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THE CURRENT ARMAMENTARIUM OF DRUGS FOR FIGHT AGAINST OBESITY

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ABSTRACT
Obesity is a condition characterized by the accumulation of excess body fat which endangers the health of an individual. It is associated with increased risk of co-morbidities like diabetes, hypertension, dyslipidemia and various cancers. Mounting evidence indicates that even a modest weight loss in obese patients would be hugely rewarding with substantial health benefits. Lifestyle modifications can produce only a small reduction in weight, and adherence to the regimen becomes poorer in long run. Thus, there is need for drugs which can augment the weight loss. At present, there is a dearth of anti-obesity drugs and the therapeutic options are limited. Till date, only five drugs are approved by the US FDA (United States Food and Drug Administration) for long term management of obesity, namely orlistat, lorcaserin, phentermine/topiramate, naltrexone/bupropion and liraglutide. This review discusses the various regulators of energy balance and appetite modulation, and highlights the salient features regarding the efficacy and safety of the current anti-obesity drugs. The data were obtained from articles present in databases of Medline and Google scholar.

KEYWORDS: Obesity, weight reduction, appetite, pharmacotherapy, energy homeostasis.

INTRODUCTION
Obesity refers to accumulation of excess body fat which causes significant impairment to the health of the individual. Objectively, it is defined by BMI (body mass index) $\geq$ 30 kg/m^2.[1] Earlier, considered to be a mere cosmetic or aesthetic problem, it is now recognized as a disease with multiple adverse health-related consequences. The prevalence of obesity is increasing at an alarming rate worldwide and has attained public health dimensions, warranting immediate attention. According to the World Health Organization (WHO), the worldwide prevalence of obesity has more than doubled between 1980 and 2014. In 2014, the worldwide prevalence of obesity and overweight in adults were 13% and 39% respectively.[2]

BMI, calculated as weight in kilograms/ (height in meter)[2] is a simple measure to assess the body fat content of an individual. According to the WHO, individuals can be classified as underweight (BMI < 18.5 kg/m^2), normal weight (BMI = 18.5 - 24.9 kg/m^2), overweight (BMI = 25 - 29.9 kg/m^2) and obese (BMI $\geq$ 30 kg/m^2). Obesity is further classified as obese class I (BMI = 30 - 34.9 kg/m^2), obese class II (BMI = 35 - 39.9 kg/m^2) and obese class III (BMI $\geq$ 40 kg/m^2).[1] However, a revised classification of BMI is used for Asians, since they are at a higher risk of developing obesity related co-morbidities at a lower BMI compared to the cut-off values used in the WHO classification. According to the revised classification for Asian Indians, BMI of 18 to 22.9 kg/m^2 is considered as normal; 23 to 24.9 kg/m^2 as overweight and $\geq$ 25 kg/m^2 as obese.[3]

Torrent of research suggest that accumulating visceral fat has a significant impact on our metabolism and predisposes to the development of various non-communicable diseases like type 2 diabetes, hypertension, dyslipidemia, GERD (gastroesophageal reflux disease)and cardiovascular diseases.[4–6] A recent meta-analysis has provided evidence for association between obesity and development of various cancers.[7] Data suggest that obese men were at a higher risk of developing malignant melanoma and carcinoma of colon, pancreas, kidney and gall bladder. Similarly, leukemia, esophageal adenocarcinoma, and carcinoma of endometrium, gall bladder, kidney, pancreas, postmenopausal breast and colon were commoner in obese women. Mounting evidence also indicate that all-cause mortality is also higher in obese individuals compared to those with normal body weight.[8]

However, evidence suggest that even a modest reduction in weight of 5 to < 10% of the baseline body weight in obese individuals can produce dramatic improvements in their health by improving their glycemic control, blood pressure and lipid profile.[9] This has created increased demand for development of treatment strategies to reduce body weight and enjoy a healthier life.

Mechanisms regulating appetite and energy homeostasis

The rising epidemic of obesity has created the need to unravel the mechanisms involved in appetite modulation so as to develop a promising anti-obesity drug which is efficacious, safe and produces sustained weight reduction. It has been demystified that a complex interaction occurs at multi-organ level to regulate various processes involved in maintenance of energy homeostasis. Energy homeostasis includes energy intake (depending on the meal size, composition and frequency of intake), energy expenditure (through basal metabolism and physical activity) and storage of energy as body fat.[10] The key to body weight maintenance lies in striking a balance between energy intake and expenditure, so as to minimize the storage of excess calories as fat.

