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The pharmacological treatment of obesity: A historical perspective

El tratamiento farmacológico de la obesidad: Una perspectiva histórica

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SUMMARY

Obesity is a highly prevalent disease associated with several metabolic pathologies such as diabetes, hypertension, metabolic syndrome, hepatic steatosis, and different types of cancer. However, since 1933, when the first pharmacological treatments for obesity appeared, their effectiveness and safety have been questioned, leading to the withdrawal of several drugs from the market. Currently, five drugs have been approved by the Food and Drug Administration (FDA) and are still in use for obesity control, of which GLP-1 analogs have demonstrated a better safety profile and moderate efficacy in reducing body weight. This literature review presents a historical analysis of anti-obesity drugs, focusing on their efficacy and adverse effects.

Keywords: *Obesity, anti-obesity drugs, anti-obesity agents.*

RESUMEN

La obesidad es una enfermedad con alta prevalencia, asociada a varias patologías metabólicas como diabetes, hipertensión arterial, síndrome metabólico, esteatosis hepática, entre otras; así como diferentes tipos de cáncer. A partir de 1933, cuando aparecen los primeros tratamientos farmacológicos para la obesidad, se ha cuestionado su efectividad y seguridad, lo que ha llevado a la retirada del mercado de varios fármacos. Actualmente 5 medicamentos cuentan con la aprobación de la Food and Drug Administration (FDA) para el tratamiento de la obesidad, de los cuales, los análagos de GLP-1 han demostrado un mejor perfil de seguridad y una eficacia moderada para la reducción de peso corporal. Esta revisión bibliográfica presenta un análisis histórico de los fármacos anti-obesidad, enfocados en su eficacia y efectos adversos.

Palabras clave: *Obesidad, drogas anti-obesidad, agentes anti-obesidad.*

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INTRODUCTION

Obesity is a pandemic with a rapidly increasing prevalence worldwide. In 2015, 107.7 million children and 603.7 million adults were obese (1), and it is estimated that by 2030, 60 % of the world's population will be overweight (2,3).

An elevated body mass index (BMI) is associated with high morbidity and mortality; therefore, weight loss in obese patients is important (1,4). Anti-obesity treatments include lifestyle changes, pharmacological treatment, and bariatric surgery (5).

Lifestyle changes in overweight patients result in significant weight loss (6); however, long-term weight loss is difficult to achieve (7) due to neurobiological mechanisms leading to weight regain (7,8), like leptin, ghrelin, peptide YY, gastric inhibitory polypeptide, cholecystokinin, among others (9).

For 100 years, a wide variety of drugs have been tested for body-weight loss with relative efficacy. Dinitrophenol appeared in 1933 (10), and since then, a wide variety of molecules have been developed, but due to their low effectiveness and severe adverse effects, the vast majority have been withdrawn from the market (11). The drugs for losing weight mediate their effects through three primary mechanisms: 1) decreasing the appetite, 2) Reducing intestinal fat absorption, and 3) Increasing thermogenesis (12). Currently, gut incretin receptor agonists are promising therapies because of the significant decrease in body weight and few adverse effects associated with this drugs (7).

Although pharmacological treatment of obesity criteria is well-established, there is a lack of prescription for these drugs (13), mainly due to physician concerns about safety and efficacy (8,14).

This review aims to describe the historical evolution of the pharmacological treatment of obesity and analyze the efficacy and adverse effects of those drugs currently available, providing evidence for decision-making within the individualized care of people with obesity.

Obesity definition

Since ancient Greece, an image evoking ideal body weight has been established. This concept was reinforced by the Hippocratic school, where excess body fat was considered a deviation from normality as a product of one of the four humors alterations (15).

