side effects than reported in clinical trials, in particular depression, was
197 then withdrawn shortly thereafter, resulting in a significant loss of investment in its development
198 (Butler & Korbonits, 2009). While a number of promising targets and drug candidates have been
199 identified for the treatment of obesity and BED, many drugs for obesity have been withdrawn
200 due to unacceptable side-effects (e.g. d-fenfluramine, sibutramine, rimonabant, lorcaserin) and
201 for BED only LDX has emerged as an approved treatment to date (Butler & Korbonits, 2009;

Dourish et al., 2008; Müller et al., 2021; Schneider et al., 2021; U.S Food and Drug Administration, 2020; Williams, 2010). Other drug candidates that have passed initial safety and drug metabolism and pharmacokinetic testing in Phase 1 clinical trials have then failed to show consistent effects in later (Phase 2 and 3) stages of clinical development (Levitan et al., 2021; Müller et al., 2021). It has been proposed that the introduction of translational experimental medicine models at the interface between Phase 1 and Phase 2 clinical trials provides a useful step to de-risk development of novel treatments for psychiatric and eating disorders and to accelerate the drug development process (Dawson et al., 2011; Dourish & Dawson, 2014). Experimental medicine studies are designed to assess potential drug efficacy, mechanisms and safety in small groups of healthy participants before expensive large-scale Phase 2 and Phase 3 trials in patients are undertaken. The rationale for these early studies is to triage a large number of drug candidates to focus on those with the highest probability of success (POS) in late-stage trials while stopping development of candidates with a low POS. Thus, the principle with the latter compounds is to "fail early and fail cheap" (Dawson et al., 2011; Dourish & Dawson, 2014).

4. Experimental medicine models for psychiatric and eating disorders

Experimental medicine models for psychiatric and eating disorders comprise testing the effects of potential new treatments on defined endpoints, often referred to as biomarkers, in healthy participants, that are predictive of clinical efficacy in the target patient population. The term biomarker is applied to a range of measures that are theorised to be related to the disorder requiring treatment such as: markers in biological material (e.g. plasma); neuroimaging-related measures (e.g. the Blood Oxygen Level Dependent (BOLD) response in functional Magnetic

225 Resonance Imaging (fMRI)); performance on behavioural and cognitive test-batteries and
226 physiological measures. In many cases, these biomarkers are hypothesised to index the
227 mechanistic processes that underlie the disorder of interest. For example, a biomarker that has
228 been used in experimental medicine models for depression is the negative bias in processing of
229 emotional information that is seen in many people with depression and is thought to be a core
230 feature of the disorder (Disner et al., 2011). Early amelioration of this emotional processing bias
231 precedes improved mood following longer term treatment with a range of antidepressants and
232 this early response has been used to screen for potential new antidepressants (Harmer et al.,
233 2009, 2011).
234
235 Healthy volunteers are recruited to participate in Phase 1 experimental medicine studies which
236 enables both a drug response on relevant biomarkers and safety issues that might pose risks for
237 vulnerable patient populations to be assessed at an early stage (Dourish et al., 2008). Recruitment
238 may also include participants who present with subclinical symptoms (termed intermediate
239 phenotypes or surrogate patients) on a measure of interest. For example, in studies of novel
240 compounds for the treatment of schizophrenia, participants scoring highly on a schizotypal
241 personality questionnaire (termed high schizotypes) have been recruited as an intermediate
242 phenotype/surrogate patient group to evaluate new drug candidates (Dourish & Dawson, 2014;
243 Koychev et al., 2012). This strategy is in line with the National Institute of Mental Health
244 Research Domain Criteria Initiative (RDoC), which encourages research on dimensions of
245 observable behaviour rather than a categorical, symptom-based approach to the study of mental
246 health (Insel et al., 2010). Recruitment of healthy volunteers or individuals with intermediate
247 phenotypes from the general population is easier than recruitment of patient groups and

assessment and interpretation of candidate drug effects is often more straightforward due to the absence of confounding effects of maintenance drug treatments that can be encountered in patients.

The experimental medicine approach also provides potential insight into the mechanisms that underlie the clinical effectiveness of a drug. If multiple biomarkers are incorporated into a model, then it may be possible to identify the markers that best predict clinical outcomes. For example, in the case of medications for depression, of several biomarkers tested, drug effects on negative emotional bias appear to be most predictive of clinical effectiveness in patients (Harmer et al., 2011). Such insight not only improves understanding of the disorder itself (suggesting that biased emotional processing may be a causal factor in depression) but also provides important information to guide the development of new treatments that can be targeted specifically at predictive biomarkers.

