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Review

New Medications for Treatment of Obesity: Metabolic and Cardiovascular Effects

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ABSTRACT

The management of obesity remains a major challenge. Dietary therapy often fails, whereas bariatric surgery, although successful, is demanding and applicable to a limited number of patients. Drug therapy has had many setbacks over the past 20 years because of serious adverse effects; however, several new drugs for the treatment of obesity are either licensed in some parts of the world, submitted for registration, or completing phase III trials. These include combinations (at low dose) of existing drugs, eg, bupropion + naltrexone (Contrave), phentermine + topiramate (Qsymia), higher doses of existing drugs licensed for other indications (liraglutide, 3 mg), and new entities (lorcaserin).

We discuss the challenges and opportunities for obesity pharmacotherapy and review in detail the efficacy of the new drugs regarding weight loss and both desirable and potential undesirable cardiovascular (CV) and metabolic risk factors. Substantial barriers remain, even if the drugs are approved, in successfully integrating these agents into weight management practice, largely related to cost, patient acceptability, and clinician willingness to be engaged in obesity treatment. Although hard clinical outcome benefit (at least for CV outcomes) has yet to be established, obesity pharmacotherapy may soon address many of the challenges in the clinical management of obesity, although newer and better drug combinations and more evidence of benefit from appropriately designed outcome trials is needed.

RÉSUMÉ

La prise en charge de l'obésité demeure un enjeu majeur. La thérapie nutritionnelle échoue souvent, tandis que la chirurgie bariatrique, malgré son succès, est exigeante et praticable que chez un nombre limité de patients. La pharmacothérapie a subi plusieurs revers au cours des 20 dernières années en raison d'effets indésirables sérieux. Cependant, plusieurs nouveaux médicaments pour le traitement de l'obésité sont soit homologués dans certaines parties du monde, soit soumis à l'homologation ou en cours d'achèvement d'essais cliniques de phase III. De ce nombre, citons les combinaisons (à faible dose) de médicaments existants, par exemple le bupropione + la naltrexone (Contrave), la phentermine + le topiramate (Qsymia), des doses plus élevées de médicaments existants homologués pour d'autres indications (le liraglutide, 3 mg) et de nouvelles substances (la lorcasérine).

Nous discutons des enjeux et des possibilités de la pharmacothérapie contre l'obésité et passons minutieusement en revue l'efficacité des nouveaux médicaments quant à la perte de poids, aux facteurs de risque cardiovasculaire (CV) et métabolique désirables et indésirables potentiels. Même si les médicaments sont approuvés, il reste d'importants obstacles à surmonter pour réussir l'intégration de ces agents à la pratique pour la prise en charge du poids, en grande partie liés au coût, à l'acceptabilité des patients et à la bonne volonté du clinicien de s'impliquer dans le traitement de l'obésité. Bien que les avantages tangibles des résultats cliniques (du moins en ce qui concerne les résultats CV) n'aient pas encore été établis, la pharmacothérapie contre l'obésité pourra bientôt relever les nombreux défis de la prise en charge clinique de l'obésité. Cependant, de plus récentes et de meilleures combinaisons de médicaments et plus de données probantes sur les avantages provenant d'essais cliniques bien conçus sont nécessaires.

The rising tide of obesity is an increasing threat to the health of populations globally. According to a recent systematic analysis, in 2013, > 2.1 billion of people were overweight worldwide, defined by body mass index (BMI) ≥ 25 kg/m^2, or obese (≥ 30 kg/m^2) compared with 857 million in 1980. The prevalence of overweight and obesity combined rose by 27.5% for adults and 47.1% for children during the same period. This trend has been true both in developed and developing countries, although it now appears to be slowing down in the former.[1] The high burden of comorbidities (such as type 2 diabetes mellitus [T2D], cardiovascular [CV] disease, and certain cancers) associated with obesity heighten the severity of this obesity crisis.[2] In 2010, overweight and

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obesity were estimated to cause 3.4 million deaths worldwide.[3] There is a close relationship between obesity, metabolic disturbances, and CV risk (so-called cardiometabolic [CM] risk), which involves a number of mechanisms, including increased inflammation, dyslipidemia, hypertension (HTN), and insulin resistance, as well as alterations in sympathetic nervous system activity. Most deaths attributable to overweight and obesity are CV deaths,[3] and this trend is true even when starting from a BMI > 23 kg/m^2.[2] Data from the 1946 British birth cohort study showed that prolonged exposure to high adiposity in adulthood had a cumulative adverse effect on carotid intima media thickness and higher blood pressure (BP) affecting the overall CV risk,[4] although weight loss at any time appeared to be protective.

