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PHARMACOTHERAPY IN THE TREATMENT OF OBESITY

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Abstract

Background and Aims: *In the last three decades, obesity and its related co morbidities has quickly increased. Sometime, obesity was viewed as a serious health issue in developed countries alone, but now is recognized as a worldwide epidemic, and its associated costs are enormous. Obesity is related with various diseases, like hypertension, type 2 diabetes mellitus (T2DM), dyslipidemia, chronic cardiovascular diseases, respiratory conditions, alongside chronic liver diseases, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). This review purpose is to provide data on the current anti-obesity drugs, also available and in the development.* ***Material and Methods:*** *We searched MEDLINE from 2006 to the present to collect information on the anti-obesity pharmacotherapy.* ***Results and Conclusions:*** *In the patients with obesity related comorbidities, there may be an adaptation of the anti-obesity pharmacotherapy to the patients' needs, in respect to the improvements of the cardiometabolic parameters. Although their efficacy was proven, the anti-obesity pharmacotherapies have presented adverse events that require a careful monitoring during treatment. The main obstacle for approve new drugs seems to be the ratio between the risks and the benefits, because of a long-time background of perilous anti-obesity drugs.*

key words: *anti-obesity pharmacotherapy, diethylpropion, lorcaserin, orlistat, phentermine/topiramate.*

Introduction

The World Health Organization (WHO) describes obesity as an excess accumulation of fat within the adipose tissue, with a health damaging potential. Since 1980, the cases of worldwide obesity have doubled [1]. WHO reported more than 1.9 billion overweight adults, aged 18 years old or older in 2014, among which over 600 million are obese. In 2014, 39% of the adults (≥ 18 years) were overweight while 13% were obese. A total of 41 million children < 5 years old were overweight or obese in 2014 [2], and this expected to reach 60 million by the year 2020 [3].

Obesity is one of the most prevalent health problem that affecting all age groups of populations, and leads to many complications. It is well known that obesity promote the development of metabolic disorders (e.g. dyslipidemia, T2DM), hypertension, stroke, ischemic heart disease, sleep apnea and other

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pulmonary problems, gallbladder disease, osteoarthritis, as well as chronic liver disease including nonalcoholic fatty liver disease (NAFLD) and its most severe group, nonalcoholic steatohepatitis (NASH) [4,5]. Due to the extent of this disease, the obesity prevention and treatment represent an important problem for health systems, with a purpose of reducing the obesity prevalence and its complications all over the world [1].

Short history of anti-obesity drugs

Since 1947, amphetamine-derivatives were authorized for the obesity treatment in the United States (US), but their abuse and addiction potential, as well as reports regarding myocardial toxicity and sudden death led to the decrease of their use [6]. During the 1980s-1990s, an amphetamine derivative called fenfluramine was considered to be anorectic, and in this new light, the relative lack of direct influence on dopaminergic and noradrenergic neurons favoured a better profile in respect to the abuse possibility. Despite of the above mentioned, the treatment was restrained in 1997. This decision was a consequence of the observations included in a heart valve injury report and an increased risk of pulmonary high blood pressure in 24 women treated with fenfluramine [7,8].

Rimonabant, a potent, selective endocannabinoid (CB1) receptor antagonist that suppresses appetite, was approved by the European Medicines Agency (EMA) in 2006, and it was withdrawn in 2008 due to concerns associated with serious psychiatric sequelae such as anxiety, depression and suicide [8,9]. Therefore, neurocognitive sequelae currently need to be assessed in all clinical trials that test anti-obesity drugs targeting endocannabinoid system [10].

Table 1. Anti-obesity drugs for long-term use approved by the FDA (Adapted after [6,8]).

Drug	Trade name	Dosage	Mechanism of action	Status
Orlistat	Xenical®	120 mg TID	Pancreatic lipase inhibitor	FDA- approved (04/1999)
Lorcaserin	Belviq®	10 mg BID	Selective 5-HT_{2C} receptor agonist	FDA- approved (2012)
Phentermine/ Topiramate ER (extended release)	Qsymia®	3.75 mg/23 mg (14 days) 7.5 mg/46 mg (thereafter)	Sympathomimetic amine with anorectic effect/blocks voltage-dependent sodium chanels, glutamate receptors and carbonic anhidrase, and augments GABA activity	FDA- approved (07/2012)
Naltrexone/ Bupropion	Contrave®	32 mg/360 mg (achieved after 4 weeks)	Blocks opioid receptors on POMC neurons, prevents feedback inhibition, increases activity of POMC neurons	Approved by FDA- (09/2014) and EMA (03/2015)
Liraglutide 3 mg	Saxenda®	3 mg	GLP-1 receptor agonist	Approved by FDA (12/2014) and EMA (03/2015)

TID = three times daily; BID = twice daily; 5-HT = 5-hydroxytriptophan; GABA = γ aminobutirate; POMC = pro-opiomelanocortin; GLP-1 = glucagon-like peptide-1.

