Review

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Regulation of food intake and the development of anti-obesity drugs

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Summary **As the most significant cause of death worldwide, obesity has become one of the world's most important public health problems, but approved anti-obesity drugs are extremely limited. This article summarizes the feeding control circuits and regulators involved in obesity development, highlight the hypothalamus, melanocortin system and brain-gut peptide actions in this process, and the five US FDA approved anti-obesity medications in long term use, namely phentermine/topiramate, lorcaserin, naltrexone/bupropion, liraglutide and orlistat.**

Keywords: Anti-obesity drugs, feed control, brain gut peptide, hypothalamus

1. Introduction

In recent years, obesity has become the leading preventable cause of death worldwide, with increasing rates in adults and children. It was named as one of the greatest public health problem threats of this century (*1*). The American Medical Association named obesity as a disease in 2013 (*2*). Now it has been identified by World Health Organization as one of the five major health threats to human beings. In 2015, the world has more than 2.3 billion overweight adults, in which 700 million are obese (*3*). During the past 20 years, the population of overweight and obese individuals increased significantly in China, Japan and Southeast Asian countries. In addition, obese children and adolescents have increased markedly. It is now the world's largest chronic disease among adult patients and listed as one of the world's four major social medical problems (*4*).

Obesity may lead to several diseases particularly, heart disease, type 2 diabetes, certain types of cancer, osteoarthritis and obstructive sleep apnea. Moreover, obesity also makes people vulnerable to injury, and makes it easy to get joint disease, and vulnerable to post-operation infections (*5*). Because of the prevalence of obesity and high costs, obesity is also a public health and policy problem. It has a number of serious consequences for individuals and government health systems (*6*). In view of the health hazards and socioeconomic burden, anti-obesity has become a hot topic, but the misunderstanding of definition is prevalence, in which many people equate obesity and heaviness. In fact, patients should have excess body fat that may influence their health to be classified as obese. It is a medical condition that may have the potential to increase health problems and/or reduce life expectancy (*5*). The most common causes of obesity are excessive food energy intake and lack of physical activity. Some people may have genetic susceptibility. However, a few cases of obesity are caused primarily by genes and patients with medications, psychiatric illness or endocrine disorders. Normally, we refer to the most common cases.

In "2014 NICE Guidelines for the identification, assessment and management of overweight and obesity in children, young people and adults", obesity is defined by a measurement of Body Mass Index (BMI) (*7*). According to BMI, the degree of overweight or obesity in adults can be subdivided as healthy weight, overweight, obesity I, obesity II and obesity III. In addition to BMI, in people with a BMI less than 35 kg/m^2, the waist circumference is also considered as a factor and subdivided as low, high and very high. Assessment of the health risks associated with being overweight or obese in adults based on BMI and waist circumference can be seen in Table 1. The four levels of intervention are: 1. General advice for healthy weight and lifestyle; 2. Diet and physical activity; 3. Diet and

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Table 1. Identification, assessment and management of overweight and obesity

BMI (kg/m^2)		Intervention level			
		Waist circumference (cm)			Comorbidities present
		Low	High	Very high	
	Male	< 94	94-102	> 102	
	Female	< 80	80-88	> 88	
Over weight (25-29.9)		1	2	2	3
Obesity I (30-34.9)		2	2	2	3
Obesity II (35-39.9)		3	3	3	4
Obesity III (≥ 40)		4	4	4	4

physical activity; consider drugs; 4. Diet and physical activity; consider drugs; consider surgery.

In addition to these two indicators, the common factors assessing obesity may also include fat percentage and waist-hip ratio. Body fat percentage refers to the proportion of fatty tissue that reflects our body fat level (degree of obesity) (*8*). Waist-hip ratio (WHtR) is the ratio of waist to hip, which is an important indicator of central obesity. The WHtR measures the body fat distribution. A higher value means the individual may have higher risk of obesity-related cardiovascular diseases. When the male WHtR > 0.9 or female WHtR > 0.8, they can be diagnosed as central obesity (*9*).

Obesity intervention may be a long and arduous task that requires coordination of all aspects. There are three major methods: lifestyle interventions, including exercise, diet and cognitive - behavioral therapy, pharmacotherapy and surgery (*10*). Among them, lifestyle intervention is the foundation, namely of all treatments for obesity must consist of dieting and physical exercise. Using drugs or surgery both must meet some strict standards. In 2015, "Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline", was published by the American Endocrine Society (*11*). It recommended that all patients with a BMI ≥ 25 kg/m^2 should be given the treatment including diet, exercise, and behavioral modification. For those who cannot adhere to behavior change, drugs may be useful and may amplify the effects of behavioral regulation. Medications can be used in patients who have a history of failing in weight control or maintaining the lost weight. Moreover, only those who meet the deemed effective standard of medication treatment, namely weight loss ≥ 5% of body weight at 3 months, and have no side effects, can be continued. If the deemed effect is not obtained or has any safety or tolerability problem, the medication should be changed to other medications or alternative treatment approaches.