In the central nervous system, arcuate nucleus (ARC) of the hypothalamus is the chief coordinating centre for regulation of food intake. The ARC has two distinct neuronal subgroups, one of which expresses the orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP). They play a pivotal role in appetite stimulation. Neighbouring the orexigenic neuronal cluster is the anorexigenic neuronal subpopulation which houses neurons expressing pro-opiomelanocortin (POMC) and cocaine-and amphetamine-regulated transcript (CART). They produce satiety signals which cause inhibition of food consumption.[11] Peripheral appetite regulating signals are relayed to these neuronal subpopulations in the ARC which produces selective activation of either of them generating orexigenic or anorexigenic nerve impulses depending on the energy requirements of the body. The neurons in the ARC project via second order neurons to the other key areas of the hypothalamus that orchestrate food intake like paraventricular nucleus (PVN), dorsomedial nucleus (DMN), ventromedial nucleus (VMN) and lateral hypothalamic area (LHA). [12]

Various hormones, biogenic amines and neuropeptides serve as peripheral regulators of feeding behaviour and play important roles in maintenance of energy balance. Leptin is an important appetite suppressing hormone produced by the white adipose tissue adipocytes. It acts on its cognate receptor in the hypothalamus, which is richly supplied with leptin receptors, to enhance the activity of anorexigenic POMC/CART neurons and inhibit the firing of orexigenic neurons expressing NPY and AgRP. The activation of POMC neurons release α-MSH (melanocyte stimulating hormone), which is a potent anorexigenic neuropeptide.[11] A multitude of gut hormones are also implicated in the intricate regulation of feeding and energy homeostasis. Ghrelin produced from the ghrelin cells located in the stomach and duodenum is the only orexigenic gut hormone that is involved in meal initiation. Other gut hormones namely cholecystokinin, GLP-1 (glucagon like peptide-1), oxyntomodulin, amylin, pancreatic polypeptide and peptide YY serve to communicate anorexigenic signals to the hypothalamus.[13] Nesfatin-1 secreted from the hypothalamus and peripheral sites like adipose tissue, pancreas, stomach and testis is another peptide involved in suppression of feeding in humans.[14]

Biogenic amines like norepinephrine, dopamine and serotonin are also involved in regulation of energy homeostasis in the hypothalamus, which is the coordinating centre for receipt and integration of orexigenic and anorexigenic signals, tipping the balance towards either side depending on the energy needs of the body. Pharmacotherapy of obesity revolves around the core concept of enhancing anorexigenic signaling and inhibiting orexigenic signaling, thus preventing unwanted body fat deposits.

Current anti-obesity drugs

Therapeutic options for management of obesity are very few and comprise lifestyle modifications, pharmacotherapy and bariatric surgery. Lifestyle modifications include reducing food intake by eating healthy foods and avoiding energy-dense foods especially processed and packaged foods rich in calories, sugar and salt. It also aims at increasing the energy expenditure by engaging in regular exercise and avoiding sedentary lifestyle. However, the long term adherence to lifestyle modifications is very poor and patients tend to regain their lost bodyweight.[15] Another option for obese patients especially in morbid obesity (BMI $\geq$ 40kg/m^2 and BMI = 35 – 39.9 kg/m^2 with at least one obesity related co-morbidity like type 2 diabetes mellitus, hypertension or dyslipidemia) is to undergo bariatric surgery. So far, this is the most efficacious treatment for morbid obesity management, producing marked and sustained weight loss. But its utility is limited by its invasiveness, high cost and association with post-operative complications.[16] Hence, an alternative for bariatric surgery in the treatment of obesity is to opt for pharmacotherapy as an adjunct to lifestyle modifications.

At present, pharmacotherapy is indicated only for obese patients with BMI $\geq$ 30 kg/m^2 or overweight patients with BMI of $\geq$ 27 kg/m^{2}with an obesity related co-morbidity like type 2 diabetes mellitus, hypertension or dyslipidemia.[17] Patients who are responders to drug treatment can be identified by monitoring their weight loss after 3 months of treatment initiation. Response is considered satisfactory if patients lose $\geq$ 5% of their body weight in 3 months and the treatment can be continued. If patient is a non-responder, then the drug must be withdrawn and another drug can be tried.[17]

Obesity, being a multifaceted disease with multiple regulators acting both centrally and peripherally in regulation of appetite and energy homeostasis, provides a multitude of drug targets. However, only a handful of anti-obesity medications are available till date. (Table no. 1) According to the US FDA (United States Food and Drug Administration), for a drug to enter the market of obesity pharmacotherapy, it has to fulfill the following requirements. The drug has to produce a statistically significant mean weight loss of at least 5% compared to placebo for at least one year. Also, at least 35% of the patients in the active drug group should have lost 5% of their baseline bodyweight and it should be double the proportion in the placebo group.[12] The anti-obesity drugs approved by US FDA are orlistat (Xenical), lorcaserin (Belviq), extended release topiramate/ phentermine (Qsymia), naltrexone/bupropion (Contrave) and liraglutide (Saxenda).[18]