The use of anthropometry to assess body composition is universally accepted because it uses non-invasive, inexpensive, and reproducible techniques (16). BMI is a practical measure that indirectly assesses body fat percentage in adults(17) through the ratio of body weight in kilograms to height in meters squared (17,18). Adolf Quetelet developed this indicator in 1832 as a practical index of relative body weight, coined as body mass index by Ancel Keys in 1972 (19). Since 1995, the World Health Organization (16) classifies a person as obese once their body mass index is greater than or equal to 30, with subclassifications that include: grade I obesity when the BMI is between 30 and 34,9, grade II obesity when BMI is between 35 and 39.9, and when the BMI is greater than or equal to 40, the person is classified as grade III obesity carrier.

The primary BMI limitation is the incapacity to assess the body fat distribution, namely, fat mass from fat-free mass discrimination. Another difficulty in using BMI to classify obese patients is the difference in body structure seen across different ethnic groups, which has led to characterizing ethnic-specific cut-off points, especially for the Asian population (20).

According to the American Association of Clinical Endocrinologists and the American College of Endocrinology, obesity is "a chronic disease characterized by pathophysiological processes that increase adipose tissue mass with an increment in morbidity and mortality". This definition bears BMI as a tool for a patient's risk assessment and considers the interaction between susceptible genes and the environment in disease development. This fact allows the classification of obesity into three stages according to the comorbidities: stage 0, those patients with BMI ≥ 30 kg/m^2 with no complications; stage 1, BMI ≥ 25 kg/m^2 with mild complications and stage 2, BMI ≥ 25 kg/m^2 with severe complications (21).

Pharmacological treatment indications

Loss of at least 5 % of body weight has been shown to have significant benefits in patients with obesity (22,23); pharmacological treatment has been established for those individuals presenting with obesity (BMI ≥ 30 kg/m^2) or those presenting with BMI ≥ 27 kg/m^2 plus comorbidities such as diabetes, pre-diabetes, hypertension, dyslipidemia, obstructive sleep apnoea, non-alcoholic fatty liver disease or other obesity-associated pathologies (24).

The past of pharmacology in obesity

In 1933 an energy chain uncoupling drug called dinitrophenol was used for the treatment of obesity due to its ability to accelerate metabolism by 50 %, with a 4 kg weight loss in approximately 40 days (10); however, three years later, severe adverse effects were reported like thrombocytopenia, granulopenia, anemia and purpura complicated by lung abscess (25).

In 1954 Simeons (26) published human chorionic gonadotropin (HCG) use associated with a 500 kcal diet resulted in a 20 to 30 pounds loss in weight in forty days. This effect was attributed to a decrease in compulsive hunger. In 1977 Shetty and Kalkhoff (27) also evaluated the effect of a restrictive diet plus HCG vs placebo, but they did not find a significant weight loss when compared with the control group, a result verified by Greenway and Bray (28) who also did not find a significant difference in either weight loss (p=0.366) or perceived hunger decrease (p= 0.709).

Around the 1960s, thyroid hormones became popular because of the general belief that obesity was associated with an underactive thyroid gland. This fact convinced that synthetic thyroid hormone administration would lead to weight loss (29). However, in 1967 Gwinup and Poucher (30) confirmed that thyroid hormone prescription does not lead to significant weight loss in patients with obesity; on the contrary, a high frequency of side effects like severe anxiety, increase in systolic blood pressure (9 mmHg), and heart rate elevation of 25 beats per minute. Similarly, Bray et al. (31) reported that 80 % of the lost weight was due to lean mass breakdown. The discouraging data regarding weight loss and three sudden death cases secondary to atrial fibrillation by L-thyroxine reported by Bhasin et al. (32) in 1981 led to the complete dismissal of this anti-obesity treatment.