A long term imbalance of energy intake and energy consumption definitely leads to overweight and obesity. In modern society, eating style and sedentary lifestyles may be the major factors in the prevalence of obesity. Cheap, high fat and prepared food and modern transportation methods increase energy intake while reducing consumption (*12*). With the urgency of dealing with this arduous task, researchers try to explain the mechanisms involved in obesity and find proper treatments with sustained effects and less toxicity. This review sums up the latest understanding of feeding control in humans and FDA approved obesity drugs.

2. Feeding control circuits and regulators

To protect the human species from extinction through famine and war, the evolutionary protective mechanism resists fat loss and maintains weight. According to metabolic needs, several homeostatic brain circuits regulate feeding behavior by promoting food intake or suppressing appetite (*13*). The homeostatic control of food intake and the regulation of energy homeostasis takes place predominantly in the Central Nervous System (CNS), especially in the hypothalamus and brainstem, and responds to peripheral hormonal and neural signals. In the CNS, hypothalamus, the brain stem and reward systems combined regulate fluids and nerve messages. Specifically the hypothalamus plays a key role in monitoring, processing and responding to peripheral signals (*14*). Hunger hormones like Orexin and Ghrelin, or high-calorie food prompt people to eat. Satiety hormones such as leptin, insulin and other so called brain-gut peptides can inhibit feeding behavior (*15*). Long-term imbalance between hunger and satiety signals lead to weight increase and obesity. Besides, cognitive structures also involved in this process such as emotions can influence human eating behavior (*16*).

The main parts of the hypothalamus are the arcuate nucleus (ARC), the paraventricular nucleus (PVN), the ventromedial nucleus (VMN), the dorsomedial nucleus (DMN), and the lateral hypothalamic area (LHA), and all of them are involved in energy homeostasis-regulation (**17**). Peripheral signals contact the CNS to regulate energy homoeostasis. Gut hormones in the gastrointestinal tract communicate information and transfer it to regulatory appetite centers based in the CNS *via* the so-called 'Gut-Brain-Axis'. There are two ways of information communication, either *via* vagal non-vagal afferent nerve signaling, or *via* blood circulation directly. The ARC is adjacent to the third ventricle and the median eminence, where there is a thin blood-brain barrier. So hormones and nutrient signals can directly

diffuse into the extracellular fluid, which means both nerve regulation and humoral regulation affect the ARC, to give it a major role in feeding control circuits (*18*).

Several neuronal populations have been listed as key players in the hypothalamus, mainly the central melanocortin system (*19*). Three main components of the central melanocortin system are: the proopiomelanocortin (POMC) and cocaine-and-amphetamine-regulated transcript (CART)-coexpressing neurons (POMC/CART), the neuropeptide Y (NPY) and agouti-related peptide (AgRP)-coexpressing neurons located in the hypothalamic arcuate nucleus (NPY/AgRP), and the melanocortin receptors (MCRs) expressing neurons located in the hypothalamic paraventricular nucleus. The first one in the lateral ARC coexpress POMC and CART can depress appetite, leads to feeding decrease and weight loss. In contrast, the second one in the medial ARC coexpress NPY and AgRP, which increase appetite and stimulate eating, leads to weight gain.

Melanocortin receptors include five, class A, G protein-coupled receptors, namely MC1R-MC5R. All of them have diverse physiological roles, in which the melanocortin 4 receptors (MC4Rs) and melanocortin 3 receptors (MC3Rs) play critical roles in mediating energy homoeostasis (*20*). MC4R mainly binds to a-melanocyte stimulating hormone (aMSH) in the hypothalamus PVN to control food intake. MC4R inactivating mutations are the single most common cause of monogenic obesity in humans (*21*). The food intake reduction and energy expenditure increasing effects of anorexigenic POMC/CART neurons are through activating MC4Rs, while the orexigenic NPY/AgRP neurons increase food intake and decrease energy expenditure by antagonizing POMC action on MC4Rs, thus increasing body weight. Moreover, enteroendocrine L cells can express MC4Rs to regulate the release of certain types of brain-gut peptides, like peptide YY (PYY) and glucagon-like peptide 1 (GLP-1). MC3R is primarily expressed in the central nervous system in the ARC of the hypothalamus and limbic areas, where it affects food utilization/partitioning and food anticipatory behavior. In mice, MC3Rs plays an important role in the maintenance of a circadian rhythm of activity related to feeding behavior while obese humans show loss-of-function mutations in MC3Rs (*22*). However, the role of MC3R in energy homeostasis is unclear.

Several bioactive peptides, like adreno corticotrophin (ACTH), α-, β-, and γ-melanocyte stimulating hormone (α-MSH, β-MSH, and γ-MSH) and β-endorphin, are generated by the POMC protein precursor. Among them, α-MSH is the most well known anorexigenic peptide and MCR agonist. By binding and activating MCRs, α-MSH regulates food intake and energy consumption. POMC plays a critical role in the regulation of metabolism, in which its gene mutation will lead to early-onset obesity. AgRP neurons co-express the orexigenic NPY, and the neuro-transmitter gamma-aminobutyric acid (GABA), directly inhibit POMC neurons. AgRP is a high-affinity MCR antagonist. However, contrary to POMC mutations, NPY/ AgRP gene mutations do not have a significant effect on food intake and body weight, which means other compensatory mechanisms may be involved in the energy homeostasis-regulating process (*23*). Besides, peripheric hormones like leptin, glucocorticoids, insulin, estrogens, ghrelin, PYY, and GLP-1, and signals from nutrients can regulate POMC and AgRP neurons. Body energy status can also influence the melanocortin system.