The EMA (European Medicines Agency) has been more stringent compared to the US FDA, in granting approval for marketing of anti-obesity drugs due to safety concerns. In Europe, the available drugs for management of obesity are orlistat (Xenical), bupropion/ naltrexone (Mysimba) and liraglutide (Saxenda).[19] Orlistat was approved as prescription only drug (Xenical) in 1998 and as over the counter drug (Alli) in 2007. In March 2015, EMA granted approval for the other two drugs, namely, bupropion/ naltrexone (Mysimba) and liraglutide (Saxenda). Lorcaserin and phentermine/topiramate were not approved by EMA due to concerns over their safety. These two drugs were known to cause cardiovascular and psychiatric complications.

Orlistat

Orlistat, also called as tetrahydrolipstatin is the oldest time-tested drug available for treatment of obesity. It was approved by the US FDA as a prescription drug in the year 1998 and as an over the counter drug in 2007. It is a reversible inhibitor of pancreatic and gastric lipases that are required for the hydrolysis of triglycerides to absorbable free fatty acids in the gut. In the presence of orlistat, triglycerides cannot be broken into free fatty acids for absorption and thus they are excreted unchanged in faeces. Thus, the therapeutic effect of the drug is exerted locally in the lumen of stomach and small intestine and systemic absorption is minimal. It inhibits the dietary fat absorption by 30%.[20]

The long term effect of orlistat as an adjunct to lifestyle modifications in weight reduction and prevention of type 2 diabetes mellitus in obese patients with either normal or impaired glucose tolerance was demonstrated in the XENDOS (XENical in the prevention of Diabetes in Obese Subjects) study. The study was conducted for a period of 4 years and it had enrolled 3,305 participants, who were randomized to receive either orlistat or placebo. At the end of 4 years, participants in the orlistat group had a significant weight loss of 5.8 kg compared to placebo group which had a reduction of only 3 kg ($p < 0.001$). Correspondingly the incidence of diabetes was lesser in the orlistat group (6.2%) compared to the placebo group (9%), which corresponded to a risk reduction of 37.3% ($p = 0.0032$).[21] In a meta-analysis of 16 double-blind randomized placebo controlled trials with 10,631overweight or obese participants, it was found that orlistat reduced body weight by 2.9 kg (95% confidence interval; 2.5 kg to 3.2 kg) more than placebo, when given at a dose of 120 mg thrice daily for a period of one year. Besides the results showed that 21% and 12% of the participants achieved $\geq$ 5% and $\geq$ 10% reduction of their body weight respectively.[22]

The faecal loss of fat is responsible for the gastrointestinal side effects like steatorrhea, flatulence and faecal incontinence.[20] These adverse effects can be avoided by consumption of a low fat diet. Thus, patients develop an aversion to intake of high fat foods while on treatment and this aids them in improving their adherence to dietary restrictions. Orlistat also prevents the absorption of fat soluble vitamins like A, D, E and K. Hence, it is advisable to supplement these patients with multivitamins. It is available as a prescription drug at a dose of 120 mg thrice daily and as an over the counter medication at half the strength of 60mg. The drug needs to be taken before meals. Although, its efficacy is limited, it has a favourable adverse effect profile compared to the other drugs approved for treatment of obesity, thus conferring it the advantage of sustaining in the unpredictable anti-obesity market which has witnessed the downfall of many initially promising drugs.

Lorcaserin

The serotonergic system in the central nervous system plays an important role in appetite modulation. Lorcaserin is a selective $5HT_{2C}$ receptor agonist approved for obesity management at a dose of 10 mg twice daily in the year 2012 by the US FDA. Stimulation of $5HT_{2C}$ receptors in the hypothalamus leads to activation of POMC neuronal subtype in the ARC. This causes release of α- MSH which acts on MC4R (melanocortin 4 receptors) expressing neurons in the paraventricular nucleus. This leads to generation of satiety signals and mediates appetite suppression and body weight reduction.

BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management) study was a double-blind randomized placebo-controlled trial of lorcaserin in overweight and obese adults (n=3182). Lorcaserin was given at a dose of 10 mg twice daily for a period of 52 weeks. At the end of one year, it was found that participants in lorcaserin group lost 5.8 ± 0.2 kg body weight, whereas participants in the placebo group lost 2.2 ± 0.1 kg ($p<0.001$). The proportion of patients losing 5% or more of their body weight was 47.5% in the lorcaserin group and 20.3% in the placebo group ($p< 0.001$). It was also demonstrated that the weight loss caused by lorcaserin was maintained over a period of 2

years. Thus, it was perceived that lorcaserin causes a significant, meaningful and sustained weight loss compared to placebo in overweight and obese participants when used as an add-on therapy to lifestyle modifications.[23]

