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The Challenge of Obesity: A Review of Approved Drugs and New

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Abstract

Obesity is a metabolic dysfunction associated with a wide range of chronic illnesses that cause significant increases in comorbidity and mortality. According to the World Health Organization, approximately 13% of the world's population is characterized as obese. Predictions state that these numbers are likely to increase exponentially in the future. Due to this scenario, it is important to highlight the available treatments for obesity and to assess their effectiveness. Although obesity is an ancient disease, studies are constantly being conducted to improve treatment effectiveness, reduce side effects of any current medications, and identify new therapeutics targets. Because the treatment of obesity is constantly evolving, treatment can be quite a challenge. Therefore, it is the objective of this review to provide a profile of the effectiveness of currently approachable pharmacotherapy and indicate possible new therapeutic targets.

Keywords: Obesity; Treatment; Pharmacotherapy

Introduction

Obesity is a potentially life-threatening, chronic disease. As the most prevalent metabolic disorder affecting humans today, obesity requires multidisciplinary, long-term treatment [1,2]. The worldwide prevalence of obesity has experienced a remarkably steady increase. Yet treatment is essential because obesity has been linked to the onset of many other chronic diseases, as well as higher rates of comorbidities and mortality [3-5].

Currently, obesity numbers reveal proportions indicative of a worldwide epidemic. Looking generally at the Canadian and U.S. population, approximately 50-60% may be classified as overweight, while specifically indicating that about 35% of Americans as being considered obese. Internationally, studies estimate that 1 billion people are overweight with approximately 500 million considered to be obese. Furthermore, weight averages are also increasing in both developed and developing countries [4-6].

It is also important to highlight that obesity has also been closely associated with an increased prevalence for cardiovascular disease, hyperlipidemia, systemic arterial hypertension and type 2 Diabetes, thus making obesity one of the most significant of nutritional diseases [3].

Height and weight are the measurements currently used in clinical practice to perform obesity diagnosis. One of the most useful parameters to correlate height and weight is the Body Mass Index, (BMI) originally proposed by Quetelet. BMI is calculated by dividing a person´s weight (in kilograms) by their height squared (in meters) [7,8]. The World Health Organization defines obesity as a BMI of over 30 (Kg/m^2) (Table 1) [9].

Table 1: Classification of obesity according to World Health Organization.

BMI (Kg/m^2)	Classification	Risk of related disease
18.5-24.9	Normal	Normal
25.0-29.9	Overweight	High
30.0-34.9	Obesity class I	Super high
35.0-40.0	Obesity class II	Super super high
>40.0	Obesity class III	Established disease
[*]Modified by World Health Organization (104)		

One of the most important requirements in the diagnosis and follow up of obesity patients is their food history. Physicians must work with the patient to determine dietary patterns and to identify errors that contribute to their obesity [10]. It is

extremely difficult, however, to assess the amount of food intake, primarily because obese patients often underestimate the amount of energy they consume [10,11]. Patient lifestyle is also another important point to investigate, which should include: the frequency of physical activity, the environment in which the patient consumes meals, and corrections for possible failures as being essential to successful treatment [10,11]. However, lifestyle changes are easier said than done, especially when considering those patients who have been found to have anxiety and their eating behavior is a manifestation of that anxiety, or in other words, it is anxiety driven. The pathophysiology of obesity is multifactorial and complex and physicians may need to use the support of anxiolytics to help their patients control their eating behaviour.

It should be noted that a reduction in body weight by 5-10% can improve blood pressure, blood glucose, serum lipids as well as improve individual health in most cases [12]. Therefore, in this report we have conducted a literature review of the latest data on the efficiency and security of the drugs used to treat obesity, as well as future therapeutic targets **(Table 2)**.

