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A REVIEW ON THE CURRENT DRUGS AND NEW TARGETS FOR OBESITY

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ABSTRACT

Obesity is defined as the condition in which the Body Mass Index (BMI) of an individual is between 25 and 29.5 that is $\geq 30\text{kg/m}^2$ and is caused by the imbalance management of energy intake and expenditure. Obesity is among the most prevalent diseases in the world and approximately over 10% of the people belong to overweight group in the world and over 5% in India. Currently many drugs are used to treat or to manage obesity. But these drugs also account for several side effects. So there is an extensive need of promising drugs which can control obesity with greater efficacy and economic viability. This review focusses on the current drugs in the market used to treat obesity and also few of the new probable targets to discover drugs.

INTRODUCTION

Obesity, the most common and complex disorders of this generation caused due to reasons like genetic heredity, diet and environmental factors [1]. Obesity can be defined as a state of an individual where the Body mass index (BMI) is more $\geq 30\text{kg/m}^2$ and is caused by the imbalance management of energy intake and expenditure. Obesity is more common in the youngsters when compared to the elder people mainly due to the lifestyle. Obesity has a major influence on social and psychological status of a person which eventually causes depression. Physiologically it will also cause many of the diseases including cardiac problems [2]. In the world approximately 10% of the population belongs to overweight group. Over 40 million children under age of 5 and 340 million above the age of 5 are obese in the year 2016 [4, 5]. USA,

China, India will occupy more than 50% of the obesity in the world. Currently, there are many drugs are used for the treatment of obesity but these drugs have numerous side effects. Therefore, there is an extensive need of such a kind of drugs which can control obesity with greater efficacy and economic viability [3].

Major pathogenesis occurs due to either over appetite or dysregulation of energy utilizing functions in the body. This kind of situation results in accumulation of fat that in turn makes more adipose tissue. This alerts the secretion of cytokine in higher amount and thereby causes vascular complications due to hyperlipidemia. This may in turn cause cardiovascular diseases and in most cases liver, gall stone and gut related diseases. Therefore management of the obesity is very much essential to restrain these diseases [5]. It is very important to

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maintain the fatty acids, triglycerides and cholesterol in the blood at very low level because higher amount of these molecules will start accumulating in the adipose all over the body called atherosclerosis and if it is not controlled may lead to myocardial infarction and stroke. This also results in the increase of oxidative stress, lipotoxicity, hypertriglyceridemia and other complications like diabetes. Managing and reducing the oxidative stress to prevent the obesity and few other complications [5].

Obesity anyhow can be managed either by reducing the appetite or by enhancing the calorie utilization. Hunger and satiety are managed by regulating the hormones which are responsible for hunger. However physical exercise can prevent the accumulation of white adipose [6]. The goal of treatment is to make the individual to attain and stay at healthy weight. The preliminary treatment target is a sudden loss of weight of 5% to 10% of the total weight. However, loss of more weight has greater benefits [7]. If the individual wants to reduce weight, the person must change eating habits and do lot of physical exercise [8]. The treatment methods which are right for the individual directly depend on the obesity severity, health and the enthusiasm in willingness in losing weight. Doctors may recommend medication for the weight loss only if the other plans like diet and exercise do not work [9]. Doctors will consider the health history of the person and possible side effects before choosing any medication for the obese patient [10]. Few of the medications can't be given to pregnant women and to the people with chronic health diseases [11]. Plethora of information available in the literature suggests that variety of drugs used treat obesity [12-26].

Medication for obesity is so interesting and confusing that one medicine can't react the same way to others and in few cases the effects may be slower as the time passes. Pausing or stopping of the medication will result in the regain of the full or little weight which was lost. Keeping these things in mind, a common, economically viable and effective drug is required to control obesity and with a proper diet plan which can substantially decrease the obesity of the individual.

Physiological study of Obesity

Development of obesity involves various pathological events at molecular level. Excess intake of food and less physical exercise leads to the condition of obesity [27]. A few number of the cases are due to genetic inheritance, medical problems or psychiatric problems [28]. Obesity occurs due to the interplay

between genetic and also environmental factors. All the People who exposed urban and rural environments will become obese, it means that there is some genetic mechanism working at the individual level. Hypothalamus expresses Leptin and Melanocortin-4 receptors, which are involved in the regulation of homeostasis in the neural circuits. Inefficiency to express those proteins also brings obesity in the individuals [29]. People with multiple copies of FTO gene (Fat mass & obesity associated gene) are found to have 1.67 times higher risk of the obesity than the people who do not possess that extra copy of gene.