Similar non-conflicting results favouring the use of lorcaserin as a complementary approach to lifestyle modification were observed in the BLOSSOM (Behavioural modification and Lorcaserin Second Study for Obesity Management) trial. This was a double-blind randomized placebo-controlled study in which overweight and obese adults were randomized in 2:1:2 ratio to receive lorcaserin 10 mg twice daily, lorcaserin 10 mg once daily, or placebo for 52 weeks in addition to counseling on dietary modifications and exercise. The results of the study showed that there was a statistically significant reduction in weight with both the doses of lorcaserin compared to placebo. The least square mean weight loss (95% confidence interval) was 5.8% (5.5 – 6.2%) and 4.7% (4.3 – 5.2%) with lorcaserin twice daily and once daily dosing. In contrast, placebo group produced least square mean weight loss (95% confidence interval) of only 2.8% (2.5–3.2%). The proportion of patients losing ≥ 5% of their body weight were 47.2 % and 40.2% in lorcaserin twice daily and once daily group respectively. This proportion was significantly higher compared to the placebo group (25 %, $p < 0.001$).[24]

In order to assess the efficacy and safety of lorcaserin in type 2 diabetic patients, the BLOOM-DM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) study was conducted. This was also a double-blind randomized placebo-controlled triple arm study which enrolled 604 patients who were randomized in 1:1:1 ratio to lorcaserin 20 mg, lorcaserin 10 mg and placebo respectively for a period of one year along with lifestyle changes. In congruence with the previous studies, there was a statistically significant greater least square mean (± SEM) reduction in body weight in the lorcaserin 20 mg group (4.5 ± 0.35 %) and lorcaserin 10 mg group (5 ± 0.5) compared to placebo (1.5 ± 0.36 %), and a significantly greater proportion of patients in the lorcaserin 20 mg group (37.5%) and lorcaserin 10 mg group (44.7%) lost ≥ 5% of their body weight compared to placebo (16.1%).[25]

Clinical trials with lorcaserin showed that headache, nausea and dizziness were the most common adverse effects with its use. Caution should be taken not to administer it with other serotonergic drugs like monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), selective serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and bupropion as it might precipitate potential life threatening serotonin syndrome or neuroleptic malignant syndrome.[26] Lorcaserin is also known to cause pulmonary hypertension, bradycardia, elevation of prolactin, priapism, cognitive impairment, psychiatric disorders like euphoria, hallucination and suicidal ideation. It can also increase the risk of hypoglycemia in type 2 diabetic patients taking anti-diabetic medications. In rare instances, it can cause valvular heart diseases which occur due to stimulation of $5HT_{2B}$ receptors in the cardiac valvular interstitial cells, although this risk is more pronounced with non-selective serotonergic drugs like fenfluramine.[26] Studies on rats have shown increased incidence of mammary adenocarcinomas and fibroadenomas with locaserin, but its relevance to humans in terms of increased risk of breast cancers remains unknown. Till date, human studies with lorcaserin have not demonstrated increased incidence of breast cancer.[27]

Phentermine /topiramate

This fixed drug combination contains immediate release phentermine and sustained release topiramate. This was the first drug combination to be approved for obesity management by the US FDA in the year 2012. It was approved as phentermine/topiramate capsules for the following dosages; 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg and 15 mg/92 mg. Phentermine is a centrally acting sympathomimetic drug similar to its congener amphetamine. It facilitates the release of norepinephrine, dopamine and serotonin into the synaptic cleft from the presynaptic nerve terminals. This leads to generation of appetite suppressing signals in the ARC of brain and thus aids in weight loss. Phentermine can cause dependence and has abuse potential.

Topiramate is an antiepileptic which is known to produce weight loss. The mechanism behind its weight reducing property is yet to be uncovered. However, various theories have been proposed to explain its mechanism of action. It causes activation of GABA (gamma aminobutyric acid) receptor mediated inhibitory potentials and modulation of voltage gated sodium and calcium channels. It is also postulated that topiramate causes weight reduction by appetite suppression as well as by increasing energy expenditure.[12]

Several clinical trials have demonstrated the efficacy of phentermine/topiramate as an adjunct to lifestyle modification in weight reduction in obese patients. The CONQUER study is a randomized double blind placebo controlled 56 week phase 3 trial conducted in 2487 overweight or obese adults. They were randomized in 2:1:2 ratio to either placebo, once-daily phentermine/ topiramate (7·5 mg/ 46 mg), or once-daily phentermine/ topiramate (15 mg/ 92 mg). At the end of the study period, there was a statistically significant reduction in bodyweight of 1·4 kg, 8·1 kg and 10·2 kg in the patients receiving placebo, phentermine/ topiramate (7·5 mg/ 46 mg), and phentermine/ topiramate (15 mg/ 92 mg) respectively. The proportion of patients who achieved ≥ 5% weight loss were 21%, 62%and 70% in placebo, phentermine/ topiramate (7·5 mg/ 46 mg) and phentermine/ topiramate (15 mg/ 92 mg) groups respectively.[28]

