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EDITORIAL

Pharmacological treatment of obesity in Europe: Waiting for the arrival of the white blackbird☆

Tratamiento farmacológico de la obesidad en Europa: a la espera de la llegada del mirlo blanco

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To decrease the impact of comorbidities associated to obesity, at least 5% of body weight should be lost. With lifestyle changes, this goal may be achieved in a few months, but most patients usually recover weight in the long-term.[1] Maintenance of weight loss is one of the most difficult challenges in the context of an unfavorable biological and environmental situation, and adjuvant treatments are therefore needed.

Innovation in drug treatment of obesity has not paralleled the disproportionate worldwide increase in obesity in the past 20 years.[2] Moreover, repeated drug withdrawal over the years due to side effects has caused regulatory authorities to be much more demanding when approving a new drug indicated for obesity as compared to drugs for any other condition.

In the therapeutic approach to obesity, use of drugs should have a prominent place between treatment based on lifestyle changes (5%–10% weight loss) and bariatric surgery (20%–30% weight loss). Therefore, the Food and Drug Administrative staff (FDA) state that for a drug to be considered effective for the treatment of obesity, it should meet the following conditions: (a) a difference in weight as compared to a >5% after 1 year of treatment, and (b) that the proportion of subjects who lose more than 5% of weight is at least 35% as compared to a placebo. The lack of drug treatments that cover this treatment gap is promoting use of endoscopic procedures or bariatric surgery for grade 1 obesity.[3] Such procedures are not free from side effects which are even more important than those caused by the drugs not marketed on the grounds of caution. Off-label use of drugs not approved for obesity, but which may induce to a significant weight loss, is also gaining ground because of this need to guarantee weight loss in the mid and short term.

Some organizations have called for approval of drugs for obesity even if they have some side effects. In the USA, the Obesity Care Continuum (OCC), represented by the Obesity Society (TOS), the Obesity Action Coalition (OAC), the American Society for Metabolic and Bariatric Surgery (ASMBS), and the American Dietetic Association (ADA), have repeatedly expressed concern for the position of the FDA, which demands greater safety in drugs for obesity as compared to other drugs. In Europe, statements by the EASO (European

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Association for the Study of Obesity) have had little or no impact on the decisions of the European Medicines Agency (EMA) on drugs submitted for evaluation and approval in Europe, despite the fact that they had been approved by its US counterpart. Such differences in opinion between the agencies are frequent. Thus, drugs approved in the US are not approved in Europe, and vice versa, despite the fact that the same dossiers are submitted in both sides of the Atlantic.

Orlistat, approved in 1988, is the only drug remaining in our shelves indicated for the treatment of obesity in Europe. Its mechanism of action is related to inhibition of gastric and pancreatic lipases, which decreases absorption of fat ingested by 30%. In practice, patients reduce their fat intake to avoid the unpleasant side effects of oily diarrhea. Different meta-analyses have shown a small but sustained effect of weight loss, with a difference of 2.9 kg as compared to placebo, which contributes to improve some comorbidities associated to obesity or to prevent diabetes mellitus.[4]

After several years in which no new drug was approved, the FDA approved in 2012 two new drugs for the treatment of obesity: lorcaserin (a selective serotonergic agonist for the 5HT2c subtype) and a combination at low and medium doses of phentermine/topiramate (PHE/TPM), a sympathomimetic agent and an antiepileptic with anorexigenic actions for which greater experience is available as monotherapy.