Another advantage of the experimental medicine approach is that biomarkers may be used to identify individuals who are more or less likely to respond to treatment, which then allows for patient stratification in future clinical trials. Selecting patients who are likely to respond and excluding patients with little likelihood of a response means that sample sizes can be reduced due to increased power to detect effects. As such, experimental medicine models can aid in the personalisation of drug treatment and more effective targeting of therapies.

Experimental medicine models have not yet been used widely in the development of drugs for treating obesity or BED. The efficacy of novel weight management drugs is primarily assessed

by weight-loss during Phase 3 Clinical Trials. Studies must demonstrate that participants lose at least 5% of their baseline body weight after 1 year compared to placebo or that at least 35% of participants lose at least 5% of their baseline body weight (FDA, 2007). The ability to assess potential for efficacy and side-effects in shorter, acute studies at an earlier stage could accelerate the development process and make it more cost effective.

The majority of drugs that have been approved for obesity are thought to act via a reduction in food intake (Williams et al., 2020). A small number of experimental medicine studies to date suggest that acute reductions in food intake are predictive of weight loss after longer term treatment. For example, the serotonin and noradrenaline re-uptake inhibitor sibutramine has been reported to reduce food intake after acute dosing and this effect is associated with long term weight loss (e.g., Barkeling et al., 2003; Fletcher et al., 2010; Halford et al., 2010). This suggests that measures of food intake provide an early indicator of efficacy for weight loss. However, there are many ways that drugs can reduce food intake and some actions may be more desirable than others. For example, a drug that enhances satiety may be preferable to a drug that has a general effect to decrease enjoyment of food and other rewarding stimuli: the latter mechanism of action may be associated with a general state of anhedonia, as was the case with the cannabinoid antagonist rimonabant and led to its withdrawal from the market. Therefore, the inclusion of biomarkers aimed at indexing the processes that lead to reduced intake would be informative.

Some studies of weight loss drugs have incorporated fMRI measures in an attempt to identify neural predictors of weight loss. Fletcher and colleagues (2010) examined the effect of

sibutramine on fMRI BOLD responses to pictures of food. Sibutramine attenuated activity in the hypothalamus and this effect was correlated with both ad-libitum food intake and subsequent weight-loss. These data suggest that reduced hypothalamic activity is a potential biomarker of future weight-loss although it should be noted that the hypothalamus is difficult to image and is susceptible to artefacts due to its proximity to the sinuses (Ojemann et al., 1997). Acute treatment with the GLP-1 receptor agonist exenatide decreased the BOLD fMRI response in reward-related brain areas including the insula, amygdala, putamen and orbitofrontal cortex in patients with obesity and the suppression of insula reactivity to food cues predicted a reduction in food intake (van Bloemendaal et al., 2014). Longer term (17 days) administration of the GLP-1 receptor agonist liraglutide to patients with diabetes increased levels of Gastric inhibitory peptide (GIP) which was inversely correlated with activation of the insula to food cues (Farr et al. 2016b). These data suggest that reduced activation to food cues in the insula may be a potential biomarker for weight loss. Overall, there is evidence that fMRI measures could have predictive power if included in an experimental medicine model to assess the potential efficacy of novel compounds to treat obesity.

An example of an experimental medicine approach that has been applied to the development of a novel treatment for binge eating is the program of research on the μ-opioid antagonist GSK1521498 that was reported to reduce food-seeking behaviour and binge-like eating of palatable food in preclinical studies (Giuliano et al., 2012). An initial open label study in healthy volunteers demonstrated target engagement (binding at μ-opioid receptors) using positron emission tomography (PET) scanning (Rabiner et al., 2011). In a follow-on study, 28-day treatment with GSK1521498 had no effect on body weight or binge eating scores in participants

317 with obesity and binge eating tendencies but did reduce food intake of a test meal and hedonic
318 responses to sweetened dairy products (Cambridge et al., 2013). GSK1521498 also reduced
319 neural responses to high calorie food pictures in reward related brain areas (pallidum/putamen)
320 and there was a significant correlation between drug-induced modulation of pallidal/putamen
321 activity to high caloric food stimuli and weight change (Ziauddeen et al., 2013). Due to the lack
322 of effect on binge eating scores, the development of GSK1521498 for BED was halted.
323 However, these studies highlight the potential for using an experimental medicine approach to
324 assess the potential efficacy of novel medications for treating BED.

