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REVIEW ARTICLE

Pharmacotherapy of Obesity: Limits and Perspectives

Pamela Rosa-Gonçalves[1] · **David Majerowicz**[1]

Abstract
Obesity is a severe worldwide epidemic. Obesity comorbidities, such as type 2 diabetes mellitus, hypertension, and atherosclerosis, are costly for patients and governments. The treatment of obesity involves several facets, including lifestyle changes, bariatric surgery, and pharmacotherapy. As changes in lifestyle require considerable patient commitment that is sometimes unachievable, and surgery is expensive and invasive, pharmacotherapy is the primary option for most patients. This review describes the pharmacotherapy currently available in the USA, Europe, and Brazil, focusing on its limitations. We then analyze the results from clinical trials of new drug candidates. Most drugs cause weight loss of < 4 kg compared with controls, and severe adverse effects have caused a number of drugs to be withdrawn from the market in several countries. Drugs under development have not shown more significant weight loss or reduced adverse effects. We conclude that a significant portion of obese patients have few treatment options because of the adverse effects and minimal weight loss associated with current pharmacotherapy. However, drugs currently under development appear unable to change this scenario in the near future. Thus, it is essential that new compounds are developed and new molecular targets studied so obesity can be efficiently treated in all patients in the future.

Key Points

The adverse effects, efficacy, and cost associated with current pharmacotherapy for obesity restricts the range of treated patients.

Drugs in development will not change this scenario in the near future.

The search for new molecular targets for the treatment of obesity is imperative.

1 Introduction

Obesity is a chronic disease with a multifactorial etiology that results from genetic, physiological, behavioral, environmental, and sociocultural factors and is not limited to developed countries [1]. It is a clinical condition characterized by an excess of body fat that may imply health risks with clinical, psychological, social, and economic effects [1]. At least 18 comorbidities are attributable to overweight and obesity, including type 2 diabetes mellitus (T2DM), cardiovascular diseases, and hypertension, among others [2].

Body mass index (BMI) data indicate that 35% of the US population was obese in 2012. In 2005, 17% of Europeans also had a BMI > 30 kg/m^2. In addition, in both regions, data indicate an alarming growth trend in obesity [3]. Furthermore, mathematical simulations have shown that 95% of the Brazilian population will be overweight or obese by 2050. Public healthcare costs are projected to reach $330 billion between 2010 and 2050 [4]. Data in the literature show that even small weight reductions promote benefits related to blood pressure [5] and lipid parameters [6]. In fact, interventions to reduce the Brazilian population's BMI by 5% will lead to savings of approximately $US60 billion in the same 40 years [4], which justifies investment in the prevention and early treatment of obesity.

✉ David Majerowicz
majerowicz@pharma.ufrj.br

[1] Departamento de Biotecnologia Farmacêutica, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Av. Carlos Chagas Filho, 373, CCS-Bloco A, 2º andar, sala 48, Cidade Universitária, Rio de Janeiro, RJ CEP 21941-902, Brazil

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Obesity involves metabolic and neurohormonal processes [7]. To understand the pharmacological treatments, it is important to know the main neurohormonal processes that regulate hunger, satiety, and the formation of body fat.

Regulation of hunger and satiety includes mechanisms involving the central nervous system (CNS), peripheral nervous system, and hormones. The primary regulation of energetic homeostasis occurs in the hypothalamus through two distinct groups of first-order neurons in the arcuate nucleus: anorexigenic and orexigenic neurons. Anorexigenic neurons express the polypeptides pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART), whereas the orexigenic neurons can coexpress the agouti-related peptide (AgRP) and neuropeptide Y (NPY). POMC/CART and AgRP/NPY neurons are projected to second-order neurons located in other regions, such as the paraventricular nucleus and the lateral hypothalamic area. POMC cleavage releases α-melanocyte-stimulating hormone (α-MSH) in the paraventricular nucleus and inhibits food intake and increases energy expenditure by stimulating the melanocortin-4 receptor. This stimulus may be inhibited by orexigenic stimulus such as that from AgRP. NPY can decrease the expression of POMC and increase the synthesis of melanin-concentrating hormone, which both have orexigenic actions.

Hormones and signals from vagal afferent neurons can regulate hunger and satiety through sensitivity to mechanical deformations, the presence of macronutrients, and changes in pH and tonicity. Ghrelin, produced by the fundic cells of the stomach, has an oxygenic effect, activating AgRP/NYP neurons. In the other direction, glucagon-like peptide-1 (GLP-1), produced by the gut in response to food, has an anorexigenic effect, activating POMC/CART neurons while inhibiting AgRP/NYP neurons. Insulin and leptin also have an anorexigenic effect.

Different neurotransmitters also regulate the hunger/satiety system. Noradrenaline activates AgRP/NYP neurons and inhibits POMC/CART neurons, increasing food consumption, whereas serotonin has the opposite effect, inhibiting AgRP/NYP neurons and activating POMC/CART neurons, leading to reduced hunger. Dopaminergic neurons in the prefrontal cortex are also involved in this regulation, and their activation causes an increase in food consumption (Fig. 1). Readers interested in the neurohormonal regulation of appetite are directed to some excellent recently published reviews [8–11].

The treatment of obesity encompasses lifestyle modifications, including physical activity, diet, cognitive–behavioral therapies, pharmacotherapy, and bariatric surgery [1]. Lifestyle changes may require a multidisciplinary team to ensure habits change, and relapse may occur in some people [12]. Although bariatric surgery promotes pronounced weight loss, it does have limitations. It is not only an expensive procedure but is also associated with significant rates of weight regain in the short term after surgery. As an invasive procedure, it is also associated with a risk of mortality and complications, which means it is reserved for cases of severe obesity or patients with comorbidities [7, 13]. An intensive clinical approach can be a useful alternative to avoid these risks [14].

With the current limitations, pharmacotherapy is necessary as an adjuvant in the treatment of obesity. It should start as a secondary prevention method, with the objective of avoiding obesity progression and increasing weight loss. However, pharmacotherapy should only be used if a hypocaloric diet and other nonpharmacological therapeutic approaches, such as exercise, have already been unsuccessful [7].

