SHAPING OBESITY CARE WITH EVIDENCE-BASED, PERSONALISED TREATMENTS

Introduction

Obesity is a chronic, relapsing disease that continues to present a serious global public health challenge, with almost 60% of adults in Europe either living with obesity or pre-obesity (overweight).[1] The morbidity and mortality risk associated with obesity is extensive, and drives increased incidence of diabetes mellitus, cardiovascular (CV) disease, chronic respiratory diseases, non-alcoholic fatty liver disease, chronic kidney disease, musculoskeletal complications, depression and other mental health conditions, and a risk of a range of cancers.[1]

Excess adipose tissue decreases life expectancy by 5 years compared with healthy weight individuals, and contributes to 1.2 million deaths (13% of the total) in Europe every year, making it the 4th biggest cause of mortality.[1] However, based on current projections, no country in Europe is expected to reach the target of halting the rise in obesity by 2025.1 The pathological effects of obesity are compounded by stigmatisation, which leads to people living with the disease to decrease their healthcare engagement, further increasing medical risks.[2] This emphasises the need to use all available treatment options to address this disease. This article will provide an overview of the currently available treatment options for obesity in Europe, the need for therapy personalisation and current treatment approaches.

Current anti-obesity treatments

Current anti-obesity treatments can broadly be divided into injectable and oral medications. Injectable medicines include glucagon-like peptide (GLP)-1 receptor agonists such as liraglutide and semaglutide, and the dual GLP-1 and glucose-dependent insulinotropic polypeptide (GDIP) receptor agonist, tirzepatide.[3-5] A further injectable option is the melanocortin-4 receptor (MC4R) agonist, setmelanotide for patients with Bardet-Biedl syndrome, loss-of-function biallelic pro-opiomelanocortin deficiency or biallelic leptin receptor deficiency.[6] Oral medications include the fixed-dose, extended-release combination of naltrexone and bupropion (NB-ER), and the gastric and pancreatic lipase inhibitor, orlistat.[7,8] The oral, dual agents (phentermine/topiramate) are also available in a limited number of European countries.[9] Each of these medication classes is associated with specific benefits resulting from the effective management of obesity including weight loss, the promotion of satiety, and increased energy suppression, amongst others (**Table 1**). Like all medication, use of these treatments in patients also requires consideration of the variety of potential side effects and contraindications (**Table 1**).

Impact of anti-obesity treatments on CV outcomes

A range of studies have investigated the effects of anti-obesity treatments on CV risk factors and outcomes. The GLP-1 receptor agonists were investigated in three studies. In the SELECT trial of 17,604 patients with CV disease (CVD), a body mass index ≥27 kg/m^2 and without diabetes, semaglutide versus placebo reduced the composite incidence of death due to CV events (CVE), non-fatal myocardial infarction, or non-fatal stroke by 20% (hazard ratio [HR]: 0.80 [95% CI: 0.72, 0.90; P<0.001) at a mean follow-up of 39.8 months.[10] Consistent with this, in the SUSTAIN-6 trial semaglutide versus placebo reduced the risk of non-fatal stroke events (HR: 0.61 [95% CI: 0.39, 0.99]; P=0.04) and overall CVE (HR: 0.74 [95% CI: 0.58, 0.95]; p<0.001) in patients with type 2 diabetes.[11] Finally, in the LEADER trial, liraglutide significantly reduced the risk of major adverse cardiovascular events (MACE) in patients with type 2 diabetes and at least one cardiovascular condition compared with placebo (HR: 0.87 [95% CI: 0.78, 0.97]; p=0.01 [superiority]).[12]

Currently, only the SURMOUNT-1 trial has assessed the CV impact of the dual GLP-1 and GDIP receptor agonist, tirzepatide.[13] This study found that tirzepatide significantly reduced key cardiometabolic risk factors, including waist circumference, systolic and diastolic blood pressure, and fasting insulin levels in patients with obesity compared with placebo.[13] Additionally, safety outcomes suggested that the incidence of MACE was similar compared to placebo.[13] The impact of tirzepatide on CV outcomes will be further investigated in the Phase III SURMOUNT-MMO trial of patients with established CVD.[14]

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Table. Benefit-risk profile of currently available anti-obesity pharmacology treatments