FDA approved fenfluramine and phentermine for obesity (33) when clinical studies demonstrated significant weight loss (p<0.001) (34). However, in 1997 these drugs were withdrawn because of asymptomatic valvular abnormalities in 32 % of patients (33) and primary pulmonary hypertension increased risk (OR 6.3; 95 % CI 3.0 - 13.2). In addition, irrespective of the prescribed drug or dose employed, pulmonary hypertension risk was ever high if the treatment was administered for three or more months (OR 23.1; 95 % CI 6.9 - 77.7) (35). Another anti-obesity drug was phenylpropanolamine, an appetite suppressant sympathomimetic amine (36) that has been off the market since 2000 due to its association with hemorrhagic stroke (RR 3.13; p = 0.08) (36,37), hypertension, seizures and death (36).

A widely used drug was sibutramine, approved in 1997 by the FDA. This compound is a serotonergic and adrenergic drug inhibiting serotonin and norepinephrine reuptake, causing appetite suppression, satiety, and increased activity thermogenesis (38). Sibutramine produced a sustained weight loss of 4.45 kg at a 2-year follow-up, along with improved lipid profile and glycaemic control associated with a slight increase in heart rate and blood pressure (39); however, in 2010, a recall was requested due to a 16 % increase in major cardiovascular events such as non-fatal myocardial infarction and stroke when compared to placebo (p = 0.02 and p = 0.03) (40,41).

Lorcaserin, approved in 2012 by the FDA as an anti-obesity treatment, is a selective serotonin 5-hydroxytryptamine 2C receptor agonist that modulates appetite (42,43) This drug demonstrated a 5 % weight loss in 38.7 % of treated patients (p<0.001) (42) and a decreased risk of incident diabetes and diabetes microvascular complications (44). The most frequent side events reported with lorcaserin included nausea, vertigo, and headache (43), with a low rate of major cardiovascular events 4.1 % (42); however, in February 2020, the FDA requested the withdrawal of this drug (45) due to

the high frequency of adverse events associated with cancer, mainly pancreatic, colorectal and lung cancer (46).

Drugs approved in the treatment of obesity

Table 1 summarizes the main developments related to the pharmacotherapy of obesity to date.

Table 1

Milestones in the pharmacological treatment of obesity

Year	Drug	Milestone
1933	Dinitrophenol	Weight loss of 4 kg in 40 days (10).
1936	Dinitrophenol	This compound is considered a poison since it causes bone marrow aplasia (25).
1954	Gonadotropina coriónica humana	Simeons attributes weight loss of 20 to 30 pounds (26).
1960	Thyroid hormones	Obesity is secondary to an underactive thyroid gland (29).
1966	Phenfluramin y Phentermin	FDA-approved as anorexigenic (33).
1977	Human Chorionic Gonadotropin	Weight loss was due to calorie restriction but not the drug (27,28).
1981	Thyroid hormone	Sudden deaths were reported during thyroid hormone administration (32).
1997	Anorexigenics	Symptomatic valvular abnormalities and pulmonary hypertension (33,35).
1997	Sibutramine	FDA-approved, it inhibits the reuptake of serotonin and norepinephrine, leading to appetite suppression, satiety, and increased thermogenesis (39).
1999	Orlistat	Pancreatic lipase inhibitor approved by FDA decreasing fat absorption by 30 (53,54). Gastrointestinal adverse events (57).
2000	Phenylpropanolamine	This drug was withdrawn from the market for association with hemorrhagic stroke (36,37).
2010	Sibutramine	This drug was withdrawn from the market for increased major cardiovascular events (40,41).
2012	Lorcaserin	FDA approves its use due to a 5% decrease in weight and a decrease in comorbidities (44).
2012	Phentermin/topiramate	Approved by FDA in 2012, it acts as an appetite suppressant and food taste modifier, resulting in weight loss of more than 10% (61,65).
2014	Liraglutide	GLP-1 analog, FDA approved for more than 5% weight loss associated with few gastrointestinal adverse effects (68,70).
2014	Naltrexone/bupropion	Anorexigen approved by FDA in 2014, is a combination of an opioid antagonist and a selective inhibitor of neuronal reuptake of catecholamines with an effect on hypothalamic pro-opiomelanocortin neurons (76,79).
2020	Lorcaserin	It was withdrawn from the market due to increased cancer, especially pancreatic, colorectal, and lung cancer (45,46).
2021	Semaglutide	GLP1 analog was approved by the FDA with weekly dosing for a decrease of almost 15% in body weight, with mild gastrointestinal effects (52,82).