Table 2: Drugs used on obesity treatment (Approved by until February 2017, FDA: Food and Drug Administration; EMA: European Medicines Agency; ANVISA: National Health Surveillance Agency, Weight loss: consider % and Kg since baseline, *have already been approved, due to side effects, require further study. α: phentermine 15.0 mg plus topiramate 92.0 mg, β: phentermine 7.5 mg plus topiramate 46.0 mg δ: topiramate 15 mg Ω: 0.6 mg, ε: 1.2 mg, λ: 2.4 mg).

Drug	Time	Weight loss	Mechanism	Approved by
Orlistat (Xenical®)	4 years (16, 18)	2.9% (16,18)	Triacylglycerol lipase inhibitor	EMA, FDA, ANVISA
Bupropion (Buproban®, Wellbutrin®, Zyban®)	24 weeks (22)	12.9% (22)	Noradrenaline and dopamine reuptake inhibitor	-
Naltrexone/ bupropion (Contrave®)	24 weeks (33)	6.1 to 9.3% (33)	Opioid receptor antagonist/ Noradrenaline and dopamine reuptake inhibitor	EMA, FDA
Bupropion/ zonisamide	12 weeks (37)	7.2 Kg (37)	Noradrenaline/ dopamine reuptake inhibitor/ Mitochondrial carbonic anhydrase inhibitor	FDA
Topiramate (Topamax®)	24 weeks (15)	6.5% (15)	inhibits excitatory glutamate receptors and carbonic anhydrase	*
Phentermine (Adipex®)	24 weeks (51)	7.2 to 8.1% (51)	Noradrenergic sympathomimetic amine	EMA, FDA
Phentermine/ topiramate (Qsymia®)	1 year (44, 56)	12.4% α (44) 9.6% β (44) 5% δ (56)	release of catecholamines and inhibits excitatory glutamate receptors and carbonic anhydrase	FDA
Sibutramine (Biomag®, Sibus®, Saciette®)	1 year (18)	4.21 Kg (18)	inhibits 5-HT and norepinephrine reuptake	ANVISA
Rimonabant (Acomplia®, Redufast®)	1 year (105)	4-7 Kg (105)	inverse agonist on the cannabinoid receptor CB1	*
Lorcaserin (Belviq®)	1 year (66, 67)	5.8% (66,67)	Selective serotonergic 2C receptor agonist	
Liraglutide (Victoza® Saxenda®)	1 year (73)	5% (73)	GLP-1 receptor agonist	EMA, FDA, ANVISA
Empagliflozin (Jardiance®)	3 years (76)	1.5 to 2.0% (76)	sodium–glucose cotransporter 2 inhibitor	Phase I
Cetilistat (Cetislim®)	12 weeks (78, 79)	3.3 to 4.1% (78,79)	inhibiting pancreatic lipase	Japan
Belonarib	12 weeks (105)	5.5 Kg Ω 6.9 Kg ε 10.9 kg λ (105)	inhibitor of methionine aminopeptidase 2	Phase II and III

Pharmacological treatment

Orlistat: Orlistat was approved in Europe in 1998 and subsequently in the United States in 1999. Olistat, an inhibitor of gastrointestinal lipase, prevents the hydrolysis of triglycerides into fatty acids and monoglycerides [13], thereby decreasing the absorption of fat in the intestines and calorie intake [13] which then results in an increase in fecal fat excretion by 30% [14].

Some studies demonstrated its efficacy in weight loss over periods of up to four years [13]. Modest effectiveness has been shown in combination with lifestyle intervention along with a reduction of 2.9 kg [95% CI, 2.27-3.51 kg] or 2.9% [95% CI, 2.5-3.4%] of body weight greater than when compared to the placebo [15-18].

When being compared with the placebo, Orlistat, in the Prevention of Diabetes in Obese Subjects clinical trial (XENDOS), showed improvements in weight loss [5.8 Kg *vs.* 3.0 Kg; $p<0.001$] [18] and revealed an important benefit in metabolic disorders [17]. Furthermore, a meta-analysis of 15 trials with Orlistat demonstrated a mean placebo-adjusted weight reduction of nearly 2.9 kg (2.9%) in a follow up study after 4 years of treatment [18].