In 1997, sibutramine, a serotonin-norepinephrine uptake inhibitor with structural similitude with amphetamines, was released in the USA. However, sibutramine was also retracted in in 2010, due to an increase in cardiovascular (CV) risks [11].

Finally, orlistat, a pancreatic lipase inhibitor was approved in 1999 by the Food and Drug Administration (FDA), for the long-term management of obesity. Among its characteristic side effects the most prominent is steatorrhea [12]. Some reports of severe liver injury determined the FDA to release a warning in May 2010. In 2011, Weir *et al.* reported the results of a study performed in Ontario, Canada evidencing that patients treated with orlistat within a seven-year timeframe showed an increase of 2% in acute renal injury within 1 year of beginning of the treatment [13].

After many years with a paucity of anti-obesity drugs, the FDA has recently approved various new anti-obesity drugs.

Current pharmacotherapeutic options for the treatment of obesity over long-term

In general, pharmacotherapy is for overweight or obese patients who do not achieve weight loss only by changing their lifestyle and with no indication for obesity surgery.

Advances in understanding the homeostatic and pathologic mechanisms underlying the development and maintenance of elevated body fat mass have led to a new pharmacological approach of obesity.

In present, five anti-obesity drugs for long-term use were approved by FDA. In Table 1, we register the long-term medications that are used at present to determine weight loss.

Orlistat

Orlistat is a semisynthetic derivative of lipstatin. Orlistat is a long-acting and strong inhibitor of pancreatic lipase. Thus, it decreases the intestinal absorption of about 30% of ingested fats [14]. Its effect is reversible. Orlistat has two available formulations: One of 120 mg that can be released on prescription only, and another of 60 mg that can be sold over-the-counter. Orlistat was also approved for the treatment of obesity in teenagers in 2003. In the Xendos study, treatment with orlistat in patients with impaired glucose tolerance at baseline led to a 45% risk reduction in the progression to T2DM [15]. Orlistat is recommended for the treatment of obesity in obese (body mass index – BMI $\geq$30 kg/m^2) or overweight (BMI 27-29.9 kg/m^2) subjects with associated risk factors, in relation with a moderately fat-reduced diet [16].

Lorcaserin

The serotonin (5-HT) role in energy homeostasis was already well established and clinically used by fenfluramine and sibutramine. These two compounds stimulate the release of 5-HT and block its reuptake from the synaptic space. Consequently, they promote satiety and reduce food intake both in rats and humans [17]. Lorcaserin distinctly differs, as it is both a potent and highly selective 5-HT$_{2C}$ agonist with ~15 times more (respectively ~100 times more) higher affinity for the 5-HT$_{2C}$ receptors vs. 5-HT$_{2A}$ and, respectively, 5-HT$_{2B}$ receptors [18]. Lorcaserin is the first serotonin-2C agonist that was approved in the USA for the long-term management of obesity. However, it is not available in Europe, because the EMA's concern about potential risk of tumors, valvular diseases and psychiatric disorders that were reported in clinical trials [19].

Phentermine/Topiramate ER

The combination of phentermine and extended-release topiramate received FDA approval for weight management in July 2012. It is recommended (in addition to a reduced calorie diet and increased physical activity) for subjects with BMI $\geq$ 30 kg/m^2 or BMI $\geq$ 27 kg/m^2 and with at least one obesity associated condition, including hypertension, T2DM, or dyslipidemia [20]. Phentermine, chemically related to amphetamines, carries out its effect mainly by reducing food intake following an increase of the

adrenergic tone, as well as by increasing the resting energy expenditure. Phentermine is approved in monotherapy for the short-term treatment (less than 12 weeks) of obesity [21]. Topiramate is an anti-epileptic drug that has been approved already from 1996 for this condition, indication expanded in 2004 for migraine prophylaxis. The weight loss mechanism of topiramate is not yet fully understood. It seems that it suppress appetite and induce satiety by a combination of actions: increased activity of gamma-aminobutyric acid (GABA), modulation of voltage-dependent calcium and sodium channels, and inhibition of carbonic anhydrase [14,20]. EMA has refused the approval of phentermine/ER topiramate due to the potential risks (cardiovascular, psychiatric and cognitive, teratogenicity) associated with its long-term use [22].

