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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 bingeeating disorder

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

Obesity and Binge Eating Disorder (BED) are prevalent conditions that are associated with 14 increased risk of morbidity and mortality. There is evidence that the use of pharmacotherapy 15 16 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 17 limited by poor efficacy and/or side effects and only one drug has been approved for the 18 19 treatment of BED. There is considerable potential to use experimental medicine models to 20 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 21 22 laboratory that incorporates both behavioural and neuroimaging measures which can be used to 23 facilitate drug development for obesity and BED. The results from validation studies conducted 24 to date using our model suggest that it is sensitive to the effects of agents with behavioural, 25 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 26 27 to evaluate the potential efficacy and side-effects of new candidate drugs at an early stage in the 28 development pipeline for both obesity and BED.

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30

31 PROVIDE MIN SIX KEYWORDS

32 Keywords: Obesity, Binge-eating disorder, Eating disorder, Pharmacotherapy, Medication, Drug,

33 Experimental medicine, Translational medicine, Behaviour, fMRI, Neuroimaging

34 1. Introduction

Obesity is characterised by a body mass index (BMI) equal to or exceeding 30 kg/m^2 and is 35 associated with increased prevalence of hypertension, type 2 diabetes, heart disease, cancer and 36 37 stroke and diminished quality of life (Agha & Agha, 2017). Individuals with obesity have 38 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., 39 40 2017). Obesity is often co-morbid with binge-eating disorder (BED) (Cossrow et al., 2016). BED 41 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 42 43 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 44 45 Association, 2013). BED is the most common eating disorder and diagnoses for women 46 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 47 48 (36.2%) and the disorder is associated with diabetes, hypertension, and chronic pain including 49 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) 50 51 (Kaisari, Dourish, & Higgs, 2017; Kessler et al., 2013). 52 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., 53 2017; Wilfley et al., 2018; Wilson et al., 2010), but high incidences of non-responders and 54 55 weight regain suggest some individuals may benefit from drug therapy (Foster, 2006; Linardon, 56 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 thepatient.

There are few approved drug therapies for obesity, and these are limited by poor efficacy 59 60 and/or side effects (Tak & Lee, 2021) and only one drug has been approved for the treatment of 61 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 62 63 pipeline but the process of clinical development is expensive and slow. In Phase 1 clinical trials, 64 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 65 66 move to the next phase. In Phase 2 clinical trials, compound efficacy and side-effects are 67 assessed in up to several hundred participants with the target disorder over a period of up to two 68 years. Approximately 33% of compounds move to the next phase. In Phase 3 clinical trials, 69 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 70 71 move to the next phase of assessment for regulatory approval (FDA, 2018). Although not yet 72 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 73 74 compound should proceed to large scale Phase 2 and Phase 3 clinical trials as well as providing 75 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 76 77 BED. Second, and more specifically, we explore the utility of an experimental medicine 78 approach in drug development and present a model developed and validated in our laboratory 79 that can be used to facilitate drug development for obesity and BED.

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81

2.1. Marketed drugs for obesity 82 83 Currently, there are five medications approved by the United States Food and Drug Administration (FDA) for long-term weight loss: orlistat (Xenical[®], Alli[®]), 84 phentermine/topiramate (Qsymia[®]), bupropion/naltrexone (Contrave[®]), liraglutide (Saxenda[®]), 85 and semaglutide (Wegovy[®]). A sixth drug, setmelanotide (ImcivreeTM), is approved only for 86 87 patients diagnosed with one of three rare genetic disorders: proopiomelanocortin, proprotein convertase subtilisn/kexin type 1 or leptin receptor deficiency. The European Medicines Agency 88 89 (EMA) has currently approved only three drug therapies for obesity (orlistat, bupropion/naltrexone (Mysimba[®]) and liraglutide) but has recently recommended the granting of 90 91 a marketing authorisation for semaglutide. This recommendation is also applicable in the UK 92 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 93 94 the action of gastrointestinal and pancreatic lipases, which reduces the absorption of fatty acids. 95 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 96 97 is an appetite suppressant and effective weight loss agent but the mechanisms underlying its 98 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). 99 100 Bupropion/naltrexone is a combination of the µ-opioid receptor antagonist naltrexone and the 101 dopamine and noradrenaline reuptake inhibitor bupropion (Sherman et al., 2016).