However, the current pharmacological arsenal for the treatment of obesity is far from efficient and safe for patients. The average weight loss with pharmacotherapy is only around 5%, and severe adverse effects are often reported. Moreover, different anti-obesity drugs were developed and approved as "magic pills", but unacceptable risks were identified, leading to their use being restricted or the drugs being withdrawn from the market [15]. In this review, we analyze the main drugs available for obesity treatment in Brazil, the USA, and Europe, with a particular focus on their limitations. We also discuss new drugs currently being studied that should be on the market shortly.

2 Methods for Selection and Assessment of Literature

We conducted a bibliographic survey in the SCIELO, LILACS, and PubMed databases using the descriptors pharmacotherapy, obesity, anti-obesity drugs, and anti-obesity agents in journals published between 2007 and April 2018 in English or Portuguese. We excluded studies with participants who were pre- or post-bariatric surgery and studies investigating the treatment of weight-related comorbidities, obesity as a secondary disease or monogenic obesity, or natural and phytotherapeutic products as anti-obesity agents.

The search located 1005 references. After duplicates were removed and the inclusion and exclusion criteria were applied, 337 articles remained, including 305 reviews.

3 Current Pharmacotherapy and Its Limits

3.1 Mazindol, Amfepramone, and Fenproporex

Amfepramone and fenproporex are compounds derived from amphetamine, and mazindol is a tricyclic derivative. Although these drugs have different chemical structures,

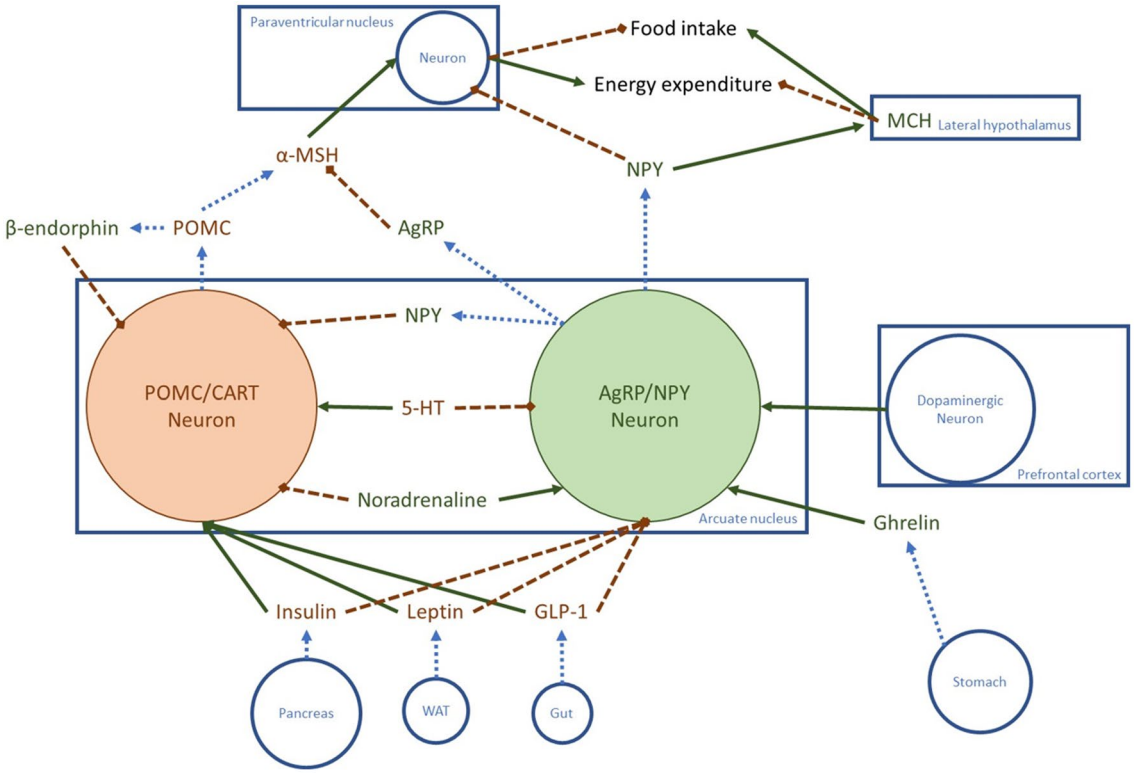

Fig. 1 An overview of the hypothalamic appetite control system. Hypothalamic appetite control is governed mainly by first-order neurons in the arcuate nucleus. Hormones released by peripheral organs, such as the digestive system, white adipose tissue, and pancreas, modulate the activity of POMC/CART and AgRP/NPY neurons. The levels of neurotransmitters in the arcuate nucleus and signals transmitted from other regions of the brain also regulate the activity of first-order neurons. POMC cleavage produces α-MSH, which activates second-order neurons in the paraventricular nucleus, reducing hunger and increasing energy expenditure. NPY production inhibits neurons in the paraventricular nucleus and induces the synthesis of MCH in the lateral hypothalamus, increasing food consumption and reducing basal metabolism. Continuous arrows indicate activation, dashed arrows indicate inhibition, and dotted arrows indicate the secretion of peptides. *AgRP* agouti-related peptide, *CART* cocaine and amphetamine-regulated transcript, *GLP-1* glucagon-like peptide 1, *MCH* melanin-concentrating hormone, *NPY* neuropeptide Y, *POMC* pro-opiomelanocortin, *WAT* white adipose tissue, *α-MSH* α-melanocyte-stimulating hormone, *5-HT* serotonin

their mechanisms of action are related to an increase in noradrenergic, dopaminergic, adrenergic, and even serotoninergic signaling in the CNS and peripheral nervous system [16]. This modulation of neurotransmitters is responsible for the sensation of satiety and reduction of food consumption (Fig. 2).