Naltrexone/Bupropion

Naltrexone/bupropion is a drug association therapy approved for long-term obesity treatment in adults, in combination with the adequate lifestyle changes (low calorie diet and exercise) [23,24]. Naltrexone is a μ-opioid receptor antagonist with a high affinity that has weight-loss effects, and approved for the alcoholism and opioid addiction treatment. The melanocortin and the reward systems in the hypothalamus contain opioid neurons [25] so naltrexone can modulate food intake through both systems. Bupropion is a reuptake inhibitor of dopamine and norepinephrine. It can stimulate satiety due to a combination of dopaminergic/ noradrenergic effects on pro-opiomelanocortin (POMC) signaling [26]. Naltrexone/bupropion combination leads to lower food intake and increased energy expenditure, both explaining the weight loss over time. The combination naltrexone/bupropion was approved in the US in 2014, and in the European Union (EU) in 2015.

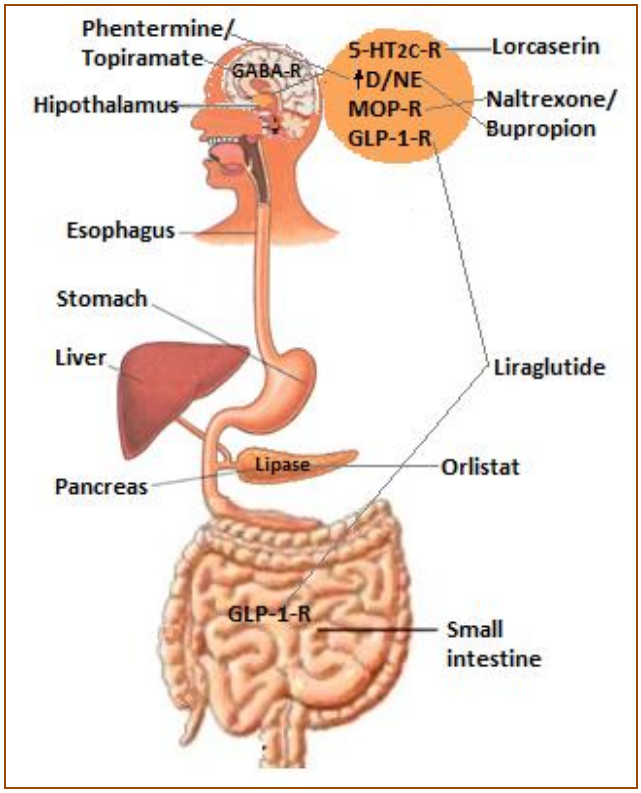

Figure 1. *Mechanism of action of long-term anti-obesity pharmacotherapies (Adapted after [26])*
5-HT_{2C}-R = 5-hydroxytryptamine 2C receptor; D/NE = dopaminenorepinephrine; GABA-R = γ-aminobutyric acid receptor; GLP-1-R = glucagon-like peptide-1 receptor; MOP-R = μ-opioid receptor.

Liraglutide

Liraglutide is a long-acting glucagon-like peptide-1 (GLP-1) receptor analogue (GLP-1RA) that was already used for the glycaemic management in T2DM adults in once daily doses of up to 1.8 mg. It is marketed under the brand name of Victoza® [27]. Clinical trials in T2DM subjects with 1.2 and 1.8 mg of liraglutide reported a robust weight loss effect and led to the clinical testing of the 3 mg once daily dose of liraglutide for weight management in patients with overweight or obesity, with or without diabetes [26,28]. Liraglutide 3.0 mg is the first GLP-1RA approved for weight management over long-term in overweight or obesity subjects. It was approved by the FDA in the USA in December 2014 and by EMA in Europe in March 2015, as an add-on to exercise and low-calorie diet in adults with BMI ≥ 30 mg/m^2 or ≥

27 kg/m^2 with at last one weight-related comorbidity [29,30].

The mechanisms of action for all the above mentioned drugs are highlighted in Figure 1.

Anti-obesity drugs in development

The history and present of anti-obesity pharmacotherapy underlies the need for additional approaches for the safe and efficient treatment/prevention of obesity. In the next part we discuss new targets that are currently investigated for the treatment of obesity and the drugs that are now under development.

