Review
Pharmacology
DOI: 10.56016/dahudermj.1271677

DAHUDER
Medical Journal
e-ISSN: 2791-9250

Current pharmacological approaches in obesity treatment

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ABSTRACT

Obesity is a complex disorder and affected by so many factors in which the balance between food consumption and calorie usage is disrupted. Drugs that act on appetite, food intake, calorie absorption or calorie consumption, or a combination of these, are basically central or peripheral agents. Diethylpropion and phentermine are preferred for short-term obesity treatment. Orlistat, lorcaserin, topiramate/phentermine, naltrexone/bupropion, and liraglutide are preferred for long-term obesity treatment. The main drugs whose experimental and clinical phase studies are still ongoing are setmelanotide, zonisamide/bupropion, neuropeptide Y antagonists, semaglutide and oral glucagon-like peptide-1 agonists, cannabinoid type-1 receptor inhibitors, amylin mimetics, amylin/calcitonin receptor activators, glucose-linked insulin-like acting peptide analogues, dual-acting glucagon-like peptide-1/glucagon receptor agonists, peptide YY, leptin analogues, beloranib, cetilistat, tenofensin, fibroblast growth factor-21 and obesity vaccines. While managing the treatment of an obese patient, considering the large costs of the disease and the high incidence of disorder, pharmacotherapeutic agents are not enough to meet the clinic spectrum like adverse effects and contraindications, but new drugs and studies in this field offer hope to the medical world in terms of efficacy and safety profile. However, it would not be rational to expect miracles from drugs without a change in lifestyle in the magement of this disorder.

Keywords: Obesity, new drugs, pharmacology, weight loss medications, weight management

Obesity is a multifactorial disorder that is described as high amount fat storage that can impair human health, alters anatomy and physiology, and therefore occurs with metabolic, biomechanical and psychosocial problems. The disease, in which the ratio between food consumption and calorie usage is disrupted, is affected by many physical and environmental situations. Although the Body Mass Index (BMI, kg/m²) does not distinguish between the proportion between fat and lean body mass, it is the most useful parameter. [1]

MEDICATIONS USED IN THE PAST FOR TREATMENT OF OBESITY

As a consequence of the observation of the relationship between hypothyroidism and obesity, the first drug used was thyroid hormone. Provided weight loss, but 80% of the weight lost is muscle tissue. After the treatment was terminated, weight gain was observed again due to thyroid gland atrophy. Obesity has been avoided due to the risk of tachycardia, cardiac arrhythmias and sudden death in excessive use.

Received: *March 29, 2023;* ***Accepted:*** *April 22, 2023;* ***Published Online:*** *April 29, 2023*

How to cite this article: *Tiryakioglu P, Yılmaz H, Demir I, Yılmaz I. Current pharmacological approaches in obesity treatment. DAHUDER MJ 2023,3(2):32-48. DOI: 10.56016/dahudermj.1271677*

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Dinitrophenol was introduced in 1933 for the treatment of obesity. It disrupts oxidation reactions and increases metabolic rate. It has been used together with thyroid hormone and has been effective. However, its use was discontinued due to its serious toxic effects (hepatotoxicity, agranulocytosis, visual impairment, dermatitis, death).

Amphetamine was preferred in the treatment of obesity in the late 1930s. Although it was used in combination therapy with thyroid hormone, digitals and diuretics between 1940-1960, it resulted in myocardial toxicity, development of addiction to some other substances in the drugs and sudden death.

Aminorex was introduced in the 1960s but was gathered from the drug stores in 1968 because of the pulmonary hypertension.

Fenfluramine is an agent that increases synaptic serotonin release and inhibits its reuptake. In 1997, fenfluramine and dexfenfluramine were withdrawn from drug stores when it was reported that they could cause valvular cardiac problems.

Phenylpropanolamine is a sympathomimetic. It was gathered from the drug stores as it raised the probability of stroke.

Sibutramine was found in the USA in 1997 and has been approved by the Food and Drug Administration (FDA). It suppresses appetite and increases thermogenesis by reuptake blockage of serotonin and norepinephrine. It improves the serum lipid profile and reduces body weight by approximately 4.5 kg in one year. In 2010, it was first removed from the market by the European Medicines Agency (EMA) after increasing the risk of MI (myocardial infarction) in clinical trials. Today, many debilitating drugs can be found illegally in non-pharmaceutical products. 1

DRUGS THAT FDA APPROVED USED IN THE SHORT-TERM TREATMENT FOR OBESITY

Phentermine

In 1959, it was authorized by the FDA for short-term (≤ 12 weeks) weight control purposes. It decreases appetite due to the release of norepinephrine in the central nervous system. The efficacy and safety of 30 mg controlled-release phentermine was evaluated in a 1.5-month clinical trial in diabetic, dyslipidemic, or obese with hypertension. [2] A significant weight loss was observed in patients given phentermine compared to placebo, and their total cholesterol and low-density lipoprotein (LDL) levels improved. There was no difference between the groups in systolic and diastolic blood pressure. In a 36-week placebo-controlled study evaluating 108 obese patients, 30 mg of phentermine daily was given regularly or intermittently. While there was a weight loss of 4.8 kg in the placebo, there was a mean weight loss of 12.2 kg and 13 kg, respectively, in the drug groups. The most common side effects in the study were dry mouth and sleep disturbances, while serious complications were palpitations, increased heart rate, and hypertension. It has been stated that longer-term, dose-adjusted clinical studies are required to confirm phentermine's efficacy and safety in treating obesity. [3]

Diethylpropion

It is a sympathomimetic amine with amphetamine-like effects and suppresses appetite by increasing the secretion of norepinephrine and dopamine and inhibiting their reabsorption. Approved by the FDA for use in less than 12 weeks. It causes about 10% weight loss in a year. It is given orally at a dose of 25 mg three times a day or in the extended pharmaceutical form at a dose of 75 mg once a day. Long-term use can cause pulmonary hypertension and heart valve disease like other appetite suppressants with amphetamine-like effects. If these symptoms occur, the drug should be discontinued, and the patient should be evaluated immediately. It is contraindicated for advanced atherosclerosis, severe hypertension, hyperthyroidism, glaucoma, agitation, history of drug dependence, MAO inhibitors during or within two weeks of use, and concomitant use with other anorectic drugs. Cardiac arrhythmia, cerebrovascular accident, hypertension, anxiety, depression, dizziness, euphoria, headache, hyperarousal, precordial pain, psychosis, alopecia, skin rashes, libido changes, gynecomastia, constipation, diarrhea, dysphagia, nausea, vomiting, Many adverse effects may occur, including xerostomia, bone marrow depression, dyskinesia, myalgia, tremor, blurred vision, and mydriasis. [4] In a meta-analysis of studies lasting 6-52 weeks involving approximately 80% of women receiving concomitant lifestyle treatments, diethylpropion produced a weight loss of 3 kg. [5]

FDA ALLOWED AGENTS USED FOR LONG-PERIOD MANAGEMENT OF OBESITY

Orlistat

It is currently the longest-licensed anti-obesity

agent for long-term management. The FDA approved it in 1999. It is prescribed at 120 mg for people over 12 years old. After oral intake, within 3-5 days, almost all of it is excreted with feces; its systemic absorption is close to zero and does not accumulate. Unlike other agents, it does not affect appetite. Its primary mechanism of action is the inhibition of intestinal absorption of triglycerides. In addition, it prevents the release of gastrointestinal system lipases and provides approximately 30% calorie reduction.

In a study of 3305 patients, a weight loss of 2.4% was achieved at the end of four years and reduced the risk of type 2 DM compared to a placebo. It also reduced fat absorption and improved lipid profiles, blood pressure, and insulin sensitivity. In another study, 91 percent of subjects given orlistat experienced gastrointestinal side effects, and 8 percent of these patients dropped out of the study because of this. [6] Common gastrointestinal adverse effects are gas, bloating, indigestion, abdominal pain, and diarrhea. It is prescribed daily multivitamins because of the risk of fat-soluble vitamin deficiency. In some cases, acute kidney injury has been reported in orlistat users with diabetes-like metabolic problems. [3]

Lorcaserin

It is a selective 5-hydroxytryptamine (5-HT) 2C receptor stimulant. The use of 10 mg twice daily was approved by the FDA in 2012, and on February 14, 2020, patients were asked to warn of potential cancer-related risks. Activating proopiomelanocortin (POMC) receptors in the body reduce calorie consumption and increases satiety with serotonin's anorectic effect. It has a high specificity against the 5-HT2C receptor. Therefore, it suppresses starvation and hunger without leading to pulmonary hypertension and heart valve defects. Existing trials have shown that it has psychological effects that contribute to weight loss, reduce appetite and the urge to eat, and increase satiety.