A similar randomized double blind placebo controlled 56 week EQUIP study using phentermine/topiramate was carried out in obese patients with BMI ≥ 35 kg/m^2 (class II and III obesity). EQUIP study, randomized 1267 obese patients to placebo, phentermine/ topiramate 3.75/23 mg, or phentermine/ topiramate 15/92 mg group. At 56 weeks, there was a statistically significant reduction in percentage bodyweight with phentermine/ topiramate 3.75/23 mg (5.1%) and phentermine/ topiramate 15/92 mg (10.9%) compared to placebo (1.6%). In addition, greater proportion of patients in phentermine/ topiramate 3.75/23 mg group (44.9%) and phentermine/ topiramate 15/92 mg group (66.7%) lost 5% or more of their body weight in comparison to the placebo group (17.3%). The study also demonstrated improvements in cardiovascular and metabolic risk factors like waist circumference, systolic blood pressure and ratio of total cholesterol and HDL cholesterol, when phentermine/topiramate was used as a supplement to low energy diet and exercise. These clinical trials have proved that the combination treatment produces a robust weight loss associated with the benefits of reduction in obesity associated co-morbidities.[29]

The common adverse effects seen with phentermine/topiramate in clinical trials are paresthesia, dry mouth, constipation, dizziness, insomnia and dysgeusia. The drug should be preferably taken in the morning and should not be consumed in the evening due to its potential to cause insomnia. The drug combination is also implicated in causing tachycardia, depression, suicidal ideation, cognitive impairment, elevation of serum creatinine and acute angle closure glaucoma. Thus, it is contraindicated in glaucoma, hyperthyroidism (due to risk of increased heart rate) and during or within 14 days of taking monoamine oxidase inhibitors (due to risk of hypertensive crisis).[28,29]

Naltrexone/bupropion

Naltrexone is a competitive antagonist of μ- and κ-opioid receptors in the central nervous system. Opioid transmission in the central nervous system especially through μ- opioid receptors is implicated in the hedonic control of feeding. In μ- opioid receptor knockout mice, it was found that they exhibited decreased motivation to feeding compared to the wild type.[30] Opioid transmission is a major contributor to the pleasurable effects of highly palatable foods. On consumption of tasty foods, there is release of endogenous opioids in the brain which activates the dopaminergic pathway and mediates reward perception. Thus, blockade of opioid receptors using naltrexone abolishes the pleasurable effects of consumption of highly appetizing foods and facilitates the adherence to reduced calorie diet. It also helps to terminate the addictive nature of food consumption in obese individuals.[31]

Bupropion is an inhibitor of dopamine and norepinephrine reuptake and is used for depression and smoking cessation. It causes activation of POMC neurons in the ARC of hypothalamus, thus releasing α-MSH (which acts on MC4R to generate satiety signals) and β-endorphins (which mediates a negative feedback to the POMC neurons and antagonizes development of satiety). Naltrexone blocks the feedback inhibition caused by β-endorphins and enhances the satiety signaling. Thus, the naltrexone/bupropion combination produces a synergistic action.[31] The combination of naltrexone/bupropion was approved for long term weight management by the US FDA in the year 2014 as naltrexone/bupropion (8 mg /90 mg) extended-release tablets (started initially as once daily dosing, dose is up titrated to maximum of two tablets twice daily i.e., naltrexone 32mg and bupropion 360 mg).

The COR-BMOD study was a 56-week, randomized, placebo-controlled trial carried out to assess the efficacy and safety of naltrexone/bupropion as an adjunct to behaviour modification in obese patients (n=793). The participants were allotted in 1:3 ratio to placebo and naltrexone/bupropion (32 mg/360 mg per day) in addition to behaviour modification and low calorie diet. The results demonstrated significantly greater percentage of weight loss with naltrexone/bupropion (7.8%) compared to placebo (4.9%). Furthermore, more than 1.5 times as many participants lost ≥ 5% body weight in naltrexone/bupropion group compared to that of placebo.[32]

CONTRAVE Obesity Research-II (COR-II) was another 56 weeks double-blind, placebo-controlled trial carried out in 1,496 obese or overweight individuals, who were randomized in 2:1 ratio to naltrexone/bupropion (32 mg/360 mg per day) and placebo. In congruence with the previous trial, this study also demonstrated a significantly greater reduction in body weight in naltrexone/bupropion group (6.4%) compared to that of placebo (1.2%). Similarly, greater proportion of participants in the combination group (50.5%) lost 5% or more of their baseline body weight in comparison to placebo (17.1%).[33]