Vagal afferent fibers can sense the signals of nutrients and transfer them to the CNS. Most of the vagal afferent fibers, that innervate the viscera and gastrointestinal tract, project to the nucleus of the solitary tract (NTS) rostral to obex (*24*). Within this region, several neurons project to the VTA and lateral hypothalamic areas, and may affect food intake through actions on dopamine signaling in motivation and reward-related areas. The pleasantness of food alongside the emotional and cognitive aspects of eating behavior is determined in the 'reward' system of the brain. This system is comprised of a number of limbic and cortical areas that communicate with each other and with the hypothalamus, predominantly through dopamine (DA), opioid and endocannabinoid neurotransmission (*25*). Moreover, metabolic pathways in the brainstem, like the orbitofrontal cortex (OFC), amygdala, insula, dorsal and ventral striatum, hippocampus, anterior cingulate cortex and dorsolateral prefrontal cortex, amongst others, also integrate and respond to short-term and long-term changes in energy homeostasis as part of a broader network.

3. Regulatory signals in the feeding control circuits

NPY, peptide YY (PYY) and pancreatic polypeptide (PP) are members of the neuropeptide Y (NPY) family. They are expressed by cell systems at different levels of the gut-brain axis (*26*). NPY is the most abundant neuropeptide in the brain. A lot of neuronal system regions, from the medullary brainstem to the cerebral cortex, can express NPY. It exerts a variety of physiological processes in humans *via* four different receptor subtypes Y1, Y2, Y4 and Y5. As one of the potent orexigenic peptides in the CNS, NPY/AgRP neurons have a critical role in feeding regulation. Y1 receptors play the main role in the orexigenic effect, although Y5 receptors also are involved in this process.

Through different neuronal circuits, neuropeptides like melanin-concentrating hormone (MCH) or orexins/hypocretins (OX) in LHA can regulate ingestion, arousal, and locomotor behavior as well as autonomic function (*27*). By activation of MCHR-1 in the nucleus accumbens (NA), MCH can coordinate energy need and feeding. This process possibly contributes to influence feeding in energy balance disorders. Central injection of the orexigenic neuropeptide MCH into the brain increases feeding in rodents and promotes obesity. Unlike strongly

orexigenic neuropeptide NPY, MCH only amplifies the size or amount of normally accepted food and water, and the forebrain can selectively control this effect.

The endocannabinoid system functions as a potent regulator of feeding behavior and energy balance through complex central and peripheral mechanisms (*28*). In general, increased endocannabinoid activity enhances food intake and favors fat storage. Endocannabinoids such as anandamide promote feeding mediated by the interaction of cannabinoid compounds with various types of receptors in the nervous system. The cannabinoid-type 1 (CB1) receptors are highly expressed in the brain, mainly in the ARC, the PVN, and the LHA. It colocalizes with opioid receptors and participates in the modulation of food palatability and ingestion. CB1 receptor inverse agonist/antagonist rimonabant was used as a weight loss drug but was withdrawn from the market for increasing the risk of psychiatric side-effects (*29*).

Highly flavored, energy-dense, "palliative foods" can override normal eating and weight-control mechanisms and generate paradoxically high but ineffective levels of appetite-suppressing hormones (*30*). There is evidence that these foods can affect the reward system through central monoamine neurotransmitters. In the reward system, neurotransmitter dopamine plays a key role in regulating feeding and emotion. However, the clear role of dopamine signaling in reward is controversial. There exists two hypotheses to explain the role of dopamine (*31*). The first one is the positive correlation between dopamine signaling and pleasure experience may overindulgence pleasurable stimuli. The second one is a compensatory response like overeating may result from decreased dopaminergic signaling.

4. Brain-gut peptides as feeding control regulators

The gastrointestinal tract is the largest endocrine organ in which many kinds of peptides are being produced and released and have several distinct effects (*32*). External cues contact the CNS to control feed and coordinate with the brain's internal signals, transferring messages about the presence and composition of foods in the gut. These gastrointestinal peptides are either orexigenic or anorexigenic related to food intake and named as brain-gut peptides. There are two types of brain-gut peptides (*33*): *i*) short-term signals, which are kept in step with each episode of eating, like, ghrelin, cholecystokinin (CCK), PP, PYY, GLP-1, nesfatin-1, oxyntomodulin (OXM), glucagon, gastric inhibitory polypeptide (GIP), amylin, and so forth.; *ii*) long-term signals, which reflect the metabolic state of adipose tissue, such as, insulin and leptin. Both of them interact with each other to determine eating behavior.

