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A BRIEF INSIGHT INTO THE PHARMACOTHERAPY OF OBESITY, DRUGS WITHDRAWN, DRUGS IN MARKET AND IN PIPELINE: A REVIEW

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Obesity, Multifactorial disorder, Energy expenditure, Melanocortin, Orlistat, Agouti gene related peptide

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ABSTRACT: A Multifactorial disorder primarily of energy balance, which occurs due to imbalance between energy expenditure and excess of calorie intake. Obesity is becoming a serious health related problem worldwide. Appropriate Treatment plans as well as Goals have been established for this disorder, when a patient presents with certain complications, for example, type-2 diabetes mellitus, cardiovascular disease presents with obesity. A number of medications have been approved by the U S Food and Drug Administration for the treatment of this disorder. However, the medications should be used in conjunction with healthy eating habits and physical activity. Several medications have been withdrawn due to serious adverse effects, yet several new drugs are in trials. This article will review the Pathophysiology of the occurrence of obesity, the neurotransmitters involved in its onset, the history of medications: why and which were withdrawn, what all medications are available, what are the future for the treatment of patients suffering from obesity.

INTRODUCTION: Obesity is the excess of fat mass, means deposition of excess fat in the body. Obesity is considered as the combination of both metabolic and neuroendocrine disease, which is ought to be occurring from the obesogenic environment and a role is also played by genetic predisposition. The Body mass index or well referred as BMI is the marker for calculating the body fat content, though it is not a direct measure of adiposity and does not take into consideration that some individuals can have a high BMI due to their large muscle mass, therefore the weight related complications should be considered and clinically assessed.

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The problem of obesity has doubled, World-wide since 1980, reason being the numerous co-morbidities associated with obesity [1, 2]. Now worldwide, Obesity represents a major and serious health as well as socioeconomic burden. When greater quantities of energy enter the body than are calories that are expended or burned, the weight increases and most of the excess energy gets stored in the body as fat. On the other side, people with increase of intra-abdominal or visceral adipose tissue and mass, are highly prone of becoming insulin resistance or getting exposed to metabolic syndrome [1, 2, 3].

As per Lung T *et al*, adults are expected to lose 3.3 years of life at age 20-29 years if they are suffering from overweight and might lose 5.6 to 10.3 years if they are suffering from severe obesity [3]. Obesity being a multifactorial disorder of energy balance (in terms of calories consumed and expended), in which long term calorie intake exceeds energy expenditure can lead to excessive weight gain.

An individual with a body mass index of 25-30 Kg/m2 is considered to be overweight and >30 Kg/m2 is regarded to be obese. It ultimately leads to an increase in the risk of Diabetes Mellitus, Ischaemic heart disease, Gallstones, Hypertension, Hypercholesterolemia.

Underling Mechanism of Obesity (In Fig. 1): Energy balance is controlled by two types of the arcuate nuclei neurons; one is proopiomelanocortin (POMC) neurons that release α-melanocortin stimulating hormone (MSH) and cocaine and amphetamine regulated transcript (CART) which leads to reduction in food intake and increasing energy expenditure. On the other hand, agouti gene related peptide (AGRP) and Neuropeptide Y (NPY) as an antagonist to Melanocortin receptors, ultimately enhances and stimulates food intake and also responsible for decreasing energy expenditure [4].

The signaling through POMC and CART induces expression of anorexigenic corticotrophin releasing hormone (CRH) and Thyrotropin Releasing Hormone ((TRH), thus induces thermogenesis and anorexia. India being on third most obese country in the world behind US and China [4]. In POMC deficiency, stimulation of Melanocortin-4 receptors decreases, which results in lack of energy regulation and in decreasing satiety.