These compounds have been used for decades in body weight control: amfepramone and mazindol were approved in the USA in 1959 and 1973, respectively. Fenproporex has never been approved by the US FDA but was commonly used in Brazil. However, few clinical trials have been conducted with sufficient quality to prove their efficacy [17]. A recent meta-analysis indicated that, discounting losses observed in the placebo groups, 6 months of treatment with amfepramone and mazindol caused a weight loss of 1.3 kg and 1.7 kg, respectively, which may be considered low weight loss. The lack of clinical trials prevented analysis of fenproporex [18], but one clinical trial [19] did report that this drug caused a weight reduction of 7.8 kg (vs. 3.1 kg with placebo) after 13 months of treatment, which can be considered a substantial loss. Furthermore, 72.4% of the patients treated with fenproporex but only 33.3 of those receiving placebo lost ≥ 5% of their initial weight.

However, adverse effects have long been reported and include constipation and irritability [16, 19]. These drugs are also associated with tolerance, which can lead to weight regain, and addiction, making them drugs of abuse [16], so they are restricted to short-term use. In fact, a study of the consumption profile of anti-obesity agents in a Brazilian university presented critical data showing that 6.8% of the participating students, with a mean age of 23.2 years, used these agents, 40.5% of which were amphetamines and derivatives of sympathomimetic amines [20].

As a result of these issues, mazindol was withdrawn from the US market in 1999. Amfepramone, fenproporex, and mazindol were banned in Europe and Brazil in 1999 and 2011, respectively. However, a recent Brazilian federal law

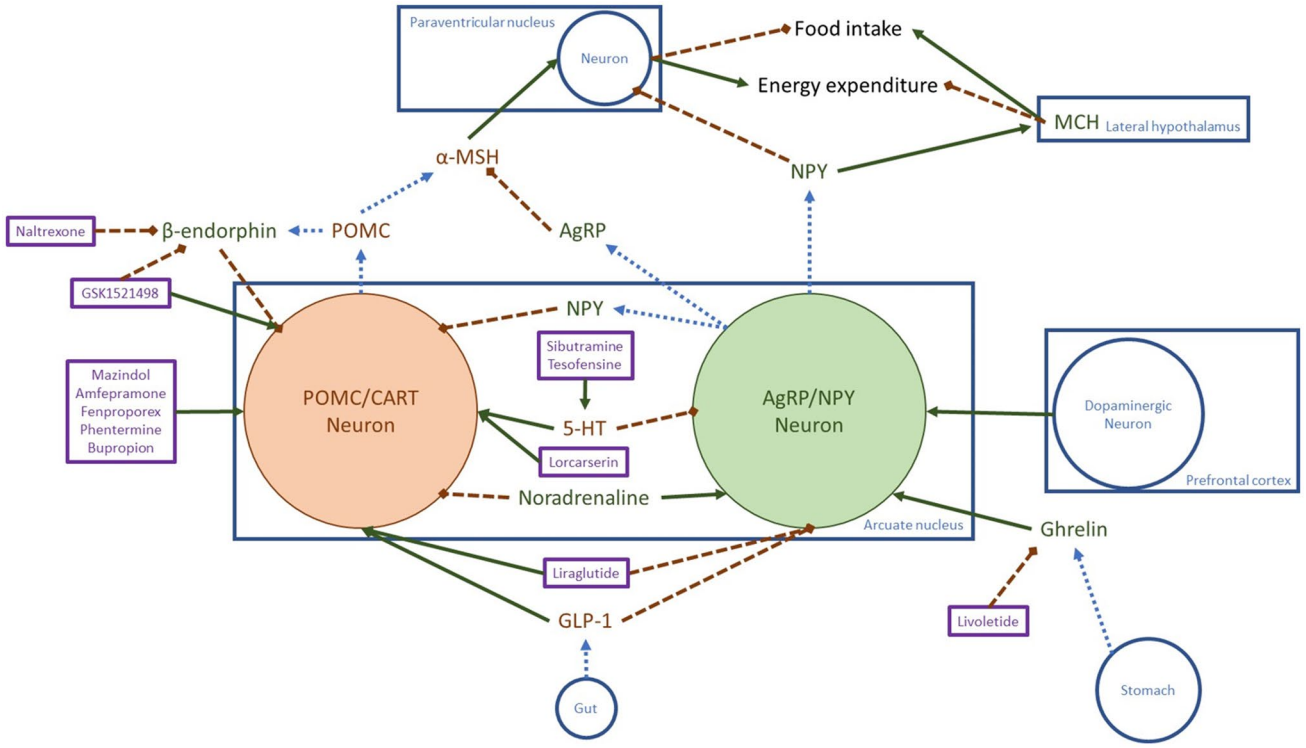

Fig. 2 Mechanism of action of current and developing anti-obesity drugs that act on appetite control. Mazindol, amfepramone, fenproporex, phentermine, and bupropion activate POMC/CART neurons. Sibutramine and tesofensine inhibit 5-HT reuptake, which increases the levels of this neurotransmitter in the synaptic cleft, activates POMC/CART neurons, and inhibits AgRP/NYP neurons. Lorcaserin is a 5-HT_{2C} receptor agonist and activates POMC/CART neurons. Liraglutide is a GLP-1 analog and activates POMC/CART neurons and inhibits AgRP/NYP neurons. Naltrexone is a β-endorphin receptor antagonist and prevents the effect of negative feedback on POMC/CART neurons. GSK1521498 is an inverse agonist of this same receptor and activates POMC/CART neurons in addition to preventing β-endorphin negative feedback effects. Livoletide is an analog of unacylated ghrelin, which inhibits the effects of endogenous ghrelin. Continuous arrows indicate activation, dashed arrows indicate inhibition, and dotted arrows indicate the secretion of peptides. *AgRP* agouti-related peptide, *CART* cocaine and amphetamine-regulated transcript, *GLP-1* glucagon-like peptide 1, *MCH* melanin-concentrating hormone, *NPY* neuropeptide Y, *POMC* pro-opiomelanocortin, *α-MSH* α-melanocyte-stimulating hormone, *5-HT* serotonin

has allowed these appetite modulators to be marketed by default and imposing on the regulatory agency [17].