The efficacy and safety of different doses of lorcaserin have been studied in clinical trials called BLOOM and BLOSSOM. All volunteers received dietary and physical activity counselling. In the BLOOM study, 3182 volunteers with a BMI of 30-45 kg/m^2 were given 10 mg of lorcaserin or a placebo for 52 weeks. The drug-administered group received the same dose of lorcaserin or placebo for another 52 weeks. Weight loss rates of 10% and above were 22.6% in the lorcaserin group and 7.7% in the placebo group. 7 The BLOSSOM study consisted of 4008 individuals with a BMI of 30-45 kg/m^2. Volunteers were given 10 mg of lorcaserin or a placebo 2 or 4 times daily. After 52 weeks, the lorcaserin group was attenuated by more than 10% compared to the placebo. 22.6% of the group taking lorcaserin 10 mg four times a day and 17.4% of the group taking it twice a day lost more than 10% of their weight. This rate was 9.7% in the placebo group. In a clinical study evaluating the risk of lorcaserin abuse, effects were assessed using a visual analog scale by giving participants ketamine, zolpidem, lorcaserin, and a placebo. This study determined that lorcaserin was well tolerated and had no risk of abuse. [8] The main adverse effects of the drug are headache, dizziness, nausea, dry mouth, hypoglycemia, cough, constipation, back pain, and fatigue. Since it activates the serotonergic system, it has been claimed that its use with other serotonergic agents may lead to serotonin syndrome. However, clinical studies are needed for this.

Phentermine/Topiramate

It was approved in 2012 for the long-term treatment of obesity. However, the EMA did not allow this combination due to the lack of long-term study data on topiramate's significant cardiovascular adverse effects, cognitive side-effect problems and the potential for abuse. [9] The mechanism of appetite suppression of this combination is not completely clear. Voltage-gated ion channel modulation, GABA-A receptor activity increase, and AMPA/Kainate glutamate receptor inhibition are thought to be effective in topiramate-induced appetite reduction. [10] Clinical studies show that topiramate can also inhibit compulsive eating and addictive behaviors. Topiramate, a GABA receptor activator, glutamate receptor inhibitor, and inhibitor of carbonic anhydrase enzyme, is also allowed for the epilepsy management and prevention of migraine attack. Significant weight reduction was seen in epileptic individuals managed with topiramate, which led to clinical studies for the obesity management. Phentermine is a noradrenergic agonist. Its central sympathetic effect occurs by increasing the norepinephrine, dopamine and serotonin release. It has been placed on the list of 4 drug groups by the FDA. This means a lower potential for abuse compared to list 3, which includes codeine and hydrocodone-like drugs. 11

EQUIP (n = 1267) and CONQUER (n = 2487) clinical studies were conducted to examine the effect of the combination of phentermine and topiramate on weight loss. The EQUIP study included non-diabetic volunteers with a BMI ≥ 35 kg/m^2, while the CONQUER study included volunteers with a BMI be-

tween 27-45 kg/m^2 and more than two obesity-related comorbidities. In the EQUIP study, the mean annual weight loss for individuals given the combination therapy was 10.9% (1.6% in the placebo group) versus 9.8% in the CONQUER study (1.2% in the placebo group). Improvements in cardiovascular system parameters were observed in both studies. A 2-year extension study, the SEQUEL study, was planned to evaluate sustained weight loss after these studies. The findings here supported the previous findings and showed that using phentermine/topiramate resulted in significant weight loss in the waist circumference by improving fasting insulin, fasting glucose, lipid profiles and blood pressure.

Common adverse effects of the combination are dry mouth, taste disturbance, constipation, dizziness, paresthesia, and insomnia. The drug can be taken in the morning to prevent insomnia. Although there is a structural similarity between phentermine and amphetamine, phentermine has no addictive potential and no risk of abuse. Even with prolonged use, amphetamine-like withdrawal is not observed when abruptly discontinued. [12] Birth control is recommended for women of childbearing age as it increases the risk of cleft palate.

Naltrexone/Bupropion

The FDA approved it in 2014 for a long-term weight loss treatment. Its mechanism is not fully understood. Naltrexone, bupropion, and dual combinations are thought to increase hypothalamic proopiomelanocortin (POMC) neuron firing frequency. Thus, by increasing proopiomelanocortin (POMC) activity, they provide modulation of the hypothalamic melanocortin system (homeostatic system) and mesolimbic dopamine reward system (non-homeostatic system).

Bupropion is used in cessation of smoking. The mechanism for anorectic action is dopamine and norepinephrine reuptake inhibition. Bupropion's alleged mechanism of action is to fire neurons that secrete α-melanocyte stimulating hormone (α-MSH). α-MSH reduces calorie intake and increases calorie consumption via MC4Rs (Melanocortin-4 Receptor). β-endorphin, a μ-opioid receptor agonist, is released in POMC neurons under physiological conditions, which inhibits the over-release of α-MSH. In this way, a negative feedback system works. Naltrexone inhibits β-endorphin-related negative feedback by blocking μ-opioid receptors, and this increase on POMC activity may be cause of its body weigtht reduction effects. Naltrexone is a drug used to treat opioid addiction. They create a synergistic effect with bupropion. [3]

The bupropion/naltrexone combination has been studied in different clinical studies COR-I (n = 1742), COR-II (n = 1496) and COR-BMOD (n = 793). Patients with diabetes, weight-related comorbidities, and patients with BMI ≥ 27 kg/m^2 were included in the 56-week studies. In the COR-I, COR-II, and COR-BMOD studies, weight loss in subjects given the 32/360 mg combination therapy was 6.1%, 6.4%, and 9.3%, respectively (1.3%, 1.2%, and 5.1% on placebo, respectively). The last study to evaluate weight loss in 505 overweight or obese diabetic patients is the COR-DM study. In this study, 5% weight loss was also observed in patients treated with a combined dose of 32/360 mg for 56 weeks (1.8% in the placebo group). In addition, HbA1c values also decreased from baseline. [13] In these studies, the bupropion/naltrexone combination improved lipid parameters in patients. Common adverse effects were headache, dizziness, gastrointestinal problems and dry mouth. The dose is gradually increased to prevent nausea. Blood pressure and heart rate may increase. There is a black box warning of an increased risk of suicidal thoughts and neuropsychiatric symptoms associated with this combination.

Liraglutide

Liraglutide is a derivative of glucagon-like peptide-1 (GLP-1) administered parenterally (3 mg/day subcutaneously). It was allowed by the FDA for type 2 DM in 2010 and for weight management in 2014. GLP-1 is released from the vagal nucleus of the solitary system, the proximal colon, and the distal ileum. It shows the effect of incretin after meals. GLP-1 shows its effect on blood sugar by increasing insulin level from principal beta cells of pancreas and reduces glucagon level in a glucose associated trait. [14] It also causes of postprandial satiety and fullness by showing ıts effects on the limbic/reward system, hypothalamus and cortex, slows gastric emptying, reduces appetite and food consumption. Liraglutide is strongly bound to plasma proteins and more stable in plasma. Thus, it provides a higher half-life (13 hours after a single injection) than endogenous GLP-1. [15] Liraglutide was approved after three large randomized controlled clinical trials: SCALE Diabetes, SCALE Maintenance, and SCALE Obesity/Prediabetes. [16] In the SCALE Obesity/Prediabetes study of 2487 obese volunteers, 61.2% of the participants were prediabetic. In the 56-week study, given liraglutide 3 mg 4 times daily or placebo, weight loss was 8% in the liraglutide group (2.6% in the placebo group). Of the patients given li-

raglutide, 63.2% lost ≥ 5% of their weight, and 33.1% lost ≥ 10%. The drug group's cardiovascular system parameters (blood pressure and lipids) were better. In addition, significant decreases were found in HbA1c and fasting blood sugar. [17] In the SCALE Diabetes study, 846 patients with type 2 DM who were overweight or obese were given liraglutide or a placebo at two different doses (3 mg 4 times a day or 1.8 mg 4 times a day) for 56 weeks. A 6%, 4.7% and 2% decrease was observed in the patient's weight, respectively. [18] The SCALE Maintenance study evaluated weight control in non-diabetic subjects on a low-calorie diet for four weeks. Four hundred twenty-two participants with 5% or more significant weight loss were randomized to subcutaneous 3 mg liraglutide/day or placebo. An additional 6.2% weight loss was observed in the drug group, compared to 0.2% in the placebo group. In addition, the improvement in cardiovascular parameters was remarkable in obese patients with type 2 DM. [19]

