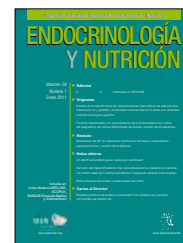




# ENDOCRINOLOGÍA Y NUTRICIÓN

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## EDITORIAL

### What is happening with antiobesity drugs?

#### ¿Qué está pasando con los fármacos para el tratamiento de la obesidad?

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Obesity is undoubtedly one of the most significant health care problems in the developed world today. The prevalence of obesity has substantially increased in the past 30 years in Europe. In many developed countries, more than half of the population is obese or overweight. In 2005, the World Health Organization estimated that there were 400 million obese adults worldwide, and predicted that the figure would increase to 700 million by 2015.

Obesity is particularly important because of the conditions with which it is associated, in addition to mechanical problems. It is very closely related to metabolic problems such as diabetes, hypertension, and dyslipidemia, which are the main determinant factors of the risk of suffering cardiovascular disease. There is also increasing evidence that obese subjects have an increased risk of developing some types of cancer<sup>1</sup>.

The management of obese patients has concerned and occupied physicians for more than ten centuries. The first successful treatment of an obese patient was reported in the 10th century in Spain<sup>2</sup>. The patient was king Sancho I (known as Sancho the Fat), the physician who treated him was Hisdai ibn Shaprut, from the Cordova caliphate, and the drug used was theriac.

Despite more than ten centuries of therapeutic attempts, the history of treatment of obesity is a history of failure. Nobody doubts that the ideal therapeutic approach is to persuade obese patients to change their lifestyle, by decreasing calorie intake and increasing physical activity,

but it must be admitted that interventions aimed at this goal have usually been poorly effective. Acute intervention to achieve lifestyle changes is invariably ineffective if not combined with a continued strategy aimed at motivating patients to maintain such changes.

The U.S. Food and Drug Administration (FDA) considers a drug to be an effective remedy for obesity when a weight decrease greater than 5% occurs in the treatment group as compared to the placebo group<sup>3</sup>. The main target of most anti-obesity drugs marketed to date has been appetite reduction. Drugs used for this purpose have achieved weight decreases ranging from 5% to 10% as compared to placebo, but weight loss is partly regained after drug discontinuation. Despite initially promising expectations, anorexigenic drugs have suffered one setback after another.

The first failure in the recent history of antiobesity drugs occurred with the fenfluramine-phentermine combination, a drug widely used in the US in the 90s. In 1996, Abenhain et al<sup>4</sup> reported a case-control study in which the use of anorexigenic drugs, particularly fenfluramine derivatives, was found to be associated with an increased risk of primary pulmonary hypertension (odds ratio [OR], 6.3), with OR increasing to 23.1 if the drug was taken for longer than three months. Conolly et al<sup>5</sup> subsequently reported a series of 24 women with no prior history of disease who took the fenfluramine-phentermine combination and were subsequently diagnosed with cardiac valve disease. All of these events led the European company that manufactured fenfluramine and dexfenfluramine to withdraw them from the market in the first half of September 1997. The Spanish Ministry of Health also subsequently withdrew these drugs from the market<sup>6</sup>.

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Next in turn was rimonabant, a drug approved in Europe in 2006 whose mechanism of action is the central inhibition of the CB1 receptors. Rimonabant reduces appetite and intake, and also has a peripheral effect on hepatic and adipocyte lipogenesis and on adiponectin secretion. Because of these additional actions, rimonabant also has metabolic effects associated with weight loss, such as improved glycemic control, decreased triglyceride levels, and increased levels of high-density lipoprotein cholesterol. However, the *Rimonabant in diabetes* (RIO) study which allowed for drug marketing had already found a 2%-5% higher dropout rate due to psychiatric side effects in the rimonabant arm as compared to placebo. The most important of these side effects was depression. Subsequently, data concerning cases of depressive disorder, suicidal ideation, and aggressiveness reported by health care professionals continued to be reviewed by the European Union. As of December 2007, 3,102 adverse reactions to rimonabant had been reported worldwide. Some form of psychiatric disturbance was found in 49.5% (1,537) of these cases, and 37% (571) of such disturbances were rated as severe. At a meeting of the European Medicines Agency (EMA) held on October 2008, it was confirmed that patients taking rimonabant had a two-fold greater risk of psychiatric disorders, and that there was no guaranteed way that this risk could be reduced. Drug marketing was therefore suspended as a precautionary measure.