Made by: The authors

Current FDA-approved anti-obesity drugs have shown to be safe and well-tolerated, with few adverse events (47,48) and limited action on cardiometabolic risk profile (49), with no influence on end-points like all-cause mortality or cardiovascular disease (50).

Until 2020, five drugs still in use for obesity treatment: orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, and lorcaserin (11), while lorcaserin was withdrawn due to adverse effects, other drugs previously used for type 2 diabetes management showed promising results in obese patients (51). In addition, in June 2021, Semaglutide was approved by the FDA for the pharmacological management of obesity (52).

Orlistat is the most popular and perhaps most prescribed anti-obesity drug. It was approved by the FDA in 1999, acting at the gastrointestinal lumen by inhibiting pancreatic lipases (53), leading to a reduction of dietary fat absorption by up to 30 % (54). The recommended dose is 120 mg 3 times daily, taken with meals (53,54) with better results at higher doses (55). The beneficial effects of orlistat are weight loss, improvement in lipid profile, and insulin levels (54).

Some multicenter studies and systematic reviews with meta-analyses have shown body weight, total cholesterol, low-density lipoprotein, and systolic and diastolic blood pressure reduction by orlistat administration (56,57). In addition, Shirai (58) 2019 also demonstrated a significant loss of visceral fat (up to 13.5 %) and waist circumference (- 2.51 cm).

Most of the orlistat adverse reactions are mild (57), mainly gastrointestinal, such as increased number and frequency of bowel defecation, steatorrhea, flatulence, and abdominal pain (53,57). In addition, fat malabsorption leads to reduced absorption of fat-soluble vitamins (59) and other drugs such as warfarin, amiodarone, cyclosporine, and thyroid hormones (60), which should be evaluated to avoid complications.

Phentermine/topiramate combines a centrally acting sympathomimetic appetite suppressant and an antiepileptic that inhibits carbonic anhydrase and Na+ channels, enhancing GABA metabolism, which is believed to modify food taste (61). The CONQUER (62) study published in 2011, a multicentre clinical trial evaluating phentermine/topiramate weight loss efficacy in obese patients, demonstrated a loss of up to 10.2 kg with phentermine/topiramate vs 1.4 kg with placebo ($p<0.0001$). Another EQUIP (63) clinical trial published in 2012 showed that phentermine/topiramate resulted in a loss of up to 10.9 % of initial body weight at doses of 15/92 mg, with significant changes in blood pressure, fasting glucose, and lipid profile. An extension study of CONQUER, the SEQUEL (64) trial, in 2012 showed a weight loss of up to 20 % with the use of the drug ($p<0.001$), also improving cardiovascular and metabolic variables. These studies were the basis for the 2012 FDA approval of phentermine/topiramate as a treatment for obesity (61,65). In different clinical trials, Phentermine/topiramate has been associated with mild adverse events such as dry mouth, paresthesia, constipation, insomnia, dizziness, and dysgeusia (62-65).

Liraglutide is a glucagon-like peptide 1 (GLP-1) analog initially developed for type 2 diabetes mellitus (DM2) management, which has been helpful in body weight reduction due to appetite suppression through specific brainstem nuclei activation and delayed gastric emptying (66). Liraglutide action at the central nervous system level is related to the right orbitofrontal cortex secondary to food signals to activation (67).