4.1. *Short-term signals*

As the first gut hormone known to affect feeding and appetite, CCK is secreted from enteroendocrine I-cells predominantly located in the proximal small intestine, mainly in response to fatty acids. After a meal, plasma CCK levels increase within 15 minutes and the life time of CCK is only a few minutes. The vagal nerve has CCK-1 receptors that can lead to early meal termination and reduce food intake once combining with CCK (*34*). The hypothalamus also has CCK-1 receptors, which means a direct communication without vagal regulation may exist. Besides, the synergistic interaction between CCK and several other anorexigenic peptides also have an important role in feeding regulation.

Ghrelin is a 28-amino-acid-long peptide that exerts its orexigenic effect *via* the growth hormone secretagogue receptor (GHS-R) to increase food intake in animals and humans (*35*). During fasting, the circulating levels of ghrelin increase and after eating, it falls to stimulate hunger. Until now, ghrelin is the only known orexigenic, peripherally active gut hormone. The plasma level of ghrelin is mainly regulated by nutrients but not water. Expressed within the ARC and PVN of the hypothalamus, ghrelin also plays a role as a neurotransmitter to adjust appetite. This effect is mediated through activation of NPY/AgRP co-expressing neurons. Both central and peripheral ghrelin administration have the same effect in reducing fat utilization and weight increase from overeating. Except for short term effects as a meal stimulator, ghrelin may also have long-term effects because its levels are inversely correlated to BMI. Further, ghrelin may influence the reward system through mesolimbic dopamine circuitry, in which the emotional wanting or reward value for highly desirable foods increased (*36*).

PP-fold peptide family includes NPY, PP and PYY. PP is a 36 amino-acid-long peptide released from the pancreas (*37*). The blood level of PP is proportional to the amount of ingested calories. It is believed that the anorectic effects of PP are transferred *via* the Y4-receptor in the brainstem and the hypothalamus. Compared to normal weight people, the circulating levels of PP in obese subjects and Pradere Willi syndrome patients are reduced and can't increase after feeding. Further, PP can reduce leptin in white adipose tissue and decrease the gene expression of ACTH-releasing factor. However, although intravenously administered PP can reduce food intake and increase energy expenditure, central administrated PP leads to increased food intake (*38*).

PYY also belongs to the PP-fold peptide family, secreted in proportion to nutrients ingested, but not affected by gastric distension. The secretion of PYY is mainly stimulated by fat. N-terminally truncated PYY3-36 is the major form of PYY that has high affinity for the Y2 receptor. Peripherally administrated PYY3-36 at physiological doses can decrease food intake in rodents, primates and humans. Circulating postprandial PYY levels are lower in obese individuals, suggesting

it may have a potential pathophysiological role in the development of obesity (*39*). However, different reports show large differences in fasting PYY levels between normal and obese patients.

Both L cells and neurons of the nucleus of the solitary tract in the hindbrain can produce GLP-1 (*40*). The release of GLP-1 is proportional to the amount of calories ingested, but normal and obese people have a different response to GLP-1 administration. Unlike PYY affected mainly by fat, the stimulators of GLP-1 are carbohydrate and fat. Protein has a relatively less effect on the release of GLP-1. By combining with GLP-1 receptor, a member of 'Family B' of the G-protein-coupled receptors widely distributed in the gastrointestinal tract, pancreas and brain, GLP-1 can activate neurons in the ARC, PVN, NTS and AP, lead to satiety and reduce hunger.

Nesfatin-1 is an 82 amino acid polypeptide. It is the cleavage product of NUCB2, mainly expressed in the CNS as part of the feeding regulatory system (*41*). As an anorexigenic modulator of feeding control, once injected into the brain, Nesfatin-1 can induce a prolonged decrease of dark phase food intake even at picomolar levels. Hypothalamic anorexigenic pathways such as corticotropin-releasing factor receptor 2 (CRF2), medullary pro-opiomelanocortin signaling, melanocortin and oxytocin can mediate the effect of Nesfatin-1.

4.2. *Long-term signals*

The long term signals of feeding regulators are leptin and insulin (*42*). The release of them are proportional to body fat content and the CNS level of them are determined by their plasma concentrations.

Insulin serves as an anorexigenic modulator of feeding control in the CNS by stimulating POMC/CART and inhibiting NPY/AgRP (*43*). It controls energy homeostasis by acting on the ARC, stimulating the synthesis of pro-opiomelanocortin that acts on melanocortin receptors MC3R and MC4R in hypothalamic nuclei. However, insulin is secreted into the blood in response to change in blood glucose concentrations, and lowered blood sugar level is a strong signal of hunger, which means it can't be used to control eating by peripheral administration. The release of insulin can also be influenced by incretin hormones such as GLP-1 (*44*). Thus, the relationship between insulin secretion and appetite regulation may be more complicated than current understanding.

Leptin acts directly on the feeding control neurons in CNS, suppressing NPY and increasing pro-opiomelanocortin, to stimulate the enzymes involved in lipid metabolism. It can reduce food intake and increase energy consumption. (*45*). It can prevent obesity by inhibiting appetite. Lacking leptin or leptin receptor dysfunction may lead to hyperphagia and obesity. Further, the expression and consolidation of learned appetitive behaviors can be depressed by leptin and dopamine signaling is influenced by leptin, as well, although the mechanism is not clear yet (*46*). It can also enhance the effect of CCK and heighten the sensitivity for sweetness.