Addition to insulin, glucagon, somatostatin, somatropin, cortisol, gastric inhibitory polypeptide/glucose-dependent insulinotropic peptide [GIP], adipopectin thyroxin, chemerin, perilipin-1, apelin, GLP-1 catecholamines and cholecystokinin-pancreozymin there are other 5 molecules which are produced endogenously have been found to regulate the appetite, satiety, storage of energy and metabolism. It includes Leptin, Obestatin, Endocannabinoids, Ghrelin and Nesfatin-1 [29].

Current Drug based therapy for Obesity

People with diabetes, sleep apnea, hypertension, arthritis and hyperlipidemia have many risk factors for the treatment of obesity using pharmacological therapy [30]. At present none of the drugs have been taken for clinical trials for more than 4 years and also most of the drugs have serious side effects. Treating obese person with drugs for a short period may have side effects but it benefits for treating obesity. For any drug to consider it as antiobesity drug, it should reduce the weight at least by 2kg within 30 days and 5-8% in the next 180 days. Pharmacotherapy will be considered effective only if the patient loses at least 10-15% of the initial weight in 1-2 years period [31]. After starting treatment, decrease in the weight should be 10-15% of the initial weight within one year, then only the demonstrated therapeutic drug will be called as anti-obesity drug. After losing weight, patients have to reduce the intake of energy by 8kcal/kg [32].

There are many agents used to treat obesity, they have different target and different mechanism of action. Appetite suppressant drugs, antidiabetic agents, anticonvulsant drugs, inhibitors of pancreatic lipase, serotonin 5-HT_{2c} agonists, antidepressants, beta 3 adrenoceptor agonists, hormones and hormone analogues and other combinational formulae are the kind of drugs used in treating obesity. Clinician should select the type

of drug for each individual using the clinical trial data available and prescribe the drug along with some diet restriction and physical exercise. Some of the approved antiobesity drugs are listed in the Table 1.

Table 1: Drugs which are approved by various authorities for treating obesity

Drug	Brand name	Treatment period	% or kg of weight loss	Mechanism of action	Drug Approved authority	Reference
Orlistat	Xenical	4 years	Approx. 3%	TAG lipase inhibitor	EMA, FDA, ANVISA	[33,34]
Bupropion	Buproban, Wellbutrin, Zyban	24 weeks	Approx. 13%	Inhibits Noradrenaline and dopamine reuptake	FDA	[35]
Naltrexone/ bupropion	Contrave	24 weeks	Between 6.1 to 9.3%	Inhibits Opioid receptor antagonist/ Noradrenaline and dopamine reuptake	EMA, FDA	[36]
Bupropion/ zonisamide	Empatic	12 weeks	Approx. 7.2 Kg	Inhibits Noradrenaline/ dopamine reuptake	FDA	[37]
Topiramate	Topamax	24 weeks	Approx. 6%	Physiologically blocks glutamate receptors and carbonic anhydrase	FDA	[38]
Phentermine	Adipex	24 weeks	Between 7.2 to 8.1%	Sympathomimetic amine and appetite suppression	EMA, FDA	[39]
Phentermine/ topiramate	Qsymia	52 weeks	Approx 9%	Physiologically blocks glutamate receptors and carbonic anhydrase and catecholamine secretion	FDA	[40,41]
Sibutramine	Biomag, Sibus, Saciette	52 weeks	4 Kg	Block the reuptake of 5-hydroxytryptamine and norepinephrine serotonin, dopamine,	ANVISA	[42]
Rimonabant	Acomplia, Redufast	52 weeks	4-7 Kg	Inverse agonist for the cannabinoid receptor CB1	EMA	[43]
Lorcaserin	Belviq	52 weeks	Approx. 5.8%	Selective agonist for serotonin 2C receptor	FDA	[44,45]
Liraglutide	Victoza, Saxenda	52 weeks	5%	Agonist for GLP-1 receptor	EMA, FDA, ANVISA	[46]
Empagliflozin	Jardiance	3 years	1.5 to 2.0%	Inhibits Sodium–glucose cotransporter 2	Phase I	[47]
Cetlistat	Cetislim	12 weeks	3.3 to 4.1%	Pancreatic lipase inhibition	Japan	[48,49]
Belonarib	Not yet given	12 weeks	Between 5-10 Kg	Methionine aminopeptidase 2 inhibition	Phase II and III	[50]

Drugs used to treat obesity in the long term

There are 5 different drugs or drug combination used in the long term to treat obesity. They are used as monotherapeutic or in combination therapy. Treatment of obesity is a long term process and involves medication, diet and physical exercise. Diet and physical exercise brings about a vast difference in the obese individual in the long term treatment.