The main side-effects of Orlistat include gastrointestinal symptoms such as: diarrhea, flatulence, abdominal pain, oily or

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liquid stool and fecal urgency [20]. These adverse effects also indicated Orlistat's potential link to liver toxicity [19-21].

In spite of its adverse effects, Orlistat is presently considered the most important obesity pharmacotherapy with long-term security and effectiveness. However, due to the adverse effects, Orlistat reveals the relatively poor efficacy of medications used for obesity phamacotherapy, especially for weight reduction and maintenance. Furthermore, the greater frequency of gastrointestinal side-effects, shown in 15-30% of patients, limits its usage [14,16].

Bupropion: Buproprion is characterized as a weak inhibitor of noradrenaline and dopamine and its metabolite, hydroxybupropion, is an amphetamine analog [22]. It is indicated for the treatment of depression and for smoking cessation [22]. A prior study, performed in 2001, demonstrated that Bupropion had been related to a minimal loss of weight when Gadde and colleagues revealed that fourteen obese patients, receiving a maximum dose of Bupropion 200 mg twice daily, experienced a mean weight reduction of 12.9% from baseline in a small-scale 24-week [22].

Efficacy in the management of obesity is related to the stimulatory effect on pro-opiomelancortin (POMC) neurons in the hypothalamus. POMC decreases caloric intake and also enhances energy expenditure by raising thermogenesis due to melanocortin secretion, primarily a α-melanocyte stimulating hormone (α-MSH) [23,24].

Although only a few studies demonstrated Bupropione's efficacy when given by itself, it has been considered most effective when given in association with other agents. It is important to note, however, that Bupropione has not been approved by any regulatory agency for individual use in obesity treatment. Nevertheless, the weight loss benefits demonstrated in non-specific studies encourage the use of Bupropione associated with other drugs for obesity treatment, as described below.

Naltrexone/Bupropion: Naltrexone, classified as an opioid receptor antagonist, was originally approved for the treatment of opiate and alcohol abuse [25]. Additionally, it has been hypothesized that Naltrexone affects appetite control using beta-endorphins on the m-opioid antagonism receptors in response to eating [25,26]. An important approach in obesity management has been the combined application of Naltrexone with Bupropione [27]. The Contrave Obesity Research (COR) trials were four, randomized, double-blind, placebo-controlled trials (COR-I, COR-II, COR-BMOD, and COR-Diabetes) designed for dose optimization and for the long-term analysis of the effectiveness and safety of extended-release Naltrexone–Bupropion [27-30].

Weight reduction by Naltrexone/Bupropion ER pharmacotherapy is mediated by inhibiting β-endorphin (an endogenous opioid) on the POMC neuron in the hypothalamus, and by suppressing the mesolimbic-dopaminergic reward system. This system regulates the hedonic food reward pathways thereby increasing food intake [31,32]. This system regulates the hedonic food reward pathways thereby increasing food intake, whereas by actively interfering with this system, the aim is to decrease food intake.

In March 2010, Naltrexone/Bupropion was delivered to the FDA, due to phase III trials in patients with no T2D, demonstrating a weight reduction between 6.1 and 9.3% from baseline. In the phase III trials, patients diagnosed with T2D showed a weight reduction of up to 5% [33,34]. Naltrexone/Bupropion was approved by the EMA, in March 2015, as therapy associated with a decrease in food intake and enhanced physical activity and for the follow up of weight in patients with a BMI ≥ 30 Kg/m^2 or ≥ 27 Kg/m^2 linked to comorbidities [35]. Important side effects of Bupropion are: tachycardia, insomnia and nausea [23].

Bupropion/Zonisamide: Zonisamide is an inhibitor of mitochondrial carbonic anhydrase and acts on GABA receptors, and yet the mechanism-of-action remains unclear. The 12-week phase II clinical trial conducted by Orexigen Therapeutics showed weight losses of 7.2 Kg with Bupropion/Zonisamide *vs.* 2.9 Kg with Zonisamide alone [36]. The main side effects were: headache, nausea and insomnia [37,38].

