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Editorial

Multidisciplinary Approaches to the Study of Eating Disorders and Obesity: Recent Progress in Research and Development and Future Prospects

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Eating disorders and obesity have an increasingly substantial negative impact on both the health of individuals and on national health care budgets. The worldwide prevalence of obesity has more than doubled since 1980 and is now 5% in children and 12% in adults and the same global trends are apparent for Type 2 diabetes (Global Burden of Disease 2015 Obesity Collaborators, 2017). In addition to Type 2 diabetes, obesity is a risk factor for a number of other chronic diseases, which reduce quality of life and life expectancy of severely obese individuals, including cardiovascular disease, kidney disease, cancer and musculoskeletal disorders (Narayanaswami and Dvoskin 2017). Overweight and obesity can be defined as abnormal or excessive fat accumulation that may impair health. Body Mass Index (BMI) is the most commonly used measure to classify overweight and obesity in adults and is defined as weight in kilograms divided by height in metres². For adults, the World Health Organisation (WHO) defines overweight as a BMI ≥ 25 kg/m² and obesity as a BMI ≥ 30 kg/m². It is a particular concern that, over the past 40 years, the global rates of obesity in children and adolescents have soared and continue to do so in low- and middle-income

countries (NCD Risk Factor Collaboration, 2017). Professor Fiona Bull, Program Manager of Non-Communicable Disease Prevention at the WHO, recently stated: “Obesity is a global health crisis today, and threatens to worsen in coming years unless we start taking drastic action. Countries should aim particularly to reduce consumption of cheap, ultra-processed, calorie-dense, nutrient-poor foods.” A report from the World Obesity Federation in October 2017 estimated that the global cost of treating ill health caused by obesity will be more than \$1.2 trillion annually from 2025. The US faces the largest cost, with a rise from \$325 billion annually in 2014 to \$555 billion per year partly because of the high cost of medical care in the US. In the UK, the cost is set to rise from \$19 billion to \$31 billion annually in 2025.

Eating disorders are severe chronic mental health disorders associated with negative health outcomes and have the highest mortality among psychiatric disorders. There are three primary eating disorders recognised in DSM-5: Anorexia Nervosa, Bulimia Nervosa and Binge Eating Disorder. Anorexia Nervosa is marked by a distorted body image, excessive dieting that leads to severe weight loss and a pathological fear of becoming fat. Bulimia Nervosa is characterised by frequent episodes of binge eating followed by inappropriate behaviour such as self-induced vomiting, excessive use of laxatives or diuretics, or excessive exercise to avoid weight gain. Binge Eating Disorder was first recognised as a separate category of eating disorder in DSM-5 and is characterised by recurrent episodes of eating significantly more food in a short period of time than most individuals would eat under similar circumstances, with episodes marked by feelings of lack of control. In contrast to Bulimia Nervosa, self-induced vomiting and laxative misuse are not present or occur only occasionally in Binge Eating Disorder. The prevalence rate of eating disorders is estimated at 0.5–3%, depending on the specific diagnosis, but disordered eating symptomatology in the general population has been reported to be as high as 12% (Nagl et al., 2016).

Individuals suffering from eating disorders rarely seek professional help due to stigma and in the case of Anorexia Nervosa and Bulimia Nervosa fear of gaining weight, which can make treatment difficult. Therefore, identification of risk factors for disordered eating in general population samples may have a significant impact on public health and could help in both the prevention and treatment of eating disorders.

Until recently, obesity and eating disorders have generally been considered as separate conditions and research has been carried out in different theoretical frameworks. Obesity has been studied within endocrinology and nutrition whereas eating disorders have lain within the domain of psychiatry and psychology. However there is increasing evidence for a higher prevalence of eating disorders in obese individuals and an increased risk of obese individuals developing disordered eating behaviour. Similarly, there is evidence for an association between obesity and other psychiatric disorders such as depression, Attention

Deficit Hyperactivity Disorder (ADHD) and schizophrenia (Simmons et al 2016; Kaisari et al 2017; Reynolds and McGowan 2017). Integrated approaches to the study of obesity and eating disorders may enable both the identification and investigation of common and separate risk factors for these disorders and provide new opportunities for prevention and treatment interventions that could simultaneously target several conditions.

There is a considerable unmet need for effective and long lasting therapy for both obesity and eating disorders. Until recently, no drug had been approved to treat eating disorders and there had been a history of failure of drug therapy for obesity with a catalogue of drugs either being assessed by the US regulatory authorities as non-approvable (e.g. rimonabant) or being approved and subsequently withdrawn due to unacceptable side-effects (e.g. fenfluramine, sibutramine). However, the recent approval by the FDA of four drugs for treating obesity (Qsymia[®], Contrave[®], Belviq[®] and Saxenda[®]) and a drug specifically for treating Binge Eating Disorder (Vyvanse[®]) suggests a change in the regulatory landscape which holds promise for the future. Therefore, it is timely to review recent progress in research and development and highlight future prospects in this Special Issue on Eating Disorders and Obesity.