Astrup et al. (66) demonstrated in 2009 that liraglutide plus nutritional plan and exercise led to a 7.2 kg maximum weight loss at a 20-week follow-up compared with placebo and orlistat. In addition, other benefits such as reduced blood pressure and pre-diabetes prevalence of 84 %-96 % were another two advantages of liraglutide. Moreover, at a 2-year follow-up, liraglutide maintained a 7.8 kg weight loss with a metabolic syndrome and pre-diabetes decrease prevalence of 50 % (68). These findings led to the FDA approval as an anti-obesity treatment in 2014 (70).

Subsequent studies showed that liraglutide monotherapy produced significant weight loss compared to placebo ($p<0.001$) (67-70), with a fat loss as high as 12.49 % (71), corresponding at least to a BMI reduction of 5 % in 43.3 % of patients (72). In addition to physical activity, the weight loss with liraglutide was 9.5 kg (70).

The SCALE (74) trial, one of the most extended studies with liraglutide (3-year follow-up), demonstrated a 6.1 % weight loss reduction with a decrease in systolic blood pressure, CRP, and an improvement in the quality of life. In addition, the cardiovascular benefits of liraglutide were decreased death from cardiovascular causes, non-fatal myocardial infarction, or stroke (73). However, gastrointestinal adverse effects may occur in up to 64.8 % of patients (69,72,75), especially nausea and constipation (75) secondary to delayed gastric emptying of solids (69).

Naltrexone/bupropion combines an opioid antagonist with a selective noradrenaline-dopamine reuptake inhibitor that has demonstrated a synergistic effect on hypothalamic pro-

opiomelanocortin neurons, with an anorectic effect (76). Greenway et al. (76) 2009 evaluated naltrexone/bupropion vs monotherapy, plus diet and exercise as adjunctive therapy for weight loss; their results showed a significant weight loss with the combination therapy versus monotherapy. The COR-BMOD trial (77) showed an 11.5 % loss in body weight with naltrexone/bupropion ($p<0.001$); also, CONTRAVE Obesity Research-II (COR-II) (78) in 2013 showed 8.2 % weight loss at 56 follow-up weeks ($p<0.001$), with an excellent cardiometabolic safety profile and mild to moderate adverse events; so in 2014 the FDA approved naltrexone/bupropion combination as a new option for obesity management. This drug increases the risk of nausea, headache and constipation (76, 78, 79) RR = 1.11 ($p = 0.0004$). However, serious adverse events have been reported at RR = 1.70 ($p < 0.00001$), leading to the discontinuation of this drug combination (80).

Initially marketed as a hypoglycemic drug for type 2 Diabetes, the GLP-1 analog Semaglutide demonstrated more significant weight loss vs its comparators (51). In 2018, O'Neil et al. (81) evaluated Semaglutide in patients with obesity without diabetes versus liraglutide and placebo; results demonstrated a 10 % loss of body weight in 37 to 65 % in Semaglutide group at 0.4 mg daily when combined with dietary advice and exercise ($p<0.001$); this drug was well tolerated and demonstrated no cardiovascular safety issues.

Wilding et al. (82) in March 2021, published the results of a double-blind clinical trial involving 1961 non-diabetic patients given 2.4 mg Semaglutide weekly vs placebo, revealing a weight loss of 15.3 kg with Semaglutide vs 2.6 kg with placebo and a total body weight loss of 14.9 % with Semaglutide vs 2.4 % with placebo ($p<0.001$). The main adverse events reported were nausea and diarrhea, which stopped the treatment in 4.5 % of patients. In June 2021, the FDA approved the use of weekly Semaglutide to treat obesity, with the specification that its use must be associated with dietary management and exercise plans (52).

CONCLUSIONS

Since the 20th century multiple drugs with different mechanisms of action have been tested for obesity treatment; however, multiple adverse neurologic and cardiovascular effects have led to the majority of these drugs being removed from the market. Due to its safety profile, the only anti-obesity drug that has remained on the market for more than 20 years is orlistat; however, its efficacy for weight loss is limited. GLP-1 agonists are the most promising of the currently available drugs due to their significant weight loss and decreased metabolic risk with few gastrointestinal adverse events.

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