Research in brief: Effective pharmacotherapy for the management of obesity

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Introduction

Obesity is increasingly prevalent worldwide, leading to significant associated morbidity and mortality, with a large impact on quality of life and health economics.[1,2] The current mainstay of management is lifestyle intervention, encouraging reduced calorie diets and exercise, however, maintaining sustained weight loss is challenging.[3] Bariatric surgery is an effective option for those with higher body mass index, but is invasive and carries risks of procedural-related and long-term nutritional complications.[4] A number of drugs have been developed for the treatment of obesity, several of which have been withdrawn due to unacceptable side effects (amphetamines, fenfluramine or larcaserin).[5] Until recently, approved drugs for the management of obesity in the US (orlistat, phentermine-topiramate and naltrexone-bupropion) had modest efficacy and significant side effects, making compliance challenging.[6]

Here, we review two recently published phase III trials for the effective pharmacological management of obesity of different aetiologies.

Weekly semaglutide in adults who are overweight or obese: The STEP-1 trial

Clinical trials of glucagon-like peptide 1 (GLP-1) agonists for the management of type 2 diabetes found that weight loss was a key side effect of the treatment.[7,8] The Semaglutide Treatment Effect in People with Obesity 1 (STEP-1) trial was set up to investigate the safety and efficacy of the GLP-1 agonist semaglutide in the management of obesity, without diabetes.[9] The study randomised 1,961 adults in a 2:1 ratio to 2.4 mg once weekly semaglutide or placebo, for a duration of 68 weeks. All participants received lifestyle intervention consisting of 4-weekly counselling sessions. There was a significant reduction in body weight in the treatment group compared with placebo (-14.9% vs 2.4%; p≤0.001), with one-third of participants losing at least 20% of their baseline body weight. Eighty-six per cent of participants in the treatment group met the primary endpoint of at least 5% weight loss. In addition to weight benefits, the authors observed a greater reduction in cardiometabolic risk factors and a greater increase in physical functioning. There was a greater incidence of side effects in the treatment group, namely nausea, diarrhoea and cholelithiasis, as is typical for this class of drug. In summary, this trial demonstrated that once weekly semaglutide was effective in achieving sustained, clinically relevant reduction in body weight in adults who are overweight or obese without type 2 diabetes.

Setmelanotide in individuals with severe obesity due to leptin receptor or pro-opiomelanocortin deficiency

The leptin-melanocortin system is a major hypothalamic pathway regulating body weight in humans. Rare, naturally occurring genetic variants in genes affecting this pathway can lead to severe early onset obesity.[10] In the last few years, directed pharmacological targeting with the melanocortin 4 receptor (MC4R) agonist setmelanotide led to significant weight loss in phase II studies of patients harbouring genetic mutations in this pathway.[11,12] In a recent edition of *The Lancet Diabetes & Endocrinology*, Clément *et al* reported the results of two phase III trials of setmelanotide in individuals with obesity secondary to deficiency of the leptin receptor (LEPR) and pro-opiomelanocortin (POMC).[13] Eleven subjects were enrolled in the LEPR trial, and 10 subjects in the POMC trial. Forty-five per cent and 80% of participants, respectively, achieved at least 10% weight loss after 1 year of treatment, with a mean percentage change in the most hunger score of –43.7% in LEPR trial and –27.1% in POMC trial. The most commonly reported adverse events were injection site reactions and hyperpigmentation. On this basis, the US Food and Drug Administration (FDA) has now licensed setmelanotide for use in these specific conditions.

Conclusion

These trials herald a new era for the management of obesity, a condition with rapidly increasing prevalence worldwide. In rare instances in which obesity is driven by specific genetic mutations, targeting the underlying mechanism promises to be an effective therapeutic strategy. In the more prevalent form of obesity, the STEP-1 trial offers great promise for more effective, meaningful

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pharmacological interventions, and could be an adjunct to the recently commissioned liraglutide for the management of obesity, without diabetes.[14] Going forward, we might expect to see further development of these classes of drug, potentially in non-injectable formulations, and with fewer side effects. ■

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