Topiramate: Topiramate is a sulfamate-substituted monosaccharide used as an anti-convulsant as well as in migraine prophylaxis. Topiramate was originally developed as an inhibitor of fructose 1,6-bisphosphatase, a key enzyme for gluconeogenesis, for the purpose of improving glycemic controls. Topiramate, however, has also been shown to suppress appetite, cause satiety and decrease overeating. It has not, however, been approved in therapy for obesity as a monotherapy [39].

The proposed mechanisms of action are antagonism of excitatory voltage-gated sodium and calcium channels, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainite (KA) receptors. They alter food taste by promoting the inhibition of carbonic anhydrase isoenzymes [40,41]. Interestingly, Topiramate improves obesity-associated metabolic disorders beyond that of weight reduction through the increase of insulin release from the pancreatic beta-cells. It is regulated by protection against lipotoxicity and the GABAA receptor that induces insulin secretion and it increases insulin-mediated glucose uptake in adipose tissue and muscle by improving the levels of adiponectin in circulation [39,42].

Studies demonstrated that Topiramate induced mean weight loss of 6.5% [95% CI, 4.8%-8.3%] in 24 weeks [15]. Its potency in weight reduction depends upon baseline body weight; therefore, obese individuals lose more weight than normal or overweight individuals [43]. However, Topiramate creates some significant adverse effects including: neuropsychiatric and neurocognitive disturbances, as well as metabolic acidosis and paresthesia *via* carbonic anhydrase inhibition, vision dysfunctions and secondary angle-closure glaucoma [44,45]. Consequently, these side effects outweigh the positive weight-loss results and thereby prevent it from gaining approval as monotherapy for the treatment of obesity. However, Topiramate has been approved for use in combination with Phentermine as will be discussed below.

Phentermine (amphetamine derivatives): Beginning in 1940, Amphetamines were presented as the first drugs to be used to treat obesity. These drugs play a role in hypothalamic receptors by releasing norepinephrine, dopamine and serotonin. By raising central nervous system activity/resting energy expenditure, decreasing appetite and food intake, amphetamines are the driving force behind the weight reduction [46,47].

In a survey of six randomized trials, lasting from 2-24 weeks, showed that patients treated with Phentermine lost 6.3 Kg when compared to patients in the placebo group who lost 2.8 Kg [48-51]. Recent trials have indicated that Phentermine promotes weight loss of up to 7.2-8.1 Kg in comparison to a placebo weight loss of 1.7-1.9 Kg over a period of 12-14 weeks. The most commonly reported side effects are: dry mouth, insomnia, elevated heart rate and blood pressure, with a potential for adverse cardiac events [52,53]. Is this strike through line intended? Or are the references to be removed?

Currently, Phentermine is classified as a controlled substance (Schedule IV drug) and is recommended for short-term use solely in monotherapy. Sympathomimetic agents are normally allowed for short-term obesity therapy only (<12 weeks), primarily due to the lack of long-term safety data with these drugs [13,48-50]. While long-term usage has been approved when in combination with other medications for weight-loss [53].

Phentermine/Topiramate ER: Phentermine and Topiramate ER have been developed as combination therapy and approved by the FDA for weight reduction in 2012. Collateral effects described by the FDA are: paraesthesia, insomnia, dizziness, altered taste sensation, constipation and dry mouth [54]. Some clinical trials fundamental in its approval include: EQUATE, CONQUER, EQUIP and SEQUEL. The EQUATE trial, a 28-week, randomized, phase III study, compared the efficacy between a combination of Phentermine/Topiramate with each component by itself [55]. This study demonstrated that patients treated with the combination treatment lost more weight than patients treated with the individual compounds.