3.2 Sibutramine

Sibutramine is selective serotonin, noradrenaline, and to a lesser extent dopamine reuptake inhibitor in the CNS [21]. Inhibition of reuptake increases serotonin levels in the synaptic clefts, and this neurotransmitter acts on the neurons of the appetite center of the arcuate nucleus of the hypothalamus. Serotonin activates the anorexigenic POMC neurons and inhibits the orexigenic NPY neurons, reducing appetite and increasing energy expenditure [22]. In this way, sibutramine suppresses hunger and reduces patient food intake (Fig. 2).

Meta-analysis data containing results from sibutramine clinical trials showed that, after 6 months, the sibutramine-treated group lost 4.2 kg of body weight (vs. 1.2 kg with placebo), which can be considered a moderate weight loss [23]. However, the sibutramine group had increased blood pressure and pulse compared with the placebo group [23–28]. These cardiovascular effects led to a specific study to assess the impact of sibutramine in overweight and obese patients with pre-existing cardiovascular disease. The results showed an increase in cardiovascular risk with sibutramine treatment for nonfatal events such as myocardial infarction and stroke. Pulses increased in the sibutramine group, corroborating the previous results [29]. Sibutramine may also increase the risk of cancer by presenting time-dependent genotoxicity [30].

The sale of sibutramine was approved in the USA in 1997, Brazil in 1998, and Europe in 1999, but this increased cardiovascular risk led the FDA and European Medicines Agency (EMA) to halt the sale of sibutramine in 2010. However, cardiovascular outcomes associated with the use of sibutramine-adulterated diet products continue to be reported, indicating the existence of an illegal market via the internet [31]. Sibutramine remains available for patients in Brazil but is contraindicated for individuals with diabetes

or increased cardiovascular risk. As many patients with obesity present some of these comorbidities, the rational use of sibutramine for the treatment of obesity is very restricted.

3.3 Orlistat

Orlistat is a compound analogous to lipstatin and is a reversible inhibitor of gastrointestinal lipases. It prevents the digestion of fat from food in the form of free fatty acids and monoacylglycerols and inhibits the absorption of about 30% of the ingested triglycerides, which end up being eliminated in the feces [32]. This inhibition reduces the number of calories absorbed and leads to loss of body weight.

Meta-analysis data showed that the use of orlistat led to an average weight loss of 8.1 kg (vs. 4.2 kg with placebo) after 6 months, which may be considered a moderate loss compared with other drugs used in the pharmacotherapy of obesity [23]. However, it is common for patients to regain weight after 1 year of treatment. Orlistat also reduced cardiovascular risk factors and the incidence of T2DM in obese patients [23, 26, 33–36].

The most common adverse effects associated with the use of orlistat are mild but are related to intestinal disorders such as urgency and fecal incontinence [26, 35–38]. These effects reduce the patient's quality of life and compromise treatment. However, a change in the patient's behavior, such as avoiding high-fat foods due to gastrointestinal accidents, helps with weight loss. Inhibition of fat absorption can also lead to problems with the absorption of liposoluble vitamins, especially vitamin D [39]. Rare events such as macrocytic anemia and thrombocytopenia have been associated with orlistat [40]. Abuse of orlistat as compensatory behavior in a case of bulimia nervosa has also been reported [41].

The half dosage of orlistat (60 mg) was approved for marketing as an over-the-counter drug in the USA and Europe in 2007 but not in Brazil. However, the adverse effects on the digestive system limit its use.

3.4 Lorcaserin

Lorcaserin is a selective agonist of the serotonin 2C (5-HT_{2C}) receptor [42] that has been proposed as an anti-obesity target for its satiety function, inhibiting the rate of food consumption [22] through the POMC neuron system [43] (Fig. 2). In preclinical studies, lorcaserin showed higher selectivity for the human 5-HT_{2C} receptor than the 5-HT_{2A} and 5-HT_{2B} receptors, with considerably conserved peptide sequences [42, 44]. The search for selective 5-HT_{2C} compounds is fundamental since activation of the 5-HT_{2A} receptor has been associated with hallucinogenic effects [45]. On the other hand, activation of the 5-HT_{2B} receptor is associated with the development of cardiac valvulopathy [46]. Thus, selective agonists for the 5-HT_{2C} receptor would prevent possible adverse effects.

Meta-analysis data showed that subjects treated with lorcaserin had a mean body weight reduction of 5.7 kg (vs. 2.5 kg with placebo) after 12 months of treatment [47], which is low compared with other anti-obesity drugs. A clinical study identified a decrease in fasting glycemia and glycated hemoglobin after 1 year of treatment in the lorcaserin-treated groups compared with the placebo group [48]. Given these results, it was suggested that lorcaserin might improve glycemic parameters and so could be used by obese patients with diabetes to establish normoglycemic levels [49]. Although two different clinical studies have observed no increase in the incidence of cardiac valvulopathy with the use of lorcaserin for up to 2 years [50, 51], concerns remain about the risk of cardiovascular events. Therefore, a clinical study to observe cardiovascular events was announced recently [52].

Lorcaserin was approved for use in the USA in 2012 and in Brazil in 2016. However, the drug was not approved in Europe because of an animal study indicating a possible carcinogenic effect [53] in addition to the poorly investigated risks of psychiatric disorders and valvulopathy. Moreover, lorcaserin is contraindicated where other serotonergic or antidopaminergic agents are being used. Lorcaserin should also be used with caution when concomitant with oral hypoglycemic agents, as the patient may present hypoglycemia. These restrictions, along with the drug's non-approval in Europe, limits its use for a substantial portion of obese target patients.

3.5 Phentermine Plus Topiramate

Phentermine and topiramate were used in clinic but for other indications. Phentermine is an atypical analog of amphetamine, such as amfepramone and fenproporex (Sect. 3.1) and is already used as an anorectic in the adjunctive treatment of obesity in the USA. Topiramate is approved for the treatment of epilepsy, bipolar disorders, and migraine. Its mechanism of action on weight loss is not fully elucidated [54, 55]. However, the combination of these drugs aims to reduce adverse effects, since phentermine has a CNS-stimulatory effect and topiramate has a sedative effect [54].