Lorcaserin (Belviq®) has an appetite-inhibiting central mechanism of action similar to that of fenfluramine and dexfenfluramine, but does not appear to have the effects on cardiac valves (related to the 5HT2 receptor subtypes A and B) which caused withdrawal from market of these two drugs. The tolerability and efficacy of lorcaserin have been tested in three 52-week randomized, placebo-controlled clinical trials (the BLOSSOM, BLOOM, and BLOOM-DM studies) where a dose of 10 mg/day achieved an additional moderate weight loss of 2.9%–3.6% as compared to placebo, with 47% of subjects experiencing a weight loss >5%.[5,6] Lorcaserin side effects (dry mouth, headache, dizziness, nausea) are mild and well tolerated by patients, and there is no evidence so far of an association to cardiac valve disease. It is very important to identify subjects who respond to lorcaserin, because the cost of the drug is estimated at $1500 per year or approximately $265/kg lost. Subjects who lose >5% at 12 weeks of follow-up achieve greater weight losses at 52 weeks (−10.6 kg, with 85.5% of patients experiencing weight losses >5% at 1 year.[7]

Lorcaserin was submitted to the EMA, which rejected marketing of the drug on May 30, 2013 on the grounds that weight loss was modest and risks outweighed the expected benefits. Specifically, experts stated that an action on the serotonergic 5HT2A/B receptors, with the resultant risk for cardiac valves or for the occurrence of serotonergic syndrome of depressive symptoms, could not be ruled out. An additional issue to be resolved would be the potential carcinogenicity shown in animals, in which cases of breast and squamous cell cancer, schwannoma, and astrocytoma have been reported.

The phentermine/topiramate combination (Qsymia®) was approved by the FDA on July 2012. Phentermine is a noradrenergic drug approved in the USA since 1956 as an appetite-inhibiting agent (15–30 mg/day) for use in obesity for periods shorter than 12 weeks. Topiramate was approved in 1996 for the treatment of partial seizures, and in 2004 for the prophylaxis of migraine. The action mechanism of topiramate is complex, but its actions on appetite appear to be related to inhibition of glutamate receptors and GABA activation. The concept underlying this combination is to use much lower doses than usual of the drugs to enhance their effects and decrease their side effects. Thus, clinical trials with Qsymia® have been conducted with low doses of the drugs in the combination, 3.75 mg of phentermine and 23 mg of topiramate (3.75/23), middle doses of 7.5/46 mg, and high doses of 15/92 mg, indicated for patients who do not achieve the weight loss goal with lower doses. In the different Phase III, randomized, double-blind, placebo-controlled studies conducted (EQUIP, CONQUER, and SEQUEL), weight losses were −1.6% for placebo and −5.1%, −7.1%, and −10.9% for PHE/TPM at low, middle, and high doses respectively (intention-to-treat analysis).[6] Side effects are characteristic of both drugs used: dry mouth, paresthesia, sleepiness, anxiety, heart rate increase by 1–3 beats per minute (bpm); there was no evidence of increased depressive symptoms. As for lorcaserin, patients who do not achieve a weight loss >5% at 12 weeks are recommended to discontinue treatment because this drug is also very expensive: approximately $2220/year or $180/kg lost.

After submission of the dossiers of this combination in Europe, the EMA refused its marketing twice (on October 18, 2012 and February 21, 2013), arguing that the benefits did not outweigh the risks of its use. They stated that the long-term safety of phentermine had not been approved (1–3 bpm increases in heart rate), and also that no long-term data were available on the potential harmful neuropsychiatric and cognitive effects of topiramate or the potential teratogenicity (harelip) in pregnant women who take topiramate. Although it was suggested to place a warning on the drug package, or even recommend control of drug prescription by the medical inspection, the regulatory authorities maintained their initial expert report.

On September 2014, the FDA approved a third drug for the treatment of obesity consisting of a sustained-release combination of naltrexone and bupropion (Contrave®). Bupropion is a drug with an inhibitory action of norepinephrine and dopamine used for smoking cessation and as antidepressant. Naltrexone is combined with bupropion to prolong the anorexigenic action of α-MSH on melanocortin receptors. Combined administration of bupropion (360 mg) and naltrexone (16 or 32 mg) in a 56-week, Phase III clinical trial (the COR study, Contrave Obesity Research) conducted on 1742 patients with obesity achieved weight losses of 1.3% (placebo), 5% (naltrexone 16 mg), and 6.1% (naltrexone 32 mg); 42% of patients using the combination achieved weight losses >5%, as compared to 17% in the placebo group.[8] The most significant side effects were headache, dry mouth, dizziness, nausea, vomiting, and constipation. The drug will be marketed with warnings stating that it should not be used in patients with history of depression, suicidal ideation, seizures, drug or alcohol addiction, uncontrolled high blood

pressure, or arrhythmia. In fact, because of the potential increase in blood pressure and heart rate, a cardiovascular safety study (The Light Study) with a 5-year follow-up period, started in 2012 and including 8900 patients, is ongoing.