The latest in a line of appetite-suppressant drugs to be marketed as a treatment for obesity, sibutramine, was first marketed in Europe in 1999 and withdrawn from the market in 2010. Sibutramine exerts an anorexigenic effect by inhibiting serotonin and norepinephrine reuptake in the central nervous system. Because of its anorexigenic effect, sibutramine increases heart rate and causes a mean 4-mmHg elevation in blood pressure<sup>7</sup>.

After more than 10 years of use, sibutramine was withdrawn from the market in January 2010 at the request of EMA following analysis of the *Sibutramine Cardiovascular Outcomes* (SCOUT) study<sup>8</sup>. The SCOUT study recruited 10,000 patients with high cardiovascular risk and analyzed the impact of weight management with sibutramine on cardiovascular disease. An increased risk of non-fatal cardiovascular events was found in the sibutramine arm of the SCOUT study. An 11.4% event rate was recorded in the sibutramine group, as compared to 10% in the placebo group. At the time of writing, the FDA has included additional contraindications on the sibutramine label, but continues to allow its use. Withdrawal of this drug has not been free of controversy, because most patients recruited into this study would not have been candidates for treatment with sibutramine based on these newly-authorized conditions for its use.

After this introduction, let us answer the question posed by this editorial. With drugs for the treatment of obesity, the precautionary principle prevails. This principle was first applied in Germany as a means of justifying regulatory intervention to eliminate the spillage of polluting waste to the sea in the absence of a consensus about their harmful effects on the environment<sup>6</sup>, and it has recently led to the closure of European airspace because of the eruption of the Eyjafjalla volcano. But

why does this principle take precedence over that of patient welfare? One could argue that the benefit of a 5% decrease in weight outweighs the damage from any side effects. However, when the problem was reviewed by health authorities, the precautionary principle prevailed in all of the above-mentioned cases. This basically occurred because these drugs induce only slight weight reductions and with no guarantee that such decreases will be maintained in the long term.

In contrast to this rigor with regard to side effects, when surgery is performed as an alternative for patients with morbid obesity, a 0.3%-1.0% of operative and perioperative mortality, much greater than that resulting from the potential complications of these drugs, is assumed. The explanation for this paradox may lie in the fact that surgery for obesity provides very significant and sustained weight reductions. Gastric bypass allows for a mean weight reduction ranging from 35% and 40%, and benefits persist after a 10-year follow-up<sup>9</sup>.

Obesity surgery has not only been a remedy for morbid obesity, but has also provided additional indications suggesting that the bowel may be a good target for research into the treatment of obesity and diabetes. To date, the bowel has only been considered as a therapeutic target for avoiding fat absorption. Orlistat is an intestinal lipase inhibitor that causes a 30% reduction in the absorption of ingested fat. The weight effects are slight, consisting again of approximately a 5% reduction. Orlistat is the only currently available drug indicated for obesity. The FDA recently issued an alert about this drug, reporting severe liver damage in 13 patients (more than 40 million people are taking or have taken this drug).

New targets in obesity, however, are not related to food absorption, but rather to substances secreted by the bowel which have very interesting metabolic effects. Glucagon-like peptide-1 (GLP-1) analogues are the principal substances of this family. Although they are approved for the treatment of diabetes, they have a greater effect on weight than e.g. orlistat<sup>10</sup>. Ghrelin is another interesting molecule, but not only incretins are being researched. The bowel is colonized by more than 15,000 bacterial species which perform a significant number of functions, such as assisting the digestion of indigestible polysaccharides. A great number of articles associating the different composition of the gut microbiota with obesity have been published in the past five years. Some elegant animal studies have shown that if the microbiota from obese mice (ob/ob) is transplanted to germ-free mice, the latter show a marked increase in weight, which does not occur if the microbiota from mice of normal weight is transplanted<sup>11</sup>.

Nobody questions the fact that drugs are needed to treat obesity. Obese people cannot be stigmatized as being unwilling to cope with calorie reduction. But the fact is that no drugs are currently available, and it is difficult to believe that companies will be prepared to assume the risk of research into drugs having anorexigenic properties only. On the other hand, clinicians are likely to be wary of new drugs launched with these mechanisms of action. We can only hope that, in the coming years, new therapeutic targets will override this therapeutic negativity regarding obesity.

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