In this issue Clifton (2017) provides an overview of how physiological responses to food ingestion interact with the rewarding properties of food to modulate the neural circuitry and neurotransmitters that control eating behaviour. Our understanding of the brain mechanisms that control eating has developed from a hypothalamo-centric homeostatic model of excitatory and inhibitory centres for appetite and satiety to the realisation that the hypothalamus is only one part of a complex system that includes numerous other structures in the forebrain and brainstem. Thus, it is now hypothesised that eating behaviour and energy balance are influenced both by homeostatic and non-homeostatic reward-related and cognitive processes. Clifton (2017) also considers current drug therapies for obesity and provides a critical appraisal of targets for drug development. He concludes by reviewing the validity and translational utility of preclinical paradigms that are used to identify novel compounds for testing in clinical trials.

An example of a novel therapy for obesity that was discovered by rational drug design is the 5-HT_{2C} receptor agonist lorcaserin. Non-selective serotonergic therapies for obesity such as fenfluramine were associated with significant cardiovascular side-effects and the discovery from genetic and pharmacological studies that the satiating effects of the drug were mediated by 5-HT_{2C} receptors (which are present in the brain but not in the cardiovascular system) led to efforts to develop selective 5-HT_{2C} receptor agonists (Vickers et al 1999, 2001). In this issue Higgins and colleagues (2017) describe the weight reducing properties of

lorcaserin which overall are modest but show marked inter-individual variation. They suggest that the identification of high responders and understanding the nature of their response could have important implications for improved therapy by more precise patient selection. An intriguing possibility is that high responders to lorcaserin may be characterised by overeating driven by maladaptive impulsivity and reward mechanisms. Higgins and colleagues (2017) review an elegant series of preclinical studies showing that 5-HT_{2C} receptor agonists reduce both the incentive motivational properties of rewarding stimuli and impulsive action. Thus, they propose that 5-HT_{2C} receptor agonists may be valuable in treating disorders characterised by exaggerated goal-directed, or incentive-driven, behaviour such as Binge Eating Disorder. To date there have been no studies in humans with lorcaserin to examine inter-individual differences in neural response to rewarding stimuli. However, a recent study with another 5-HT_{2C} receptor agonist meta-chlorophenylpiperazine (mCPP) reported marked individual variability in both the behavioural and neural responses to mCPP in female volunteers (Thomas et al 2017). Some participants did not reduce their intake of a palatable snack after treatment with mCPP and this lack of response was associated with enhanced ratings of snack pleasantness and enhanced baseline Blood Oxygen Level Dependent functional Magnetic Resonance Imaging (BOLD fMRI) responses to food images in key reward and appetite circuitry (Thomas et al 2017). Thus, further investigation of stratification of response to 5-HT_{2C} receptor agonists is warranted to identify individuals who are most likely to benefit from treatment with lorcaserin.

As described by Clifton (2017) the brain dopamine system has long been associated with the control of eating, reward process and impulsivity. In this issue, Robertson and Rasmussen (2017) describe the use of a Diet Induced Obesity (DIO) model in which rats are given a high-fat, high-sugar cafeteria diet that causes weight gain, altered sensitivity to reward and alterations in D₂ dopamine receptor mechanisms. The DIO model was used in conjunction with a delay discounting task (which measures preference for smaller immediate versus larger delayed food rewards to assess impulsive choice) to characterise diet-induced behavioural alterations in reward processing. The antipsychotic dopamine D₂ receptor antagonist haloperidol unmasked diet-related differences by dose-dependently reducing choice for a larger, later reinforcer. Rats fed a cafeteria diet showed a leftward shift in the dose-response curve, suggesting increased sensitivity to haloperidol compared to rats fed a standard diet. Robertson and Rasmussen (2017) suggest that chronic exposure to a cafeteria diet increases impulsivity and that this may be mediated by D₂ dopamine receptor mechanisms. These findings are relevant for obesity and in particular for obesity and diabetes associated with schizophrenia and treatment with antipsychotic drugs which act as antagonists at D₂ dopamine receptors.

