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Obesity: Diagnosis and Treatment

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Abstract

Obesity is a condition characterized by an excessive accumulation of body fat, generally due to incorrect nutrition and a sedentary life, which can adversely affect both the quality and life expectancy. In recent years, awareness has grown that a balanced weight is a necessary condition for good physical and mental health. On a psychological level, in fact, obesity can completely upset a person's life: those who are obese are often isolated and can run into anxiety and depression. In particular, overweight children tend to develop a difficult relationship with their body and with their peers, with consequent isolation which often results in further sedentary habits. We are studying whether and to what extent obesity can also be the result of genetic risk factors. Although studies are still preliminary, given the multifactorial nature of obesity, it is likely that there are combined genetic factors capable of promoting or not the ability to lose weight and keep it low.
Other health problems associated with excess body weight are: hypertension, hypercholesterolemia, sleep apnea and respiratory problems, asthma, increased surgical risk, complications in pregnancy, hirsutism and menstrual irregularities. A particularly serious problem is that of the onset of obesity among children and adolescents, exposed since childhood to respiratory difficulties, joint problems, reduced mobility, but also digestive and psychological disorders. Those who are obese in childhood are often obese as adults: the risk of developing cardiovascular risk factors (hypertension, coronary heart disease, tendency to heart attack) and conditions of impaired metabolism, such as type 2 diabetes or hypercholesterolemia. The main treatment is prevention: in order to control your weight, you need to adopt healthy lifestyles, i.e. proper nutrition and adequate physical activity. In the diagnosis of obesity and especially in all subsequent therapies and dietary treatments, it is necessary to avoid self-diagnosis, but to rely on a specialist. The treatment consists in reducing body weight, under close medical supervision and in specialized centers and in maintaining a weight appropriate to one's height. Alongside the diet, which must be studied on the individual, physical activity (appropriate to the type of patient) and possibly also behavioral therapy must be combined.
Below we report a brief summary of pharmacotherapy for the reduction of body weight

Key words: *diet, overweight, obesity, therapy*

Introduction

From an etiological point of view, obesity has a multifactorial origin and is connected to several risk factors: behavior styles, life conditions life and genetic determinants [1-5]. Obesity develops as a consequence of a positive energy balance resulting from a calorie intake that exceeds the energy expenditure. A person can therefore become obese if, despite having a normal energy expenditure, the caloric intake is excessive or if, despite feeding properly, he has a deficit in the energy metabolism [6]. The complexity of the problem is determined by the fact that there are multilevel, interpersonal (family, social networks), community (school, workplaces, institutions), governmental influences (local, regional, national context and policies). Even behavioral risk factors, including incorrect eating habits and sedentary lifestyle, which are often considered the main determinants of overweight and obesity, are strongly affected by complex collective dynamics involving large sectors of society: from families to schools, from health institutions to social organizations and the mass media [7]. In parallel with the increase in the incidence of obesity and the progression of obese individuals towards BMI values that are gradually increasing, there is an increased risk of the appearance of comorbid phenomena. In Europe overweight and obesity are responsible for about:

Ø 80% of cases of type 2 diabetes

Ø 55% of cases of high blood pressure

Ø 35% of cases of ischemic heart disease

All this translates into 1 million deaths and 12 million patients a year, worldwide [8]. All the main obesity guidelines indicate very clearly that the first step of therapy is the modification of lifestyles through nutritional intervention, the increase in structured physical activity and behavioral changes.

Methods

However, long-term treatment is very problematic and requires an integrated approach, which uses the tools available in a complementary way, making use of different professional skills, which share the same therapeutic objective [8]. It is now an established and commonly accepted opinion for many years that, in order to face the obesity epidemic, it is necessary to resort to various therapies (nutritional, cognitive-behavioral, pharmacological and surgical), differently combined in the individual patient [8]. The clinical goal must be to reduce body weight sufficient to significantly improve the risks associated with obesity, especially cardiovascular ones.

However, when this first strategy is insufficient or completely ineffective, it is possible to resort to drug therapy, taking into account that a chronic disease such as obesity must be managed flexibly and that the treatment must be as much adapted as possible to the individual patient, as underlined by the new guidelines 2016-1017 of the Italian Obesity Society (SIO) and of the Italian Association of Dietetic and Clinical Nutrition (ADI) [8].

Results

Bupropion/Naltrexone is a combination in prolonged-release tablets, consisting of two molecules, bupropion hydrochloride (90 mg, equivalent to 78 mg bupropion) and naltrexone hydrochloride (8 mg, equivalent to 7.2 mg naltrexone). The Scientific Committee, of the European Medicine Agency (EMA) had already expressed a positive opinion recommending its placing on the market on March 26, 2015, following the registration of the product in the USA for a few months [9].

In combination with a low calorie diet and increased physical activity, the combination is indicated for

weight management in adult patients (≥ 18 years) with an initial body mass index (BMI):

• ≥ 30 kg / m2 (obese)

• ≥ 27 kg / m2 - 30 kg / m2 (overweight) in the presence of one or more weight-related comorbidities (type 2 diabetes, dyslipidemia and arterial hypertension in particular) [10].