Currently there are five drugs which are approved by the US FDA for the long term treatment of obesity. These medications should be taken in combination with physical exercise and proper diet. Orlistat, Lorcaserin, Liraglutide, Phentermine/ Topiramate and Naltrexone/ Bupropion are approved in the US and out of these, phentermine/ topiramate and lorcaserin are prohibited in Europe because of the safety issues [51, 52].

Orlistat

Orlistat was first approved in 1998 and it is the longest licensed drug to treat obesity. In United Kingdom and United States Orlistat sold as Alli by

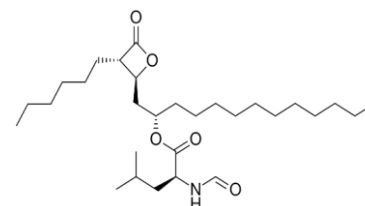


Figure 1: Orlistat

GlaxoSmithKline and in most other countries as Xenical by Roche [53]. For the adults and adolescents of ≥ 12 years of age orlistat-120mg prescribed 3 times a day before meals [54].

Mechanism of action:

Orlistat is highly potent and selective inhibitor of gastric and pancreatic lipase and thus inhibits the digestion of triglycerides into fatty acids. So, absorption of fatty acids becomes limited and undigested triglycerides excreted through feces.

Absorption of Fatty acids decreases by at least 30% after taking Orlistat [55]. It has to be noted that people who take low lipid containing diet have less significance in taking Orlistat.

Side effects

Some of the major side effects include gastrointestinal symptoms like diarrhea, abdominal pain, oily stool, fecal urgency and flatulence [55]. Gastrointestinal issues can be resolved by co-prescribing a fiber containing supplement like psyllium or by increasing the fiber content in the diet.

Efficacy

Studies have been done for 4 years to comprehend the efficacy of the medication [56]. Ideal impacts have been found in association with diet and physical exercise brought about the decrease of 2.9 kg that is 95% CI, 2.27-3.51 kg of the body weight when compared with placebo treatment. Critical loss in the weight of 5.8 kg versus 3.0kg; $p < 0.001$ when compared with placebo treatment in the diabetic prone obese patients [57-60].

Lorcaserin

Lorcaserin is a specific agonist of 5-hydroxytryptamine (5-HT)_{2C} receptor found in the hypothalamus region of the brain, which is known to control appetite. Lorcaserin was approved in 2012 for long term treatment of obesity, however in 2020 Lorcaserin was withdrawn from sale in USA because of the increased risk of cancer [61].

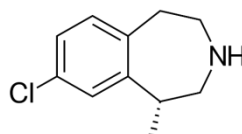


Figure 2 : Lorcaserin

Mechanism of action

Activation of 5-HT_{2c} receptors present in the hypothalamus of the brain leads to the stimulation of proopiomelanocortin (POMC), which in turn decreases the appetite by satiety. Lorcaserin is a selective 5-HT_{2C} receptor agonist, upon binding to the receptor, reduces the feel of appetite, mood and also endocrine secretion. The appropriate mechanism of regulation of appetite is not yet fully understood [62, 63]. Lorcaserin has also found to interact with the 5-HT_{2C} related receptors like 5-HT_{2B} and 5-HT_{2A} at a ratio of 100x and 17x times less than that of 5-HT_{2C} receptor [64].

Side effects: Nausea, dizziness, fatigue, headache, dry mouth, constipation, back pain, cough and hypoglycemia are the few of the major side effects.

Efficacy:

A randomized, placebo treatment controlled, double blind investigation with more than 3000 individuals called BLOOM

(Behavioral Modification and Lorcaserin for Overweight and Obesity Management) clinical trial has been conducted to analyze the efficacy of lorcaserin 10mg twice day by day with placebo treatment. To summarize the trial, some of the patients who got lorcaserin in the first year asked to keep taking lorcaserin for the subsequent year and the rest of the patients were given the placebo treatment. 47.5% of patients who got Lorcaserin in the subsequent year lost more than 5% of their initial baseline body weight in year 1 and just 20.3% of the placebo treatment patients shed weight by over 5% ($p < 0.001$) [65, 66].

