Editors' view

Editorial for BJCP Special Obesity Edition

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The obesity epidemic (with the associated co-morbidities) poses a major health-care challenge for the 21st Century [1]. A 'Westernised' lifestyle (calorie dense diets and reduced physical activity) fuel this epidemic, on the background of genetic susceptibility [2, 3]. Therapeutic options for clinically significant weight-loss and weight-loss maintenance are currently limited. Whilst appropriate public-health measures need instigated to reduce the obese burden, the development of new anti-obesity agents is much awaited.

In Caucasians a body mass index (BMI) ≥ 25 kg/m² represents overweight, a BMI ≥ 30 kg/m² is defined as obese. The aim of treatment of the obese patient is to cause a satisfactory maintained weight-loss, with the improvement of either biochemical markers (e.g. glucose tolerance or improved lipid profile) or physical conditions associated with obesity (e.g. hypertension or sleep apnoea). Treatment is not aimed at causing merely 'cosmetic' weight-loss. The first-line of treatment for the obese patient is lifestyle intervention (i.e. a reduced calorie intake, with increased daily exercise underpinned by long-term behaviour-change). If this lifestyle intervention does not cause medically significant weight-loss, it can be supplemented by drugs, usually now either the pancreatic lipase inhibitor orlistat or the centrally acting monoamine uptake inhibitor sibutramine. These agents typically produce a modest weight-loss (1 year mean pooled weight loss for orlistat 2.89 kg and sibutramine 4.45 kg [4, 5]) which is often insufficient to satisfactorily treat the more severely obese patient.

Bariatric surgery is the definitive treatment for the morbidly obese patient. In the UK NICE recommend bariatric surgery (which includes gastric band insertion, sleeve gastrectomy or Roux-en-Y gastric bypass (RYGB)) for patients with BMI >35 kg/m² with co-morbidities or BMI >40 kg/m² with evidence of previous significant attempts of weight-loss [6]. In addition, NICE recommends bariatric surgery as first-line treatment option for patients with BMI >50 kg/m² [6]. The evidence for bariatric surgery provision is compelling, as it causes a maintained clinically significant weight-loss (up to 25% in some series [7]). Studies have shown

that bariatric surgery can lead to a significant reduction in co-morbidities (which includes diabetes, sleep apnoea, dyslipidaemia and hypertension) and mortality [7].

This edition of the journal provides a timely overview of the subject of obesity and its future management. The aim of this edition is to provide an understanding of potential developments in this important field of medicine. A long-term challenge is to replace the need for bariatric surgery with improved medical therapies.

The understanding of the pathophysiology behind the development of obesity is essential for the development of preventative and treatment options. Family and twin studies have shown that genetic factors contribute up to 40–70% to the interindividual variation in common obesity [8]. Whilst some rare monogenetic causes of obesity have been reported [9], the understanding of the genetics behind the aetiology of common obesity is less well known. In this Journal, Ruth Loos provides an important review on the genetics of common obesity by discussing the discovery of obesity susceptibility loci, and their potential impact on public health and clinical practice [10]. This review describes how the use of genome-wide association has revolutionised the field of genetic epidemiology and has recently led to the discovery of 15 loci associated with obesity-related; one such gene being fat mass and obesity associated gene (FTO), the first gene associated with common obesity. Whilst these advances do provide important insights into the pathophysiological development of obesity, to date, the established loci in combination explain $<2\%$ of interindividual variation in BMI and the review outlines the great challenges that thus remain in this field.

An understanding of current pharmacological therapy for obesity is essential. Li and Cheung provide a detailed review here of currently available anti-obesity agents [11]. This review highlights the fact that although only modest weight-loss is achieved by these agents, such weight-loss is clinically significant with regards to relevant biochemical markers and hypertension. This review is complimented by the paper of current paediatric prescribing by Viner *et al.*, which provides an insight into the challenging area of paediatric obesity management [12]. Both of these papers do

outline the need for long-term studies investigating efficacy and safety of anti-obesity agents in most age ranges, as obesity does affect all ages.

The development of new therapeutic agents is crucial. Body-weight maintenance is achieved by careful regulation of appetite and energy expenditure. Our better understanding of these homeostatic mechanisms is leading to the development of new anti-obesity drugs. Sargent and Moore provide a clear overview of the centrally acting therapies that are in current development [13]. Predominantly these agents act via hypothalamic nuclei, although future agents may act via either the brainstem or higher centres. What this review highlights is the difficulties that have been encountered with the centrally-acting drug development with regards to untoward side-effects and lack of efficacy. One approach to improve drug efficacy, as outlined in this review, is to use combinations of agents (e.g. bupropion and naltrexone). What is clear, however, is that further research is required to develop more efficacious centrally therapeutic agents with less side-effects.

The investigation into the underlying mechanisms that mediates the weight loss achieved by bariatric surgery potentially may provide novel therapeutic agents. Field *et al.* in their review provide a clear overview of this subject and highlight the potential for gut-peptides (or gut-peptide analogues) as future obesity therapies [14]. Gut peptides (notably peptide YY₃₋₃₆, glucagon-like peptide-1 (GLP-1) and oxyntomodulin) are elevated in gastric bypass surgery. These peptides act at higher centres (hypothalamus and hind-brain) to apparently cause decreased appetite [15]. These three peptides are all anorectic when administered to healthy lean and obese volunteers [15]. The authors rightly stress that the gut hormones thus present great opportunities for novel obesity agents and that they probably currently have less non-specific side-effects than centrally acting drugs. The review discusses the progress in the treatment of type 2 diabetes with the successful development of GLP-1 analogues (e.g. exenatide or liraglutide); this is as direct a consequence of gut peptide research. The paper also puts forward the intriguing prospect that combinations of these anorectic gut peptides may be used in combination (thus at lower individual doses) thereby reducing potential side-effects (predominantly nausea and vomiting). The papers by Doogue *et al.* and by Lim *et al.* both build on previous gut hormone research.

The regulatory hurdles that exist for licensing of novel therapeutic agents have to be recognised. Heal *et al.* here provide a detailed review of the history of such regulation, (including how previous adverse events have influenced these regulatory barriers) and outlines the potential difficulties that may be encountered in drug development [16]. The review highlights the requirement by the regulatory authorities for the primary efficacy endpoint of >5% placebo subtracted weight-loss maintained for 1 year, with secondary improvements in cardiovascular risk factors being prerequisite. The review underlines the fact that

'Metabolic Syndrome' is not recognised as a discreet disease by the regulatory bodies and hence these agencies will not licence drugs for treatment of 'Metabolic Syndrome'. Ultimately, the review thus stresses how the regulatory landscape may be changed for anti-obesity drugs and the spectrum of conditions for which they are approved, if positive data is obtained from the forthcoming publication of the phase IV SCOUT trial (Sibutramine Cardiovascular Outcome).

Obesity is a major international health problem. This edition of the Journal reviews some aspects of the pathophysiology underling obesity and describes how novel obesity agents may be discovered. The Journal also reviews the regulatory hurdles that have to be overcome for these new drugs to be licensed. In the future, such new anti-obesity agents may either be used with traditional lifestyle interventions, or perhaps in conjunction with more aggressive weight-loss strategies (e.g. low energy liquid diets). This though will all take time. The hope has to be that such advances will significantly reduce the need for bariatric surgery and that together with public health initiatives, reduce the burdens of obesity on our societies.

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