325 The model developed to test the effects of GSK1521498 did not include measures related to
326 cognition but given evidence that loss of impulse control is a causal factor in bingeing on
327 palatable foods in BED (Galanti et al., 2007; Lavagnino et al., 2016), it has been argued that the
328 ideal drug treatment for BED should demonstrate a combination of effects to reduce food intake
329 (preferably of binge type foods) as well as effects on cognitive control (Heal & Smith, 2021).
330 This argument is supported by the results of a recent meta-analysis and systematic review of
331 preclinical and clinical studies which suggested that LDX likely reduces binge eating through
332 combined effects on satiety, food reward, and cognitive control (Schneider et al., 2021).

333 Drugs for obesity and BED must have an acceptable safety profile and for some drugs that have
334 effects on food intake due to action at receptors in the brain, neuropsychiatric adverse effects
335 (e.g. depression, suicidality as observed with rimonabant) and abuse liability (as observed with
336 stimulants) are side effects of concern. The requirements and endpoints for ensuring psychiatric
337 safety of drugs for weight management are less well defined by the regulatory authorities than
338 those for weight-loss. The use of cognitive test batteries such as the P1vital® Oxford Emotional

Test Battery (ETB), that measure emotional processing offer an approach to the assessment of psychiatric safety. The assessment of behavioural indicators of mood and emotion are less influenced by demand characteristics than are self- reports using rating scales. The ETB can be used in short term studies over days and has been found to have good test-re-test reliability (Thomas et al., 2016). In a study on rimonabant, negative effects of the drug on emotional processing were detected after a single dose, in the absence of any change in standard questionnaire measures of mood, emotion, and psychiatric functioning (Horder et al., 2009). Thus, the use of a cognitive test battery as part of an experimental medicine model for obesity and BED would aid in the identification of drugs with psychiatric safety concerns.

In summary, there is great potential to exploit experimental medicine models to advance development of drug for obesity and BED. In the following section we describe the development and validation of such a model in our laboratory. We assessed the effects of a number of compounds on a range of biomarkers using multimodal methods (See Figure 1 for a schematic diagram of the model). To our knowledge, our model is the most comprehensive to date and improves on previous experimental medicine approaches because we include detailed assessment of eating behaviour and fMRI biomarkers as well as the behavioural assessment of cognitive processes (attention, impulsivity and memory), emotion and mood, which has not been done previously.

5. An experimental medicine model for investigation of new drug treatments for obesity and BED

5.1 Eating measures

Our model involves assessing the effects of drug administration on consumption of both a staple main meal (pasta) and a palatable snack (cookies), eaten a short time after the main meal, in the laboratory. The inclusion of the cookie snack allows us to model eating in the absence of hunger and the tendency towards binge eating in participants with binge eating symptoms. Eating snacks in the absence of hunger has been found to be associated with loss of control over eating and weight gain in women (Feig et al., 2018). Assessing intake of a main meal and snacks also enables insight into the mechanisms underlying any changes in intake because we can distinguish between drug treatments that have a selective effect on cookie intake from drugs that decrease intake of both pasta and cookies. The former effect may be indicative of a reduction in the palatability of rewarding foods, whereas the latter effect may indicate enhancement of the satiating effects of the main meal with a consequent effect on food reward when full.

Insight into the specific processes underlying changes in food intake can also be gained from the assessment of within-meal measures, including eating rate and rated palatability using a universal eating monitor (UEM) (Kissileff, Kilngsberg, & van Italie, 1980; Yeomans, 1996). The UEM, which was first devised by Kissileff and colleagues (1980) enables constant monitoring of food consumed during a meal. The participant's plate is placed upon a weighing balance that is located underneath, but protruding through, the surface of a table. A placemat rests on top of the table, disguising the balance (although we have found that awareness of the balance has no effect on food intake, Thomas et al., 2015) and providing a surface on which to place a plate of food. The balance is connected to a computer and the progressive reductions in the weight of the plate as food is eaten are recorded. This method was adapted by Yeomans (1996) who configured it to allow visual analogue scale (VAS) ratings to be completed after a specified amount of food has been consumed (the Sussex Ingestion pattern Monitor or SIPM). In

385 the SIPM, participants are presented with a dish of 200g pasta. After each 50g of food consumed,
386 the computer interrupts the participant to prompt completion of ratings of appetite and liking of
387 the food. After 150g of the pasta has been consumed, there is another prompt, this time the
388 participant is asked to pause eating while the dish is replaced with another 200g serving. The
389 participant may continue to eat in this fashion for as long as they wish. Manipulations that
390 enhance satiety have been found to reduce eating rate in the SIPM whereas manipulations which
391 reduce food reward tend to decrease the initial rated palatability of a meal (Yeomans 1996).

