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SIBUTRAMINE: THE MAGIC PILL TO LOSE WEIGHT AND INCREASE CARDIOVASCULAR RISKS

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Abstract: Obesity is a complex and multifactorial condition that affects an increasing number of people around the world. While lifestyle changes such as the diet and exercise are the cornerstone of obesity treatment, in some cases pharmacological treatment may be necessary. Sibutramine is a drug that has been widely used for the treatment of obesity, acting as a serotonin and noradrenaline reuptake inhibitor, resulting in appetite suppression and increased satiety. However, several clinical trials and observational studies have found significant associations between sibutramine use and adverse cardiovascular effects, including increased blood pressure, heart rate, and risk of cardiovascular events such as myocardial infarction and stroke. Faced with the side effects of sibutramine, many countries suspended the marketing of this drug, restricting its use only to extreme cases of obesity. Nowadays, the most used drugs for the treatment of obesity include orlistat, liraglutide and phentermine/topiramate, which have a lower risk of adverse cardiovascular effects. In summary, pharmacological treatment of obesity may be an option for patients with severe obesity who have not had success with lifestyle changes. However, it is essential to carefully assess the risks and benefits of each medication before prescribing it, taking into account the patient's comorbidities and clinical conditions. Sibutramine, despite its effectiveness in weight control, should be used with caution due to its adverse cardiovascular effects.

UNDERSTANDING OBESITY

Obesity is a complex chronic condition that involves complex interactions between genetic, environmental and behavioral factors. It is characterized by excessive accumulation of body fat that can lead to a series of metabolic, cardiovascular and other comorbidities. The pathophysiology of obesity involves a complex interaction between energy metabolism, central and peripheral nervous systems, as well as endocrine function.[1]

Excessive adiposity in obese individuals is attributed to an imbalance between calorie intake and energy expenditure. Body fat is stored in the form of triglycerides in adipocytes, which are also responsible for producing and secreting a series of hormones and cytokines that affect metabolism throughout the body.[2] For example, leptin, produced by adipose tissue, plays an important role in regulating satiety, energy expenditure and overall energy homeostasis. Furthermore, chronic low-grade inflammation associated with obesity can lead to insulin resistance and the development of type 2 diabetes mellitus (T2DM). Adipocytes also produce hormones such as adiponectin and resistin, which are involved in the regulation of glycemic homeostasis. Thus, the resulting insulin resistance can lead to an increase in blood glucose levels, which, if not properly controlled, can lead to the development of T2DM.[3,4]

The pathophysiology of obesity is complex and involves interactions between several factors. Recent studies also suggest that the gut microbiome may play an important role in regulating energy metabolism and the development of obesity. With this, a better understanding of these underlying mechanisms may help guide therapeutic interventions to treat obesity and its associated complications.[4]

The central and peripheral nervous system plays a key role in the pathophysiology of obesity. The hypothalamus is a brain region that plays an important role in regulating food intake and energy expenditure. Neurons in the hypothalamus respond to hormonal, metabolic, and neural signals to adjust food intake and energy expenditure according to the body's energy needs.[1,5] However, in obese individuals, these regulatory mechanisms are disrupted, leading to excessive food intake and reduced energy expenditure. The peripheral nervous system, including the nerves that innervate adipocytes, also plays a role in regulating energy metabolism. Studies suggest that dysfunction of the sympathetic nerves that innervate adipose tissue may contribute to the development of obesity and insulin resistance.

The pathophysiology of obesity also involves a complex interaction between several hormones, including insulin, ghrelin, peptide YY, and thyroid hormones. These hormones regulate food intake, energy expenditure, and overall energy metabolism. Changes in these hormones, such as insulin resistance, ghrelin dysregulation and reduced levels of thyroid hormones, are associated with the development and progression of obesity.[1]

THE NON-PHARMACOLOGICAL TREATMENT

Obesity is a multifactorial condition that requires an integrated therapeutic approach that involves both pharmacological and non-pharmacological interventions. Non-pharmacological treatment includes lifestyle changes such as dietary modifications, increased physical activity, behavioral therapy and social support.[6] Diet is one of the main factors that contribute to the development and progression of obesity. A healthy diet should include a variety of foods that are low in saturated fat, trans fat, and added sugars, as

well as being rich in fruits, vegetables, whole grains, and lean protein. Reducing portion sizes and limiting your intake of high-calorie, processed foods is also important for weight loss and long-term weight loss maintenance.[7]

Increasing physical activity is an important intervention for the non-pharmacological treatment of obesity, helping to increase energy expenditure and improve overall energy metabolism. In addition, physical activity may also have mental health benefits and reduce the risk of cardiovascular disease.[6,8]

Behavioral therapy and social support play an important role in the treatment of obesity. Behavioral therapy helps individuals identify and modify behavior and thinking patterns that contribute to weight gain, while social support helps promote adherence to lifestyle changes by providing encouragement and motivation.[8]

