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THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

Cardiovascular Effects of the New Weight Loss Agents

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ABSTRACT

The global obesity epidemic and its impact on cardiovascular outcomes is a topic of ongoing debate and investigation in the cardiology community. It is well known that obesity is associated with multiple cardiovascular risk factors. Although life-style changes are the first line of therapy, they are often insufficient in achieving weight loss goals. Liraglutide, naltrexone/bupropion, and phentermine/topiramate are new agents that have been recently approved to treat obesity, but their effects on cardiovascular risk factors and outcomes are not well described. This review summarizes data currently available for these novel agents regarding drug safety, effects on major cardiovascular risk factors, impact on cardiovascular outcomes, outcomes research that is currently in progress, and areas of uncertainty. Given the impact of obesity on cardiovascular health, there is a pressing clinical need to understand the effects of these agents beyond weight loss alone. (J Am Coll Cardiol 2016;68:849-59) © 2016 by the American College of Cardiology Foundation.

With the designation of obesity as a disease by the American Medical Association in 2013, 35% of adults in the United States became bearers of a chronic illness associated with adverse cardiovascular outcomes—and one that is mandated by consensus guidelines to require treatment (1,2). Obesity, through either associations with other disease states (e.g., dyslipidemia, diabetes, hypertension, obstructive sleep apnea) or direct endocrinologic, inflammatory, and prothrombotic effects, is an important contributor to the global burden of cardiovascular disease (3-8).

Despite advice on caloric restriction and increased physical activity, the majority of obese patients either fail to lose weight or regain weight that is lost. As an adjunct to life-style modification, medications approved by the Food and Drug Administration (FDA) for the treatment of obesity include orlistat, lorcaserin, phentermine/topiramate, liraglutide, and naltrexone/bupropion (9-13). However, the effect of these agents on cardiovascular risk factors and outcomes has not been well described. As nonpharmacological weight loss is known to have beneficial effects on cardiovascular risk factors, the effects of pharmacological weight loss agents on these parameters is important to distinguish from the effects produced from weight loss alone. Previously approved weight loss agents, such as sibutramine and fenfluramine, despite showing

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

FDA = Food and Drug Administration

GLP = glucagon-like peptide

HbA_{1c} = glycosylated hemoglobin

HDL-C = high-density lipoprotein cholesterol

HR = hazard ratio

hsCRP = high-sensitivity C-reactive protein

LDL-C = low-density lipoprotein cholesterol

POMC = pro-opiomelanocortin

SBP = systolic blood pressure

efficacy for weight loss, were withdrawn from the market due to adverse cardiovascular effects (increased myocardial infarction and stroke with sibutramine, valvular heart disease and pulmonary hypertension with fenfluramine) (14–16).

The recent approval of 2 new weight loss medications, a naltrexone/bupropion combination and liraglutide, raises an important question as to the true impact of these agents on cardiovascular risk factors and outcomes. Using the available evidence, this review focuses on the known effects of these medications on cardiovascular risk factors as well as clinical cardiovascular outcomes, reviews important safety data, and highlights areas where a knowledge gap exists.

LIRAGLUTIDE

WEIGHT LOSS EFFECTS. Liraglutide (Saxenda, Novo Nordisk, Bagsværd, Denmark) is a glucagon-like peptide (GLP)-1 receptor agonist, a modified form of human GLP-1 with enhanced albumin binding, self-oligomerization, and resistance to breakdown by dipeptidyl peptidase 4 (17). Liraglutide exerts its action through binding the GLP-1 receptor on pancreatic beta cells, increasing their sensitivity to glucose. It also suppresses glucagon production by pancreatic alpha cells, diminishing hepatic gluconeogenesis, inhibiting gastric emptying, and promoting satiety and weight loss (18). Liraglutide also binds to GLP-1 receptors located in the arcuate nucleus of the hypothalamus, as well as mesolimbic neurons, acting on known central pathways of hunger and satiety (**Central Illustration**) (19,20). Originally approved for the treatment of type 2 diabetes mellitus on the basis of the LEAD (Liraglutide Effect and Action in Diabetes) series of trials, liraglutide was noted to promote significant weight loss at a dose of 1.8 mg daily (21). A phase II weight loss trial evaluating liraglutide at doses up to 3 mg daily also showed favorable results compared with orlistat and placebo, prompting the phase III SCALE (Satiety and Clinical Adiposity - Liraglutide Evidence in Nondiabetic and Diabetic Individuals) trials (12). The SCALE Maintenance, SCALE Obesity and Prediabetes, and SCALE Diabetes trials showed placebo-adjusted weight loss ranging from 4.0% to 6.1% of initial body weight (22–24). Liraglutide was approved by the FDA in 2014 for the treatment of obesity in patients with a body mass index (BMI) >30 kg/m^2 or >27 kg/m^2 with an obesity-related comorbidity and can be used in patients with known cardiovascular disease (25). The dose of liraglutide approved for weight loss is 3 mg injected once daily, compared with 0.6 to 1.8 mg daily for the treatment of diabetes.

CARDIOMETABOLIC VARIABLES. Glycemic effects. The beneficial effects of liraglutide on blood sugar are well documented, and the phase III LEAD studies showed its efficacy in treating type 2 diabetes mellitus, with reductions in glycosylated hemoglobin (HbA_{1c}) ranging from 0.33% to 1.85%, depending on the comparator (26–32). Additionally, the SCALE trials showed a reduction in HbA_{1c} of 0.2% to 0.9% with liraglutide compared with placebo (22–24). A natural concern with the use of a diabetic agent is the incidence of hypoglycemia, particularly in nondiabetic patients. This is of particular concern, as hypoglycemia is known to be a risk factor for cardiovascular events (33). Although the incidence of symptomatic hypoglycemia was not significantly different between groups in the SCALE Obesity and Prediabetes trial (1.3% with liraglutide vs. 1.0% with placebo), there was an increased incidence with liraglutide in the SCALE Maintenance trial (5.2% vs. 2.4%) (22,23). The risk of hypoglycemia was also increased by liraglutide in diabetic patients in the SCALE Diabetes trial (87 per 100 patient-years vs. 31 per 100 patient-years) (24).

Lipid effects. The effects of liraglutide on the lipid profile have also been examined. A network meta-analysis of 35 trials showed a mean decrease in high-density lipoprotein cholesterol (HDL-C) of 0.4 mg/dl, a decrease in low-density lipoprotein cholesterol (LDL-C) of 4.6 mg/dl, a decrease in total cholesterol of 6.2 mg/dl, and a decrease in triglycerides of 23 mg/dl (34). The SCALE trials showed a reduction in triglycerides (−10 to −25 mg/dl), as would be expected from an agent improving glycemic control, and more neutral effects on HDL-C (neutral to +3 mg/dl) and LDL-C (−4 to +3 mg/dl) (22–24).

Blood pressure and heart rate effects. Regarding liraglutide's effects on blood pressure, a patient-level meta-analysis of the LEAD trials showed that liraglutide treatment resulted in a systolic blood pressure (SBP) reduction of approximately 2.8 mm Hg, as opposed to 0.5 mm Hg with placebo. Treatment was also associated with an increase in heart rate of 3 beats/min (35,36). In the SCALE trials, a minor improvement was seen in blood pressure with liraglutide over placebo, with decreases in SBP of between 2.6 and 3.1 mm Hg (22–24). Of potential concern, heart rate in the SCALE trials generally increased with liraglutide when compared with placebo (+0.6 to +3.5 beats/min). Increases in heart rate have been previously noted with sympathomimetic