No meta-analysis has evaluated all clinical trials of this drug combination. Weight losses in the treated groups ranged from 1.4 kg (2-week treatment) to 10.2 kg (14-month treatment), whereas patients in the placebo groups lost between 0.2 and 1.4 kg [56, 57]. This is the most effective available combination of drugs for weight reduction. In addition to weight loss, the treatment slows gastric emptying, reducing calorie consumption, and leads to improvements in cardiometabolic risk parameters and diabetes [56, 58–61].

However, adverse effects associated with depression and anxiety were observed alongside less severe problems such as paresthesia, constipation, insomnia, dry mouth, dysgeusia, and dizziness [57, 61, 62]. The combination of phentermine and topiramate was approved for use in the USA in 2012 [63], but a new assessment of the benefits and risks was required [64]. Its use is contraindicated in patients with cardiovascular diseases [52], which limits the number of obese patients who can benefit from the treatment. These drugs are not available in combination in Europe or Brazil.

3.6 Liraglutide

Liraglutide is an acylated GLP-1 receptor agonist with 97% homology to endogenous human GLP-1. Liraglutide was produced by modifying GLP-1 to improve its pharmacokinetic properties [65, 66]. This drug was initially developed for the treatment of T2DM, but clinical studies have also shown its ability to promote weight loss [67]. Liraglutide induces the sensation of satiety when binding to the GLP-1 receptors present in neurons expressing POMC in the arcuate nucleus (Fig. 2) so reduces food consumption and consequently results in weight loss. Another interesting point is a possible action in the decrease of the sensation of pleasure in the meals per action in the limbic system [68].

A meta-analysis found that liraglutide induced a weight loss of 5.6 kg vs. the 1.7 kg observed in the placebo group [69], with treatment duration ranging from 3 to 14 months. Liraglutide also caused a reduction in cardiometabolic risk factors, such as waist circumference, blood pressure, and inflammatory markers [69, 70]. As GLP-1 is an incretin, liraglutide treatment also reduced postprandial and fasting blood glucose and improved pancreatic β-cell function and insulin sensitivity [70].

Liraglutide was released to the market in the USA in 2014, Europe in 2015, and Brazil in 2016. Although the drug promotes high weight loss, the price of treatment and its injectable form limit the group of patients who can be treated and their commitment to treatment.

3.7 Naltrexone and Bupropion

Like phentermine and topiramate (Sect. 3.5), both naltrexone and bupropion were already known in the clinic [52]. Bupropion is approved for the treatment of depression or smoking cessation, and naltrexone is approved for alcohol or opioid dependence, as it is an opioid antagonist. Bupropion inhibits dopamine and noradrenaline reuptake and activates POMC neurons (Fig. 2). However, cleavage of POMC also produces β-endorphin, which acts as an inhibitor of POMC neurons themselves in a negative feedback system (Fig. 1). Naltrexone works as a β-endorphin receptor antagonist in these neurons, disrupting the retro-inhibition and keeping POMC neurons active longer (Fig. 2). This effect potentiates the satiety signal, reducing food intake and body weight [71, 72].

No meta-analysis has been conducted on the combination of naltrexone and bupropion. Weight loss with treatment varies between 9.5% (14-month treatment) and 7.8% (6.5-month treatment) of initial weight (vs. 4.9–0.9% with placebo) [73, 74]. No clinical trial has information on weight loss in kilograms, which makes comparison with the other drugs analyzed here difficult. Treatment also caused a reduction in the levels of glycated hemoglobin, high-density lipoprotein cholesterol, triglycerides, and other parameters of cardiometabolic diseases [74–76]. However, nausea, constipation, vomiting, headache, dizziness, and dry mouth were identified as adverse effects [73, 74, 76–78]. Changes in blood pressure have also been observed [78], although no significant changes in cardiovascular risk were observed in an additional study in populations at cardiac risk [54]. However, this combination remains contraindicated for patients with uncontrolled hypertension.

The use of naltrexone together with bupropion was approved by the FDA in 2014 and by the EMA in 2015 but has not yet been analyzed by the Brazilian agency. This, along with the contraindications, limits the group of patients that can be assisted by these drugs.

Table 1 provides a summary of the information on current pharmacotherapy.

4 Future Pharmacotherapy and Its Perspectives

4.1 Drugs with Actions on the CNS

As discussed briefly, the CNS, especially the arcuate nucleus of the hypothalamus, plays a crucial role in regulating energy metabolism and feelings of hunger and satiety [79]. The activity of neurons in this brain region is regulated by the body's nutrient levels and the hormones released by peripheral organs, such as pancreas, intestines, and adipose tissue [79]. Thus, drugs that can regulate the activity of these neurons could act on energy expenditure and food consumption, leading to reductions in body weight. However, the risks of behavioral adverse effects, such as depression and dependence, are high. All the described drugs, except orlistat, act on the CNS as appetite modulators.