392

393 The UEM system has been used to examine the mechanisms underlying the effects of drugs that
394 reduce food intake. For example, it has been reported that sibutramine reduces eating rate
395 (Halford et al., 2010), which is indicative of an effect to enhance satiety. In contrast, the opioid
396 receptor antagonist naltrexone reduces food intake via a decrease in rated food pleasantness at
397 the start of a meal suggesting an effect on reward processes (Yeomans & Gray, 1997). Hence, it
398 is possible to discriminate between drugs with differential effects on satiety and palatability
399 using this approach.

400

401 5.2 fMRI measures

402 To provide insight into the neural mechanisms that may underlie the effect of drug treatment on
403 appetite and body weight we include in our model assessment of the fMRI BOLD response when
404 viewing pictures of foods (Chechlacz et al., 2009). The food picture paradigm has been used in
405 studies that have contrasted the patterns of activation seen when viewing food versus non-food
406 pictures (for review see García-García et al., 2013). Viewing food pictures is associated with
407 activity in food reward-related brain regions (e.g. Anterior Cingulate Cortex (ACC), Orbito-

Frontal Cortex (OFC), insula, amygdala and nucleus accumbens) that underpin appetitive motivation (Neseliler et al. 2017). Hence, the fMRI picture paradigm can provide information on whether a drug is acting to reduce the reward value of foods. However, merely observing a reduction in activation in these regions does not provide information on the origin of the response. It is known that neural systems of food reward are closely connected with regions of the brain that process and integrate signals from the periphery about nutrient status e.g. the hypothalamus. Therefore, reductions in food reward could result from a primary effect on brain reward circuits or from an indirect effect on homeostatic systems. Indeed, activity in brain reward circuitry is enhanced by hunger and attenuated by satiety (e.g. Cornier et al., 2009; Goldstone et al., 2009; Smeets et al., 2012;. Thomas et al., 2015) and influenced by gut hormones (Farr et al., 2016; Zanchi et al., 2017). In addition, reward processing is influenced by higher order goals such as health concerns and so reductions in food reward could also stem from an effect of a drug or therapy on cognitive processes in areas of the brain, such as the dorsolateral prefrontal cortex, that are implicated in cognitive control (Higgs and Spetter 2018; Higgs et al. 2017). This means that the interpretation of fMRI data will depend upon the overall pattern of activity observed and additional insight may be gained from analysis of the connectivity between reward related regions and other areas of the brain involved in nutrient detection and/or cognitive processes.

fMRI may also be used to index potential psychiatric side effects. Just before Rimonabant was withdrawn from the market due to adverse effects on mood, it was found to decrease activation in the OFC and ventral striatum in response to rewarding chocolate stimuli but *increase* activation in the lateral OFC in response to aversive mouldy strawberry stimuli (Horder et al., 2010). This pattern of activity suggests a blunting of reward but also a bias towards negative

aversive stimuli, which may reflect the anhedonia and depression-like effects induced by the drug which led to its withdrawal from the market (Horder et al., 2009, 2012; see also Kumar et al., 2013 for a review of neuroimaging biomarkers in anhedonia and depression).

5.3 Cognitive measures

Manipulations that disrupt the amount of attention paid to food such as watching TV while eating increase the amount of food consumed during a meal (Bellisle et al., 2004) and at a later eating opportunity (e.g., Higgs & Woodward, 2009). Both obesity and BED have been associated with a reduced ability to inhibit appetitive responses to food (e.g., Nederkoorn et al., 2006). In addition, ADHD, which is characterised by impaired attention and inhibitory control, is associated with increased rates of disordered eating including binge eating (Kaisari et al., 2017). LDX is effective in the treatment of ADHD and its efficacy in treating BED may stem in part from its ability to improve attention and inhibitory control, which suggests that other drugs with similar effects on cognitive function may help control of food intake and reduce binge eating (Schneider et al., 2021). Therefore, we include in our model computer-based tests of cognition including attention and inhibitory control.