The CONQUER clinical trial, a 56-week, double-blind, randomized, placebo-controlled, phase III trial used two Phentermine/Topiramate ER arms (15 mg and 7.5 mg) and placebo. Patients began the drug in conjunction with a diet of a 500 kcal/day deficit. By the termination of the full-year treatment, patients showed a 12.4% reduction in body weight with Phentermine/Topiramate ER 15/92 mg, and 9.6% reduction with Phentermine/Topiramate ER 7.5/46 mg, when compared to a 1.6% reduction in the placebo group [44].

The EQUIP trial used two Phentermine/Topiramate ER treatment arms (15 mg and 3.75 mg) and a placebo arm. The majority of patients (67%) in the 15 mg group lost 5% of their body weight, while 47% of patients lost 10% of their body weight. In the 3.75 mg group, the subjects who presented a 5-10% body weight reduction from baseline averaged 45% and 19%, respectively [54-56].

The SEQUEL trial, a 2-year extension trial of CONQUER, developed and confirmed the results and durability of the CONQUER trial [57].

Sibutramine: Sibutramine functions by inhibition of 5-HT and norepinephrine reuptake in the hypothalamus [58]. Clinical trials included 46 surveys with 9,303 overweight or obese patients. Of the 9,303 patients, 5,812 (62%) were treated with Sibutramine. Clinical Trials demonstrated efficacy in weight loss with a mean placebo-subtracted weight loss of 4.2 kg in over 12 months [18].

Sibutramine was FDA approved in 1997 for long-term weight management based upon the results of the STORM trial (Sibutramine Trial of Obesity Reduction and Maintenance). The study showed that at least 80% of the weight loss achieved during the six months of therapy was maintained after two years in 43% of patients receiving Sibutramine when compared to 16% of those in the placebo group (odds ratio (OR), 4.64; 95% confidence interval [CI]; p<0.001; 2.59-8.28) [59].

In another study, SCOUT (Sibutramine Cardiovascular Outcomes) investigated the long-term safety of Sibutramine in patients with preexisting cardiovascular disease. SCOUT assessed the first time cardiovascular event occurrences with Sibutramine (nonfatal myocardial infarction [MI], stroke, cardiovascular resuscitation after cardiac arrest, or cardiovascular death) and showed a 16% increase in the risk of a primary outcome event among users. And yet, interestingly, SCOUT data reanalysis indicated that Sibutramine actually decreased the risk of cardiovascular events and mortality in patients who lost weight. In the reanalysis, it was determined that the increase in cardiovascular risk was, in fact, due to high-risk patients who had not incurred any weight reduction, but had, instead, continued taking the drug only to fulfill the trial's protocols [60].

Rimonabant: In 2006, Rimonabant was approved in Europe. By inverting the agonist on the cannabinoid receptor CB1, it achieves a reduction in appetite [61]. Unfortunately, because clinical trials have shown an increased occurrence of some psychiatric disorders, such as: anxiety, suicidal ideation and depression, only a few studies have been performed which reveal the true effectiveness of this treatment in obesity [62]. In June 2007, the US Endocrine and Metabolic Drugs Advisory Committee decided against its approval in the USA, due to the suspected association with psychiatric safety concerns [63]. The EMA also suspended the production of Rimonabant in October 2008 because of the psychiatric risk/slant to prohibit it in Europe [64]. Although this drug had demonstrated a benefit in weight loss, more clinical trials are needed to assess its safety in obese patients who present no history of psychiatric disorders.

Lorcaserin: Locarserin is classified as a serotonergic antiobesity agent, through the agonism of 5-HT 2C receptors and exhibits an affinity 100 times greater for 5-HT 2C receptors than for 5-HT 2B receptors. Locarserin was approved in 2012 as a long-term weight loss therapy [65].