5. Nutrients served as feeding control regulators

Nutrients can also transfer satiating signals to the hypothalamus. Specific receptors or transporters sense the signals from nutrients like carbohydrate, fat and protein. These receptors located in the entero-endocrine cells (EEC) in the intestinal epithelium can trigger the release of gastro-intestinal regulatory peptides such as CCK, ghrelin, PYY, serotonin, GLP-1 among others (*47*).

After absorption, glucose released in the portal vein bound to SGLT3, and served as a second message to the brain to reduce hunger (*48*). A broad range of G-protein-coupled receptors in the lumen sense the signal from non-esterified fatty acids (NEFA) in a length dependent manner. Among them, NEFA1 receptor and GPR120 respond to medium- and long-chain NEFA(C>12) and NEFA2 and NEFA3 receptors detect short-chain fatty acids (SCFA). After digestion, protein degrade to peptides in the portal vein, which antagonize MORs present in the peri-portal afferents to the brain. By vagal and spinal signals, these message are transferred to the brain by MOR-controlled ascending nerves.

6. Weight-loss products

Excessive body weight can lead to various diseases, such as diabetes mellitus type 2, cardiovascular diseases, certain types of cancer, obstructive sleep apnea, asthma and osteoarthritis. As a result, obesity may reduce life expectancy. With the dramatic increase in obesity in the population, a variety of weight-loss products have emerged, but effectiveness and safety are uncertain (*49*). To date, there are no regulations for the safety and effectiveness of weight-loss products and no strict criteria. The most common weight-loss products can be divided into four categories, which include: prevent the absorption of fat or carbohydrates to reduce the absorption of energy from food; promote metabolism, namely increasing energy expenditure; change the distribution of nutrients in body to reduce body fat while increasing lean tissue; reduce the body's energy intake by suppressing appetite and increasing satiety.

A-amylase inhibitor (*50*) and chitin (*51*) are two materials that can reduce energy intake by decreasing the absorption of carbohydrates and fat, respectively. These products have less toxicity but can cause stomach discomfort. Besides, there is no evidence or proof for the weight-loss effect of these products compared with placebo.

The body's metabolism determines the rate of energy consumption. Fast metabolism people can consume more energy compared with slower ones. Metabolism boosters reduce body weight by speeding up the body's calorie-burning furnace (*52*). Caffeine, ephedra (ephedrine), green tea, and cocoa are among this type of weight-loss products. However, the safety of metabolism boosters is uncertain and commodities on the market usually contain an excessive quantity of doping products, leading to serious side effects.

Calcium, conjugated linoleic acid, and chromium picolinate can change the ratio of fat tissue to muscle tissue in the body, and namely reduce fat and increase muscle (*53*). However, the weight loss effect of these products is insignificant with an uncertain mechanism. Moreover, relative high toxicity restrains their application.

As undigested carbohydrate, dietary fiber can be used as a physiological barrier to interfere with energy intake by replacing the available nutrients to promote weight reduction (*54*). Fiber reduces the absorption efficiency of the intestine. Dietary fiber can increase anaerobic microorganisms' reproduction, stimulate intestinal peristalsis, accelerate the discharge of food residues and reduce nutrient digestion and absorption. Further, fibers need more chewing action, which can limit food intake and promote gastric and saliva secretion, causing gastric distension and increasing satiety. Although inadequate dietary fiber intake can cause many diseases, excessive dietary fiber will affect the absorption of nutrients, resulting in malnutrition.

7. The history of anti-obesity drugs

Obesity is one of the world's most important public health problems, but the approved anti-obesity drugs are extremely limited. Currently, only two types of anti-obesity drugs for long term weight loss are on the market, pancreatic lipase inhibitors and central nervous system appetite suppressants. Those that can increase energy consumption and metabolism were withdrawn due to side effects. Until now, there are five drugs (orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion and liraglutide) approved for long-term use and four sympathomimetic drugs approved for short-term treatment of obesity by the US FDA.

Medical treatment of obesity can be traced to the late 19th and early 20th century (*55*). Between 1887 and 1940 thyroid hormone, dinitrophenol and amphetamine were used to treat obesity. All of them were finally stopped due to side effects. Neuropathy and cataracts induced by dinitrophenol and trityl alcohol were named as one of the disasters caused by medicine in the 20th century (*56*). In the early 1950s, amphetamine and its congener methamphetamine, became widely abused street drugs. The side effects and addictive effect of them lead to the search for safer alternatives. Serotonergic agents like fenfluramine opened a new area of anti-obesity drugs, although the side effects like primary pulmonary hypertension lead to withdrawal later (*57*). Combination therapy for treatment of obesity was popular between 1973 and 1996, and one of the most popular combination drugs was d,l-fenfluramine and phentermine. However, they were removed from the market worldwide in 1997 because more than 30% of patients have the potential to develop valvular heart disease (*58*). A number of nervous system appetite suppressants were developed after 1996, but only a few approved by the FDA to treat obesity. The mechanism of these drugs were inhibiting monoamine action and modulating neuropeptides. However, nearly all of them were withdrawn from the market several years later. In 2001, the appetite suppressant phenylpropanolamine (PPA) was withdrawn from the market due to serious consequences like hemorrhagic stroke (*59*). In 2003, ephedrine was removed from the market because of heart disease and stroke (*60*). In 2009, rimonabant was withdrawn for enhancing suicidal tendency (*61*). Sibutramine is also a central appetite inhibitor, which inhibits norepinephrine and serotonin reuptake, leading to satiety and reducing appetite. After its approval by the US FDA, similar products swept the world, and became the gold standard for anti-obesity drugs. However, in 2010, it was withdrawn because of the risk of cardiovascular disease and stroke (*62*). Most recently, in early 2011, a pharmaceutical scandal in France shocked the world. The country's pharmaceutical giant Servier's anti-obesity drug Mediator lead to the death of hundreds of people because its main component benfluorex causes valvular side effects and death (*63*). Thus, since approved in 1999, lipases inhibitor orlistat (tetrahydrolipstatin) has long been the only drug available on the market (*64*).

