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EXPERT OPINION

Overview of new antiobesity drugs

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A short overview of new drugs approved for the treatment of obesity (lorcaserin, phentermine/topiramate combination) as well as those with a perspective for approval as antiobesity drugs (cetilistat, naltrexone/bupropion combination, liraglutide) is presented. All these drugs produce significant weight loss accompanied by reductions in cardiometabolic health risks. Although the adverse events were rather rare and tended to decrease with the duration of treatment with most of these medications, the drug-specific safety concerns should be seriously considered. In order to ensure an appropriate, efficient and safe implementation of novel antiobesity drugs into the comprehensive treatment of obesity, it will be necessary to establish a network of physicians and other health-care providers well educated in obesity management.

Keywords: antiobesity drugs, cetilistat, liraglutide, lorcaserin, naltrexone/bupropion, phentermine/topiramate

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1. Introduction

Antiobesity drugs are employed to enhance both weight loss and reductions in cardiometabolic health risks achieved by lifestyle modification alone [1-3]. They should further reduce visceral obesity, improve program adherence and weight loss maintenance, improve quality of life and be preferentially administered orally, devoid of serious adverse events, and distributed at affordable prices. Withdrawal of several antiobesity drugs from the market and discontinuation of clinical trials led to skepticism concerning their role in the treatment of obesity [3]. After voluntary withdrawal of sibutramine from the market in 2010 due to cardiovascular risk concerns [4], orlistat remained the only medication indicated for the long-term treatment of obesity.

2. New antiobesity drugs approved for treatment of obesity

In 2012, both lorcaserin and phentermine/topiramate extended-release (PHEN/TPM ER) combination were approved by the US FDA for treatment of patients with body mass index ≥ 30 or ≥ 27 kg/m^2 with comorbidities. A recently published review article by Gadde summarized the main issues concerning the efficacy, safety and tolerability of drugs currently approved for obesity management [5]. Three essential clinical trials were carried out with each novel antiobesity drug: EQUIP, CONQUER and SEQUEL with PHEN/TPM ER and BLOOM, BLOSSOM and BLOOM-DM with lorcaserin. SEQUEL [6] and BLOOM [7] trials were carried out for 2 years.

Lorcaserin acts as a selective serotonin 2C receptor agonist that due to a reduction of food intake leads to a mean total weight loss of 5% (2.9 – 3.6% placebo-subtracted weight loss) after 1 year of administration. PHEN/TPM ER combination provides immediate release of sympathomimetic amine phentermine (used over 50 years as anorectic drug for the short-term weight management in the US

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and several other countries) and extended release of topiramate (approved as an anticonvulsant drug). This drug is highly effective in terms of total weight loss, which reaches about 10% (7.5 – 8.7% placebo-subtracted weight loss). The combination led to a reduction of side effects in comparison with administration of each component alone. Both drugs demonstrated beneficial influences on abdominal obesity, lipid and glucose profile, blood pressure and fibrinogen levels as well as on the quality of life. It is well known that obesity is characterized by a chronic low-grade inflammation that is linked to the development of cardiovascular risks. High-sensitivity C-reactive protein, as an inflammatory marker, significantly decreased after 1 year of treatment with both lorcaserin and PHE/TPM ER. Subsequent studies with PHEN/TPM ER also revealed significant reduction in the incidence of type 2 diabetes, improvements in liver function and functional tests in sleep apnea and reductions of concomitant medications for cardiometabolic diseases. Adverse events were dose dependent and rather rare with both novel medications and tended to decrease with the duration of treatment. Incidence of side effects was lower with lorcaserin than with PHEN/TPM ER treatment. Most trials with antiobesity drugs exhibited rather high discontinuation rates. Somewhat higher drop-out rate in lorcaserin than in PHEN/TPM ER trials might have been due to its lower efficacy in terms of weight loss. Serious safety concerns for both drugs include cognitive and psychiatric adverse effects. Awareness of potential development of serotonin syndrome after lorcaserin and oral clefts and mild metabolic acidosis after PHEN/TPM ER should be considered. Although the heart valvulopathy has not been demonstrated with lorcaserin administration, safety concerns with regard to cardiac valvulopathy should be taken into account in patients treated with lorcaserin. A small, usually transient, increase in pulse rate although accompanied by a decrease in both systolic and diastolic blood pressures after PHEN/TPM ER should be considered in patients with established cardiovascular diseases [8]. Permeability glycoprotein (Pgp) transport system represents a hot topic in drug-drug interactions as well as in issues related to drug's efficacy and resistance. It should be taken into account that topiramate is a substrate for Pgp, and brain levels of topiramate may be affected by overexpression of Pgp as observed in patients with intractable epilepsy [9].