Currently, clinical trials are being conducted to assess the efficacy and safety of Lorcaserin over one and two year periods, as well as in patients with type 2 diabetes mellitus. The BLOOM trial (Behavioral Modification and Lorcaserin for Overweight and Obesity Management) was a randomized, placebo-controlled, double-blind trial conducted in more than 3,000 patients over a

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two year period. Its aim was to analyze the safety and efficacy of Lorcaserin 10 mg twice daily compared to placebo

Patients receiving Lorcaserin (n=1,595) during the first year were reassigned to either continue receiving Lorcaserin (n=564) or to receive the placebo (n=959) during second year [66,67]. Test results showed Lorcaserin to be efficacious with primary endpoints, which are weight loss. Therapy was associated with a mean weight loss of 5.8% from baseline in patients who were switched from Lorcaserin to placebo during year 2. The 5.8% weight loss was found to be less likely to ocurr than in those who continued using Lorcaserin in order to maintain the weight loss they attained during year 1. Of the patients receiving Lorcaserin, 47.5% lost 5% or more of their baseline body weight in year 1, as compared to the 20.3% of patients who received the placebo ($p<0.001$). The aim of the BLOOM study was to assess the mean reductions in the BMI together with the waist circumference in the Lorcaserin group in year 1. In this context, subjects showing a mean baseline weight of approximately 100 kg, Lorcaserin therapy implicated up to a 6% weight reduction compared to the 2-3% reduction in the placebo group ($p=0.001$) [66,67].

Since there is a low specificity for the 5-HT 2B receptor (about 100 times lower than that of the 5-HT 2C receptor), Lorcaserin represents a low risk of heart valve abnormalities with long-term use [65,68]. The most common side effects are: nausea, headache, dizziness, dry mouth, fatigue and constipation. In patients with Type 2 Diabetes, these side effects also include hypoglycemia back pain, headache, cough and fatigue [69].

Liraglutide: Liraglutide is an analogue of endogenous GLP-1 with a longer half-life (the half-life of native GLP-1 is ~1.5 min) that increases activation of the GLP-1 receptor. By activating this receptor, it improves the stimulation of glucose-dependent insulin secretion and many other effects besides just glucose control [70,71]. Currently prescribed for patients in treatment for Type 2 Diabetes Mellitus, Liraglutide treatment involves subcutaneous injection with daily doses ranging from 0.6 to 1.8 mg [72].

Clinical trials showed that after 56 weeks, subjects in the Liraglutide group decreased their body weight by a mean of (± SD) of 8.0 ± 6.7% (8.4 ± 7.3 kg), whereas, the placebo group showed a decrease by a mean of 2.6 ± 5.7% (2.8 ± 6.5 Kg). These results were maintained for over 56 weeks. Also seen was a greater number of subjects in the Liraglutide group decreased their body weight by at least 5%, 10% and 15% (63.2% *vs.* 27.1%), (33.1% *vs.* 10.6%), (14.4% *vs.* 3.5%), respectively, when comparing them to the placebo group. Therefore, it was revealed that 92% of the subjects in the Liraglutide group and 65% of the subjects in the placebo group had a decrease in their weight [73].

In this context, recent trials demonstrated a dose-dependent, weight reduction in obese and overweight patients without diabetes with efficacy in reducing waist circumference as well as BMI. This dose-dependent weight reduction, however, emphasizes that Liraglutide may be less effective in subjects with a mean BMI of 40 or higher than what was seen in patients with a lower BMI [29,74].

In addition to these studies regarding Liraglutide and obesity management, a one year extension, follow up study evaluated the efficacy and safety of higher doses of Liraglutide compared to Orlistat in 398 patients. The extension phase was completed by 67% of the participantes (n=268). Of those who completed the trial and went on to the extension phase, they received an increased dose of Liraglutide of up to 3 mg daily, in comparison to their 2.4 mg daily dosage during the original 56-week trial. The study demonstrated, in 2 years, the effectiveness and durability of the weight loss/maintenance while using Liraglutide [74].

The SCALE Maintenance study occurred over a 56-week period and studied 422 overweight and obese subjects presenting chronic diseases, all using Liraglutide (3 mg daily), and demonstrating a maintenance of weight reduction previously achieved through caloric dietary restriction (≥ 5% initial weight reduction). In this case, Liraglutide improved weight reduction when compared with placebo [29].