The fact that obesity is increasingly more serious and treatment is extremely limited led to the development of new drugs and re-combination of old drugs (Table 2). To handle this global problem, FDA approved phentermine/topiramate (*65*) and lorcaserin (*66*) in 2012, then naltrexone/bupropion (*67*) and liraglutide (*68*) in 2014. However, to date, the anti-obesity drug market has one and only OTC drug, orlistat (*69*).

7.1. *Pancreatic lipase inhibitor approved by FDA for long-term use: Orlistat (marketed by prescription as Xenical and OTC as Alli)*

As the only long term used drug approved worldwide, orlistat was approved by FDA in 1999. It has long been the only long term used weight-loss medicine on the market until 2012. It is a potent long-acting gastrointestinal lipase inhibitor, directly blocking the absorption of fat (*70*). Serval long term clinical trials of orlistat have been published. Orlistat at a therapeutic

Table 2. Currently approved anti-obesity drugs

Name	Mechanism of Action	Average weight lost at 1 year (kg) *vs.* for placebo	Percentage of patients achieving > 5% loss of body weight at 1 year *vs.* for placebo	Safety warning	Contraindications
Orlistat	Pancreatic lipase inhibitor	10.3 kg	68.50%	Cyclosporine exposure, rare liver failure, concomitant	Chronic malabsorption, gall bladder disease
Lorcaserin	5-HT2C agonist	5.8 kg	47.50%	Serotonin syndrome, valvular heart disease, cognitive impairment, depression, hypoglycemia, priapism	MAOIs, use with extreme caution with serotonergic drugs (SSRIs, SNRIs), pregnancy
Phentermine/ topiramate	Sympathomimetic Anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)	8.1 kg (7.5/46 mg) 10.2 kg (15/92 mg)	62% (7.5/46 mg) 70% (7.5/46 mg)	Fetal toxicity; acute myopia, cognitive dysfunction, metabolic acidosis,	Glaucoma, hyperthyroidism, MAOIs, pregnancy
Naltrexone/ bupropion	Opioid receptor antagonist dopamine reuptake inhibitor	6.1 kg (360/32 mg)	39%	Boxed waning: suicidality; Warning: BP, HR, seizure risk, glaucoma, hepatotoxicity	Seizure disorder, uncontrolled HTN, chronic opioid use, MAOIs, pregnancy
Liraglutide 3.0 mg	GLP-1 receptor agonist	7.4% (*vs*. 3.0% for placebo)	62.3% (*vs*. 34.4% for placebo)	Boxed warning: thyroid c-cell tumorsin rodents. Warnings: acute pancreatitis, acute gallbladder disease, serious hypoglycemia if used with insulin secretagogue, heart rate increase,use caution in renal impairment; hypersensitivity reactions can occur, monitor for depression or suicidal	Patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia, pregnancy

dose (120mg, 3 times per day) will reduce fat absorption up to 30%. Patients in a one year treatment can lose 9% of their body weight by using orlistat, while the placebo group only lost 5.5%. It can also reduce waist, blood pressure, fasting glucose, BMI, glycated hemoglobin concentration in diabetic patients, as well as decrease low-density lipoprotein cholesterol (LDL-C), total cholesterol and increase high-density lipoprotein cholesterol (HDL-C) (*71*).

Orlistat can't be transfered into the bloodstream, so the side effects mainly involved triglyceride digestive dysfunction in the intestine, including fat diarrhea, abdominal distension, fecal urgency, fecal incontinence and oily stools (*72*). The incidence rate of these side effects can be 15% to 30%, and some patients considered this unacceptable. Certain researchers even consider the anti-obesity effect of orlistat mainly comes from the "punishment" of a high-fat diet that can lead to these embarrassments, so people will consciously decrease fat absorption to avoid them. Studies have shown that few people can stick to the treatment longer than 1 year (less than 10%), let alone 2 years (less than 2%). Further, absorption of fat soluble vitamins can be impaired by orlistat, so patients should take multivitamins with more than a 2 hour interval. Moreover, patients treated with orlistat may develop gall bladder disease (> 2%) and it can influence the absorption of cyclosporine. Very few cases of liver failure were reported recently.