Liraglutide

Liraglutide is an incretin mimetic agent which is an agonist for the

glucagon like peptide -1 receptor. This drug was approved by FDA in the year 2014 for subcutaneous injection of 3mg per day [67].

Mechanism of action

Glucagon like peptide-1 (GLP-1) binds to glucagon like peptide -1 receptor and enhances glucose dependent insulin secretion. GLP-1 has very less half-life of 1.5 to 2 minutes in the blood. Liraglutide is very stable in plasma and its half-life is found to be 13 hours [68]. The insulin produced will assist in managing blood glucose. GLP-1 is also known to induce postprandial satiety, slows down gastric emptying and decrease appetite [69].

Side effects

Some of the major side effects subtracted with placebo were nausea (25.0%), diarrhea (11.6%), vomiting (12.2%), constipation (11.0%), and dyspepsia (6.4%) [70-72] Long term use of Liraglutide also leads to decrease in the level of HbA_{1c} and blood pressure [73, 74].

Efficacy

A 8 month clinical trial of liraglutide in 564 obese-but-non-diabetic patients following the 5 month dose dependent placebo-controlled experiment of liraglutide in contrast with orlistat treatment (a normal weight reduction of 6.0 kg with liraglutide contrasted and orlistat 4.1 kg and with placebo 2.8 kg) revealed that liraglutide at higher dose prompted 5.5 to 6.0 kg placebo-adjusted weight reduction in one year [75].

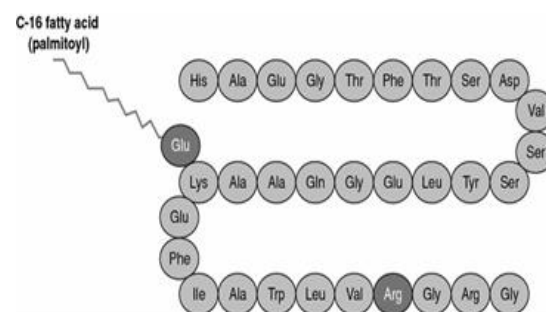
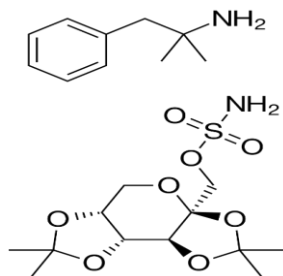


Figure 3 Liraglutide

Phentermine/topiramate

It was the first combination drug approved by FDA in 2012 for the longer treatment of obesity. However it is not approved by EMA due to lack of long term studies related to cardiac related issues. Phentermine is a **Figure 4: Phentermine/topiramate** controlled drug substance since it comes under DEA schedule IV [76].



Mechanism of action

This combination drug works by suppressing the appetite in an unknown mechanism. Phentermine is a noradrenergic agonist and it enhances the release of norepinephrine, serotonin and dopamine by its sympathetic action [77]. Topiramate is a glutamate antagonist, γ -aminobutyric acid agonist and carbonic anhydrase inhibitor and was approved for treating epilepsy and migranes. But the epilepsy patients who received topiramate have significantly lost the weight and it paved the way to study topiramate for clinical trials to treat obesity. The action of topiramate have not been understood properly, however studies on rats suggest that topiramate is a neurostabilizer and enhances thermogenesis [78-80].

Side effects

Dizziness, paresthesia, dysgeusia, insomnia, dry mouth, tingling, constipation and sleeping trouble are few of the major side effects of the phentermine/ topiramate. Use of this drug is not recommended during pregnancy [81].

Efficacy

In clinical trials, individuals treated with the maximum dose of phentermine/topiramate along with a plan of diet and exercise lost 10% to 11% of their body weight contrasted with 1% to 2% for the individuals who got placebo. Moreover, 62% to 70% of subjects accepting the suggested dose or highest dose of phentermine/topiramate accomplished $\geq 5\%$ weight decrease by week 56 (ITT-LOCF) compared with 17% to 21% of those getting a placebo [82].

Naltrexone/ Bupropion

Naltrexone/bupropion is a drug combination for long term treatment of obesity. This combination was approved by FDA in 2014. Individual drugs were used in 1980s for various health conditions. This is not controlled substance since it poses no potential abuse [76].

Mechanism of action

Synergistic effect of both Naltrexone and bupropion regulates the appetite and energy utilization. Naltrexone acts by inhibiting the reuptake of dopamine and norepinephrine and in turn it activates POMC in the hypothalamus. Naltrexone is opioid antagonist and it further increases the activity of Bupropion [83].

