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Obesity: State of the Art

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Abstract

Paradoxically, given the degree of malnutrition existing on the planet, obesity is today one of the most visible and yet neglected public health problems. Despite the degree of malnutrition existing on the planet, obesity represents one of the main public health problems in the World. In fact, we are facing a real global epidemic, which is spreading in many countries and which can, in the absence of immediate action, cause very serious health problems in the coming years. A Global Epidemic affecting 50% of the adult population of industrialized civilizations. According to data provided by the WHO, the number of obese people in the World has almost tripled since 1975; in 2016, over 1.9 billion adults, aged 18 and over, were overweight; of these over 650 million are obese. In addition, 41 million children under the age of 5 are overweight or obese. This led the European Association for the Study of Diabetes (EASD) to recognize the importance of obesity prevention and treatment, considered "the most important public health problem in the World".

In Italy 35% of the population is overweight and about 10% is obese equal to about 6 million compatriots. The differences on the territory show a North-South gap in which the southern Regions have the highest prevalence of obese adults (Molise 14.1%, Abruzzo 12.7% and Puglia 12.3%) and overweight (Basilicata 39, 9%, Campania 39.3% and Sicily 38.7%) compared to the northern ones (obese: Bolzano PA 7.8% and Lombardy 8.7%; overweight: Trento PA 27.1% and Valle d'Aosta 30.4%). The percentage of overweight population increases with increasing age and, in particular, the overweight goes from 14% of the 18-24 age group to 46% between 65-74 years, while obesity passes, from 2.3% to 15.3% for the same age groups. In addition, the condition of excess weight is more common among men than women (overweight: 44% *vs* 27.3%; obesity: 10.8% *vs* 9%).

Keywords: Diet; Overweight; Obesity; Therapy

Introduction

From an etiological point of view, obesity has a multifactorial origin and is connected to modifiable risk factors (behaviors, stylesand conditions of life) and to non-modifiable risk factors (genetic determinants) [1].

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 normal energy expenditure, the caloric intake is excessive or if, despite feeding properly, he has a deficit in the energy metabolism. 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 [2].

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:

- 80% of cases of type 2 diabetes
- 55% of cases of high blood pressure
- 35% of cases of ischemic heart disease

All this translates into 1 million deaths and 12 million patients a year, Worldwide. 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 [3].

Literature Review

The role of diet in weight control

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. 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. The clinical goal must be to reduce body weight sufficient to significantly improve the risks associated with obesity, especially cardiovascular ones [4].

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 of the Italian Obesity Society (SIO) and of the Italian Association of Dietetic and Clinical Nutrition [5].

The new drug for the reduction of body weight

The combination Bupropionr/Naltrexone was recently introduced on the Italian market (Mysimba is the commercial name). It 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 following the registration of the product in the USA for a few months [6].

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/m^2 (obese)
- ≥ 27 kg/m^2-30 kg/m^2 overweight in the presence of one or more weight-related

Mysimba is the association of bupropion (antidepressant also used in disuassuefazione from smoke) and naltrexone (antagonist of μ opioid receptors, 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 [7].

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 [8].

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 [9].

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. The reward/reward system, modulated by dopamine, mediate the rewarding effects of pleasant stimuli (food, gender and drugs of they abuse) and play 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:

- Reduction of adverse effects
- Reduction of the number of doses
- Better compliance for the patient
- Less variability of the plasma concentrations of the drug
- More uniform action of the drug
- 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 evening.

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 [11,12].

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. 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 [13].

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. 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 [14].

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 [15].

Conclusion

In conclusion, obesity remains an urgent challenge for the a 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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