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

Bupropion/naltrexone is an effective weight loss agent but side effects include nausea, headache 102

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.

110

111 2.2. Drug development pipeline for obesity

112 There is a broad range of potential new mechanisms and drugs in the pipeline to treat obesity 113 and we provide a brief overview of these below (see Table 1). Tesomet is a combination of the 114 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/). 115 116 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-117 118 ongoing-review-tesofensine-mexico). Dual acting GLP-1/ Gastric Inhibitory Polypeptide [also known as Glucose-dependent Insulinotropic Polypeptide] (GIP) receptor agonists are being 119 120 developed for obesity. GIP is a peptide hormone released by K-cells of the small intestine in 121 response to food that increases insulin release and enhances the effects of GLP-1 (Bergmann et 122 al., 2019). For example, tirzepatide is a long-acting GIP/GLP-1 receptor agonist that is in Phase 123 3 clinical trials (https://www.lilly.com/discovery/clinical-development-pipeline). There is also 124 interest in analogues of amylin (a peptide co-secreted with insulin that has satiety-enhancing 125 effects) such as cagrilintide and combinations of amylin analogues with other weight loss agents

e.g. cagrilintide and semaglutide (Sonne et al., 2021;

127 <u>https://clinicaltrials.gov/ct2/show/NCT04940078</u>). Similarly, peptide tyrosine tyrosine (PYY)

fragments are being developed for the treatment of obesity. (PYY) 3-36 is a preferential Y2

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

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)
- administration of PYY does not induce nausea (<u>https://www.gilatherapeutics.com/technology/</u>)

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

results, NPY5 receptor antagonists such as S-237648 are being developed as potential therapies

- 139 for obesity (<u>https://www.shionogi.com/global/en/innovation/pipeline.html</u>).
- 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

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
- 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 binge-eating episodes and BED-related symptoms and subsequent studies have confirmed the 151 efficacy of LDX in the treatment of BED (for review see Schneider, Higgs, & Dourish, 2021). 152 153 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 $\sim 24\%$ - 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

In contrast to obesity, there are few potential new mechanisms and drugs in the pipeline for 164 treating BED. Several other stimulant drugs marketed and/or developed for the treatment of 165 166 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 therapy (Quilty et al., 2019). Dasotraline was in development for both ADHD and BED and 168 169 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 discontinued as further clinical studies would be needed to support regulatory approval for both 171

- 172 indications (https://news.sunovion.com/press-releases/press-releases-details/2020/Sunovion-
- 173 <u>Discontinues-Dasotraline-Program/default.aspx</u>). The hypothalamic neuropeptide orexin
- increases eating which is thought to be mediated by OX₁ receptors (Tsujino & Sakurai, 2013)
- and the OX_1 receptor antagonist ACT 539313 is in Phase 2 clinical development for the
- 176 treatment of BED (<u>https://www.idorsia.com/about-idorsia/idorsia-today/our-pipeline</u>). Drugs
- 177 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
- 180 causes weight loss would be contraindicated for these patients. See Table 1 for a summary of
- 181 approved drugs and drugs in the pipeline for treatment of obesity and BED.
- 182
- 183 Table 1. An overview of currently approved drugs and drugs in development for treatment of
- 184 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	
β1 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

The journey from identifying a new drug candidate to its launch as a marketed treatment is long 187 188 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, largely due to lack of efficacy in late stage clinical trials or failure during the regulatory approval 193 194 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;