Liraglutide´s side effects are: nausea, vomiting, diarrhea, constipation and hypoglycemia, all of which are more prevalent in subjects taking higher doses of Liraglutide. Less common side effects are: pancreatitis, cholecystitis, renal impairment and suicidal ideation. Additionally, the FDA states that Liraglutide is not recommended for patients with a personal or family history of medullary thyroid cancer or Multiple Endocrine Neoplasia syndrome (MEN) type 2, due to the high incidence of thyroid C-cell tumors found in rodents [29,74].

The FDA and the EMA assessed several studies suggesting a possible association of incretin-based drugs with acute pancreatitis and/or pancreatic cancer, however these results are inconsistent. Nevertheless, pancreatitis will continue to be considered a risk associated with these medications until there is more available data [75].

SGLT2 inhibitors: The mechanism of action of these drugs is the inhibition of sodium-glucose cotransporter 2. In a recent study using Empagliflozin, an SGLT2 inhibitor, in patients with Type2 Diabetes Mellitus (T2DM) at high risk for cardiovascular events, demonstrated a reduction in the hospitalization for heart failure by 35%, a reduction of cardiovascular death by 38%, and a reduction of all-cause mortality by 32% [76].

In this context, clinical trials also revealed implications in weight loss mainly in patients with T2DM. Empagliflozin has shown a sustained weight loss of 1.5-2.0 kg over 3 years. It is important to highlight that this result adds Empagliflozin to a select group of glycemic control medications that have established cardiovascular benefits and favorable weight outcomes [76]. However, it is important to highlight that this class of drugs (SGLT2 inhibitors) is not presently approved for obesity treatment. Looking towards the future, it is possible the availability of these drugs for weight management therapy, especially when considering the weight loss results in T2DM patients with cardiovascular benefits and low risk of hypoglycemia. New trials for obesity treatment are needed with these drugs.

Cetilistat: Similar to Orlistat, Cetilistat is a pharmacotherapy that acts by inhibiting pancreatic lipase [77].

Studiesdemonstrated that subjects lost 3.3-4.1 kg during a 12 week period. Like Orlistat, the most important side effects of Cetilistat were gastrointestinal disorders [78,79]. Although Cetilistat has been approved in Japan in September 2013, an application for approval for its usage has not yet been filed either in the US or Europe [80].

Belonarib: Belonarib is a methionine aminopeptidase 2 inhibitor that decreases lipid biosynthesis. Weight loss occurs as a side effect. First described as drug class that causes weight loss by reducing fat biosynthesis and stimulating fat oxidation and lipolysis, patients using Belonarib expressed markedly decreased appetites and body weight [52].

Studies over a 12-week period in a phase II randomized trial, demonstrated that Beloranib, at doses of 0.6 mg, 1.2 mg and 2.4 mg, improved weight loss of 5.5 ± 0.5 kg, 6.9 ± 0.6 kg and 10.9 ± 1.1 kg, respectively, when compared with placebo. Adverse effects were dose-dependent and include: nausea, vomiting, insomnia and abnormal dreams. Thromboembolic events have also been reported in ongoing and prior clinical trials, leading the FDA to issue a partial clinical hold in order to institute measures to ensure patient safety [52,81]. As a result, the safety of Beloranib usage is currently under review, thereby rendering its progress in the future uncertain.

Mirabegron (Myrbetriq): Mirabegron (Myrbetriq) is a β3-adrenergic receptor (AR) agonist used in the treatment for overactive bladders. The most important characteristic is the higher *in-vitro* binding affinity/specificity for the human β3-AR [82]. The Mirabegron class of medications was initially studied in 1970 for obesity management and metabolic disease [83-85]. This therapy, however, was not successful enough to be considered for approval primarily due to such side effects as cardiovascular outcomes correlated with their substantial cross-reactivity with β1-AR [86].