GLP-1 receptor analogues can increase amylase and lipase in a dose-independent manner, which raises concerns in terms of acute pancreatitis. However, it is stated that this risk does not increase significantly in long-term studies. In experimental studies, it is stated that liraglutide may be risky in patients with a predisposition for thyroid carcinoma. However, the findings of a long-term clinical study did not find a significant difference between liraglutide (≤ 1.8 mg/day) and placebo in terms of calcitonin levels and medullary thyroid carcinoma rates. [20] Although the optimal dose of liraglutide for weight loss is 3 mg per day, treatment should be started with 0.6 mg, and the dose should be increased gradually to avoid gastrointestinal complaints. A recent meta-analysis showed that liraglutide had the highest discontinuation rate due to adverse effects among all FDA-approved obesity drugs (13% of patients). [21]

COMBINED ANTI-OBESITY DRUGS

Due to the multifactorial factors in the development of obesity, a single anti-obesity drug may not show sufficient efficacy in the treatment or it may be necessary to increase the doses of the drug that cause unacceptable side effects. Anti-obesity drug combinations; It aims to increase to maximum the effect on weight, while being complementary, safe and tolerable. However, to date, there is no allowed combination drug for obesity treatment other than topiramate/phentermine and bupropion/naltrexone. Firstly, most of the combinations aims to controlling hunger/appetite/satiety with decreasing peripheral calorie absorption.

Sodium-glucose-co-transporter 2 (SGLT-2) inhibitors have been approved by the FDA for use with diet and exercise to lower blood sugar in type 2 diabetics. Drugs in this group include canagliflozin, dapagliflozin, and empagliflozin. These drugs inhibit renal glucose uptake and increase urinary glucose excretion. They are mainly used to regulate the blood sugar of people with DM. Interestingly, the efficacy of these agents in people without a diagnosis of diabetes is limited. While 8 kg of weight loss was observed in patients with diabetes for more than one year, in another study only 2 kg of weight loss was observed in diabetics. It has been claimed that this is due to compensatory eating behaviour and increased appetite. Based on this information, a combination of an appetite suppressant such as phentermine and an SGLT2 inhibitor drug might be reasonable for weight management. Indeed, significant weight loss was observed in clinical studies examining the combination of canagliflozin and phentermine. The weight loss observed with the combination therapy was 6.9%, compared to 1.3% with canagliflozin alone and 3.5% with phentermine alone. In another recent study, combination therapy was more successful than the use of drugs alone. [16]

The anorectic efficacy and safety of the combination of topiramate and diethylpropion were investigated in experimental studies. The drugs were given alone or in combination at dose ratios of 1:1, 1:3, and 3:1. The ED30 of these combinations is significantly higher than the experimental ED30 of non-deprived or 12-hour food-restricted mice. Interaction indices and confidence intervals also confirmed the possible potential between these two drugs. The theoretical ED30 value of this combination did not affect blood pressure. The data showed that low doses of the diethylpropion+topiramate combination deserve further study in clinical trials. The anorectic effects of these drugs appear to be potentiated with safer doses. [22]

Table 1 presents clinical studies on the safety and efficacy of FDA-approved anti-obesity drugs currently in use. Table 2 summarises the safety profiles of FDA-approved anti-obesity drugs currently in use.

TREATMENT PRINCIPLES IN OBESITY DRUGS

Despite accessibility, anti-obesity drugs are not used enough by healthcare workers. Just 2 percent of obese people eligible for obesity drug therapy receive

Table 1. Currently Used FDA-Approved Anti-Obesity Drugs and Efficacy Trials

Anti-Obesity Drugs	Clinical trials	Patient (n)	Clinical Trial Duration	Weight Loss
Orlistat		3305	4 years	%2,4
Lorcaserin	BLOOM	3182	2 years	> %10
	BLOSSOM	4008	52 weeks	> %10
Phentermine / Topiramate	EQUIP	1267	1 year	%10,9
	CONQUER	2487	1 year	%7,8
	SEQUEL		2 years	
Bupropion / Naltrexone	COR-I	1742	56 weeks	%6,1
	COR-II	1496	56 weeks	%6,4
	COR-BMOD	793	56 weeks	%9,3
	COR-DM	505	56 weeks	%5
Liraglutide	SCALE Obezite ve Prediyabet	2487	56 weeks	%8
	SCALE Diyabet	846	56 weeks	%6
	SCALE Maintenance	422	4 weeks	%6,2

a prescription from doctors. It is high ratio stigmatized disorder, there is a misunderstood that obesity is caused by a willpower deficiency and laziness. It is often thought that these patients do not deserve appropriate management with drugs or operation. The expensive prices of these drugs also blocks them from being adequately prescribed for long-term treatment. Achieving and maintaining weight loss is extremely difficult, and long-period treatment of obesity often needs additional pharmacological therapy options. In obese patients, it would be prudent to plan treatment by initiating drug therapy after a risk/benefit analysis. Consideration should be given to the growing evidence that these agents may delay the onset of obesity-related morbidities and achieve better metabolic and cardiovascular outcomes. More importantly, these drugs' risk/benefit ratios should be evaluated individually for each patient. Management strategy should be clear and unambiguous. Patient compliance affects the treatment and may even lead to the termination of the treatment. At each examine, physicians should evaluate the adverse effects associated with a particular agent and evaluate the agent's weight reduction effect.

The main management goal with an obesity drug in obese people should be permanent weight loss and improvement in general health. Physicians should convey these important messages to their patients when medication is started. Firstly, not every agent can cause efficient results in individuals, and wide variable responses can be seen. Secondly, when the maximum therapeutic effect of a agent is seen, weight loss reaches a plateau and then weight gain should normally be expected when drug therapy is discontinued. Management results of these agents should be considered for approximately 12 weeks usage of maintenance dose. 3-4 months trial period is needed to predict whether a person will observe significant weight reduction in one year. Lastly allowed anti-obesity drugs have FDA and EMA-recommended "Stop Rules" to help physicians identify individuals who can see > 5% weight loss within one year. Stopping rules can prevent harmful usage of drugs and increase the benefit/risk ratio. If, after 12 weeks, there is less than 5% weight loss with full-dose therapy (less than 4% weight loss in 4 months for liraglutide), the drug should be discontinued, and treatment with other medications should be initiated. However, it can be difficult for the physician to decide which obesity medication to continue after 12 weeks of full-dose therapy. In addition, only drug therapy is not considered when determining the withdrawal rules. All these are considered together, including anti-obesity medications and drastic lifestyle changes. Drug administration without calorie restriction and increased energy expenditure may result in less than 5% body weight loss after 12 weeks. [3, 11, 16]

ANTI-OBESITY DRUGS CURRENTLY UNDER RESEARCH

Melanocortin receptor (MC4R) agonists (Setmelanotide)

Known about the melanocortin receptor agonists (RM-493, BIM-22493, IRC-022493), which reg-

Table 2. Safety Profiles of Currently Used FDA-Approved Anti-Obesity Drugs (modified fromSrivastava G &Apovian C, 2018)

Anti-Obesity Drugs*	Contraindications	Warnings and Precautions	Advers Effects
Phentermine	Cardiovascular disease, the use of MAO inhibitor in 14 days, hyperthyroidism, glaucoma	Rarely primary pulmonary hypertension cases, increase in heart rate and blood pressure	Insomnia, dry mouth, constipation, agitation
Orlistat	Chronic malabsorption Syndromes, cholestasis	Decrease in vitamin absorption (multivitamin supplementation recommended)	Diarrhea
Phentermine / Topiramate	Glaucoma, hyperthyroidism, use of MAO inhibitor in 14 days	Fetal toxicity, metabolic acidosis, cognitive disorder	Paresthesia, dizziness, taste disorder, insomnia, constipation and dry mouth
Lorcaserin	Pregnancy	Risk of reaction like serotonin syndrome and neuroleptic malignant syndrome (medication is discontinued if there are symptoms of valve disease	In non-diabetic patients: headache, dizziness, fatigue, nausea, dry mouth and constipation and diabetic patients: hypoglycemia, headache, back pain, cough and fatigue
Bupropion / Naltrexone	Uncontrolled hypertension, seizures, anorexia nervosa or bulimia, chronic opioid use, simultaneous use with MAO inhibitors in 14 days	Suicide behavior and thought, increase in heart rate and blood pressure, hepatotoxicity, narrow angle glaucoma	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth and diarrhea
Liraglutide	Medullary carcinoma or Multiple endocrine neoplasia in personal or family	Thyroid C-cell tumors seen in rats and mice; Rarely, acute pancreatitis, acute gallbladder disease, renal failure, increase in heart rate, suicide tendency and behavior, serious hypoglycemia when used in insulin	Nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decrease in appetite, indigestion, fatigue, dizziness, abdominal pain and lipase increase