5.4 Mood and emotional responding

The ETB (see above and www.p1vital.com) comprises a number of validated cognitive tests that can be used to assess emotional processing (e.g., Murphy et al., 2008; Thomas et al., 2016). The ETB has been validated in studies with clinical and at-risk populations, including individuals at risk of depression (Chan et al., 2007; Mannie et al., 2007; Le Masurier et al., 2007), bipolar disorder (Harmer et al., 2002; Rock et al., 2010) and panic disorder (Reinecke et al., 2013). The

tests assess biases in emotional responding and emotional memory. For example, the Emotional Categorization Task (ECAT) displays positive and negative self-referent personality descriptors (e.g. “cheerful” versus “hostile”, respectively). Participants are asked to indicate whether they would like or dislike to be referred to as such. Participants with depression take longer to respond to positive self-referent personality adjectives than healthy controls (Ruhe et al., 2019). In the Emotional Recall Task (EREC) participants are asked to recall as many words as they can remember from the ECAT. Participants with depression are worse at recalling positive self-referent personality adjectives compared with healthy controls (Ruhe et al., 2019). Similarly, rimonabant which induces anhedonia and depressed mood after chronic treatment reduced recall of positive self-referent adjectives after a single dose (Horder et al., 2009) in the absence of changes in subjective mood measures.

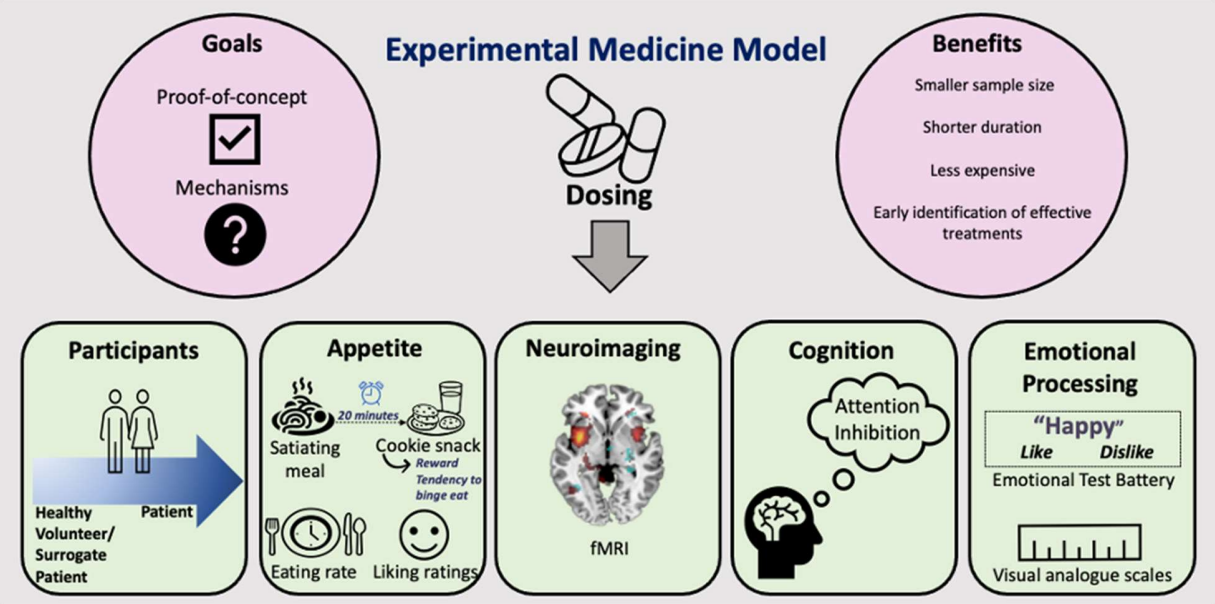

Figure 1. Multimodal experimental medicine model for the assessment of potential new treatments for obesity and BED.

6. Validation of the model

We have conducted a series of studies to validate our model. This comprised testing the effects of a drug with a pharmacological mechanism of action shown to be clinically effective in inducing weight loss (5-HT_{2C} receptor agonist). In addition, we have examined the effects of a hormone with a different mechanism of action that has been found to reduce food intake and body weight but has yet to be tested in clinical trials for obesity (intranasal insulin). Finally, we have tested the effects of LDX to allow us to establish a standard against which it will be possible to compare potential future drug treatments for BED. The model has been augmented across these studies but consists of the same basic elements in all studies facilitating cross-study comparison.