PHARMACOLOGICAL TREATMENT OF OBESITY

Several pharmacological treatment options are useful to help control obesity along with lifestyle changes. Drugs approved by the US Food and Drug Administration for the treatment of obesity include orlistat, lorcaserin, phentermine/topiramate, naltrexone/bupropion, and liraglutide. Orlistat is an intestinal lipase inhibitor that prevents fat absorption, while lorcaserin is a selective serotonin receptor agonist that helps control appetite. [6]

The Phentermine/Topiramate composition is a drug combination that suppresses appetite and increases feelings of fullness, and the Naltrexone/Bupropion is a combination that helps control appetite and reduce food intake. Liraglutide, on the other hand, is a GLP-1 receptor agonist that reduces appetite and improves glycemic control. Other pharmacologic treatment options for obesity include melanocortin receptor agonists, pancreatic amylase inhibitors, GLP-1 receptor agonists, appetite suppressants, fat absorption inhibitors, and pancreatic lipase inhibitors. [6,9,10]

In Brazil, there is still the circulation of Sibutramine, a medicine used as an appetite suppressant, increasing the feeling of satiety. Approved by the FDA in 1997, sibutramine was widely prescribed for obese or overweight patients. The drug works by inhibiting the reuptake of serotonin, noradrenaline and dopamine, brain chemicals that regulate appetite and mood, leading to a decrease in appetite and a faster feeling of fullness during meals. [11,14]

In 2010, the FDA decided to withdraw sibutramine from the market due to cardiovascular safety concerns. Several clinical studies have indicated an increased risk of heart attack and stroke events in patients taking the drug compared to those taking a placebo. Additionally, sibutramine may interact with other medications, such as antidepressants, increasing the risk of side effects. Since then, its use is limited in many countries. However, some healthcare professionals still prescribe sibutramine in selected cases, especially in morbidly obese patients who do not respond to other treatment interventions.[12-20]

A study published in 2010 in the New England Journal of Medicine evaluated the use of sibutramine in patients with high cardiovascular risk. The study was stopped prematurely after a safety analysis showed a significant increase in the risk of serious cardiovascular events, such as myocardial infarction, stroke and cardiovascular death, in treated patients compared to the placebo group. According to the results found, the absolute risk of serious cardiovascular events was 11.4% in the group treated with sibutramine, compared to 10% in the placebo group.

The European Heart Journal published an article evaluating the use of sibutramine in patients with a history of cardiovascular disease. The study was also stopped early due to a significantly increased risk of cardiovascular events in patients on treatment compared to those on placebo. The absolute risk of serious cardiovascular events was 16.4% in the sibutramine-treated group, compared with 10% in the placebo group.

Other clinical trials have also found associations between sibutramine use and adverse cardiovascular effects. A randomized trial of over 10,000 overweight or obese patients at high cardiovascular risk found a significant association between sibutramine use and an increased risk of serious cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. This study led to the withdrawal of sibutramine from the market in several countries.

Furthermore, in patients with coronary artery disease and obesity, the use of sibutramine was associated with a significant increase in resting heart rate and systolic blood pressure. Furthermore, a study in patients with high blood pressure and obesity showed that the use of sibutramine increased systolic and diastolic blood pressure, as well as heart rate. An analysis of more than 3000 overweight or obese patients with coronary artery disease found that sibutramine use was associated with a significant increase in resting heart rate and systolic blood pressure, as well as an increased risk of cardiovascular events. The risk of cardiovascular events increased by 16% in patients who used sibutramine compared to those who did not.

Another prospective observational study of over 12,000 patients with obesity associated sibutramine with a significantly increased risk of myocardial infarction, stroke, and cardiovascular death. Specifically, the risk of myocardial infarction increased by 16% and the risk of stroke increased by 34% in patients who used sibutramine compared to those who did not. To leave no doubt on the matter, a retrospective study of more than 21,000 patients with obesity and cardiovascular disease associated the use of the drug with a 50% increase in the risk of myocardial infarction and a 60% increase in the risk of stroke compared to those who did not use the drug.

Although pharmacological treatment can help improve weight loss, it is important to remember that these medications should not be used as a one-stop solution for obesity. Lifestyle changes, such as dietary modifications and increased physical activity, remain the main interventions for the treatment of obesity. Furthermore, pharmacological treatment should be closely monitored by a physician and should only be used in obese or overweight individuals at increased risk of obesity-related health complications.

CONCLUSION

Although sibutramine has been widely used in the past to treat obesity, its safety and effectiveness are now questionable. It is important for healthcare professionals to carefully weigh the risks and benefits before prescribing sibutramine, due to its broad effect in increasing heart attacks and strokes, and to consider other non-pharmacological treatment options such as lifestyle changes and behavioral interventions.

CONFLICT OF INTERESTS

There is not any.

FINANCING

The own researchers.

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