As described in Sect. 3.2, sibutramine acts by inhibiting the uptake of mainly serotonin, which leads to increased serotonin levels in the synaptic cleft and activation of anorexigenic neurons [21]. Tesofensine is another inhibitor of the reuptake of biogenic monoamines, including serotonin, dopamine, and noradrenaline; it was developed by Saniona, initially for the treatment of Parkinson and Alzheimer

Table 1 Detailed information on current pharmacotherapy for the treatment of obesity in the USA, Europe, and Brazil

Therapeutic action	ATC code	INN	Brand name, developer	Pharmaceutical form classification/administration route	Posology	Mechanism of action	Approved	Major studies	Marketing status	Patent
CNS action	A08AA03	Amfepramone (diethylpropion)	Tenuate®/Artegodam and Tenuate Dospan®/Actavis Labs UT Inc.	Solid oral (also XR)	Diethylpropion hydrochloride 25 mg TID (1 h before meals) or diethylpropion hydrochloride XR 75 mg OD, preferably mid-morning	Sympathomimetic amine appetite suppressant	FDA 1959	–	FDA: prescription; EMA: withdrawn in 1999; ANVISA: withdrawn in 2011 but authorized by federal law in 2017	Expired
	None	Fenproporex	Desobesi-M®/Aché	Solid oral	Fenproporex hydrochloride 20–40 mg OD	Sympathomimetic amine appetite suppressant	–	–	EMA: withdrawn in 1999; ANVISA: withdrawn in 2011 but authorized by federal law in 2017	Expired
	A08AA05	Mazindol	Sanorex/Sandoz Pharmaceuticals	Solid oral	Mazindol 1–3 mg OD	Serotonin, norepinephrine, and dopamine reuptake inhibitor	FDA 1973	–	FDA: prescription; EMA: withdrawn in 1999; ANVISA: withdrawn in 2011 but authorized by federal law in 2017	Expired
	A08AA10	Sibutramine	Meridia®/Abbott Laboratories	Solid oral	Sibutramine hydrochloride monohydrate 10 or 15 mg OD	SNRI in the CNS	FDA 1997; EMA 1999; ANVISA 1998	[27, 28]	FDA: withdrawn in 2010; EMA: withdrawn in 2010; ANVISA: prescription	Expired
	A08AA11	Lorcaserin	Belviq®/Arena Pharmaceuticals and Eisai (distribution)	Solid oral	Lorcaserin hydrochloride 10 mg BID	5-HT_{2C} selective agonist	FDA 2012; ANVISA 2016	BLOOM [50]; BLOSSOM [51]; BLOOM-DM [48]	FDA: prescription; ANVISA: prescription	Vigent
				Solid oral XR	Lorcaserin hydrochloride (XR lorcaserin) 20 mg OD		FDA 2016		FDA: prescription	Vigent

Table 1 (continued)

Therapeutic action	ATC code	INN	Brand name, developer	Pharmaceutical form classification/administration route	Posology	Mechanism of action	Approved	Major studies	Marketing status	Patent
	A08AA01	Phentermine and topiramate	Qsymia® or Qnexa or Qsiva/Vivus	Solid oral topiramate XR	Two escalation doses: starting with combination of phentermine hydrochloride 3.75 mg + topiramate XR 23 mg in the morning for 14 days then increase to 7.5 mg/46 mg for 12 weeks. To evaluate the weight, if responsive, escalate to 11.25 mg/69 mg for 14 days, then increase to maximum of 15 mg/92 mg until 12 wk	Not fully understood; possibly an association between sedative effect and sympathomimetic amine appetite suppressant action	FDA 2012	EQUIP [61]; CONQUER [57]; SEQUEL [60]	FDA: prescription	Vigent
	A10BJ02	Liraglutide	Saxenda®/Novo Nordisk	Liquid (injectable solution)/parenteral (subcutaneous)	4 wk of dose escalation (liraglutide 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, 3.0 mg); the last dose should be maintained during the treatment	GLP-1 RA, as an analog of human GLP-1	FDA 2014; EMA 2015; ANVISA 2016	SCALE-Obesity and Prediabetes [70]	FDA: prescription; EMA: prescription; ANVISA: prescription	Vigent

Table 1 (continued)

Therapeutic action	ATC code	INN	Brand name, developer	Pharmaceutical form classification/administration route	Posology	Mechanism of action	Approved	Major studies	Marketing status	Patent
	A08AA62	Naltrexone and bupropion	Contrave® or Mysimba®/ Orexigen Therapeutics	Solid oral XR	3 wk of dose escalation: (1) one tablet morning (naltrexone hydrochloride XR 8 mg and bupropion hydrochloride XR 90 mg); (2) two tablets: one morning, one evening; (3) three tablets: two morning, one evening; (4) four tablets: two morning, two evening. Last dose should be maintained during the treatment	Dopamine and noradrenaline reuptake inhibitor (bupropion) and β-endorphin receptor antagonist (naltrexone)	FDA 2014; EMA 2015	COR-I [78]; COR-II [76]; COR-BMOB [74]; COR-Diabetes [75]	FDA: prescription; EMA: prescription	Vigent
Digestive lipase inhibition	A08AB01	Orlistat	Xenical®/Roche	Solid oral	Orlistat 120 mg TID	Gastrointestinal lipase inhibitor	FDA 1999; EMA 1998; ANVISA 1999	XENDOS [33]	FDA: prescription; EMA: prescription; ANVISA: prescription	Expired
			Alli®/Glaxo-SmithKline Cons	Solid oral	Orlistat 60 mg TID		FDA 2007; EMA 2007		FDA: OTC; EMA: OTC	Expired

5-HT serotonin, *ANVISA* Agência Nacional de Vigilância Sanitária, *ATC* Anatomical Therapeutic Chemical, *BID* twice daily, *CNS* central nervous system, *EMA* European Medicines Agency, *FDA* US Food and Drug Administration, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *INN* international nonproprietary name, *OD* once daily, *OTC* over the counter, *SNRI* selective serotonin and noradrenaline reuptake inhibitor, *TID* three times daily, *wk* week(s), *XR* extended release

disease (Fig. 2). The drug was inefficient for those indications and is now in phase III clinical trials for the treatment of obesity. In studies with obese rats, the compound led to weight reduction via hypophagia [80–83]. The treated animals also had smaller deposits of abdominal and subcutaneous fat. Reduced lipidemia and increased sensitivity to insulin were also observed [81]. Pharmacological tests have indicated that the effect of tesofensine on food intake occurs via dopamine receptors [80]. In the tests with obese animals, tesofensine normalized brain levels of dopamine and altered the expression and availability of dopamine receptors [82, 83]. In humans, treatment with tesofensine led to weight loss [84–86]; a meta-analysis indicated that the average weight loss was 4% of the initial weight after 3.5 months of treatment more than the placebo treatment, which can be considered a moderate loss [87]. The compound also increased the rates of satiety and fullness, leading to lower food intake. It also induced metabolic changes, increasing nocturnal energy expenditure, and fatty acid oxidation [86]. Tesofensine is well-tolerated in general, but mild adverse effects such as constipation, insomnia and dry mouth have been reported [84, 85, 88]. Concern about cardiac effects is high because of the sibutramine case; in fact, studies have reported that tesofensine caused an increased heart rate but had no effect on blood pressure [84, 85, 87]. An animal study showed that the hypophagic effect of the compound is independent of the cardiovascular effect, which opens the way for the heart rate to be controlled without loss of effect on the control of food intake [89]. Tesofensine also has little potential for abuse [90]. These results indicate that tesofensine may be a future substitute for sibutramine.