202 Dourish et al., 2008; Müller et al., 2021; Schneider et al., 2021; U.S Food and Drug 203 Administration, 2020; Williams, 2010). Other drug candidates that have passed initial safety and 204 drug metabolism and pharmacokinetic testing in Phase 1 clinical trials have then failed to show 205 consistent effects in later (Phase 2 and 3) stages of clinical development (Levitan et al., 2021; 206 Müller et al., 2021). It has been proposed that the introduction of translational experimental 207 medicine models at the interface between Phase 1 and Phase 2 clinical trials provides a useful 208 step to de-risk development of novel treatments for psychiatric and eating disorders and to 209 accelerate the drug development process (Dawson et al., 2011; Dourish & Dawson, 2014). 210 Experimental medicine studies are designed to assess potential drug efficacy, mechanisms and 211 safety in small groups of healthy participants before expensive large-scale Phase 2 and Phase 3 212 trials in patients are undertaken. The rationale for these early studies is to triage a large number 213 of drug candidates to focus on those with the highest probability of success (POS) in late-stage 214 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, 215 216 2014).

217

218 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 mechanistic processes that underlie the disorder of interest. For example, a biomarker that has 227 228 been used in experimental medicine models for depression is the negative bias in processing of emotional information that is seen in many people with depression and is thought to be a core 229 feature of the disorder (Disner et al., 2011). Early amelioration of this emotional processing bias 230 231 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 may also include participants who present with subclinical symptoms (termed intermediate 238 239 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 personality questionnaire (termed high schizotypes) have been recruited as an intermediate 241 242 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 Research Domain Criteria Initiative (RDoC), which encourages research on dimensions of 244 245 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 phenotypes from the general population is easier than recruitment of patient groups and 247

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.

251

252 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 253 254 model, then it may be possible to identify the markers that best predict clinical outcomes. For 255 example, in the case of medications for depression, of several biomarkers tested, drug effects on 256 negative emotional bias appear to be most predictive of clinical effectiveness in patients (Harmer 257 et al., 2011). Such insight not only improves understanding of the disorder itself (suggesting that 258 biased emotional processing may be a causal factor in depression) but also provides important 259 information to guide the development of new treatments that can be targeted specifically at 260 predictive biomarkers.

261

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.

268

269 Experimental medicine models have not yet been used widely in the development of drugs for270 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.

276

277 The majority of drugs that have been approved for obesity are thought to act via a reduction in 278 food intake (Williams et al., 2020). A small number of experimental medicine studies to date 279 suggest that acute reductions in food intake are predictive of weight loss after longer term 280 treatment. For example, the serotonin and noradrenaline re-uptake inhibitor sibutramine has been 281 reported to reduce food intake after acute dosing and this effect is associated with long term 282 weight loss (e.g., Barkeling et al., 2003; Fletcher et al., 2010; Halford et al., 2010). This suggests 283 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 284 285 than others. For example, a drug that enhances satiety may be preferable to a drug that has a 286 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 287 288 cannabinoid antagonist rimonabant and led to its withdrawal from the market. Therefore, the 289 inclusion of biomarkers aimed at indexing the processes that lead to reduced intake would be informative. 290

291

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

294 sibutramine on fMRI BOLD responses to pictures of food. Sibutramine attenuated activity in the 295 hypothalamus and this effect was correlated with both ad-libitum food intake and subsequent 296 weight-loss. These data suggest that reduced hypothalamic activity is a potential biomarker of 297 future weight-loss although it should be noted that the hypothalamus is difficult to image and is 298 susceptible to artefacts due to its proximity to the sinuses (Ojemann et al., 1997). Acute 299 treatment with the GLP-1 receptor agonist exenatide decreased the BOLD fMRI response in 300 reward-related brain areas including the insula, amygdala, putamen and orbitofrontal cortex in 301 patients with obesity and the suppression of insula reactivity to food cues predicted a reduction 302 in food intake (van Bloemendaal et al., 2014). Longer term (17 days) administration of the GLP-303 1 receptor agonist liraglutide to patients with diabetes increased levels of Gastric inhibitory 304 peptide (GIP) which was inversely correlated with activation of the insula to food cues (Farr et 305 al. 2016b). These data suggest that reduced activation to food cues in the insula may be a 306 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 307 308 of novel compounds to treat obesity.