Cetilistat is a novel, orally active, gastrointestinal and pancreatic lipase inhibitor developed by Takeda and approved by Japanese Ministry of Labor Health and Welfare (MHLW) as a drug for treatment of obese patients having both type 2 diabetes and dyslipidemia (*73*). Cetilistat acts similarly as orlistat with relatively mild side effects. Adverse events and discontinuation rates with cetilistat are less common than with orlistat.

7.2. *Serotinin-2C receptor agonist approved by FDA for long-term use: Lorcaserin (marketed as Belviq)*

In 2012, FDA approved a long-term medication for obesity, lorcaserin. It is a highly selective serotonin 2c receptors (5HT-2C) agonist that reduces appetite and increase satiety by binding to the 5HT-2C receptors on anorexigenic POMC neurons in the hypothalamus (*74*). Some removed anti-obesity drugs such as fenfluramine

and dexfenfluramine, also act on 5-HT receptors but increased the risk of serotonin-associated cardiac valvular disease by activating the 5HT-2B receptor (*75*). As a highly selective 5HT-2C agonist, the cardiac valvular effects of lorcaserin may not be serious (long-term data was asked for by FDA).

Three randomized, placebo-controlled trials of locraserin have been reported. Two of them were in nondiabetic patients (BLOOM29 (N=3182; 50% attrition) and BLOSSOM30 (N=4004; 45% attrition)) and one was in adults with type 2 diabetes (BLOOM-DM31 (N=603; 34% attrition)). It shows that compared with placebo, lorcaserin can cause decrease of more body weight, approximately 3.2 kg (≈3.2%of initial body weight) (*76*). Although the weight lost is modest, when it comes to the weight lost of at least 5% standard, patients treated with lorcaserin 10mg twice daily gave better data than with placebo (BLOOM (47% *vs.* 20%), BLOSSOM (47% *vs*. 25%), BLOOM-DM (37% *vs*. 16%)), and the weight lost of at least 10% standard shows the same results (BLOOM (23% *vs*. 8%), BLOSSOM(23% *vs*. 10%), BLOOM-DM(16% *vs*. 4%)). The only study involved where patients took lorcaserin for 2 years shows that an average weight loss of 5.6 kg, compared with 2.4 kg in the placebo group. Using locraserin can also decrease blood pressure, triglycerides, total cholesterol and low-density lipoprotein cholesterol. For diabetic patients, lorcaserin treatment can reduce body weight and improve glycated hemoglobin concentrations.

As one of the central appetite suppressants, lorcaserin is relatively well-tolerated. Common side effects of locraserin were headache, dizziness, nausea, dry mouth, constipation and fatigue (*77*). However, selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors (MAOIs) should not be used with locraserin to avoid the risk of serotonin syndrome. Warnings of valvular heart disease and hypoglycemia are on the drug label. Last but not the least, like all the other weight loss medications, lorcaserin should be avoided in pregnancy.

7.3. *Combination of phentermine-topiramate approved by FDA for long-term use: Phentermine/Topiramate ER (marketed as Qsymia)*

The first FDA approved long-term anti-obesity combination drug was an extended release (ER) combination of phentermine and topiramate (marketed as Qsymia) in 2012 (*78*). Phentermine is an adrenergic agonist that reduces weight by activating the sympathetic nervous system and releasing endorphins to reduce energy intake and increase expenditure. Topiramate was approved by FDA to treat epilepsy and migraine prophylaxis. It has the effect of reducing weight through promoting taste aversion and reducing caloric intake. Combining these two with lower doses, at starting dose phentermine 3.75 mg and topiramate 23 mg, a recommended dose 7.5 mg and 46 mg respectively, and full dose 15 mg and 92 mg respectively, can reduce side effects and obtain weight loss results.

Three essential clinical trials were carried out (EQUIP, CONQUER and SEQUEL) (*79*). Treatment with Qsymia 56 weeks can obtain percent weight loss of approximately 10.6% (15/92 mg), 8.4% (7.5/46 mg,), and 5.1% (3.75/23 mg), respectively ($p < 0.0001$). 2 years study (SEQUEL) shows 9.3% (7.5/46mg) and 10.5% (15/92 mg) weight loss from baseline were sustained ($p < 0.0001$). Qsymia treatment can also reduce fasting triglycerides, fasting glucoses and waist circumference in obese patients.

Using a lower dose of these two drugs minimizes risks and adverse effects. The most common side effects of Qsymia were dizziness, paraesthesias, insomnia, dysgeusia, dry mouth and constipation. Like the other than-orexiants or nonselective monoamine oxidase inhibitors, Qsymia may induce the potential risk of cardiovascular and central nervous system effects (*80*). Besides, Qsymia may increase the risk of oral clefts and other craniofacial defects, and thus it should be avoided during pregnancy and lactation.

7.4. *Combination of Naltrexone and Bupropion approved by FDA for long-term use: Naltrexone SR/Bupropion SR (marketed as Contrave)*

Contrave is an extended-release tablet combining an opioid receptor inhibitor (naltrexone) and a dopamine and norepinephrine reuptake antagonist (bupropion) (*81*). It is the fourth long-term weight management medication approved by US FDA, in September 2014. Bupropion has been approved to treat depression and smoking cessation. Bupropion reduces weight by inhibiting reuptake of dopamine and norepinephrine to decrease the food activated reward system. Naltrexone has been approved to treat opioid and alcohol dependence and inhibiting opioid receptors may slow weight gain.