As described in Sect. 3.7, naltrexone is an opioid receptor antagonist and prevents the feedback inhibition of POMC neurons by β-endorphins, thus maintaining the feeling of satiety for longer. GlaxoSmithKline is developing a μ-opioid receptor inverse agonist, currently called GSK1521498 [91]. As an inverse agonist, this compound would be superior to naltrexone because it can not only prevent the inhibition of POMC neurons but also cause their activation (Fig. 2). In rats, GSK1521498 reduced food intake, weight, amount of white adipose tissue, and animal preference for sugary solutions [92]. In binge-eating rat models, the compound also reduced the compulsion for palatable food and the search for food before and after the meal. Moreover, GSK1521498 prevented the anticipatory hyperphagia typical in these animals [93]. The compound was well-tolerated in human trials but did have a moderate effect on attention span and pain threshold [94, 95]. GSK1521498 reduced the pleasure from and consumption of caloric foods [94, 96], lowering the attentional bias for food but without affecting other aspects of cognition [97]. The compound appears to act by modulating brain responses, especially in the amygdala [91], putamen, and globus pallidus [98], reducing the motivation to see images of caloric food [98]. Although no effects on weight or fat mass of patients were observed in the phase I clinical trials [96], GSK1521498 was tested in a phase II clinical trial.

Ghrelin is an acylated peptidic hormone produced by the stomach, being the main orexigenic sign and acting directly on NPY and AgRP neurons in the arcuate nucleus of the hypothalamus [99]. However, the unacylated ghrelin, long considered a degradation product of this hormone, has been shown to be a function inhibitor of ghrelin, with beneficial effects on obesity and diabetes [100]. Millendo Therapeutics is developing an unacyl-ghrelin analog cyclic peptide that is currently in phase II clinical trials for the treatment of patients with Prader–Willi syndrome, who present with hyperphagia and obesity as symptoms [101] (Fig. 2). In mice that are obese because of a high-fat diet, the peptide, called livoletide, prevented food-induced inflammation and stimulated the expression of mitochondrial function markers in brown adipose tissue. Treatment with livoletide also prevented the development of prediabetes in these animals [102]. In human tests, livoletide was well-tolerated [103, 104]. The peptide reduced glycemia without increasing plasma insulin levels, glycated hemoglobin, or body weight (2.6 kg on average vs. 1.3 kg in the placebo group, considered a small effect) after a 2-week treatment [103]. In tests in patients with Prader–Willi syndrome, livoletide reduced hyperphagia, waist circumference, adipose mass, and postprandial glucose levels [104]. These results indicate that livoletide may have potential as a treatment in obese patients as well as those with Prader–Willi syndrome.

4.2 Inhibitors of Digestive Lipases

Excessive consumption of fats, which are highly energetic, contributes to the development of obesity [105]. Thus, the reduction of digestion and absorption of fats by enterocytes is an efficient way to control body weight. The therapeutic success of orlistat is proof of this concept. However, the adverse effects of this drug mean the development of new lipase inhibitors is necessary. Cetilistat was developed to be the second drug of this class. In rats receiving a high-fat diet, treatment with cetilistat reduced intestinal fat absorption, increasing the amount of fat in the stool. The animals also had lower weight and amount of adipose tissue and reduced plasma levels of leptin, triglycerides, and cholesterol. It is important to note that no oil droplets were shed in the feces of the treated rats [106]. In clinical trials, patients lost weight after 3 months of treatment (~4.0 kg more than the placebo group, which is similar to the current pharmacotherapy), and blood levels of cholesterol and glycated hemoglobin were reduced [107, 108]. The release of fat in the feces increased. Adverse effects from cetilistat were milder than those from orlistat, and the dropout rate in the cetilistat

group was lower than in the orlistat group [109]. This drug is currently approved only in Japan; however, drugs sold as orlistat but containing small quantities of cetilistat have been found [110].

4.3 Drugs Acting on the Metabolism

Food consumption and fat absorption are essential for the development of obesity but are not the only factors. Energy expenditure and the metabolism and accumulation of lipids are also crucial points. In that sense, compounds capable of increasing muscle metabolism [111] and brown adipose tissue [112] or modulating white adipose tissue activity [113], for example, would be attractive candidates for the treatment of obesity. Currently, no approved drug acts directly on the metabolic character of obesity, which opens several possibilities in the search for new therapeutic and compound targets.

Adipotide is a modified peptide that has apoptotic action and affinity for the prohibitin protein. In this way, the biopharmaceutical induces apoptosis of endothelial cells specifically of white adipose tissue [114]. In rodents, adipotide caused loss of weight and mass of white adipose tissue and improved metabolic parameters such as plasma levels of non-esterified fatty acids, glycerol, triglycerides, and leptin, and the amount of hepatic fat [114–116]. The animals also presented an increase in the generation of heat, higher tolerance to glucose, and lowered insulinemia [114, 116]. It is interesting to note that, even with reduced leptin and hypothalamic expression of POMC, the animals reduced their food consumption [115]. This result may indicate that part of the weight loss effect is due to the decrease in calorie consumption. The adipotide also corrected the expression of genes involved in mitochondrial dysfunction, oxidative phosphorylation, and degradation of amino acids, which was altered by the high-fat diet [116]. The drug has also been tested in monkeys, who lost weight, with reduced white adipose tissue mass and insulin resistance. However, the treatment caused changes in renal function, which were reversed after the experiment ended [117]. The peptidic character of the adipotide means it must be given via injections, which may affect commitment to the treatment. However, one study has shown that a nanoencapsulated version of adipotide for controlled release is more efficient and allows for dose reduction [118]. This result may indicate that this formulation will lead to fewer injections in future treatment. Adipotide is in phase I clinical trials.