6.1 Effects of a 5-HT_{2C} receptor agonist

5-HT_{2C} receptors were first identified over 25 years ago as a target for appetite suppressant drugs (Dourish, 1995), and in 2012 the selective 5-HT_{2C} receptor agonist lorcaserin (Belviq) was approved by the FDA to treat obesity (although it has since been withdrawn due to increased occurrence of cancer in post-marketing safety trials (FDA, 2020). We chose to examine the effects of another 5-HT_{2C} receptor agonist, meta-chlorophenylpiperazine (mCPP), in our model. In the first study, healthy lean men and women were randomly assigned to receive an acute dose of placebo, 15mg mCPP, or 30mg mCPP (Thomas, Dourish, Tomlinson, Hassan-Smith, & Higgs, 2014). Participants consumed a pasta meal *ad libitum* from a UEM. Emotional processing was assessed using the ETB and physical state, mood and appetite were assessed via standardised questionnaires. mCPP had no effect on amount of pasta consumed but decreased self-reported appetite in men and women and increased satiety, indicated by enhanced within-

meal satiation quotients, in women. Participants self-reported greater physical effects of the drug than placebo (faint, lightheaded, nausea), but there were no effects of mCPP on negative affect and reports of the physical effects did not correlate with effects on food intake.

In a second study, in addition to the pasta meal, participants were offered chocolate chip cookies to eat after a short delay to enable assessment of eating in the absence of hunger (Thomas et al., 2018). We also included an fMRI scan to assess neural activity in response to viewing food pictures. Lean women were administered 30 mg mCPP and placebo in a randomised, placebo-controlled, crossover design. As we observed in our first study, mCPP had no effect on pasta intake but we observed a reduction in cookie intake relative to placebo. mCPP also reduced eating rate of both pasta and cookies. Across the test day, mCPP reduced self-reported hunger and desire to eat but had no effects on emotional processing. Participants in the mCPP condition reported increased ratings of physical effects (faint, lightheaded, nausea) but these ratings did not correlate with intake. While viewing high-calorie food images, mCPP attenuated activity in reward-related brain areas including the insula, caudate, ACC and dorsolateral prefrontal cortex (dlPFC) and increased activity in the ventromedial prefrontal cortex (vmPFC). A similar pattern of results was observed when viewing low calorie pictures.

Post-hoc analysis of the data revealed that, while on average most participants ate fewer cookies after mCPP, some participants had no change in intake or even ate more cookies after mCPP. We therefore compared responders and non-responders on measures of interest to investigate the potential factors that might contribute to participant response. Non-response to mCPP was associated with enhanced rated cookie pleasantness and enhanced baseline BOLD

responses to food in key reward areas suggesting that heightened reward response might be responsible for blunting the hypophagic effect of mCPP.

In summary, across two studies, we found that mCPP reduces appetite and eating rate as well as intake of a cookie snack eaten after a pasta meal but had no effect on consumption of the pasta meal. These data suggest that 5-HT_{2C} receptor agonists act to enhance satiety signals (as reflected in the reduction in eating rate for pasta) which then reduces the reward value of palatable food eaten when full (as reflected in the reduction in rated pleasantness and intake of cookies, and reduced reward-related neural activity). Novel agents with this profile may be effective for treating obesity because reductions in reward-related responding that are specific to the satiated state are likely to be effective in helping individuals to curb their appetite but are unlikely to reduce hedonic responding in general or depress mood. However, further investigation is required to assess whether individuals with high reward responsiveness who may be less responsive to such agents would therefore benefit more from treatment with compounds with a different mechanism of action.

6.2 Insulin

Intranasal (IN) insulin has been reported to reduce food intake and body weight in lean men and men with obesity in short term studies but long term effectiveness for weight management has yet to be evaluated. In humans, IN insulin is a safe, effective, and rapid means of exogenous insulin delivery to the brain (Leary et al., 2005; Schmid et al., 2018). Reductions in food intake brought about by IN insulin may be mediated by enhanced postprandial signals that reduce food reward when satiated because effects are observed after a satiating lunch, but not in the fasted state (Hallschmid et al., 2012). This suggestion is supported by findings from fMRI studies that