Reynolds and McGowan (2017) review the association between schizophrenia and obesity and describe how treatment with antipsychotics can cause weight gain by actions at both 5-HT_{2C} receptors and dopamine D₂ receptors in addition to histamine H₁ and muscarinic M₃ receptors. There is some evidence from first episode studies that schizophrenia may be a risk factor for obesity and diabetes in the absence of antipsychotic therapy but results to date are inconsistent. However, it is clear that some antipsychotics (e.g. clozapine, olanzapine) have a high propensity to cause high weight gain whereas others (e.g. aripiprazole, asenapine) have little or no effect on body weight. In addition to drug-induced differences, there are large individual differences in antipsychotic drug-induced weight gain. This variation in response is correlated with genetic variation in several neurotransmitter receptors, including the 5-HT_{2C} receptor, in addition to genes involved in obesity and metabolic disturbances. Inter-individual variation is a recurring theme in associations between 5-HT_{2C} receptor mechanisms (see Higgins et al 2017; Thomas et al 2017) and Dopamine D₂ receptor mechanisms (see Evers et al 2017) and obesity and Reynolds and McGowan (2017) conclude that predictive genetic testing for drug-induced weight gain would be an important step forward to improve antipsychotic therapy.

In this issue Evers and colleagues (2017) report the effects of the antipsychotic olanzapine in Roman High and Low Avoidance (RHA/RLA) rat strains. The RHA shares many behavioural and physiological characteristics with schizophrenia in humans, such as increased central dopaminergic sensitivity, whereas the RLA has been shown to be prone to diet-induced obesity and insulin resistance. Their results show that only RHA rats are susceptible to olanzapine-induced weight gain and it is suggested that this could be related to enhanced dopaminergic sensitivity through increased expression of Dopamine D₁ mRNA in the prefrontal cortex and of Dopamine D₂ mRNA in the nucleus accumbens of RHA rats. Thus, individual differences in dopamine receptor expression in the cortico-mesolimbic system may be responsible for susceptibility to olanzapine-induced weight gain.

In addition to their widespread use for the treatment of schizophrenia, antipsychotic drugs are increasingly used to treat bipolar disorder (Singh et al 2012) and patients with bipolar disorder have been reported to have a higher prevalence of obesity and metabolic syndrome (Toalson et al., 2004). In this issue Akgün and colleagues (2017) report evidence that another common therapy for bipolar disorder the anticonvulsant valproic acid may contribute to metabolic disturbances in bipolar patients such as decreased serum adiponectin and increased serum leptin levels.

As discussed above (see Clifton 2017), most models of appetite control have focussed on the role of homeostatic and hedonic mechanisms and interactions between the neural

substrates of the two systems. Higgs and colleagues (2017) review evidence that higher level cognitive functions such as learning, memory and attention also play an important role in the control of eating and similarly that homeostatic signals play a role in cognition. Higgs and colleagues (2017) provide evidence that metabolic signals from the gastrointestinal tract that are triggered by food consumption interact with neural homeostatic and reward processes to determine how much a food is wanted. This cascade can influence subsequent food consumption in both the short term through appetite and satiety processes and in the longer term by the development of food preferences. Further studies will be required to fully understand the process by which metabolic signals influence complex food-related decision processes making in humans and to provide a comprehensive model of the control of appetite that integrates cognitive mechanisms with homeostatic and reward mechanisms. However, there are immediate implications of this new approach for the treatment of psychiatric disorders such as schizophrenia which is associated with obesity and diabetes (see Reynolds and McGowan 2017). Thus, metabolic adaptations occurring as a result of weight gain could worsen cognitive impairment in schizophrenia (Bora et al., 2017). Similarly, subgroups of patients with depression (Simmons et al 2016) and ADHD (Kaisari et al 2017) can exhibit either overeating or restrictive eating and these symptoms can be exacerbated by drug therapy for their illness. Higgs and colleagues (2017) discuss the implications of their new model for understanding the factors that may contribute to such disordered patterns of eating and point to opportunities for developing more effective treatments for eating disorders and weight management such as combining cognitive therapy with drug therapy.

Brain imaging techniques, in particular fMRI, are increasingly used to study the neural substrates of appetite, satiety, disordered eating and obesity and to characterise the effects of drugs on eating (Porubska et al 2006; Führer et al 2008; Fletcher et al 2010; Thomas et al 2015). Thus, it has been shown that meal size and frequency are influenced by activity in brain circuits which process signals on nutritional state and food reward and that natural satiation attenuates activity in reward-related brain regions and increases activity in the dorsolateral prefrontal cortex, which may indicate higher cognitive control of satiation (Thomas et al 2015; Higgs et al 2017). In this issue Avery and colleagues (2017) and Stice and Shaw (2017) describe the use of brain imaging to study obesity and eating disorders (including Anorexia Nervosa, Bulimia Nervosa and Binge Eating Disorder) respectively.