3. Medications with a perspective of approval as antiobesity drugs

Cetilistat acts similarly as orlistat and inhibits gastrointestinal lipase. Decreased fat absorption induces only modest weight loss associated with improvement in glucose and lipid profile [10]. Adverse events and discontinuation rates with cetilistat are less common than with orlistat. Phase III trials with cetilistat performed in obese patients with type 2 diabetes and dyslipidemia in Japan resulted there in its subsequent approval in 2013 as a drug for the treatment of obese patients having both type 2 diabetes and dyslipidemia.

Naltrexone sustained release (SR)/bupropion SR combination (NB) consists of two already existing medications: an opioid antagonist naltrexone and an antidepressant bupropion. The drug improves control over eating and food craving by its effects on both anorexigenic hypothalamic melanocortin pathway and rewarding mesolimbic system. Obese patients treated over 12 months with NB achieved 4.6% greater weight loss than controls. The drug induced an improvement in blood sugar control, lipid profile and weight-related quality of life [11]. Due to concerns about cardiovascular safety of NB, FDA declined its approval in 2011. In November 2013, the manufacturer announced that the interim analysis of the cardiovascular outcome trial (The Light Study), which included 8900 patients, did not lead to a significant increase in cardiovascular adverse events. Applications for marketing authorization have already been submitted to the drug regulating agencies in the US and Europe. An approval of this drug is expected in 2014.

Analogs of naturally occurring gut hormones (glucagon-like peptide-1/GLP-1/, oxyntomodulin, peptide YY, ghrelin) engaged in energy balance regulation may in the future represent a specific and low side-effect approach in the treatment of obesity. A GLP-1 analog liraglutide was approved for the treatment of type 2 diabetes. Clinical trials conducted over 2 years with liraglutide (3 mg/day) in obese patients confirmed significant weight loss and reduction of cardiometabolic health risks [12]. Transient nausea and vomiting occur in some treated patients. An observed increase in heart rate after liraglutide is opposed by its cardioprotective properties [13]. Preclinical evidence does not support the safety concerns with regard to β-cell proliferation and risks of pancreatitis and pancreatic cancer with incretin-based therapies. A need for a parenteral administration and formation of antibodies will limit the use of gut hormone analogs in some patients.

4. Advantages of combination drugs

Recently, 107 randomized placebo-controlled studies with antiobesity drugs have been analyzed [3]. The greatest weight loss (about 10 kg after 1 year of treatment) was achieved with combination medications. It appears that greater weight loss leads to enhanced reduction in cardiometabolic health risks. However, some antiobesity drugs similar to lifestyle intervention may also improve metabolic profile independently of weight loss. Drug combinations in reduced dosage may result in increased efficacy and reduction of side effects (e.g., PHEN/TPM, NB) or in potentiation of side effects caused by drug interactions (e.g., phentermine/fenfluramine). Phentermine suppresses the clearance of serotonin, and this way enhances the serotoninergic effects of serotonin releasing drugs such as fenfluramine [14]. Due to safety concerns, adverse events documented in individual components of

the combined antiobesity drugs have still been declared although their occurrence has not been demonstrated in clinical trials.

5. How to achieve successful involvement of the new antiobesity drugs in weight management

Realistic goal in the weight management should be focused on reduction of health risks. We have to persuade both patients and physicians that 5 – 10% weight loss is already associated with reduction of cardiometabolic health risks and represents a realistic goal in a nonsurgical weight management [1,2].

Indications and contraindications of antiobesity drugs should be strictly kept in mind. After the experience with the SCOUT Study [4] where almost 90% of the recruited patients were contraindicated to sibutramine according to the drug labeling, a requirement of the European Medicines Agency (EMA) for cardiovascular outcome trials in elderly subjects with established cardiovascular disease does not seem reasonable. Antiobesity drugs should be indicated for the treatment of obesity and related health risks in order to prevent cardiovascular diseases, particularly in young and middle-aged subjects, but not primarily for the treatment of elderly patients with established cardiovascular diseases.