* All anti-obesity drugs are contraindicated during pregnancy

ulates eating behavior and feeling of fullness in the brain and affects insulin sensitivity, was advanced in 1992 with the POMC mRNA melanocortin peptides discover and the melanocortin cloning. Again, it has been clearly demonstrated that MC4R loss-of-function variants, which are highly prevalent in the Pima Indian population, cause energy dysregulation that causes monogenic type 2 DM and obesity. Compared to the MC4R gene, the MC3R gene is more critical in maintaining energy balance and foraging behavior after food deprivation. [23, 24] The effects of setmelanotide (infused continuously at 1 mg/day for 72 hours) on resting energy use in obese subjects were studied in a clinical study. [25] Male and female patients with a mean body mass index of 35.7 ± 2.9 kg/m^2 were evaluated with diet and half-hour physical activity once a day. While the resting energy expenditure of the patients increased by 6.4% compared to the placebo, wherewithal, the total daily energy expenditure increased, and the respiratory coefficients decreased. No side events were observed on blood pressure or heart rate. In another crossover study, setmelanotide treatment was associated with increased serum fasting glucose, triglyceride, free fatty acid, insulin, C-peptide, peptide YY, and total glucagon-like peptide-1. [26] Although MC4R activators have previously been observed to raise blood pressure and heart rate, no side events on blood pressure or heart rate have been seen. Other transient side effects include arthralgia, nausea, headache, female genital tenderness, and spontaneous penile erection. While cetmelanotide is currently allowed for some rare genetic diseases of obesity, it continues to be evaluated in others. These diseases include POMC deficiency obesity (FDA approval in

2020), LepR deficiency obesity (FDA approval in 2020), proprotein convertase subtilisin / kexin type-1 (PCSK1) deficiency (FDA approval in 2020), Bardet -Biedl syndrome, Prader-Willi syndrome (FDA approval in 2022), POMC heterozygous deficiency obesity, Alström syndrome, and POMC epigenetic diseases (FDA approval in 2022). Setmelanotide also has potential as replacement treatment for genetic obesity disorders like MCR4 pathway deficiences.

Neuropeptide Y Antagonist (Velneperit)

Velneperit (S-2367) blocks the binding of Neuropeptide Y (NPY) to Y5 receptors. Thus, it reduces hunger and strengthens the feeling of satiety. It was considered an anti-obesity drug because of its effect on hunger. But, it was abandoned for further studies after disappointing results in phase II clinical trials that showed moderate weight loss. [27, 28] Patients on a restricted calorie diet (RCD) or a low-calorie diet (LCD) were given two different doses of the drug (800 versus 1600 mg) in combination. The efficacy and safety of the drug were studied versus placebo in 1566 obese patients. Patients taking 800 mg of the drug lost an average of 3.8 kg. 35% lost more than 5% of their initial body weight. A weight loss of 7.1 kg was observed in the LCD trial in those who were given 1600 mg of medication for 54 weeks. 52% of these patients lost more than 5% of their baseline body weight. Results from the trial reported that velneperitin met the primary goal for weight reduction endpoints and the secondary endpoints of improvement and reduction in total lipid parameter. [2]9 However, Y5 receptor antagonists are considered to have the potential to be successful as an anti-obesity agent. A new combination drug of velneperit and orlistat is currently under investigation in different clinical trials.

Zonisamid/Bupropion

In many clinical studies, this combination has been shown to cause weight loss. Zonisamide is an antiepileptic used in the treatment of partial seizures. It blocks sodium and calcium channels, inhibits carbonic anhydrase enzyme, and has a dopamine-serotonin transmission effect. The known side effect of antiepileptic therapy is weight loss in patients. Bupropion is a dopaminergic agent and allowed for the management of smoking cessation and depression and provides weight loss when used as monotherapy because it reduces appetite. The depression-sedation effects and antiepileptic properties caused by zonisamide, when combined with the proconvulsant and anti-depressive effects of bupropion, form a complementary combination. [29] A pilot trial of 18 obese women demonstrated that the combination was superior to monotherapy. The mean weight loss of the combination of zonisamide and bupropion was 7.2 kg (7.5%) and 2.9 kg (3.1%) at 12 weeks against to placebo, respectively. %44 of the zonisamide administered monotherapy group dropped out because of poor tolerance and adverse events against to the combination therapy group with percentage of. [22] In a 24-week phase IIb study involving 729 obese patients given the combination of zonisamide and bupropion, more significant weight loss was observed in patients receiving the combined drug treatment than in monotherapy of both drugs and placebo. The proportion of subjects who lost more than 5% of their baseline body weight was approximately half of the patients in the bupropion (360 mg) + zonisamide (120 mg) combination and 60% of the patients in the bupropion (360 mg) + zonisamide (360 mg) group. The most commonly reported adverse effects were headache, insomnia, and gastrointestinal complaints. There were no differences in cognitive disorders, depression, anxiety, and suicidal ideation between the placebo and treatment groups. Phase II trials of this combination therapy have been completed, and phase III trials have been initiated.

Type-1 Cannabinoid Receptor Inhibitors

Stimulation of cannabinoid type-1 (CB1) receptors enhances orexigenic signaling, while antagonism of CB1 receptors inhibits food intake by activating anorexigenic signaling. Rimonabant (also known as SR141716) and AM251 are CB1 receptor antagonists/inverse agonists and have increased body weight reduction in experimental studies. [30] These former CB1 therapeutic antagonist aims also have the potential for centrally mediated effects. Rimonabant causes mood disturbances in 10% of patients and suicidal thoughts in approximately 1%. Other expected adverse effects include gastrointestinal complaints, flu symptoms, upper respiratory tract infections, anxiety, nervousness, sleep problems, hot flashes, dry skin, tendinitis, muscle cramps and spasms, and fatigue. Side effects such as similar symptoms and raised risk of falls have been reported. Clinical studies and post-marketing surveillance data have shown a double risk of psychiatric problems such as depressive disorders, anxiety and thoughts of suicide in people taking rimonabant. Due to these risks, rimonabant was withdrawn from the stores in 2009. [31, 32]

Semaglutide and Other Oral GLP-1 Agonists

GLP-1 receptors are found in the brain. They can directly affect various neural circuits, including GLP-1 signals from the periphery to regulate calorie consumption and weight maintenance. [33] Liraglutide is a GLP-1 analogue used parenterally (3 mg/day subcutaneous injection). It is approved for the treatment of obesity. This drug is effective in obese and type 2 diabetic patients. However, its extended-release pharmaceutical form is still not approved for treating obesity. Semaglutide (NN9536), a long-acting GLP-1 analogue, is currently being studied. Clinical data both in treating obesity and in people with type 2 diabetes are promising. At the end of 3 months of treatment, the energy intake of patients given subcutaneous semaglutide once weekly decreased by 24%, and their body weight decreased by 5 kg. [34] In clinical trials evaluating the effects of once-weekly use in type 2 diabetics, a decrease in HbA1c and weight loss were observed. Its safety profile is similar to other GLP-1 receptor activators. The main adverse effects observed with these drugs are gastrointestinal complaints. There was no increased risk of pancreatitis and pancreatic cancer in controlled clinical trials. However, caution should be studied regarding cholelithiasis. [35] Other minor GLP-1 activators, such as TTP054/TTP-054 and ZYOG1, which can be administered orally, are being investigated as an alternative to parenteral drugs with low side effects. [36]

Amylin Mimetics and Dual Amylin-Calcitonin Receptor Agonists

Amylin is a pancreatic beta-cell hormone. It creates a central effective satiety signal, reducing calorie consumption by affecting the area postrema, where the peripheral peptide signal may directly connect with cerebral neurons. It also increases gastric motility and reduces postprandial glucagon release. The area postrema also connects to the nucleus solitarius and other brain autonomic control centers. As a result, amylin signaling shows a regulator effect over energy metabolism by reducing the orexigenic neuropeptides expression. Subtypes of human amylin receptor are complexed with receptor activity-modifying proteins of the calcitonin receptor. [37] Due to their mechanism of action, amylin mimetics coupled with dual-acting amylin and calcitonin receptor activators (also known as DACRA) have emerged as promising new anti-obesity drug target. Davalintide (AC2307), an amylin-mimetic peptide, decreased calorie consumption and weight with increased metabolism on amylin in animal trials. [38, 39] In last trials, DACRA (KBP-088 and KBP-042) achieved superiority against to davalintide in efficacy for in vitro receptor pharmacology, in vivo calorie consumption, and weight loss. [40] DACRA improved oral glucose tolerance and hyperinsulinemia in rats fed a high-fat diet. It also reduced adipose tissue cell hypertrophy, resulting in weight loss. A long-acting amylin analogue given once daily is being tested in phase I clinical trial.