The application dossier for marketing of this combination in Europe was submitted to the EMA Committee on October 2013, but many clinicians think that, based on what happened with previous applications, approval for marketing in Europe is difficult.

Also on September 2014, the FDA advisory panel approved by 14 votes in favor and one against to submit for consideration by the evaluating committee the indication of liraglutide 3.0 mg (Saxenda®) for the treatment of obesity, based on experience with the drug in diabetes and on an ongoing cardiovascular safety study (the LEADER study: the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results). In the Phase III trials conducted with liraglutide 3.0 mg, enrolling 5344 patients, mean weight loss at 56 weeks in non-diabetic patients was 8% (vs 2.6% with placebo; intention-to-treat data). Weight losses >5% were achieved in 63.5% of patients (26.6% with placebo).[9,10] The interesting thing with this drug is that it has no central side effects and only causes gastrointestinal symptoms, usually transient (nausea, vomiting, or diarrhea), which promotes low treatment discontinuation rates (29%). There are some questions pending clarification, including the higher frequency of acute pancreatitis and cholelithiasis in patients treated with liraglutide, the heart rate increase by 1–3 bpm, and a higher-non-significant-number of some thyroid and breast tumors in the group treated with liraglutide.

Obesity accounts for thousands of deaths every year, with high direct and indirect medical costs (absenteeism and productivity losses). Strategies for prevention and treatment of obesity are therefore urgently needed measures. As recently stated by Herman Toplak, elected chairman of EASO, in the opening session of the last EASO meeting, ''we cannot solve the problem of obesity by surgery; we know that therapies based on lifestyle changes fail in 80%–90% of patients, and since we are living in a difficult environment, we need drugs''. US patients currently have at least three drugs available for the treatment of obesity, for two of which (lorcaserin and the PHE/TPM combination) there are 2 years of post-marketing experience with no serious adverse effects reported. In Europe, the EMA sets the bar higher than in the US as regards surveillance of these drugs, particularly since marketing of sibutramine was discontinued in January 2010, after more than 10 years of experience, based on the results of the SCOUT (Sibutramine Cardiovascular OUTcome) clinical study, conducted on more than 10,000 patients at high cardiovascular risk for 6 years.[11] Cardiovascular risk increased 16% (hazard ratio 1.161; 95% CI 1.029–1.311) at the expense of an increased incidence of myocardial infarction and non-fatal stroke, but not of overall mortality. Although patients participating in the clinical trial were not usual candidates to receive sibutramine because they did not meet the label criteria, the final report of the Committee of Medicinal Products for Human Use of the EMA considered that ''those results are relevant for withdrawal of the medicinal product because benefit-risk was unfavorable for sibutramine, taking into account that patients with overweight usually have greater cardiovascular risk and this may be difficult to identify''. This peculiar decision to place all obese patients under the same umbrella of cardiovascular risk as the study subjects continues to be controversial among healthcare professionals.

Prospects for fighting obesity with drugs continue to be gloomy. On the one hand, we are at a disadvantage as compared to the US with regard to drugs available to treat obesity, but if the financing policies of European health systems do not change, even if a wide drug offer was available, only a few patients with a high purchasing power will be able to benefit from these new drugs. It is therefore not surprising that we begin to see that such revindication may become a chimera.

Conflicts of interest

The author has received fees for lectures and/or consulting from Abbott, Astra-Zeneca, Lilly, Merck-Serono, MSD, Novo-Nordisk, Nestlé Healthcare, Nutricia, Sanofi, Vegenat.

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