Physicians should seriously consider potential increased risk/benefit ratio of drug-induced weight loss in polymorbid elderly patients, frequently treated with multiple medications. Long-term administration of antiobesity drugs should be indicated only in responders, that is, only in those who lost at least 5% of their body weight (patients with diabetes achieving weight loss $\geq$ 3%) after initial 3-month treatment.

Perception of obesity and antiobesity drugs must be changed. It is generally agreed that the current global epidemic of obesity is mainly due to lifestyle changes induced by the obesogenic environment [15]. Obesity, however, cannot be considered simply as a lifestyle disease and should be accepted as a complex disease with serious health consequences by health-care providers, national health-care authorities and drug regulating agencies. In addition to environmental factors, the development of obesity is affected by multiple additional factors: hereditary, psychological, biological, etc. It should be kept in mind that not only weight gain itself, but also the weight loss in response to weight management is greatly influenced by hereditary factors. Antiobesity drugs cannot be perceived just as lifestyle medications as they normalize or improve regulatory and/or metabolic disturbances that lead to the development of obesity. They should be handled in a similar way as the drugs designated for the treatment of other complex diseases as hypertension or diabetes. Taking into account the mechanisms of action of antiobesity drugs, it is apparent that they should be administered lifelong in order to normalize, frequently inherited, multiple dysfunctions characterizing different obesities. Genetically determined body weight set point is however vigorously defended. It has been shown that the discontinuation of treatment with antiobesity drugs or their replacement with placebo results in weight regain and deterioration of cardiometabolic profile of an obese individual. This experience justifies a need for continuous administration of antiobesity drugs in order to preserve their beneficial effects on metabolic and/or regulatory disturbances that contribute to the development of obesity. Pharmacotherapy of obesity should be implemented in the individually tailored weight management program considering degree and character of obesity, gender, age, individual pathogenic factors, response to previous weight loss attempts and presence of comorbidities. In order to ensure comprehensive obesity management including appropriate prescriptions of antiobesity medications to the indicated patients, a multilevel obesity management network that includes obesity management centers, obesity specialists, other specialists and primary care physicians was proposed in Europe in 1999 [16]. However, currently, in some aspects, better conditions have been provided for obesity management in the US than in Europe. Two new antiobesity drugs have been available in the US, but none of the new antiobesity medications have been approved by the EMA [17]. Coverage of antiobesity medications for the US Federal Employees was announced in March 2014 while there has still not been a reimbursement for these drugs by health insurance in most European countries. The first round of the American Certification Examination for Obesity Medicine Physicians will be conducted in December 2014 while a specialization in Obesity Medicine has not been recognized in Europe.

6. Expert opinion

New antiobesity drugs produce additional weight loss and reduction of cardiometabolic health risks to that achieved by lifestyle modification alone. Approval of lorcaserin and PHEN/TPM ER by the FDA and expected negotiations on approval of additional antiobesity drugs is a good news for clinicians. Until now only a lipase inhibitor orlistat that induces only a minor weight loss has been available for the long-term treatment of obesity. Moreover, clinical experience revealed that lifestyle intervention alone is effective only if applied intensively and continuously in highly motivated patients. Most clinicians cannot provide this expensive and time-demanding treatment on long-term basis. However, antiobesity drugs applied after the lifestyle intervention may not only provide additional weight loss but also ensure a long-term weight loss maintenance. I believe that it will be necessary to establish a network of physicians well educated in obesity management in order to guarantee an efficient and safe implementation of new antiobesity drugs into the comprehensive treatment of obesity. In future, appropriately designed clinical trials on

efficacy and safety of novel antiobesity agents are required covering the long-term studies on their effects on morbidity and mortality. Further analysis is also needed with regard to rather high dropout rates in clinical trials with antiobesity medications. Special attention should be paid to overcoming the development of tolerance to some antiobesity medications as well as to potential use of antiobesity drugs in adolescents and to efficacy of their intermittent administration. If more antiobesity drugs with different mode of action will be available, specific individually tailored treatment of obesities focused on their complications can be expected.

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Declaration of interest

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