The COR-DIABETES study was double-blind, placebo controlled study executed to find out the efficacy and safety of naltrexone/bupropion in overweight or obese patients with type 2 diabetes mellitus. It included 505 patients' randomized 2:1 ratio to naltrexone/bupropion (32 mg/360 mg per day) or placebo for 56-weeks. This study also demonstrated results consistent with the previous trials. Patients in the naltrexone/bupropion group had significantly greater reduction in body weight (5 vs 1.8 %; $p < 0.001$) and greater proportion of patients with ≥ 5% weight loss when compared to placebo group (44.5 vs. 18.9%, $p< 0.001$).[34]

These clinical trials have uncovered the common adverse effects associated with its use. The combination is implicated in causing nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth and diarrhea. In rare instances, it can cause seizures, hypertension,

tachycardia, hepatotoxicity and angle closure glaucoma. It is contraindicated in patients receiving monoamine oxidase inhibitors, either during or within 14 days of therapy.[32–34] It has a black box warning stating that it produces increased risk of causing suicidal thoughts and behaviors, and neuropsychiatric reactions.[35]

Liraglutide

Liraglutide was a recent addition to the armamentarium of drugs for fight against obesity. It was already licensed for treatment of type 2 diabetes mellitus and by using the drug repurposing strategy, it was tried for weight reduction. The attempt was fruitful and it was granted approval by the US FDA in the year 2014 for management of obesity and it owns the credit of being the only parenteral drug approved for weight reduction. It is a GLP-1 receptor agonist which is 97% homologous to endogenous GLP but resistant to degradation by dipeptidyl peptidase IV and thus has a longer half-life. It is available as a solution for subcutaneous injection in pre-filled pen devices that deliver doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3 mg.

GLP-1 plays a dual role of being a gastrointestinal hormone and a neurotransmitter. It acts on the GLP-1 receptors in the ARC of hypothalamus to produce satiety signals and inhibit feeding. Liraglutide, being an agonist of GLP-1activates the anorexigenic POMC/CART neurons and inhibits the orexigenic NPY/AgRP neurons by acting on the GLP-1 receptors in the ARC of hypothalamus. Thus, it stimulates satiety and suppresses feeding and leads to weight reduction. Besides an appetite modulator, it also stimulates brown adipose tissue thermogenesis leading to an increase in the energy expenditure, thus augmenting the weight loss.[36]

In order to determine the efficacy and safety of liraglutide in weight reduction in obese patients, a 56-week, randomized double-blind placebo controlled trial (SCALE Obesity and Prediabetes trial) involving 3731 patients was conducted. The patients were randomized in a 2:1 ratio to liraglutide (3mg once daily subcutaneous injection) and placebo in addition to lifestyle modifications. The patients in liraglutide group had an increased weight reduction of 5.6 kg (95% confidence interval of 5.1 kg to 6 kg) compared to placebo group. In addition, significantly greater proportion of patients in the liraglutide group (63.2%) lost ≥ 5 % of their body weight compared to the placebo group (27.1%). These results provided favourable evidence for the use of liraglutide in weight management as an adjunct to lifestyle modifications.[37]

Gastrointestinal side effects like nausea, vomiting, decreased appetite, dyspepsia, diarrhea, constipation, abdominal pain were the most common adverse effects. Others include hypoglycemia, headache, fatigue, dizziness, and increased lipase levels. Unusually, it can cause acute pancreatitis, cholelithiasis and anaphylactic reactions.[37] It has a black box warning of causing thyroid C-cell tumours and is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).[38]

Future prospects

Multiple drug targets have been identified for management of obesity and many of them have the potential to be developed into a promising drug candidate for weight reduction. The various drug targets include central hypothalamic pathways, gut hormones, leptin, peripheral fatty acid oxidation pathways and fatty acid absorption.

Accumulating evidence indicate that the central melanocortin system especially melanocortin 4 receptors (MC4R) present in the ARC of hypothalamus play an important role in transmission of satiety signals and this has paved way for the development of MC4R agonists in the management of obesity. One such MC4R agonist in clinical trial is RM-493, which was found to increase the resting energy expenditure in humans.[39] However, its implications in weight reduction in obese patients remain unknown and warrant further studies.

Tesofenasine is an inhibitor of dopamine, norepinephrine and serotonin reuptake in the presynaptic nerve terminals. It is found to suppress feeding in diet-induced obese rat models by stimulation of α1 adrenoceptor and D1 dopamine receptor pathways.[40] Also, a meta-analysis of tesofenasine trials investigating its role in the management of Parkinson's or Alzheimer's disease, has unveiled its potential to cause bodyweight reduction in humans.[41] However, further clinical trials are required to explore its safety and efficacy as a weight reducing tool.