Therefore, obesity is associated with very high preventable costs, and this economic burden is beginning to raise global political awareness.[5] Although prevention of obesity is the strategic imperative, treatment of obese patients, preferably at a stage before end-organ damage has occurred, should also be an urgent priority. Lifestyle modification is the first step in weight management. Intervention programs focusing on diet or exercise, or both, are effective in inducing weight loss and weight loss maintenance in the short to medium term but lose efficacy in the long term; despite this patients may retain clinical benefits in the long term from reduced CV and all-cause mortality and reduced T2D incidence.[6-11] In most guidelines, bariatric surgery is reserved for patients with severe or complicated obesity (BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 in the presence of at least 1 obesity-related comorbidity) and is the most effective treatment regarding weight loss achieved and maintained and amelioration of obesity-related comorbidities.[12-14] A recent meta-analysis of 11 trials that included 796 participants and was randomized to either bariatric surgery or nonsurgical treatment found that bariatric surgery resulted in greater weight loss, remission of T2D and metabolic syndrome, and lipid profile improvement.[15] Bariatric surgery also reduces all-cause and CV mortality.[13] However, surgery will never be able to be performed on a scale large enough to address the pandemic proportions of obesity, and it is also subject to an increasing number of recognized medical and surgical complications and weight regain.[16,17] Clearly, effective alternative approaches are required, and it is appropriate that pharmacologic treatment should be considered as a treatment option.[18,19] In this review, we discuss the CV and metabolic benefits and risks of new antiobesity drugs.

Dichotomies in Obesity Pharmacotherapy

Past experience

Despite efficacy in producing weight loss and CM improvement, previous antiobesity drugs have also had serious adverse CV side effects. The fenfluramines, developed in the 1980s, were effective satiety-enhancing drugs that acted mainly through enhancing central serotoninergic neuronal transmission (by both release and reuptake inhibition of serotonin) but were found to cause (fatal) pulmonary HTN and cardiac valve abnormalities (especially when combined with phentermine) and were withdrawn from use in 2004.[20] Sibutramine, a selective serotonin and norepinephrine uptake inhibitor had been licensed and in use worldwide since the 1990s. Concerns that the drug had unwanted, and potentially dangerous, sympathomimetic effects that could raise BP and pulse led to a demand from the European Medicines Agency (EMA) for a CV outcome trial. The findings from the **S**ibutramine **C**ardiovascular **Out**comes (SCOUT) trial of an increased incidence of nonfatal myocardial infarction and stroke led to its withdrawal in the United States and Europe (although it is still licensed in some Latin American countries).

From the Clinician to the Patient

Patient and clinician expectations of antiobesity drugs differ. The clinician expects an antiobesity drug to normalize deranged factors involved in the pathogenesis of obesity, reduce body fat stores, ameliorate obesity-related comorbidities, reduce mortality, and improve quality of life with minor or acceptable side effects; yet the Look AHEAD: Action for Health in Diabetes study, an intensive diet and lifestyle intervention trial based on that used in the Diabetes Prevention Program but that also included the use of meal replacements and orlistat, suggested that 8% weight reduction in obese patients with T2D was insufficient to reduce CV disease.[21] Patients, however, often focus on weight loss alone and often have unrealistic expectations and may not wish to remain on a drug long term.[22-25] Thus, although lifestyle and pharmacologic interventions can reverse metabolic syndrome, the lack of data on whether these benefits are sustained and translate into longer term prevention of T2D or CV disease, or both,[26] may undermine confidence in this approach by both clinicians and patients.

From Europe to the United States

The US Food and Drug Administration (FDA) and the EMA differ in the criteria they set for efficacy of antiobesity drugs.[27] Efficacy is determined by mean and categorical weight losses at 1 year:

1. Mean efficacy is defined as the percentage of placebo-subtracted weight reduction.
2. Categorical efficacy requires that the significantly greater proportion receiving the medication doubles the placebo loss and maintains weight loss from their initial weight.

The FDA requires that mean efficacy is a $\geq 5\%$ difference in mean weight loss and that $\geq 35\%$ of drug-treated patients lose $\geq 5\%$ of body weight from baseline.[28] The EMA regards weight reduction from baseline as being more clinically relevant than placebo-subtracted weight loss and requires evidence for a mean weight loss $\geq 10\%$ at 1 year, which must also be $\geq 5\%$ greater than that achieved on placebo. Few drugs previously approved, or being considered for approval, have met both agencies' criteria. None of the weight-loss medication most recently approved by the EMA (orlistat, sibutramine, rimonabant) met the 10% criterion but were approved as meeting an alternative efficacy target, namely, a significantly greater proportion of patients losing more than 10% of their baseline body weight in the active treatment group compared with those in the placebo group at the end of a 12-month period.