IN insulin reduces activation in the hypothalamus, a key centre of homeostatic control (Timper & Brüning, 2017) that modulates the dopaminergic reward system (Tyree & de Lecea, 2017). However, there is some evidence that individuals with obesity may be less sensitive to the neural effects of IN insulin (Kullmann et al., 2015) and the effects of IN insulin on food intake in women with obesity are unknown. Therefore, we evaluated the effects of IN insulin in our model to examine its potential efficacy as a weight management tool in women (Schneider et al., 2022, under review). In line with the paradigm reported by Hallschmid et al. (2012), and because the effects of IN insulin on intake in women were only observed in a postprandial and not in a fasted state, we administered 160 IU to lean women and women with obesity in a satiated state. IN insulin reduced cookie intake and self-reported liking of the cookie snack at the beginning of the meal (but not the end of the meal) and these effects were stronger for women with obesity. IN insulin also reduced self-reported ratings of appetite and increased self-reported ratings of positive affect in women with obesity. IN insulin had no effect on cognition or emotional biases assessed by the ETB. In response to viewing pictures of food, IN insulin increased activity in the insula in both lean women and women with obesity. The insula is hypothesised to integrate interoceptive and exteroceptive appetite and food reward signals (Simmons et al., 2013). Since the participants were in a post-prandial state when insulin was administered and cookies were offered, the pattern of results we observed might reflect enhanced post-prandial signals that nutrients have been consumed, which in turn decreases the attractiveness of food and reduces intake. Given the co-morbidity of obesity, diabetes and mood disorders, the effect of IN insulin to decrease appetite and food intake in women with obesity at the same time as enhancing mood in our model is promising in terms of its potential therapeutic use.

559 6.3 Lisdexamfetamine dimesylate (LDX)

560 As the only drug currently approved for the treatment of BED, LDX represents the standard
561 against which to compare potential new drug therapies. Therefore, we assessed the effects of an
562 acute dose of 50mg LDX and placebo in women with binge-eating symptoms (an intermediate
563 phenotype for BED) in our model using a randomised, placebo-controlled, crossover design
564 (Schneider et al., 2022). Given the potential importance of cognitive control for the action of
565 compounds to treat BED we added tasks measuring inhibitory control and attention, which are
566 key components of cognitive control. We found that LDX reduced both pasta and cookie intake
567 and eating rate for pasta only. LDX had no effect on liking ratings for cookies but decreased
568 pasta liking ratings at the end of the meal. LDX decreased self-reported appetite and increased
569 ratings of arousal and physical effects. LDX had no effect on emotional processing but enhanced
570 inhibitory control and sustained attention. LDX also attenuated activity in the thalamus, which is
571 an area of the brain involved in processing of incentive sensory information (Matsumoto et al.,
572 2001) including driving attention to motivationally salient external cues. This pattern of results
573 suggests that LDX may generate its therapeutic effects via several mechanisms. First, the
574 reduction in eating rate of pasta and reduced rated palatability at the end of the meal in the
575 absence of an effect on initial palatability ratings is indicative of enhanced satiety, which is
576 consistent with an action of LDX to increase serotonin transmission (Rowley et al., 2014).
577 Second, the finding that LDX reduced cookie intake suggests that the drug also reduces
578 motivation to eat when satiated possibly via a state-dependent reduction in the reward value of
579 food. Third, the fMRI results suggest that LDX may reduce food intake due to a shift in the
580 relative influence of exteroceptive versus interoceptive signals in response to food cues.
581

582 6.4 Summary of model validation

583 The results from studies conducted to date using our experimental medicine model suggest that it
584 is sensitive to the effects of agents with behavioural, neurophysiological and
585 neuropharmacological mechanisms of action known to be associated with weight loss (mCPP,
586 intranasal insulin) and reductions in binge eating (LDX). A strength of our model is that it also
587 provides insight into the changes in behaviour and associated neural effects that likely underlie
588 the therapeutic effects of LDX in BED and 5-HT_{2C} receptor agonists in obesity and the potential
589 therapeutic effects of IN insulin in obesity. The overall profile of effects observed differed
590 according to the compound tested suggesting that the model is able to discriminate between
591 treatments that reduce food intake but have different mechanisms of action (see Figure 2). All
592 compounds tested decreased intake of a palatable snack eaten in the absence of hunger but mCPP
593 reduced eating rate whereas IN insulin and LDX had no effect on eating rate of cookies. mCPP
594 and intranasal insulin reduced rated palatability of cookies but LDX had no effect on liking for
595 cookies. mCPP reduced eating rate for pasta but did not affect intake of a pasta meal whereas
596 LDX reduced both eating rate and intake of pasta (the effect of IN insulin on pasta intake was not
597 evaluated). These effects were associated with different patterns of neural activity when viewing
598 food pictures, with mCPP reducing activity in key reward related areas, IN insulin increasing
599 activity in insula and LDX reducing activity in thalamus. None of the compounds tested induced
600 adverse effects on emotional processing and IN insulin was actually associated with increased
601 positive mood in women with obesity. LDX had additional effects to improve cognitive control
602 in women with binge eating symptoms. Taken together these data suggest that future obesity
603 treatments might be more effective if they specifically enhance the actions of post-prandial
604 signals on food reward processes to decrease eating rate and liking for palatable foods in the