The association of bupropion (antidepressant also used in disuassuefazione from smoke) and naltrexone (antagonist of μ opioid receptors), is used for the treatment of opioid dependence and alcohol. These two substances act on two brain areas responsible for controlling food intake and energy consumption, as well as on reward circuits associated with the act of eating. The action of the two active ingredients administered simultaneously determines a reduction in appetite and the amount of food consumed by patients and increases their energy expenditure, helping them to adhere to a low-calorie diet and to lose weight.

To explain the synergistic action of the two components, bupropion and naltrexone , it is necessary to consider that the hypothalamus plays a key role in regulating food intake and energy expenditure. Bupropion and naltrexone predominantly affect two areas of the brain, the arched nucleus of the hypothalamus and the mesolimbic dopaminergic gratification system [10].

In the arcuate nucleus of the hypothalamus, bupropion, following the inhibition of the reuptake of dopamine and norepinephrine and the consequent increase in the concentrations of these two molecules in the synaptic space, stimulates the pro- opiomelacortine neurons (POMC). These cells release α-MSH (alpha-melanocyte stimulating hormone), which binds and stimulates melanocortin 4 receptors (MC4-R), decreasing appetite, increasing energy expenditure and producing a global slimming effect overall. In addition to α-MSH, POMC neurons simultaneously release β-endorphin, an endogenous μ-opiate receptor antagonist. The binding of β-endorphin to these receptors expressed on POMC neurons exerts negative feedback, inducing a reduction in the release of α-MSH. Blocking this negative feedback by naltrexone is believed to facilitate more potent and lasting activation of POMC neurons, amplifying the effects of bupropion. Preclinical data suggest that naltrexone and bupropion, administered together, may induce more than additive effects in reducing food intake and stimulating energy expenditure , if administered together [10]. The reward / reward system, modulated by dopamine, mediates the rewarding effects of pleasant stimuli (food, sex and drugs of abuse) and plays a central role in regulating eating behavior. Activating the Mesolimbic reward / gratification system can increase the consumption of highly pleasing foods [10].

Correct use of the drug

The triple-layer tablet has two prolonged-release layers, one for each active ingredient, physically separated by an inert layer. The advantages of prolonged release are

a) reduction of adverse effects,

b) reduction of the number of doses,

c) better compliance for the patient,

d) less variability of the plasma concentrations of the drug,

e) more uniform action of the drug,

f) the best efficacy/safety ratio.

At the start of treatment, the dose of the drug should be progressively increased over the course of 4 weeks:

First week : one tablet in the morning

Second week: one tablet in the morning and one tablet in the evening

Third week: two tablets in the morning and one tablet in the evening

From the fourth week onwards: two tablets per day and two tablets in the evening10

The need to continue treatment should be assessed after 16 weeks and reassessed annually. Treatment should be stopped after 16 weeks if patients have not lost at least 5% of their initial weight [10].

In older people who are more likely to have a decrease in kidney function, the dose should be selected with caution and it may be helpful to monitor kidney function. The combination is not recommended in patients over 75 years of age [10].

It is a medicinal product subject to a limited medical prescription, to be renewed from time to time, sold to the public on the prescription of hospital centers or specialists such as the endocrinologist, cardiologist, internist and specialist in food science. The prescription required a non-repeatable recipe.

Efficacy was evaluated in over 4,500 obese and overweight subjects, and / or subjects with controlled hypertension and/or dyslipidaemia or type II diabetes mellitus, enrolled in four multicenter, phase 3, double-blind, controlled placebo, called Contrave Obesity Research (COR), lasting 56 weeks [11-15]. All enrolled patients were asked to change their lifestyle by following a low-calorie diet and regular physical activity. In all studies, the effectiveness of the combination was already demonstrated at 4 weeks, and was maintained throughout the study period. Patients who were treated with the new combination achieved clinically relevant weight loss (≥5% or ≥10%), greater than those treated with placebo. The efficacy of the treatment was greater in subjects who finished 56 weeks of treatment [10].

The most common side effects were nausea, constipation, headache, vomiting and dizziness. Cardiovascular safety and tolerability has yet to be monitored. For this reason, the FDA has requested a study to evaluate the incidence of major cardiovascular events in patients at increased cardiovascular risk. The multicenter, double-blind study, the LIGHT Cardiovascular Outcomes Study of Naltrexone SR / Bupropion SR in Overweight and Obese Subjects with Cardiovascular Risk Factors) Trial, however, was stopped prematurely by the coordinating committee led by researchers from the Cleveland Clinic following the premature communication part of the intermediate results. A new long-term monitoring study on cardiovascular safety began in late 2015 and will end in 2022 [16,17].

Conclusions

In conclusions, obesity remains an urgent challenge for public health, it is a chronic and evolutionary disease, whose treatment must continue for a long time even after reaching weight loss, often for life. It must be addressed by a multidisciplinary team, in which the figure of the specialist doctor must be accompanied by those of the psychologist, the expert in motor rehabilitation and other specialists (diabetologist, internist, cardiologist, bariatric surgeon, plastic surgeon) with the aim of achieve a reasonably optimal weight and above all maintain it over time.

The care and follow-up of the patient must continue even after the achievement of the weight loss, given the very high frequency of relapses, always remembering that the success of the therapy cannot be based only on drugs, even if effective, but on a multidimensional management that provides for the maintenance of an active lifestyle and a conscious and balanced diet, with the support of a qualified care team.

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