A plethora of drug development opportunities are provided by various gut hormones which relay signals to the central nervous system for regulation of appetite. Potential drug candidates include CCK_A (cholecystokinin A) receptor agonists, oxyntomodulin analogs, Y-2 receptor agonists and Y-4 receptor agonists. However they are still in the initial stage of drug development and have a long way to travel in the drug development process. Ghrelin antagonists, leptin analogs and amylin analogs are also being developed. A combination of leptin agonist (metreleptin) and amylin analog (pramlintide) is under development and has completed phase II clinical trials which showed promising results.[42]

The unmet need of efficacious and safe therapeutic drugs for weight reduction has been a driving force in unearthing of new drug targets, which would open a new era of efficacious and safe pharmacotherapeutic drugs for obesity.

Summary

Obesity is a global public health problem and is associated with many obesity related co-morbidities like

diabetes, hypertension, dyslipidemia, GERD and various cancers. Although the various mechanisms involved in modulation of appetite and energy expenditure have been elucidated, at present, there is a dearth of drugs for management of obesity. According to the US FDA, only five drugs, namely orlistat, lorcaserin, phentermine/topiramate, naltrexone/bupropion and liraglutide were licensed for this indication. To make the situation still worse, in Europe, only a handful of drugs consisting of orlistat, naltrexone/bupropion and liraglutide were approved by the EMA for management of overtly increased body weight.

There is still a lacuna of an ideal drug which is efficacious, safe, produces sustained weight reduction, and leads to the improvement in the cardio-metabolic biomarkers, to combat obesity and its associated co-morbidities. However, developing such a drug has been a challenging endeavor till now. The unmet need of efficacious and safe drugs for weight reduction has been a driving force in unearthing of new drug targets for obesity. Hopefully, in the future, breakthrough research would lead to sweeping changes in management of obesity for the betterment of mankind.