309

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 of effect on binge eating scores, the development of GSK1521498 for BED was halted. 322 323 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 combined effects on satiety, food reward, and cognitive control (Schneider et al., 2021). 332

Drugs for obesity and BED must have an acceptable safety profile and for some drugs that have effects on food intake due to action at receptors in the brain, neuropsychiatric adverse effects (e.g. depression, suicidality as observed with rimonabant) and abuse liability (as observed with stimulants) are side effects of concern. The requirements and endpoints for ensuring psychiatric safety of drugs for weight management are less well defined by the regulatory authorities than those for weight-loss. The use of cognitive test batteries such as the P1vital[®] Oxford Emotional 339 Test Battery (ETB), that measure emotional processing offer an approach to the assessment of 340 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 341 342 used in short term studies over days and has been found to have good test-re-test reliability 343 (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 344 345 questionnaire measures of mood, emotion, and psychiatric functioning (Horder et al., 2009). 346 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. 347 348 In summary, there is great potential to exploit experimental medicine models to advance 349 development of drug for obesity and BED. In the following section we describe the development 350 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 351 352 diagram of the model). To our knowledge, our model is the most comprehensive to date and 353 improves on previous experimental medicine approaches because we include detailed assessment 354 of eating behaviour and fMRI biomarkers as well as the behavioural assessment of cognitive 355 processes (attention, impulsivity and memory), emotion and mood, which has not been done previously. 356

357

358 5. An experimental medicine model for investigation of new drug treatments for obesity and359 BED

360

361 5.1 Eating measures

362 Our model involves assessing the effects of drug administration on consumption of both a staple 363 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 364 365 and the tendency towards binge eating in participants with binge eating symptoms. Eating snacks 366 in the absence of hunger has been found to be associated with loss of control over eating and 367 weight gain in women (Feig et al., 2018). Assessing intake of a main meal and snacks also 368 enables insight into the mechanisms underlying any changes in intake because we can 369 distinguish between drug treatments that have a selective effect on cookie intake from drugs that 370 decrease intake of both pasta and cookies. The former effect may be indicative of a reduction in 371 the palatability of rewarding foods, whereas the latter effect may indicate enhancement of the 372 satiating effects of the main meal with a consequent effect on food reward when full. 373 Insight into the specific processes underlying changes in food intake can also be gained from the 374 assessment of within-meal measures, including eating rate and rated palatability using a 375 universal eating monitor (UEM) (Kissileff, Kilngsberg, & van Italie, 1980; Yeomans, 1996). 376 The UEM, which was first devised by Kissileff and colleagues (1980) enables constant 377 monitoring of food consumed during a meal. The participant's plate is placed upon a weighing 378 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 379 380 balance has no effect on food intake, Thomas et al., 2015) and providing a surface on which to 381 place a plate of food. The balance is connected to a computer and the progressive reductions in 382 the weight of the plate as food is eaten are recorded. This method was adapted by Yeomans 383 (1996) who configured it to allow visual analogue scale (VAS) ratings to be completed after a 384 specified amount of food has been consumed (the Sussex Ingestion pattern Monitor or SIPM). In the SIPM, participants are presented with a dish of 200g pasta. After each 50g of food consumed, the computer interrupts the participant to prompt completion of ratings of appetite and liking of the food. After 150g of the pasta has been consumed, there is another prompt, this time the participant is asked to pause eating while the dish is replaced with another 200g serving. The participant may continue to eat in this fashion for as long as they wish. Manipulations that enhance satiety have been found to reduce eating rate in the SIPM whereas manipulations which reduce food reward tend to decrease the initial rated palatability of a meal (Yeomans 1996).