Dapagliflozin is an inhibitor of sodium-glucose cotransporter-2, mainly expressed in the renal system. This transporter allows the reabsorption of glucose in the kidneys, and its inhibition causes an increase in the excretion of glucose in the urine and consequent reduction of glycemia. Thus, dapagliflozin has been approved in the USA and Europe for the treatment of T2DM. However, the observation of weight loss in treated animals and humans was recurrent. Thus, the drug is in phase II trials for the treatment of obesity. In different animal models, treatment with dapagliflozin induced glucose excretion in the urine but increased food and water intake [119]. A reduction in energy expenditure was also observed [119, 120]. However, significant weight loss and reduced plasma triglyceride levels were still observed [119, 121], as were reductions in glycemia and insulinemia [119, 121, 122]. In the kidneys, treatment with dapagliflozin decreases inflammation and oxidative stress, lipid accumulation, and damage to renal tissues [121, 122]. The drug also improves hepatic physiology, decreasing lipid accumulation and fibrosis, and plasma levels of hepatic aminotransferases [121]. In humans, reduction of glycated hemoglobin, fasting blood glucose, and systolic blood pressure were observed

Table 2 Detailed information on some drugs under development for the treatment of obesity

Therapeutic action	Promising drugs in clinical development	Developer	Proposed mechanism of action	Relevant clinical studies	Clinical phase
CNS action	Tesofensine or NS-2330	Saniona	Biogenic monoamines uptake inhibitor	Phase I/II [86]; phase II [85]	II completed
	GSK1521498	GlaxoSmithKline	μ-Opioid receptor reserve agonist	Phase I [91, 94, 96]; phase II [96–98]	II completed
	Livoletide or AZP-531	Millendo Therapeutics	Unacylated ghrelin analog	Phase I [103]; phase II [104]	II completed
Digestive lipase inhibition	Cetilistat or ATL-962	Norgine and Takeda	Gastrointestinal lipase inhibitor	Phase I [109]; phase II [107, 108]	III completed
Metabolic action	Prohibitin-TP01 or Adipotide®	Arrowhead Research	Apoptosis of endothelial cells in white adipose tissue induction	Phase I—main identifier: NCT01262664	I active
	Dapagliflozin or BMS-512148-05	Bristol-Myers Squibb and AstraZeneca	Sodium–glucose cotransporter-2 inhibitor	Phase I [129]; phase II [130]	II completed

CNS central nervous system

[123]. A meta-analysis showed that the average weight loss caused by dapagliflozin was 1.6 kg more than in the placebo group after 6 months of treatment [124], which is a small effect compared with the currently available pharmacotherapy. The treatment caused increased urine excretion of glucose [123] and, probably because of this, the primary adverse effect observed was a higher incidence of urinary and genital infections [123].

Table 2 summarizes the information on developing pharmacotherapy.

5 Conclusion

Although new pharmacotherapeutic options have emerged over the last few years, data from studies in the USA indicate that pharmacotherapy is of interest to many patients. However, few of those who need it have access, with a socioeconomic disparity regarding access to both medication and commercial diet-related weight-loss programs [125].

On the other hand, obese patients with the intention of unrealistic weight loss can use pharmacotherapy incorrectly, uncorrelated to current treatment approaches, because of their unwillingness to endure difficulties for weight loss [126]. These patients tend to use anti-obesity drugs without medical and physical activity [127]. The expectation of weight loss with pharmacotherapy is 5–10%, which should be respected by physicians and patients [7]. Weight loss of at least 5% is associated with an improved inflammatory state and decreased insulin resistance, in addition to substantially reducing all components of metabolic syndrome [5]. However, the patient is often more interested in aesthetics than health.

The interaction between the current pharmacotherapy and the diet composition of treated patients is another point not yet explored in clinical trials and meta-analyses. The macronutrient composition of food alters the satiety response [128]. For example, the gastrointestinal system responds to a high-protein diet with a more significant release of cholecystokinin, peptide tyrosine–tyrosine, and GLP-1, all with anorexigenic action. On the other hand, a high-fat diet has little satiety effect and can lead to an increase in food consumption. Thus, it would be fascinating to investigate the effects of different diet compositions on the action of the drugs discussed here. For example, could a high-protein diet increase the satiety capacity of liraglutide? Is the effect of sibutramine reduced in a high-fat diet?

Although the amount of weight loss is attractive, this is not what determines the treatment. In general, it is difficult to compare the weight loss between each drug described in this review because of variations in treatment durations between the cited studies. Moreover, each drug has its limitations and therapy recommendations should consider the needs of patients and their clinical characteristics, which often renders the use of certain medications unfeasible. As such, new drugs are required so that all obese patients may be treated.

However, the future of pharmacotherapy for obesity is not encouraging. Half of the drugs being tested in humans currently target the CNS. Thus, it is likely that the same adverse effects of current pharmacotherapy will continue to restrict the use of new drugs. The new generation of lipase inhibitors has milder adverse effects on the gastrointestinal system, but they do remain, which further compromises treatment [109]. Drugs targeting metabolism also have problems. Weight loss with dapagliflozin treatment is low, and an increased incidence of urinary and genital infections has been observed in almost all clinical trials and confirmed in meta-analyses [123]. The effect of adipotide on weight in the preclinical test was good, but the injectable administration route may disrupt commitment to treatment [117].

Thus, the search for new compounds for the treatment of obesity remains imperative, especially for drugs with novel and as-yet unexplored molecular targets.

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Compliance with Ethical Standards

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