Side effects

Gastro-intestinal discomforts like nausea, vomiting, constipation, diarrhea and other side effects such as headache, dizziness and dry mouth. In long term use, patients with CVD may pose increased level of Blood pressure and heart rate [84].

Efficacy

In a clinical trial III, patients with no T2DM medicated with Naltrexone/Bupropion showed effective weight decrease of up to 9.3% from the baseline and patients with T2DM medicated with Naltrexone/Bupropion showed weight decrease of up to 5% and the data was submitted to FDA [85,86]. In 2015, Naltrexone/Bupropion affirmed by EMA following its treatment related to weight reduction in patients having BMI ≥ 30 Kg/m² [87]

New probable targets:

Individual can continue taking these medications as long as they are benefiting from treatment and not having unpleasant side-effects. The increase of severe obesity in the patient population along with the co-morbidities, demands the development of novel drugs for treating obesity. This development is due to the proper understanding of the energy regulation and neuronal pathways which are involved in the energy homeostasis.

There are many new distinctive pathways have been studied which are involved in peripheral metabolic pathways. Many of the researchers are developing agonists for various pathways of peripheral metabolism like GLP-1R/Glucagon receptor twin agonists, triagonists for GLP-1 and GIP. One of the animal studies shows promising results in glycaemic management and weight reduction when injected with GLP-1/GIP/glucagon receptor triagonists [88]. Velneperit, one other drug which stops the binding of Neuropeptide Y to the Y5 receptor which reduces the hunger and thereby it manages energy balance.

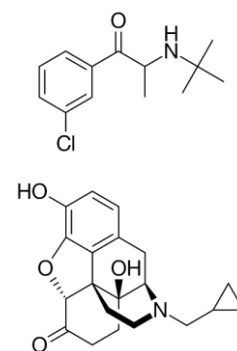


Figure 5: Naltrexone/ Bupropion

Velneperit showed high degree of positive response in clinical trials along with few side effects [50]. Cannabinoid receptor type 1 is one more achievable target [89]. Rimonabant is the antagonist and reverse agonist for CB1 receptor which reduced the weight rats in the animal studies [90, 91]. It is found to be very effective for the people who have inflated medication tolerance [92]. However, in 2008 due to its psychiatric side effects like anxiety, depression and suicide ideation Rimonabant was withdrawn from US market. Taranabant, one more CB1 receptor antagonist and it also works same as Rimonabant also had same psychiatric issues. So, it is believed that, CB1 receptor antagonists are associated with major psychiatric issues and the antagonist which were at the developing stage were halted [93].

Discovery of a new kind of cells called beige fat cells which are a kind of adipose cells, help in enhancing the hormone sensitivity and also involved in antiobesity effects [94]. So the manipulation of these beige cells would result in loss of energy through thermogenesis and Physical activity [95, 96]. Further research on those cells should be done in order to get a complete picture of the fact on beige cells. Some evidences also reveal that inflammatory mediators like fat and macrophages have very important role in developing obesity induced hormone resistance [97-99]. Demonstrations by Lee et al. and Lumeng et al. also revealed that obesity induces inflammation by changing variety of inflammatory mediators like WBC, Neutrophils and also Ly6chi pro-inflammatory monocytes [100-101]. Salicylates and pioglitazone able to decrease the inflammation caused in animal models [102]. Some anti-obesity vaccines are also under development for including ghrelin, somatostatin and adenovirus36. Ghrelin is an orexigenic molecule secreted by stomach. Anti-ghrelin vaccine is shown to decrease food intake and increase energy expenditure [103]. Somatostatin is produced by hypothalamus, and is known to inhibit the secretion of growth hormone and insulin like growth factor-1. Somatostatin vaccination increases the GH and IGF-1 and decreases obesity [104]. Adenovirus36 (ad36) known to increase the risk of obesity by causing inflammation and adiposity [105].

CONCLUSION

Treating obesity is still one of the complicated challenges till today. As this review encompasses, even though the cases of obesity increasing, there are drugs which can work at various pathways and mechanisms which can manage hunger, satiety

and appetite. By keeping the target to progress in finding the better medication for obesity, existing drugs and new targets have to be understood properly. With the development of new therapeutics, anti-obesity drugs have a potential to largely expand and allow better as well as personalized treatment options. Further, studies should be carried out to prove the ability of the drug to reach to its target site in the body and the ability of the drug to adapt into environment and the lifestyle of the individual. Switching to healthy diet and adequate physical exercise as well as proper medication may be the better road to success.

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Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

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