Glucose Linked Insulinotropic Polypeptide (GIP) Analogue

Gastric Inhibitory Peptide is a polypeptide hormone consisting of 42 amino acids. However, inhibition of gastric secretion could not be confirmed in subsequent human studies. The fact that it shows a glucose-dependent insulinotropic effect in further studies suggests a role of incretin. GIP shows effect on stabilizing blood sugar levels, in contrast to glucose associated effects on insulin and glucagon release, respectively. [41] High-level GIP signaling in adipocytes can lead to lipid deposition, hepatic steatosis associated with visceral fat deposition, and insulin resistance. In animal trials, the GIP analogue ZP4165 did not change body weight in obese subjects, similar to the GLP-1 receptor activators, although it exerted an insulinotropic effect in rats and decreased HbA1c levels in diabetic mice. GLP-1-induced significant weight loss suggests that the combined treatment of GIP and GLP-1 agonists should be further studied instead of GIP monotherapy in treating obesity and diabetes. [42]

Dual Action GLP-1/Glucagon Receptor Agonists, GC-CO-Agonist 1177, and Triple Agonist Glucagon-GIP-GLP-1 Agonist (Tri-agonist 1706)

For over 50 years, glucagon has been known to reduce food intake and increase human satiety. Further studies investigating the use of GLP-1 receptor activator and glucagon combinations (Oxyntomodulin, MEDI0382, G530S (Glucagon analogue+semaglutide)) revealed that glucagon reduces hunger by neuronal stimulation in the area postrema and central nucleus. [43] Oxyntomodulin is a dual receptor activator peptide of GLP-1/glucagon and secreted by endocrine enteral L cells and is reduce hunger, reduce calorie consumption, and raise energy consumption. Overweight and obese subjects have been seen to decrease body weight by 2.3 ± 0.4 kg in the management group over the trial time against to the control group following 4 weeks of management. [44] Tirzepatidine, a novel glucose-dependent insulinotropic polypeptide,

and GLP-1 agonist, achieved a significant and sustained reduction in body weight in an approximately 1.5-year clinical trial in 2539 obese patients (dosed at 5 mg, 10 mg, or 15 mg/week). Further studies of its efficacy and safety in obese individuals are planned. [45]

Peptide YY (PYY)

It is secreted from L cells of the colon and ileum in response to food intake and has anorexigenic effect. It is a 36 amino acid peptide with a U-shaped fold. [46] Its two main forms are PYY3-36 and PYY1-36. The most abundant biologically active form in the bloodstream is PYY3-36, which binds to the Y2 receptor (Y2R) of the Y receptor family and shows structural homology. PYY decreases gastric motility and increases satiety. It decreases appetite and food consumption through NPY receptor blockade. [47] Obese individuals have lower levels of PYY. In addition, the increase in PYY is blunted after satiety. Infusion of PYY has also achieved to decrease levels of the ghrelin which an oroxigenic hormone. [48] Failure to maintain high PYY levels also causes weight gain after bariatric surgery. [49] Although it is an important anti-obesity agent target to study, it has a few restrictions, firstly its short half-life that affects usage and stability. Phase I and II clinical trials are currently testing strategies to develop different pharmaceutical drug forms, such as long-acting subcutaneously administered analogs, oral-intravenous forms, and nasal sprays.

Leptin Analogues

Since animal studies of leptin, a hormone secreted by adipocytes, have linked leptin deficiency with severe obesity, it was initially considered a successful treatment for obesity. Conversely, however, obese people are leptin-resistant and have much more leptin levels. [50] Therefore, combination therapies have been tried to block leptin resistance. Metreleptin is a parenteral leptin analog. It corrects hyperglycemia and hypertriglyceridemia and reduces hepatic adiposity. It has been associated with lipodystrophic diseases that cause congenital or familial loss of adipocytes. It has been approved in Japan and the US for limited indications in individuals with lipodystrophy and leptin deficiency. Decreased treatment efficacy and weight regain after meterleptin treatment may be observed in patients. This has been attributed to the development of anti-metreleptin antibody immunogenicity. The most commonly expected drug-related adverse effects (≥ 10%) are headache, weight loss, hypoglycemia, and abdominal pain. T-cell lymphoma has occurred in individuals with acquired generalized lipodystrophy independent of metreleptin treatment.

Pramlintide is a synthetic analog of amylin peptide hormone with anorexigenic action. It reduces food intake, and weight gain is released in response to calorie consumption and has a glucose-regulating effect. It is approved for treating diabetes mellitus and reduces calorie consumption and weight in obese individuals regardless of diabetes. Pramlintide produces a shorter-lasting satiety signal in contrast to leptin. It has been shown to improve the leptin pathway in experimental studies. This suggested that the neurohormonal combination may have a synergistic or additive effect. In phase II clinical trials comparing the combination of pramlintide/metreleptin with monotherapies, more significant weight loss was achieved without any plateau phase being observed. In the 52-week extension study of this trial, weight loss continued in the treatment group, while the placebo group regained all lost weight. [11] The most seen side events are mild or moderate nausea that subsides over time.

OTHER PROMISING NEW DRUG TARGETS

Beloranib

This fumagillin analogue drug is a methionine aminopeptidase 2 (MetAP2) inhibitor that reduces the synthesis of new fatty acids in the liver and converts stored fat into usable energy.

It was first used as an anti-angiogenetic agent in cancer treatment. After the role of MetAP2 in obesity was understood, antiobesity effects started to be studied. Different doses of beloranib given parenterally twice a week resulted in significant weight loss compared to placebo. It also showed improvements in lipids, C-reactive protein, and adiponectin. In a phase II study investigating the tolerability and efficacy of the drug, it improved weight loss and cardiometabolic risk factors. [51] Although gastrointestinal side effects and sleep disturbances were reported most frequently in relation to beloranib, it was generally found to be safe and well tolerated. It has led to significant weight loss and hypophagia in experimental hypothalamic and genetic models of obesity. Due to patient deaths, the FDA halted a phase III clinical trial in Prader-Willi patients in December 2015. [52]

Lipase Inhibitor

Cetilistat (ATL-962) has a similar effect to orlistat. It is an inhibitor of pancreatic and gastric lipase.

Reduced weight gain and improved lipid parameters in diet-induced obese rats. In a multicenter, randomized, placebo-controlled, phase II parallel group trial, the cetilistat group significantly reduced mean body weight against to placebo, resulting in improvement in lipid profiles. Treatment-emergent side effects were similar between treatment groups. More gastrointestinal adverse events were reported in the cetilistat group against to placebo. [53] In another phase II clinical trial, cetilistat was better tolerated than placebo and orlistat groups, and fewer patients discontinued the drug due to adverse effects. Cetilistat shows more promise than orlistat due to milder potential gastrointestinal adverse events (such as diarrhea, bloating, and oily stools). [54]

Inhibitors of Triple Monoamine Reuptake

Tesofensine (TE) is a recently discovered potent triple monoamine (dopamine, norepinephrine, and serotonin) reuptake inhibitor. In animal models, it increased dopamine levels in the forebrain and induced weight loss in diet-induced obese rats. In a phase II study involving obese patients given TE at dosages of 0.25, 0.5, or 1 mg/day for 24 weeks, an average of 4.5%, 9.2%, and 10.6% more weight loss was observed than placebo, respectively. Clinical studies have shown that it is effective in the treatment of anti-obesity. It has similar pharmacological properties to sibutramine. Therefore, it can potentially increase heart rate, blood pressure, and psychiatric disorders, and further studies on its safety are needed. [55]

Fibroblast Growth Factor (FGF) 21

It is a member of the FGF family, produced in the liver but can also be released from adipocytes, skeletal muscle, and the pancreas. It regulates metabolism by promoting both weight loss and glycemic control. [56] While the molecule acts on multiple organs, it is a triple autocrine, paracrine and endocrine factor. FGF21 stimulates uptake of glucose and release of adiponectin by transforming sensitive white adipocytes stores into brown adipose tissue. Activates both uptake of glucose and thermogenesis in brown adipose tissue. Its ability to raise energy consumption makes it a potential drug target for obesity. Reduces hepatic growth hormone signaling and regulates fatty acid oxidation. In experimental studies, it preserved lipid homeostasis in both fasted, and mice fed a low-carbohydrate and high-fat ketogenic diet. It is also known to have anti-inflammatory, anti-oxidative stress effects related to increased levels of this molecule during muscle-related or critical stress periods. [57]