Treatment	Benefits beyond weight loss[3-8]	Common side effects[3-8, 35]	Contraindications[3-8, 35]	CV risk[7, 10-13, 15, 18, 19, 21]
Semaglutide and Liraglutide	• Promotes satiety • Improved glycaemic control	• Gastrointestinal disorders: • Nausea, • Diarrhoea, • Constipation • Vomiting	• Hypersensitivity to the active substance or to any of the formulation excipients	• Semaglutide: Reduced risk of death due to (vs placebo): – CVE – Non-fatal MI – Non-fatal stroke • Liraglutide: Reduced risk of MACE (vs placebo)
Tirzepatide	• Appetite suppression • Improved glycaemic control	• Gastrointestinal • Disorders, mostly mild or moderate in severity. • The incidence of • nausea, diarrhoea and • vomiting was higher during the dose escalation period and decreased over time	• Hypersensitivity to the active substance or to any of the formulation excipients	• Reduced cardiometabolic risk factors including waist circumference, systolic and diastolic blood pressure, and fasting insulin levels • Incidence of MACE similar to placebo
Setmelanotide	• Appetite suppression	• Hyperpigmentation disorders • Injection site reactions • Nausea • Headache	• Patients without confirmed genetic diagnoses of POMC deficiency, PCSK1 deficiency, LEPR deficiency, or Bardet-Biedl Syndrome • Hypersensitivity to setmelanotide or any of its components	• No adverse CV effects or complications
Naltrexone/ bupropion ER	• Appetite suppression	• Nausea • Constipation • Vomiting • Dizziness • Dry mouth	• Hypersensitivity to the active substance or to any of the formulation excipients • Uncontrolled hypertension • History of seizures or bipolar disorder • CNS tumour • Alcohol or benzodiazepine withdrawal • Current or previous bulimia or anorexia nervosa diagnosis • MAOI use within 14 days • Long-term opioid use • Severe hepatic impairment or end-stage renal failure	• No apparent increase in CV risk (vs lorcaserin) • Improvements in cardiometabolic risk factors including waist circumference (including patients with type 2 diabetes), triglycerides, HDL-C and LDL-C/HDL-C ratio (vs placebo)
Orlistat	• Inhibited fat absorption	• Gastrointestinal disorders which are very common: • Oily spotting • Flatus with discharge • Faecal urgency • Fatty oily stool • Oily evacuation • Flatulence • Soft stools	• Hypersensitivity to the active substance or to any of the formulation • Concurrent treatment with ciclosporin • Chronic malabsorption syndrome • Cholestasis • Pregnancy • Breast-feeding • Concurrent treatment with warfarin or other oral anticoagulants	• Lower rates of (vs placebo): – Overall MACE – New-onset heart failure – Renal failure – Mortality

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Table. Continued

Phentermine/ topiramate	• Appetite suppression • Increased satiety	• Dry mouth • Paraesthesia • Constipation	• Hypersensitivity to the active substance(s), to any other sympathomimetic amine, or to any of the formulation excipients Pregnancy and in women who may become pregnant, who do not use safe methods of • contraception • MAOI use within 14 days • With other medicines intended for weight loss.	• No apparent increased risk of MACE • Decreased blood pressure (vs placebo)

CNS=central nervous system; CV=cardiovascular; CVE=cardiovascular event; ER=extended release; HDL-C=high-density lipoprotein cholesterol; LDL-C=high-density lipoprotein cholesterol; LEPR=Leptin receptor deficiency; MAOI=monoamine oxidase inhibitor; MACE=major adverse cardiovascular events; MEN=multiple endocrine neoplasia; MI=myocardial infarction; PCSK1=Proprotein convertase 1; POMC=proopiomelanocortin

CV outcomes with the MC4R agonist, setmelanotide have been extensively assessed. In a systematic review and meta-analysis of 12 studies including 376 patients, no significant adverse CV effects including on blood pressure were identified while patients were on treatment.15 Additionally, slight reductions from baseline in low-density lipoproteins cholesterol (-8.0%) and triglycerides (-16.4%), and increases in high-density lipoproteins cholesterol (+14.1%) were noted.[14] Although the study did not specifically measure the incidence of MACE, no clinically significant CV complications were reported during the follow-up period of up to 52 weeks across studies.[15]