New targets for treatment of obesity

It was established that the endocannabinoid system contributes to the regulation of appetite and food intake, energy spending, insulin sensitivity, glucose and lipid metabolism. From this point of view, this system represents a focus for research for new anti-obesity drugs development. Whether the blockade of the cannabinoid receptor type 1 (CB1) receptor seems to be a promising alternative for obesity treatment, a reasonable approach in order to avoid the central nervous system (CNS) side effects previously reported for rimonabant would be to project selective CB1-antagonists that cannot cross the blood-brain barrier [31]. Other strategies targeting the endocannabinoid system include approaching other cannabinoid receptors including the cannabinoid receptor type 2 (CB2), the G protein-coupled receptor 55 (GPR55) and GPR119, and the Transient Receptor Potential Vanilloid 1 (TRPV1) [10]. Deveaux *et al* showed that CB1 and CB2 exhibit congruent effects, *via* complementary pathways. Thus, CB2 was shown to increase the low-grade inflammation associated with obesity, fatty liver and insulin resistance in high fat diet mice [32]. Thus, CB2 blockage may represent a new approach for the management of metabolic alterations associated with obesity [32].

Currently, Ghoshal *et al* show that inositol hexakisphosphate kinase-1 (IP6K1) removed, protects mice against high fat diet induced obesity (DIO) and insulin resistance. If this pathway is a valid pharmacologic target in obesity/T2DM, it is not known yet. They reported that TNP [N2-(m-Trifluorobenzyl), N6-(p-nitrobenzyl) purine], a pan-IP6K inhibitor, has strong anti-obesity and anti-diabetic effects in DIO mice and this study can arouse the enthusiasm for exploring the possibility of pharmacologic inhibition of the inositol pyrophosphate pathway in human obesity, fatty liver diseases, or T2DM [33].

Anti-obesity drugs in development

Bupropion/Zonisamide

Bupropion, already used in combination with naltrexone as discussed above, is also currently evaluated in another combination with zonisamide, a potent inhibitor of carbonic anhydrase that has been used as an antiepileptic drug. Some short-term studies with zonisamide in the treatment of epileptic patients revealed weight loss as a secondary effect. In a phase IIb trial, that evaluated 729 patients for a 24-weeks period, 164 patients treated with bupropion/zonisamide (both 360 mg) lost 7.5% of their body weight at baseline, while 81 patients treated with the 360 mg/120 mg dosage lost 6.1% of their body weight at baseline. This was significantly ($p \leq 0.001$) better than placebo treated patients who decreased their body weight by 1.4% [34,35].

Beloranib

Beloranib represents a novel class of obesity drugs that was discovered by Zafgen's researchers, acting as selective methionine aminopeptidase 2 inhibitor, a mechanism by which fat biosynthesis is reduced, and fat oxidation and lipolysis, are increased [36]. A

phase II trial investigated the subcutaneous administration of a beloranib suspension (0.6 mg, 1.2 mg and 2.4 mg) compared to placebo in 147 obese subjects. After 12 weeks treatment, weight loss totaled 5.5–10.9 kg (5.3–10.6%) for the beloranib 0.6–2.4 mg twice weekly group in comparison with 0.4 kg (0.3%) for placebo treated subjects (all $p < 0.0001$ vs. placebo) [37]. In this study, beloranib exhibited a good safety profile for the 0.6 mg and 1.2 mg doses that were well tolerated, while patients treated with the 2.4 dose reported adverse events like sleep disturbance, nausea and vomiting [37]. However, Zafgen announced, in July 2016, that the company ceased the development of beloranib for the treatment of obesity in patients with Prader-Willi Syndrome (PWS), because in December 2015, the FDA placed beloranib on full clinical hold suspending all development work following two deaths in the best PWS trial that resulted from pulmonary embolism in two patients who receiving beloranib [38].

Tesofensine (NS2330)

Tesofensine is a potent, non-selective serotonin–noradrenaline–dopamine reuptake inhibitor that was initially considered for clinical development in the treatment of Alzheimer or Parkinson disease. Currently it is evaluated for obesity therapy [39]. In their recent review, Martin *et al* showed that tesofensine already completed Phase 1 and 2 trials. It seems that tesofensine acts mainly as a suppressor of appetite, but other effects such as increasing resting energy expenditure cannot be excluded [40]. The most common tesofensine side effects include high blood pressure and increased heart rate, headache, insomnia, dry mouth and other gastrointestinal symptoms [40].

Conclusion

Weight-loss pharmacotherapies can be a therapeutic alternative in patients who have not achieved their target weight with lifestyle changes alone and who may not eligible for bariatric surgery. In the treatment of obesity, an individualized therapy in which the correct drug is combined with advice for positive lifestyle changes seems to be the best approach, with no one single treatment being effective for all patients.

The hypothalamic food intake regulation centers generated a large aria of new molecular targets for the development of anti-obesity drugs. As the worldwide obesity epidemic shows no signs of slowing down, there is a high hope for a new generation of anti-obesity drugs with increased efficacy and safety.

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