Obesity Vaccines (Ghrelin, Somatostatin, AD36)

While the focus has so far been on anti-obesity agents that directly or indirectly increase anorexigenic signals, vaccines are a potential new therapeutic approach to prevent or treat obesity. The main point in the producing of obesity vaccines is to decrease appetite activating hormones and/or prevent food intake. Ghrelin has an important vaccine potential. Experimental data have shown that the anti-ghrelin vaccine reduces calorie intake, increases calorie utilization, and reduces hypothalamic orexigenic stimulation. In clinical trials, a strong response in ghrelin autoantibodies was achieved after four different doses of the anti-ghrelin vaccine. However, despite all these, the lack of significant weight loss has lowered hopes. [11] Somatostatin hormone inhibits insulin-like growth factor-1 and growth hormone (GH) release. Decreased basal GH release is associated with obesity and adiposity. Somatostatin vaccination aims to counteract the inhibitory effects of somatostatin and increase endogenous GH and immunoglobulin levels. Experimental studies showed a 10% reduction in body weight gain due to vaccination despite a fatty diet, while food intake remained unchanged. [58] Adenovirus 36 (AD36) has been shown to affect obesity risk in humans, increasing inflammation and adiposity. In mice injected with the AD36 vaccine, inflammatory cytokines and macrophages in adipose tissue were reduced after 14 weeks compared to the control group. In addition, more than a 17% reduction in body weight and more than 20% reduction in the epididymal fat increase were observed in the vaccinated group. Virus-induced vaccine prophylaxis may become an important treatment management target against obesity in the near future. [59]

The pharmacological profiles of novel drugs and drug-target agents currently under development are summarized in Table 3.

CONCLUSION

In the treatment management of obese patients, given the enormous costs and high burden of disease, current pharmacologic treatment options are not sufficient to meet clinical heterogeneity. Despite this shortcoming, anti-obesity drug studies and currently approved anti-obesity drugs give hope to the medical community. In this respect, it is important to increase medical options for obesity treatment with more effective management strategies. With the increase in

Table 3. New Drugs Currently in Development and Drug Targets (modified from Srivastava G & Apovian C, 2018)

Anti-Obesity Drugs	Other Names	Mechanism of Action	Effects	Adverse Effects	Clinical Benefits
Setmelanotide	RM-493 BIM-22493 IRC-022493	MC4R agonism	Decreased body weight, increased energy consumption	Headache, arthralgia, nausea, spontaneous penile erections, female genital area sensitivity	Trial for rare genetic diseases
Bupropion / Zonisamide	Empatic	Combination of a dopaminergic agent with an antiepileptic that provides sodium and calcium channel blockade, carbonic anhydrase inhibition and dopamine-serotonin transmission	More significant weight loss than monotherapy, stabilization of depression and proconvulsant effects with combination therapy	Nausea, headache, insomnia	Phase II trials completed
Cannabinoid type-1 receptor blockers	SR141716, AM251, AM6545	Cannabinoid type-1 receptor antagonism: anorexigenic signal attenuates	Weight loss in experimental studies	Depression and mood swings	
Semaglutide	NN9536; oral GLP-1 agonists: Semaglutid, TTP054/TTP-054 and ZYOGI	GLP-1 agonism	Decreased HbA1c, weight loss	Safety profile similar to GLP-1 agonists, fewer hypoglycemic events	Type-2 DM, obesity
Amylin mimetics	Davalintide (AC2307), KBP-088, KP-042 (dual amylin and calcitonin receptor agonists)	Pancreatic β-cell hormone (generates a central satiety signal that reduces food intake, slows gastric emptying, reduces satiety glucagon secretion); human amylin receptor subtypes are complexes of the calcitonin receptor	Reduces food intake and body weight improves oral glucose tolerance	Hypoglycemia	Type-2 DM, obesity

Table 3. (continued)

Anti-Obesity Drugs	Other Names	Mechanism of Action	Effects	Adverse Effects	Clinical Benefits
Velneperit	S-2367	Noropeptide Y5 receptor antagonist	Anorexia	Discontinued due to insufficient weight loss in phase II clinical trial	
Glucose-dependent insulinotropic polypeptide analogues	ZP4165	Increased GIP signalling in adipose tissue-induced insulin resistance, lipid storage and hepatic steatosis; GLP-1-induced weight loss enhancement by the combination of GLP-1 agonist and GIP	Insulinotropic effects and reduced HbA1c levels in diabetic mice, no effect on weight loss		Type-2 DM, obesity
	Pramlintide-Metreleptin	Synthetic analog of amylin peptide combined with the leptin analog; pramlintide is approved 30ort he treatment of type- 1 or 2 DM	Reduced food intake, with an average weight loss of 11% in combination trials	Mild-moderate nausea	Type-2 DM, obesity
Dual action GLP-1/glucagon receptor antagonist	Oxyntomodulin(OXM), MED10382, G530S (glucagon analogue + semaglutide), GC-co-agonist 1177	Glucagon monotherapy is hyperglycemic, but combining GLP-1 agonist and glucagon induces anorexia	Appetite suppressed, food intake reduced, and energy consumption increased	The short duration of action, limited clinical benefit	Long half-life drug development studies
Peptide YY	PYY	Decreases gastric motility, increases satiety, inhibits NPY receptors	Decreases appetite and food intake	Short half-life and stability limit the clinical utility	PYY infusion reduces the orexigenic hormone ghrelin levels. A blunt increase in postprandial PYY levels is associated with lower PYY levels in obesity

Table 3. (continued)

Anti-Obesity Drugs	Other Names	Mechanism of Action	Effects	Adverse Effects	Clinical Benefits
Leptin analogues	Metreleptin	Human recombinant leptin injectable analog	Improves hyperglycemia and hypertriglyceridemia, reduces hepatic fatty steatosis	Common adverse effects are headache, hypoglycemia, weight loss and abdominal pain.	Approved in Japan for lipodystrophic disorders, in the USA for non-HIV generalized lipodystrophy
Beloranib		Fumagillin analogue that inhibits methionine aminopeptidase 2 (reduces new fatty acid molecules in the liver, converts stored fat into usable energy); a novel angiogenesis inhibitor	It induced potent weight loss and hypophagia in 31ouse hypothalamic and genetic models of obesity. It also showed improvements in lipids, C-reactive protein, and adiponectin in clinical trials	Sleep disturbance and gastrointestinal side effects	Phase III clinical trial in Prader-Willi patients terminated in 2015 after 2nd patient's death
Lipase inhibitor	Cetilistat (ATL-962	Inhibitor of pancreatic and gastric lipase	Improved lipid profile and weight loss	Gastrointestinal side effects are better tolerated than orlistat	Obesity, hyperlipidemia, prediabetes, DM
Anti-Obesity vaccines	Ghrelin	An orexigenic hormone secreted by gastric fundus cells	Decreased food intake, decreased hypothalamic orexigenic signalling and increased energy expenditure in experimental studies	No weight loss in clinical trials	
	Somatostatin	Peptide hormone which inhibits growth hormone and insulin-like growth factor 1 secretion (IGF-1)	Decreased GH secretion is associated with obesity and increased adiposity. The somatostatin vaccine can eliminate the inhibitory effects of somatostatin and increase endogenous GH and IGF-1 levels	Vaccination did not affect changes in food intake in experimental studies	
	Adenovirus 36 (AD36)	Associated with obesity, inflammation, and increased adiposity	Vaccinated mice showed a more significant reduction in body weight and a reduction in inflammatory changes in adipose tissue in experimental studies		

the knowledge of the disease process, it will be possible to achieve new successes regarding these drugs and to approach this complex disease more rationally from a therapeutic point of view.

Authors' Contribution

Study Conception: PT, IY, HY,; Study Design: PT, IY, ID,; Supervision: IY, HY, ID,; Literature Review: PT,HY,; Manuscript Preparation: PT, HY, IY and Critical Review: IY, ID.