More recent studies have shown that Mirabegron increases energy expenditure, which is associated with a higher metabolic rate of 203 ± 40 kcal/day versus placebo (+13%; p=0.001) [87]. It is important to note that this result occurred in patients taking a high dose of Mirabegron. These patients also experienced additional activation of β1-AR and tachycardia [82,87].

At this moment there is no safety assessment described for this medication. Consequently, more studies are needed to reveal whether lower doses, selective only for β3-AR, will stimulate thermogenesis, improve weight loss and/or decrease side effects.

Tesofensine: Tesofensine is characterized as a monoamine reuptake inhibitor and has been studied for obesity therapy. The primary objective was to investigate it as potential therapy for both Alzheimer's and Parkinson's diseases, however weight loss reduction was a notable side effect. Because Tesofensine's mechanism of action prevents the reuptake of serotonin, noradrenaline and dopamine, Tesofensine suppresses appetite and ameliorates thermogenesis [88].

Unfortunately, as seen with other therapies that act upon the noradrenergic pathways, an increase in heart rate was observed in phase II clinical trials [88]. More studies need to be performed in this regard.

New targets: Additional new fields of study focus upon identifying and developing multiple peripheral metabolic pathways, such as GLP-1R/glucagon receptor dual agonists, GLP-1, glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptor triagonists. Studies in animals demonstrated that a GLP-1/GIP/glucagon receptor triagonist ameliorate body weight, glycemic control and hepatic steatosis [89].

Another agent, the Y5 receptor antagonist Velneperit, revealed a positive perspective in phase II clinical trials. Velneperit prevents the binding of NPY to the Y5 receptors thereby reducing hunger and stabilizing energy balance. Studies showed some side effects such as respiratory infection, including nasopharyngitis, sinusitis, and headache. In regards to weight reduction, this agent still requires more efficacy trials [88].

The CB1 receptor is another possible success target [90]. Differing from Rimonabant, that presented both antagonist and inverse agonist activity on the CB1 receptor, this newer and more pure CB1 receptor, acts as a neutral antagonist agent with fewer reported side effects [91,92]. Studies in rodents of peripheral-selective CB1 receptor antagonists revealed significant weight reduction and an increased medication tolerance that was comparable to Rimonabant's effectiveness in weight loss [93].

A notable new finding comes from the discovery of beige fat cells, a type of adipocyte, which were found to improve insulin sensitivity and action with anti-obesity effects [94]. Therefore, by manipulating these fat cells for obesity treatment, the likely result would be an increase in caloric loss during physical activity and thermogenesis [95,96]. However, studies still remain unclear about the factors that enhance the differentiation of these cells and more research is needed.

Recent surveys reveal that inflammatory mediators, such as adipose tissue and macrophages, play an important role in the development of obesity-induced insulin resistance [97-100]. In this case, M1 macrophages in adipose tissue are characterized by CD11c+, and several studies showed that obesity increases CD11c+ ATM numbers Lee et al. [101,102] demonstrate that obesity induces systemic inflammation by modulating the amount of inflammatory mediators, such as white blood cells, neutrophils and the Ly6 Chi pro-inflammatory monocytes. In animal models, salicylates and Pioglitazone are able to decrease this systemic inflammation. Thus, these data may provide new insights into how the modulation of systemic inflammation could possibly function in obesity treatment [103-106].

Conclusion

Obesity treatment has always been and will continue to be a challenge. Presently existing and new targets are being assessed constantly with the aim of progressing in treating this worldwide epidemic. As our review has shown, several drugs are acting through different mechanisms to control hunger, satiety and desire to eat, and yet the prevalence of obesity continues to increase. Why, then, is it so difficult to locate the right

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medication to treat obesity and achieve long-term, treatment success? Are drugs missing the real target or is there a lack of drugs that assist in lifestyle change strategies? Perhaps, in having created expectations too high, basing them solely upon the success of pharmacological obesity treatments, thereby setting ourselves up for major failure. Probably, the road to success is a three-set p process: to increase efforts in improving exercise, to modify eating behavior and to make life-style alterations coupled with the assistance of pharmacology.

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