Four unique phase 3 studies of Contrave, all named as CONTRAVE Obesity Research (COR), involving approximately 4500 overweight and obese participants have proved efficacy and safety (*82*). COR-I trial shows that the mean change in body weight was 25.4% in 360/32 mg Contrave group, while 21.3% in the placebo group. As to clinically significance of at least 5% reduction in body weight, 42% patients in Contrave group and 17% in placebo group met this standard. In the COR-Diabetes trial, 44.5% in Contrave group and 18.9% in placebo group met the at least 5% reduction in body weight standard ($p < 0.001$). Contrave can also reduce HbA1c (0.6% *vs*. 0.1% in placebo group) and reduce waist circumference, visceral fat, triglycerides and increase HDL cholesterol.

For bupropion, the safety concerns are hypertension, depression and seizures, and for naltrexone, opioid

overuse and acute opioid withdrawal should be considered (*83*). On the label, Contrave warns the increased risk of depression and suicidal behavior, which is the side effect of bupropion alone, but not shown in the clinical trials of the combination. Contrave can't be used in patients with uncontrolled high blood pressure because of the potential of raising blood pressure and heart rate. Seizure patients and those already taking opioids should avoid using Contrave

7.5. *GLP-1 receptor agonist approved by FDA for long term use: Liraglutide 3.0 mg (marketed as Saxenda)*

It has long been considered that analogs of naturally occurring gut hormones (GLP-1, oxyntomodulin, PYY, ghrelin, *et al*.) engaged in energy balance regulation may represent a specific and low side-effect approach in the treatment of obesity. Liraglutide is a GLP-1 receptor agonist that has 97% homology to native GLP-1. After approval by US FDA to treat type 2 diabetes at a 1.5 mg dosage in 2010, the 3.0 mg dosage of liraglutide (marked name Saxenda) was approved to treat obesity in December 2014 (*84*).

Phase III studies have shown that compared with placebo and cognitive behavioral intervention, Saxenda treatment can achieve more weight loss, in the range of 26% to 28%. Data confirm that after using Saxenda, patients have shown improvements in systolic and diastolic blood pressure, LDL and triglycerides reduction, HDL cholesterol increasing and waist circumference reduction (*85*). Besides, Saxenda can improve glycemic control in a weight loss independent manor.

As to the side effects, some patients have shown transient nausea and vomiting. Of note is that Saxenda can increase heart rate slightly, which is opposed by its cardioprotective properties. A black box warning of Saxenda said it may increase the risk of thyroid C-cell tumors because Saxenda causes C-cell tumors in rodents but not in humans. Patients with a personal or family history of Multiple Endocrine Neoplasia or medullary thyroid carcinoma should avoid liraglutide for safety concerns. As with all the other weight loss drugs, Saxenda is contraindicated in pregnancy or hypersensitivity patients. Clinical trials have shown the potential risks of mild or moderate pancreatitis, thus the drug should be stopped if acute pancreatitis is suspected (*86*). Phase 3 studies also report cholecystitis and cholelithiasis, but whether it was caused by the drug or weight loss is uncertain.

7.6. *Noradrenergic drugs approved for short-term use*

Lots of sympathomimetic drugs, like diethylpropion, benzphetamine, phentermine and phendimetrazine, have a similar mechanism as norepinephrine and were tested to treat obesity before 1973 (Diethylpropion (1959), Phentermine (1959), Benzphetamine (1960), and Phendimetrazine (1959). These compounds work by stimulating adrenergic neurotransmitter pathways in the brain, however, they have varying degrees of amphetamine-like side effects, including insomnia, nervousness and irritability (*87*). They are approved only for use of less than 12 weeks (short-term use) and have the potential for abuse. There are no studies that support long-term use of these agents and the evidence that weight regain occurs when administration of these drugs is ceased limit the application of them.

8. Conclusion

Obesity has been recognized as a worldwide epidemic of the 21st century. In the past 30 years, obesity increased rapidly and obesity-related diseases surged. It is a complex medical problem with poor pharmacotherapy-based management. The major goal of obesity treatment is to reduce body weight, diminish the risk of weight associated disorders and to prevent regaining the lost weight. Despite the fact that obesity has become the most significant problem worldwide, efficient medication is limited and potential serious side effects associated with these drugs always outweigh the advantages. Bariatric surgery achieves greater and more sustained weight loss than non-surgical management in patients with severe obesity. However, not all patients can accept surgery.

Until now, studies show that the most effective way to prevent overweight and obesity during menopause is to follow a proper diet and do physical activity. That's why lifestyle interventions are required for all treatments. In the foreseeable future, lifestyle changes, like reducing fat intake and regular exercise, are still the most reliable way to lose weight. In order to achieve the desired outcomes, all patients (taking drugs or not) must combine treatment with lifestyle intervention to achieve sustained weight loss.

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