Conflict of interest

None to declare

Financing

None to declare

REFERENCES

1. Pilitsi E, Farr OM, Polyzos SA, Perakakis N, Nolen-Doerr E, Papathanasiou AE, Mantzoros CS. Pharmacotherapy of obesity: Available medications and drugs under investigation. Metabolism. 2019 Mar;92:170-192. doi: 10.1016/j.metabol.2018.10.010.
2. Kang JG, Park CY, Kang JH, Park YW, Park SW. Randomized controlled trial to investigate the effects of a newly developed formulation of phentermine diffuse-controlled release for obesity. Diabetes Obes Metab. 2010 Oct;12(10):876-82. doi: 10.1111/j.1463-1326.2010.01242.x.
3. Narayanaswami V, Dwoskin LP. Obesity: Current and potential pharmacotherapeutics and targets. Pharmacol Ther. 2017 Feb;170:116-147. doi: 10.1016/j.pharmthera.2016.10.015.
4. Obezite Tanı ve Tedavi Kılavuzu. 8. ed. Ankara: Türkiye Endokrinoloji ve Metabolizma Derneği; 2019.
5. Rodríguez JE, Campbell KM. Past, Present, and Future of Pharmacologic Therapy in Obesity. Prim Care. 2016 Mar;43(1):61-7, viii. doi: 10.1016/j.pop.2015.08.011.
6. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care. 2004 Jan;27(1):155-61. doi: 10.2337/diacare.27.1.155. IR N
7. Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, Stubbe S, Bays H, Shanahan WR; Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med. 2010 Jul 15;363(3):245-56. doi: 10.1056/NEJMoa0909809.
8. Shram MJ, Schoedel KA, Bartlett C, Shazer RL, Anderson CM, Sellers EM. Evaluation of the abuse potential of lorcaserin, a serotonin 2C (5-HT2C) receptor agonist, in recreational polydrug users. Clin Pharmacol Ther. 2011 May;89(5):683-92. doi: 10.1038/clpt.2011.20.
9. Patel DK, Stanford FC. Safety and tolerability of new-generation anti-obesity medications: a narrative review. Postgrad Med. 2018 Mar;130(2):173-182. doi: 10.1080/00325481.2018.1435129.
10. Bray GA, Hollander P, Klein S, Kushner R, Levy B, Fitchet M, Perry BH. A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. Obes Res. 2003 Jun;11(6):722-33. doi: 10.1038/oby.2003.102.
11. Srivastava G, Apovian C. Future Pharmacotherapy for Obesity: New Anti-obesity Drugs on the Horizon. Curr Obes Rep. 2018 Jun;7(2):147-161. doi: 10.1007/s13679-018-0300-4.
12. Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, Tam PY, Troupin B, Day WW. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). Obesity (Silver Spring). 2012 Feb;20(2):330-42. doi: 10.1038/oby.2011.330.
13. Jeon WS, Park CY. Antiobesity pharmacotherapy for patients with type 2 diabetes: focus on long-term management. Endocrinol Metab (Seoul). 2014 Dec 29;29(4):410-7. doi: 10.3803/EnM.2014.29.4.410.
14. van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WH. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. Int J Obes (Lond). 2014 Jun;38(6):784-93. doi: 10.1038/ijo.2013.162.
15. Farr OM, Tsoukas MA, Triantafyllou G, Dincer F, Filippaios A, Ko BJ, Mantzoros CS. Short-term administration of the GLP-1 analog liraglutide decreases circulating leptin and increases GIP levels and these changes are associated with alterations in CNS responses to food cues: A randomized, placebo-controlled, crossover study. Metabolism. 2016 Jul;65(7):945-53. doi: 10.1016/j.metabol.2016.03.009.
16. Tak YJ, Lee SY. Anti-Obesity Drugs: Long-Term Efficacy and Safety: An Updated Review. World J Mens Health. 2021 Apr;39(2):208-221. doi: 10.5534/wjmh.200010.
17. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, le Roux CW, Violante Ortiz R, Jensen CB, Wilding JP; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. N Engl J Med. 2015 Jul 2;373(1):11-22. doi: 10.1056/NEJMoa1411892.
18. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, Andreasen AH, Jensen CB, DeFronzo RA; NN8022-1922 Study Group. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. JAMA. 2015 Aug 18;314(7):687-99. doi: 10.1001/jama.2015.9676.
19. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, Aronne L; NN8022-1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond). 2013 Nov;37(11):1443-51. doi: 10.1038/ijo.2013.120.
20. Hegedüs L, Sherman SI, Tuttle RM, von Scholten BJ, Rasmussen S, Karsbøl JD, Daniels GH; LEADER Publication Committee on behalf of the LEADER Trial Investigators. No Evidence of Increase in Calcitonin Concentrations or Development of C-Cell Malignancy in Response to Liraglutide for Up to 5 Years in the LEADER Trial. Diabetes Care. 2018 Mar;41(3):620-622. doi: 10.2337/dc17-1956.
21. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, Loomba R, Camilleri M, Singh S. Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events: A Systematic Review and Meta-analysis. JAMA. 2016 Jun 14;315(22):2424-34. doi: 10.1001/jama.2016.7602.