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

400

401 5.2 fMRI measures

To provide insight into the neural mechanisms that may underlie the effect of drug treatment on appetite and body weight we include in our model assessment of the fMRI BOLD response when viewing pictures of foods (Chechlacz et al., 2009). The food picture paradigm has been used in studies that have contrasted the patterns of activation seen when viewing food versus non-food pictures (for review see García-García et al., 2013). Viewing food pictures is associated with activity in food reward-related brain regions (e.g. Anterior Cingulate Cortex (ACC), Orbito408 Frontal Cortex (OFC), insula, amygdala and nucleus accumbens) that underpin appetitive 409 motivation (Neseliler et al. 2017). Hence, the fMRI picture paradigm can provide information 410 on whether a drug is acting to reduce the reward value of foods. However, merely observing a 411 reduction in activation in these regions does not provide information on the origin of the 412 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 413 414 hypothalamus. Therefore, reductions in food reward could result from a primary effect on brain 415 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; 416 417 Goldstone et al., 2009; Smeets et al., 2012; Thomas et al., 2015) and influenced by gut 418 hormones (Farr et al., 2016; Zanchi et al., 2017). In addition, reward processing is influenced by 419 higher order goals such as health concerns and so reductions in food reward could also stem from 420 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; 421 422 Higgs et al. 2017). This means that the interpretation of fMRI data will depend upon the overall 423 pattern of activity observed and additional insight may be gained from analysis of the 424 connectivity between reward related regions and other areas of the brain involved in nutrient 425 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).

434

435 5.3 Cognitive measures

436 Manipulations that disrupt the amount of attention paid to food such as watching TV while 437 eating increase the amount of food consumed during a meal (Bellisle et al., 2004) and at a later 438 eating opportunity (e.g., Higgs & Woodward, 2009). Both obesity and BED have been associated 439 with a reduced ability to inhibit appetitive responses to food (e.g., Nederkoorn et al., 2006). In 440 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). 441 442 LDX is effective in the treatment of ADHD and its efficacy in treating BED may stem in part 443 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 444 (Schneider et al., 2021). Therefore, we include in our model computer-based tests of cognition 445 including attention and inhibitory control. 446

447

448 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 454 tests assess biases in emotional responding and emotional memory. For example, the Emotional 455 Categorization Task (ECAT) displays positive and negative self-referent personality descriptors (e.g. "cheerful" versus "hostile", respectively). Participants are asked to indicate whether they 456 457 would like or dislike to be referred to as such. Participants with depression take longer to 458 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 459 460 remember from the ECAT. Participants with depression are worse at recalling positive self-461 referent personality adjectives compared with healthy controls (Ruhe et al., 2019). Similarly, rimonabant which induces anhedonia and depressed mood after chronic treatment reduced recall 462 463 of positive self-referent adjectives after a single dose (Horder et al., 2009) in the absence of 464 changes in subjective mood measures.



465 Figure 1. Multimodal experimental medicine model for the assessment of potential new

treatments for obesity and BED.

467

468 6. Validation of the model

469 We have conducted a series of studies to validate our model. This comprised testing the effects 470 of a drug with a pharmacological mechanism of action shown to be clinically effective in 471 inducing weight loss (5-HT_{2C} receptor agonist). In addition, we have examined the effects of a 472 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 473 474 have tested the effects of LDX to allow us to establish a standard against which it will be 475 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 476 477 comparison.

478

479 6.1 Effects of a 5-HT_{2C} receptor agonist

480 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 481 482 approved by the FDA to treat obesity (although it has since been withdrawn due to increased 483 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. 484 485 In the first study, healthy lean men and women were randomly assigned to receive an acute dose 486 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 487 488 was assessed using the ETB and physical state, mood and appetite were assessed via 489 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-490

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

494

495 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 496 497 (Thomas et al., 2018). We also included an fMRI scan to assess neural activity in response to 498 viewing food pictures. Lean women were administered 30 mg mCPP and placebo in a 499 randomised, placebo-controlled, crossover design. As we observed in our first study, mCPP had 500 no effect on pasta intake but we observed a reduction in cookie intake relative to placebo. mCPP 501 also reduced eating rate of both pasta and cookies. Across the test day, mCPP reduced self-502 reported hunger and desire to eat but had no effects on emotional processing. Participants in the 503 mCPP condition reported increased ratings of physical effects (faint, lightheaded, nausea) but 504 these ratings did not correlate with intake. While viewing high-calorie food images, mCPP 505 attenuated activity in reward-related brain areas including the insula, caudate, ACC and 506 dorsolateral prefrontal cortex (dlPFC) and increased activity in the ventromedial prefrontal 507 cortex (vmPFC). A similar pattern of results was observed when viewing low calorie pictures. 508 Post-hoc analysis of the data revealed that, while on average most participants ate fewer 509 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 510 511 investigate the potential factors that might contribute to participant response. Non-response to 512 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 beresponsible for blunting the hypophagic effect of mCPP.