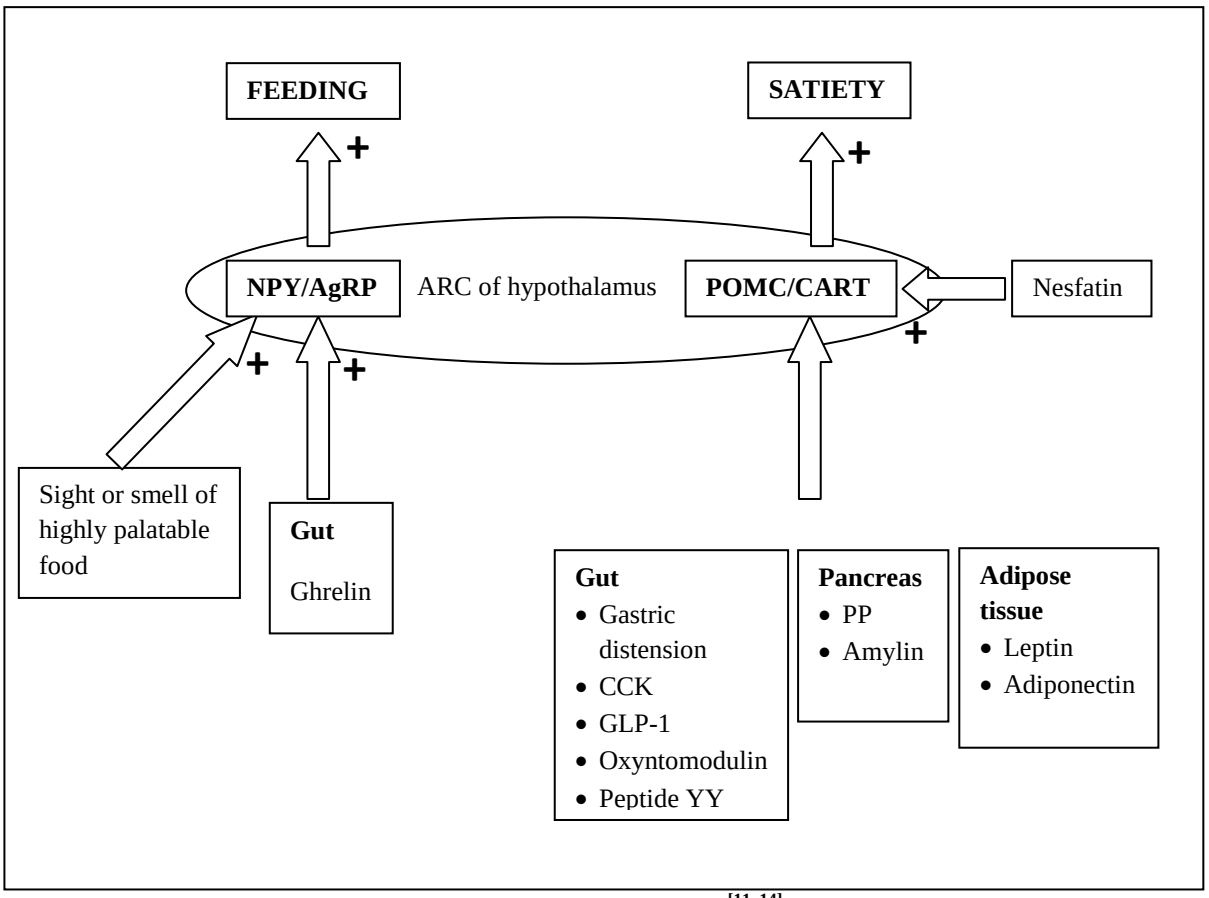

Figure 1: Central and peripheral modulators of appetite control.[11–14] NPY - neuropeptide-Y; AgRP - agouti related peptide; POMC - pro-opiomelanocortin; CART - cocaine-and amphetamine-regulated transcript; CCK – cholecystokinin; GLP-1 - glucagon like peptide-1; PP - pancreatic polypeptide.

Table no.1 Anti-obesity drugs approved by United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA).[18,19]

S.No.	Anti-obesity drugs	Approval status by US FDA	Approval status by EMA
1.	Orlistat	Approved in 1998	Approved in 1998
2.	Lorcaserin	Approved in 2012	Not approved
3.	Topiramate/ phentermine	Approved in 2012	Not approved
4.	Naltrexone/bupropion	Approved in 2014	Approved in 2015
5.	Liraglutide	Approved in 2014	Approved in 2015

Table no.2: Summary of major findings in clinical trials with anti-obesity drugs.

S.No.	Drug	Clinical trial	Participants	Duration of study	Weight loss achieved	Proportion losing ≥ 5% body weight (%)		Major adverse drug reactions	
					Drug	Placebo	Drug	Placebo	
1.	Orlistat	XENDOS [21]	3,305obese patients with either normal or impaired glucose tolerance	4 years	5.8 kg	3kg	52.8	37.3	Gastrointestinal side effects like steatorrhea, flatulence and faecal incontinence
		Meta-analysis [22]	10,631 overweight or obese participants	1-4 years	2.9 kg(95% C.I = 2.5 kg to 3.2 kg) more than placebo		21	-	Gastrointestinal side effects like steatorrhea, faecal urgency, and oily spotting
2.	Lorcaserin	BLOOM [23]	3182overweight and obese adults	52 weeks	5.8 kg	2.2 kg	47.5	20.3	Upper respiratory infections, headache, dizziness, nasopharyngitis, nausea, suicidal thoughts and cardiac valvulopathy
		BLOSSOM [24]	4008 overweight and obese adults	52 weeks	LS mean weight loss 5.8%	LS mean weight loss 2.8%	47.2	25	Headache, upper respiratory infection, nausea, dizziness, fatigue, depression and suicidal ideation
		BLOOM-DM [25]	604 type 2 diabetic patients	1 year	LS mean weight loss 4.5%	LS mean weight loss 1.5 %	37.5	16.1	Headache, back pain, nasopharyngitis, nausea and depression
3.	Phentermine /topiramate	CONQUER [28]	2487 overweight or obese adults	56 weeks	10.2 kg	1.4 kg	70	21	Dry mouth, paraesthesia, constipation, insomnia, dizziness, dysgeusia and depression
		EQUIP [29]	1267obese patients with BMI ≥ 35 kg/m^2	56 weeks	10.9%	1.6 %	66.7	17.3	Paresthesia, dry mouth, constipation, dysgeusia, and insomnia.
4.	Naltrexone/bupropion	COR-BMOD [32]	793obese patients	56 weeks	7.8%	4.9 %	54.3	41.6	Nausea, constipation, dizziness, dry mouth, tremor, upper abdominal pain and tinnitus
		COR-II [33]	1,496 obese or overweight individuals	56 weeks	6.4%	1.2 %	50.5	17.1	Nausea, headache, and constipation
		COR-DIABETES [34]	505 type 2 diabetic patients	56 weeks	5 %	1.8 %	44.5	18.9	Nausea, constipation, vomiting and diarrhea
5.	Liraglutide	SCALE Obesity and Prediabetes [37]	3731 obese patients	56 weeks	5.6 kg (95% C.I =5.1 kg to 6 kg) more than placebo		63.2	27.1	Nausea, vomiting, cholelithiasis, cholecystitis and pancreatitis

C.I: Confidence interval; LS: least square

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