Editorial

Pharmacotherapy in conjunction with lifestyle for the treatment of obesity complications, is it enough?

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Type 2 diabetes and its precursor 'prediabetes' are common complications of obesity. While the rates of those diseases are reaching dangerous levels globally, effective non-invasive remission methods of the diseases are still lacking. The CAMELLIA-TIMI 61 in *The Lancet* shed light on the use of lorcaserin for the prevention and remission of type 2 diabetes for people with overweight and obesity (1). Lorcaserin is an FDA approved selective agonist for 5-hydroxytryptamine 2C serotonin receptors (5-HT2C) for the management of obesity as it reduces the symptoms of obesity (excess hunger and lack of satiety) via actions on the subcortical areas of the brain which regulate appetite (2,3).

Patients with prediabetes or type 2 diabetes are asked to lose weight to control the progression of the disease. Lifestyle interventions are used as the first line therapy towards achieving moderate weight loss targets. Only 1 in 8 men and 1 in 7 women are able to lose 5% of their weight (4) with even fewer achieving the 10% weight loss target required to substantially improve type 2 diabetes (5). Once overweight or obesity occurs, the probability of attaining a normal weight with lifestyle and pharmacotherapy becomes 1 in 210 for men and 1 in 124 for women, and 1 in 1,290 for men and 1 in 677 for women with morbid obesity (4). These figures have made us aware on the complexity of treating this disease and the importance of personalizing treatments to obtain better success. However, the response to treatment is governed by biology and not external motivation. The central nervous system controls many biological parameters in the body to keep different systems at a balance including hormones, fluid, and food intake and energy expenditure. It is now accepted that body fat is also regulated by this system. The body fat set-point is still a theory, but it allows us a theoretical framework to understand the importance of adjusting treatments.

Lorcaserin results in a dose-dependent weight loss when given in conjunction to lifestyle modification (6). Bohula *et al.* [2018] showed that in a general population of patients with obesity, lorcaserin resulted in a net weight loss of 3.3 kg at 12 months, this translated to a 5% weight loss in 37.4%, 39.7%, and 42.3% of patients with diabetes, prediabetes, and normoglycemia, respectively. Previously 5% weight loss was thought to be sufficient to reduce risks of obesity related complications. This is true for certain complications but not all. For example, as little as 5% weight reduction can improve glycaemic control in type 2 diabetes (7), whereas to get remission of type 2 diabetes, or clinical improvement of sleep apnoea, weight loss of 10–15% may be required (5,8). The rates of patients achieving 10% weight loss in Bohula *et al.* [2018] was 14%, 15%, and 18% of patients with diabetes, prediabetes, and normoglycemia, respectively. The higher doses of lorcaserin can result in 22.6% of patients achieving more than 10% weight loss (6) which should really become the new target.

Lorcaserin resulted in a reduction in HbA1c of 0.33% at 12 months in patients with diabetes (baseline HbA1c 53 mmol/mol or 7.0%) and slightly lower reduction in

those patients with prediabetes 0.09% or normoglycemia 0.08%. Despite the modest reduction in HbA1c in patients with prediabetes, Bohula *et al.* [2018] reports that lorcaserin may be used to prevent the development of type 2 diabetes in patient with prediabetes by 19%, what corresponds to treating 56 patients with prediabetes to prevent one diabetes event over 3 years, and by 23% in patients with normoglycemic (1). The authors report that improvement in HbA1c may not be weight dependent as the reduction in glycaemic parameters peak at around 3 months before the nadir in weight.

Hypoglycaemia is common in patients with diabetes taking insulin or sulfonylurea, and can cause disability or even be life threatening. There was a numerical imbalance for severe hypoglycaemia with serious complication that required hospitalization or considered life threatening or disabling in patients with diabetes taking lorcaserin [12 cases (0.4% of all patients)] *vs.* placebo [4 cases (0.1% of all patients)] (P=0.054). The number of cases of hypoglycaemia in patients without diabetes at baseline was 9 (4 mild, 2 moderate, 2 severe, and 1 severe with serious complications) in those taking lorcaserin *vs.* 3 in placebo (2 mild, and 1 moderate).

Lorcaserin lowered diabetes related microvascular complications by 21% in patients with diabetes (1) and lowered the rate of new onset or progression of renal impairment in patients with obesity and overweight (9).

Undesired side effects included headache, nausea, and dizziness (6), which put people at risk of stopping the treatment, particularly, if patients are not rewarded with significant reduction of the numbers on their scales early on. Initial weight loss response is a helpful indicator to identify "early responders" and "early non-responders", which may help to determine follow-up treatments or changes in approaches that may help the patient. Following up with patients closely and setting milestone targets can help determine who is responding to the treatment. For example, at 16 weeks, those who lose 5% of their weight should continue on the medication, while at 32 or 52 weeks only those who lose 10% of their weight should continue to be prescribes the medication. At each those milestone targets, if weight loss was not achieved then a different treatment should be considered, which can include a change to another diet, medication or even bariatric surgery.

Obesity cannot be cured but must be managed for life similar to how we manage all other chronic diseases such as asthma, hypertension or familial hypercholesterolemia. Successful obesity treatments point towards the subcortical brain regions where the body fat set point is regulated. Lorcaserin as a selective agonist for 5-HT2C addresses the pathology of the disease of obesity in the hypothalamus (3) by reducing the symptoms of obesity. Together with GLP-analogues and combination of naltrexone and bupropion which also address the symptoms of obesity by activating receptors in the subcortical areas of the brain, they can have beneficial effects and lower body weight set point. The next step would be to assess whether using combination pharmacological approaches plus or minus lifestyle interventions have any additive benefit, but for now we are able to offer a more personalized medicine approach for patients with obesity as we attempt to get the right treatment to the right patient at the right time.

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Footnote

Conflicts of Interest: CW le Roux serves on advisory boards for Novo Nordisk, Johnson & Johnson, GI Dynamics, Fractyl, Keyron and Herbalife. W Al-Najim has no conflicts of interest to declare.

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