satiated state and that future treatments for BED should incorporate similar effects alongside enhancement of cognitive control.

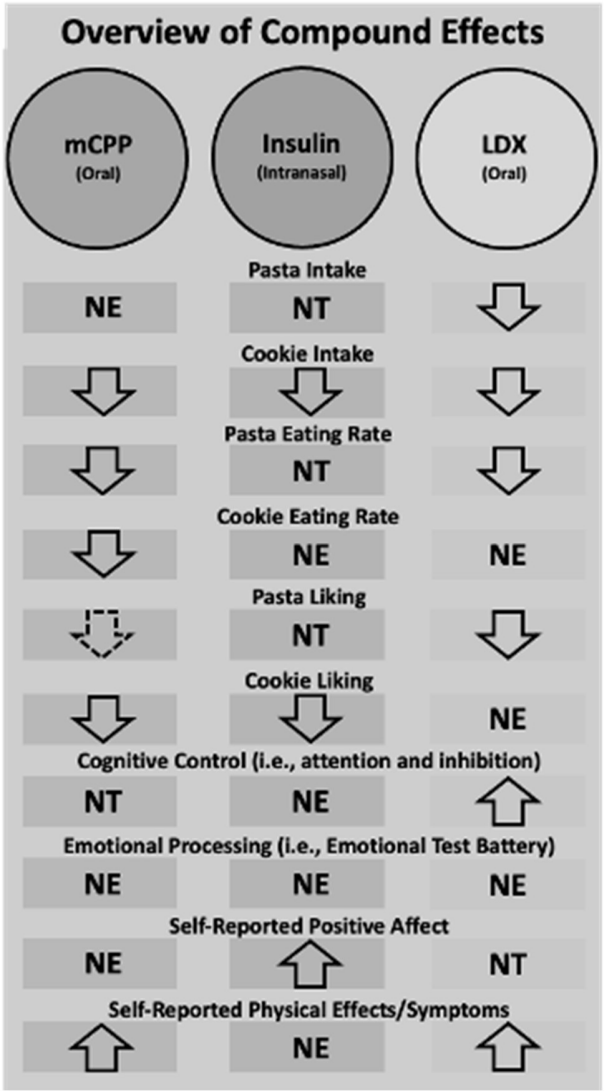

Figure 2. Overview of effects of compounds tested in the obesity and BED experimental medicine model. Down arrow = decrease (dotted line indicates a marginal effect that only approached significance). Up arrow = increase. NE = No Effect. NT = Not tested.

7. Conclusions

There continues to be a need for novel drug therapies to help people living with obesity and BED. The drug development processes is both lengthy and expensive and drugs may fail to make it to market due to lack of efficacy in late phase clinical trials in patients but also because of their tolerability and/or adverse side effects. The chances of success of new treatments for obesity and BED may be increased if co-morbidities such as depression and cognitive control are also addressed. There is potential for experimental medicine models, such as the model we have developed and validated that is presented here, incorporating both behavioural and neuroimaging measures, to aid in the development of future compounds. Our model has been shown to identify drugs that reduce appetite and food intake without adverse effects on mood/emotional processing and that have desirable effects on cognition e.g. reduced impulsivity/increased attention. However, the number of compounds tested to date has been limited. Future studies using the model will be valuable to evaluate the potential efficacy and side-effects of other marketed compounds and new candidate drugs at an early stage in the development pipeline for both obesity and BED.

Author Contributions

Authors ES, CD, and SH were responsible for designing, drafting, and editing the final version of this work.

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data; in the writing of the report; and in the decision to submit the paper for publication. Colin T Dourish is a Director and Co-Owner of P1vital Limited and a Director and Co-Owner of P1vital Products Limited.

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