The fixed-dose NB-ER was assessed for CV outcomes in individuals with obesity at increased CV risk in the LIGHT trial, although early termination of the trial prevented assessment of non-inferiority at pre-specified thresholds.[16] More recently, a systematic review and meta-analysis of 12 randomised controlled trials, indicated no apparent increased incidence of MACE compared with placebo.[17,18] Similarly, the real-world retrospective Cardiovascular Health Outcomes Analysis of 24,600 patients, with an average follow-up of 1700 days, demonstrated no statistically significant difference in the rate of MACE between NB-ER and the appetite suppressant, lorcaserin.[18] These findings are also consistent with >10 years of post-authorisation safety monitoring in over 600,000 patient-years of NB-ER exposure globally.[19] The Phase IV INFORMUS trial of patients with obesity and at increased risk of adverse CV outcomes will further investigate CV outcomes during real-world use of NB-ER.[20]

Finally, in patients with obesity, a retrospective, propensity-score matched study, found that the gastric and pancreatic lipase inhibitor, orlistat was associated with lower rates of overall MACE, new-onset heart failure, renal failure, and mortality compared with those not receiving orlistat.[21] The CV effect of the dual agents, phentermine/topiramate, have been investigated in both real-world and clinical studies[22,23] In a real-world retrospective study of 14,586 current and former uses of phentermine/topiramate, no statistically significant increase in the risk of MACE was found in current users of the treatment.[23] Similarly, a randomised clinical trial of phentermine/topiramate indicated a reduction from baseline in blood pressure compared with placebo.[22]

Together, these results suggest that all currently available anti-obesity treatments do not increase the risk of adverse CV outcomes and in many cases, may improve outcomes.

The need for personalised treatment in obesity

Patient goals are central to treatment outcomes, and can increase the proportion of patients achieving and maintaining healthy weight loss.[24] Furthermore, a study evaluating the perspective of patients with obesity on personalised medicine, revealed that this approach has the potential to empower patients and reduce stigma.[25] An additional consideration is that some patients prefer oral treatments over injections due to their convenience and ease of administration.[26-28] Therefore, treatment goals should be personalised based on clinical efficacy and patient needs, including preference for method of administration, body composition and comorbidities.[29,30]

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A range of treatment options including therapeutic nutrition and movement, psychological and behavioural interventions, bariatric surgery when indicated, and pharmacotherapy allow treatment choices to be orientated around patient treatment goals using a comprehensive, multi-disciplinary strategy.[31] Additionally, as early treatment responses are indicative of longer-term responses and are difficult to predict before treatment is initiated,[32] multiple options are required for patients who do not respond to particular treatments.

Treatment approaches

Obesity treatment approaches should be interdisciplinary, involving healthcare professionals across multiple specialties to address the diverse phenotypes of the condition to maximise effectiveness.[33] Additionally, a comprehensive, patient-centred treatment plan must consider factors such as comorbidities, obesity severity, and patient preferences.[33] However, the current approach to anti-obesity pharmacological treatment limits access to patients being treated in secondary care, a particular problem given the large number of patients with obesity and limited number of specialist physicians to treat them.[33]

Given the current undertreatment of obesity and acceptable benefit-risk profile of available anti-obesity pharmacological treatments, there is a need to expand obesity management in the primary care setting.[33] This reflects guideline recommendations for treating obesity as a chronic disease,[34] and the model used for the treatment of other diseases such as hypertension, where prescribing is done by primary care physicians. Overall, personalising obesity treatment pathways based on patient needs may promote better long-term success in weight management and adherence.

Summary

The burden of obesity continues to grow, emphasising the need for a range of pharmacological treatment options to address the problem. Current anti-obesity pharmacological treatments have demonstrated a range of benefits in patients including weight loss, maintenance of weight loss, improved metabolic parameters, the promotion of satiety, and increased energy suppression, with no apparent adverse effect on CV outcomes. Considering the importance of personalised care to achieving obesity management goals, the full range medication options, including all available medications, are required to meet patient needs.

This report was developed as part of the touchINSIGHT activity, Shaping obesity care with evidence-based, personalised treatments. To view the full touchINSIGHT activity, which also includes an interview, please visit: https://www.touchendocrinology.com/obesity/learning-zone/shaping-obesity-care-with-evidence-based-personalised-treatments/

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