22. Cortés-Moreno GY, Roa-Coria JE, Zúñiga-Romero Á, Huerta-Cruz JC, Lara-Padilla E, Del Valle-Laisequilla CF, Rocha-González HI, Reyes-García JG. Anorectic efficacy and safety of the diethylpropion-topiramate combination in rats. Drug Dev Res. 2018 Aug;79(5):225-233. doi: 10.1002/ddr.21434.
23. Fani L, Bak S, Delhanty P, van Rossum EF, van den Akker EL. The melanocortin-4 receptor as target for obesity treatment: a systematic review of emerging pharmacological therapeutic options. Int J Obes (Lond). 2014 Feb;38(2):163-9. doi: 10.1038/ijo.2013.80.
24. Kievit P, Halem H, Marks DL, Dong JZ, Glavas MM, Sinnayah P, Pranger L, Cowley MA, Grove KL, Culler MD. Chronic treatment with a melanocortin-4 receptor agonist causes weight loss, reduces insulin resistance, and improves cardiovascular function in diet-induced obese rhesus macaques. Diabetes. 2013 Feb;62(2):490-7. doi: 10.2337/db12-0598.
25. Chen KY, Muniyappa R, Abel BS, Mullins KP, Staker P, Brychta RJ, Zhao X, Ring M, Psota TL, Cone RD, Panaro BL, Gottesdiener KM, Van der Ploeg LH, Reitman ML, Skarulis MC. RM-493, a melanocortin-4 receptor (MC4R) agonist, increases resting energy expenditure in obese individuals. J Clin Endocrinol Metab. 2015 Apr;100(4):1639-45. doi: 10.1210/jc.2014-4024.
26. Greenfield JR, Miller JW, Keogh JM, Henning E, Satterwhite JH, Cameron GS, Astruc B, Mayer JP, Brage S, See TC, Lomas DJ, O'Rahilly S, Farooqi IS. Modulation of blood pressure by central melanocortinergic pathways. N Engl J Med. 2009 Jan 1;360(1):44-52. doi: 10.1056/NEJMoa0803085.
27. George M, Rajaram M, Shanmugam E. New and emerging drug molecules against obesity. J Cardiovasc Pharmacol Ther. 2014 Jan;19(1):65-76. doi: 10.1177/1074248413501017.
28. Yukioka H. [A potent and selective neuropeptide Y Y5-receptor antagonist, S-2367, as an anti-obesity agent]. Nihon Yakurigaku Zasshi. 2010 Nov;136(5):270-4. Japanese. doi: 10.1254/fpj.136.270.
29. Powell AG, Apovian CM, Aronne LJ. New drug targets for the treatment of obesity. Clin Pharmacol Ther. 2011 Jul;90(1):40-51. doi: 10.1038/clpt.2011.82.
30. Colombo G, Agabio R, Diaz G, Lobina C, Reali R, Gessa GL. Appetite suppression and weight loss after the cannabinoid antagonist SR 141716. Life Sci. 1998;63(8):PL113-7. doi: 10.1016/s0024-3205(98)00322-1.
31. Bergamaschi MM, Queiroz RH, Chagas MH, Linares IM, Arrais KC, de Oliveira DC, Queiroz ME, Nardi AE, Huestis MA, Hallak JE, Zuardi AW, Moreira FA, Crippa JA. Rimonabant effects on anxiety induced by simulated public speaking in healthy humans: a preliminary report. Hum Psychopharmacol. 2014 Jan;29(1):94-9. doi: 10.1002/hup.2374.
32. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet. 2007 Nov 17;370(9600):1706-13. doi: 10.1016/S0140-6736(07)61721-8.
33. Kanoski SE, Hayes MR, Skibicka KP. GLP-1 and weight loss: unraveling the diverse neural circuitry. Am J Physiol Regul Integr Comp Physiol. 2016 May 15;310(10):R885-95. doi: 10.1152/ajpregu.00520.2015.
34. Blundell J, Finlayson G, Axelsen M, Flint A, Gibbons C, Kvist T, Hjerpsted JB. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab. 2017 Sep;19(9):1242-1251. doi: 10.1111/dom.12932.
35. Monami M, Nreu B, Scatena A, Cresci B, Andreozzi F, Sesti G, Mannucci E. Safety issues with glucagon-like peptide-1 receptor agonists (pancreatitis, pancreatic cancer and cholelithiasis): Data from randomized controlled trials. Diabetes Obes Metab. 2017 Sep;19(9):1233-1241. doi: 10.1111/dom.12926.
36. Fosgerau K, Hoffmann T. Peptide therapeutics: current status and future directions. Drug Discov Today. 2015 Jan;20(1):122-8. doi: 10.1016/j.drudis.2014.10.003.
37. Bailey RJ, Walker CS, Ferner AH, Loomes KM, Prijic G, Halim A, Whiting L, Phillips AR, Hay DL. Pharmacological characterization of rat amylin receptors: implications for the identification of amylin receptor subtypes. Br J Pharmacol. 2012 May;166(1):151-67. doi: 10.1111/j.1476-5381.2011.01717.x.
38. Mack CM, Smith PA, Athanacio JR, Xu K, Wilson JK, Reynolds JM, Jodka CM, Lu MG, Parkes DG. Glucoregulatory effects and prolonged duration of action of davalintide: a novel amylinomimetic peptide. Diabetes Obes Metab. 2011 Dec;13(12):1105-13. doi: 10.1111/j.1463-1326.2011.01465.x.
39. Mack CM, Soares CJ, Wilson JK, Athanacio JR, Turek VF, Trevaskis JL, Roth JD, Smith PA, Gedulin B, Jodka CM, Roland BL, Adams SH, Lwin A, Herich J, Laugero KD, Vu C, Pittner R, Paterniti JR Jr, Hanley M, Ghosh S, Parkes DG. Davalintide (AC2307), a novel amylin-mimetic peptide: enhanced pharmacological properties over native amylin to reduce food intake and body weight. Int J Obes (Lond). 2010 Feb;34(2):385-95. doi: 10.1038/ijo.2009.238.
40. Gydesen S, Andreassen KV, Hjuler ST, Christensen JM, Karsdal MA, Henriksen K. KBP-088, a novel DACRA with prolonged receptor activation, is superior to davalintide in terms of efficacy on body weight. Am J Physiol Endocrinol Metab. 2016 May 15;310(10):E821-7. doi: 10.1152/ajpendo.00514.2015.
41. Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: Similarities and differences. J Diabetes Investig. 2010 Apr 22;1(1-2):8-23. doi: 10.1111/j.2040-1124.2010.00022.x.
42. Nørregaard PK, Deryabina MA, Tofteng Shelton P, Fog JU, Daugaard JR, Eriksson PO, Larsen LF, Jessen L. A novel GIP analogue, ZP4165, enhances glucagon-like peptide-1-induced body weight loss and improves glycaemic control in rodents. Diabetes Obes Metab. 2018 Jan;20(1):60-68. doi: 10.1111/dom.13034.
43. Parker JA, McCullough KA, Field BC, Minnion JS, Martin NM, Ghatei MA, Bloom SR. Glucagon and GLP-1 inhibit food intake and increase c-fos expression in similar appetite regulating centres in the brainstem and amygdala. Int J Obes (Lond). 2013 Oct;37(10):1391-8. doi: 10.1038/ijo.2012.227.
44. Wynne K, Park AJ, Small CJ, Patterson M, Ellis SM, Murphy KG, Wren AM, Frost GS, Meeran K, Ghatei MA, Bloom SR. Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects: a double-blind, randomized, controlled trial. Diabetes. 2005 Aug;54(8):2390-5. doi: 10.2337/diabetes.54.8.2390.
45. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, Stefanski A; SURMOUNT-1 Investigators. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med. 2022 Jul 21;387(3):205-216. doi: 10.1056/NEJMoa2206038.
46. Steinert RE, Feinle-Bisset C, Asarian L, Horowitz M, Beglinger C, Geary N. Ghrelin, CCK, GLP-1, and PYY(3-36): Secretory Controls and Physiological Roles in Eating and Glycemia in Health, Obesity, and After RYGB. Physiol Rev. 2017 Jan;97(1):411-463. doi: 10.1152/physrev.00031.2014.

47. Troke RC, Tan TM, Bloom SR. The future role of gut hormones in the treatment of obesity. Ther Adv Chronic Dis. 2014 Jan;5(1):4-14. doi: 10.1177/2040622313506730.
48. Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, Ghatei MA, Bloom SR. Inhibition of food intake in obese subjects by peptide YY3-36. N Engl J Med. 2003 Sep 4;349(10):941-8. doi: 10.1056/NEJMoa030204.
49. van der Klaauw AA, Keogh JM, Henning E, Trowse VM, Dhillo WS, Ghatei MA, Farooqi IS. High protein intake stimulates postprandial GLP1 and PYY release. Obesity (Silver Spring). 2013 Aug;21(8):1602-7. doi: 10.1002/oby.20154.
50. Farooqi IS, O'Rahilly S. 20 years of leptin: human disorders of leptin action. J Endocrinol. 2014 Oct;223(1):T63-70. doi: 10.1530/JOE-14-0480.
51. Kim DD, Krishnarajah J, Lillioja S, de Looze F, Marjason J, Proietto J, Shakib S, Stuckey BGA, Vath JE, Hughes TE. Efficacy and safety of beloranib for weight loss in obese adults: a randomized controlled trial. Diabetes Obes Metab. 2015 Jun;17(6):566-572. doi: 10.1111/dom.12457.
52. Elfers CT, Roth CL. Robust Reductions of Excess Weight and Hyperphagia by Beloranib in Rat Models of Genetic and Hypothalamic Obesity. Endocrinology. 2017 Jan 1;158(1):41-55. doi: 10.1210/en.2016-1665.
53. Yamada Y, Kato T, Ogino H, Ashina S, Kato K. Cetilistat (ATL-962), a novel pancreatic lipase inhibitor, ameliorates body weight gain and improves lipid profiles in rats. Horm Metab Res. 2008 Aug;40(8):539-43. doi: 10.1055/s-2008-1076699.
54. Kopelman P, Groot Gde H, Rissanen A, Rossner S, Toubro S, Palmer R, Hallam R, Bryson A, Hickling RI. Weight loss, HbA1c reduction, and tolerability of cetilistat in a randomized, placebo-controlled phase 2 trial in obese diabetics: comparison with orlistat (Xenical). Obesity (Silver Spring). 2010 Jan;18(1):108-15. doi: 10.1038/oby.2009.155.
55. Hansen HH, Jensen MM, Overgaard A, Weikop P, Mikkelsen JD. Tesofensine induces appetite suppression and weight loss with reversal of low forebrain dopamine levels in the diet-induced obese rat. Pharmacol Biochem Behav. 2013 Sep;110:265-71. doi: 10.1016/j.pbb.2013.07.018.
56. Giralt M, Gavaldà-Navarro A, Villarroya F. Fibroblast growth factor-21, energy balance and obesity. Mol Cell Endocrinol. 2015 Dec 15;418 Pt 1:66-73. doi: 10.1016/j.mce.2015.09.018.
57. Gómez-Sámano MÁ, Grajales-Gómez M, Zuarth-Vázquez JM, Navarro-Flores MF, Martínez-Saavedra M, Juárez-León ÓA, Morales-García MG, Enríquez-Estrada VM, Gómez-Pérez FJ, Cuevas-Ramos D. Fibroblast growth factor 21 and its novel association with oxidative stress. Redox Biol. 2017 Apr;11:335-341. doi: 10.1016/j.redox.2016.12.024.
58. Takagi K, Legrand R, Asakawa A, Amitani H, François M, Tennoune N, Coëffier M, Claeyssens S, do Rego JC, Déchelotte P, Inui A, Fetissov SO. Anti-ghrelin immunoglobulins modulate ghrelin stability and its orexigenic effect in obese mice and humans. Nat Commun. 2013;4:2685. doi: 10.1038/ncomms3685.
59. Yamada T, Hara K, Kadowaki T. Association of adenovirus 36 infection with obesity and metabolic markers in humans: a meta-analysis of observational studies. PLoS One. 2012;7(7):e42031. doi: 10.1371/journal.pone.0042031.