In summary, across two studies, we found that mCPP reduces appetite and eating rate as well 515 516 as intake of a cookie snack eaten after a pasta meal but had no effect on consumption of the pasta 517 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 518 519 palatable food eaten when full (as reflected in the reduction in rated pleasantness and intake of 520 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 521 522 the satiated state are likely to be effective in helping individuals to curb their appetite but are 523 unlikely to reduce hedonic responding in general or depress mood. However, further 524 investigation is required to assess whether individuals with high reward responsiveness who may 525 be less responsive to such agents would therefore benefit more from treatment with compounds with a different mechanism of action. 526

527

528 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 536 IN insulin reduces activation in the hypothalamus, a key centre of homeostatic control (Timper 537 & 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 538 539 effects of IN insulin (Kullmann et al., 2015) and the effects of IN insulin on food intake in 540 women with obesity are unknown. Therefore, we evaluated the effects of IN insulin in our model 541 to examine its potential efficacy as a weight management tool in women (Schneider et al., 2022, 542 under review). In line with the paradigm reported by Hallschmid et al. (2012), and because the 543 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 544 545 insulin reduced cookie intake and self-reported liking of the cookie snack at the beginning of the 546 meal (but not the end of the meal) and these effects were stronger for women with obesity. IN 547 insulin also reduced self-reported ratings of appetite and increased self-reported ratings of 548 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 549 550 insula in both lean women and women with obesity. The insula is hypothesised to integrate 551 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 552 553 offered, the pattern of results we observed might reflect enhanced post-prandial signals that 554 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 555 556 to decrease appetite and food intake in women with obesity at the same time as enhancing mood 557 in our model is promising in terms of its potential therapeutic use.

558

559 6.3 Lisdexamfetamine dimesylate (LDX)

As the only drug currently approved for the treatment of BED, LDX represents the standard 560 against which to compare potential new drug therapies. Therefore, we assessed the effects of an 561 562 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 (Schneider et al., 2022). Given the potential importance of cognitive control for the action of 564 565 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 and eating rate for pasta only. LDX had no effect on liking ratings for cookies but decreased 567 568 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., 2001) including driving attention to motivationally salient external cues. This pattern of results 572 573 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 motivation to eat when satiated possibly via a state-dependent reduction in the reward value of 578 579 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

is sensitive to the effects of agents with behavioural, neurophysiological and 584 585 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 provides insight into the changes in behaviour and associated neural effects that likely underlie 587 588 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 cookies. mCPP reduced eating rate for pasta but did not affect intake of a pasta meal whereas 595 596 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 food pictures, with mCPP reducing activity in key reward related areas, IN insulin increasing 598 599 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 positive mood in women with obesity. LDX had additional effects to improve cognitive control 601 602 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

The results from studies conducted to date using our experimental medicine model suggest that it

satiated state and that future treatments for BED should incorporate similar effects alongside

- 606 enhancement of cognitive control.
- 607



608

609 Figure 2. Overview of effects of compounds tested in the obesity and BED experimental

- 610 medicine model. Down arrow = decrease (dotted line indicates a marginal effect that only
- 611 approached significance). Up arrow = increase. NE = No Effect. NT = Not tested.
- 612
- 613

614 7. Conclusions

There continues to be a need for novel drug therapies to help people living with obesity and 615 BED. The drug development processes is both lengthy and expensive and drugs may fail to make 616 617 it to market due to lack of efficacy in late phase clinical trials in patients but also because of 618 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 619 620 also addressed. There is potential for experimental medicine models, such as the model we have 621 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 622 623 drugs that reduce appetite and food intake without adverse effects on mood/emotional processing 624 and that have desirable effects on cognition e.g. reduced impulsivity/increased attention. 625 However, the number of compounds tested to date has been limited. Future studies using the 626 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 627 628 obesity and BED.

629

630 Author Contributions

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

633

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