Avery and colleagues (2017) highlight the important role that interoceptive neural pathways may play in the control of eating and body weight. It has been previously reported that the interoceptive insula is sensitive to markers of energy signalling (Page et al 2011; Simmons et al 2013) and that successful weight loss is associated with increased insula activity (Mata

et al 2016). Avery and colleagues (2017) now report that obese and lean individuals showed contrasting patterns of eating-related functional connectivity between the dorsal mid-insula and brain regions involved in reward and satiety. Thus, in lean individuals there was a significant positive relationship between changes in hunger and in medial orbitofrontal functional connectivity whereas in obese individuals a negative relationship between hunger and ventral striatum connectivity to the mid-insula was observed. This suggests that behavioural strategies to improve interoceptive sensitivity through increased attention and awareness of interoceptive signals could help to promote eating that is more appropriate to energy needs.

Stice and Shaw (2017) review results from prospective studies that identify risk factors which predict the onset and persistence versus remission of eating disorders and core symptom dimensions. Factors that predicted the onset of any eating disorder included perceived pressure to be thin, body dissatisfaction, dieting, negative mood, poor family social support, parental obesity and alcohol use. Brain imaging studies of Binge Eating Disorder suggest that patients may have enhanced reward region responsivity to food cues and blunted reward region responses to palatable food intake. Thus, interventions that reduce reward region responses to food cues and valuation of high-calorie foods, such as cognitive reappraisal and response inhibition training could be useful for the prevention and treatment of Binge Eating Disorder. There is also evidence for neural deficits in inhibitory control that may increase the risk of binge eating and purging in Bulimia Nervosa and that excessive inhibitory control can increase the risk for Anorexia Nervosa but the data are inconsistent. Most studies on biological risk and maintenance factors for eating disorders have been cross-sectional, which limits conclusions on etiology and maintenance processes. However, Stice and Shaw (2017) propose that the use of high-risk designs in future prospective studies offers a viable method for identifying biological risk factors for maintenance processes. It is suggested that the use of this approach could improve the outcome of prevention and treatment interventions for eating disorders.

The final two papers in this Special Issue consider therapies to reduce food intake and body weight. In the first of these Stice and colleagues (2017) describe the results of a study in which the effect of Gymnemic acids on consumption of chocolates was examined. Gymnemic acids decrease the sensation of sweetness from sugar and sugar substitutes by inhibiting sweet taste receptors on the tongue (Sanematsu et al 2014). Thus, Gymnemic acids decrease the consumption of sugary foods because they reduce the pleasantness of a sweet taste. In this issue Stice and colleagues (2017) report that Gymnemic acids reduced the desire to eat chocolates, measured by pleasantness ratings, prior to tasting the chocolates. These results suggest that Gymnemic acids may provide an effective method to

reduce the consumption of sweet foods such as chocolates which has been suggested to predict future excessive weight gain.

In the final paper of this issue, Wilding (2017) reviews pharmacotherapy for obesity and in particular recent developments in the use of combination drug therapy. Combination drug therapy for obesity has a chequered history with a notable example being the combination of fenfluramine and phentermine (known as fen-phen) in the 1990's. The rationale for this combination and for most subsequent drug combinations for obesity was that the modest weight loss achieved by either drug alone could be improved by the combination while minimising side-effects. Unfortunately, this hypothesis proved ill-founded in the case of fen-phen as valvular heart disease was identified in a large number of patients that had taken the drug combination (Connolly et al 1997) a finding which eventually led to the withdrawal of fenfluramine from the US market by the FDA. Nevertheless, more recently approved drug combinations for obesity have been more successful and better tolerated. The two drug combination therapies that are currently approved by the FDA are Qsymia[®] (phentermine/topiramate) and Contrave[®] (naltrexone/bupropion) and a number of other combinations including compounds that act on neuropeptide receptors are in clinical development. Wilding (2017) concludes that the aim of reducing body weight to a similar extent to that seen with bariatric surgery remains elusive, but that it may be achievable in the future if the development of neuropeptide analogues that can reach multiple gastrointestinal and neural targets is successful.

The contributions to this issue illustrate that the investigation of eating disorders and obesity is a fast moving field of research where significant progress has been made in recent years. Although the challenge of a considerable unmet need remains, an increasing emphasis on a multidisciplinary approach to the study of eating disorders and obesity and co-morbid psychiatric disorders including depression, schizophrenia and ADHD is likely to identify improved therapies for patients.

Finally we would like to thank the authors of this Special Issue for their insightful and authoritative contributions and the referees whose comments have further enhanced the excellent quality of the manuscripts to provide a comprehensive and timely overview of this increasingly significant subject.

Declaration of conflicting interests

CT Dourish is an employee, Director and shareholder of P1vital Ltd and a Director and shareholder of P1vital Products Ltd. No conflicts are reported by PG Clifton.

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