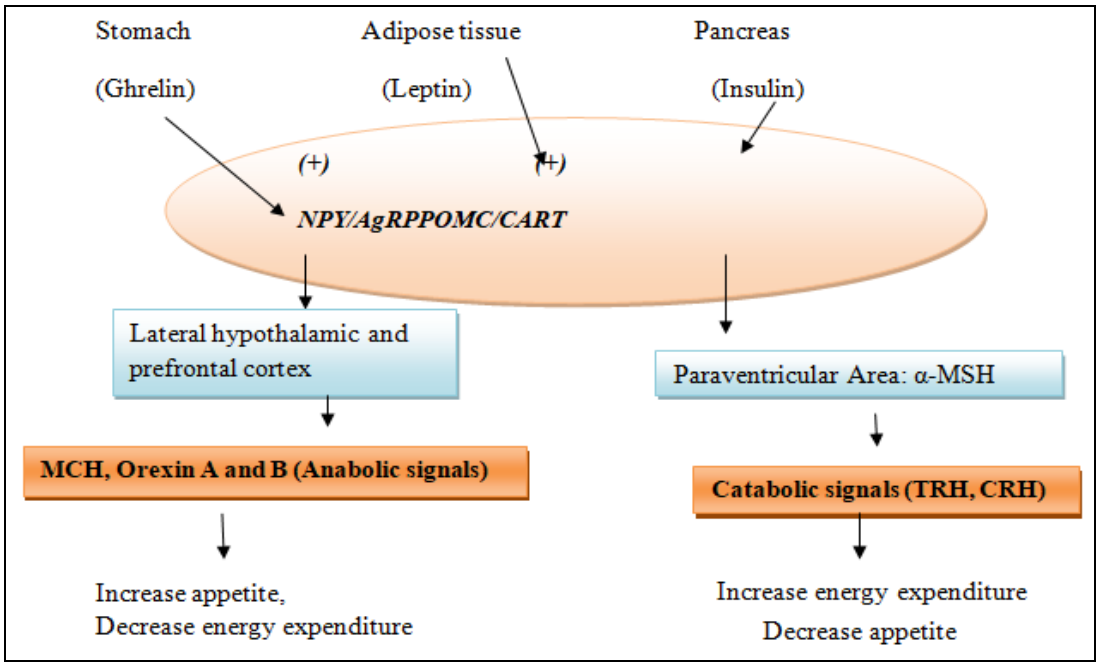

FIG. 1: NEURONS AND NEUROTRANSMITTERS INVOLVED IN PATHOGENESISOF OBESITY [4]

Therapy of Obesity: Management for weight reduction includes both incorporation of physical interventions as well as pharmacological treatment. Lifestyle changes and modifications can significantly reduce the health risks by helping in reduction of the calorie intake and increase in the physical activity and exercise ("exercise pill"). Drugs act through different mechanisms as appetite suppressants, by interference with nutrients absorption from gastrointestinal tract or peripheral tissues, increase metabolism, reducing inflammatory process in adipose tissues and modulation of the body fat distribution [5].

Non-Pharmacological Management: Recent recommendations given by American college of cardiology, the obesity society and American heart association recommends an initial weight loss target to be of 5-10% of baseline weight within initial 6 months. Modest weight loss that can be done with lifestyle modification Programmes, can have long-term health benefits including improved lipid and glycaemic control.

However attrition rates from these programs are high and adherence and compliance is poor, that may result in decreased efficacy. Increasing energy expenditure (by brisk walk or staying active or exercising) has a much more positive role in reducing fat storage and adjusting the energy balance in the obese. Recently, Intermittent fasting

trend is getting popular amongst people, to reduce weight with the help of various fasting periods.

Candidates for Pharmacotherapy: Individuals with a body mass index of more than or equal to 30kg/m^2 or a BMI of 27 to 29Kg/m^2 with co-morbidities but have not met their weight loss of at least 5% of total body weight at three to six months [6]. The history of Pharmacotherapy of obesity dates back to the year 1930s. In 1947, 1st obesity drug Desoxyephedrine or methamphetamine was approved by FDA.

TABLE 1: LIST OF ANTIOBESITY DRUGS WITHDRAWN FROM THE MARKET

Drug	Introduced	Mechanism	FDA Status
Fenfluramine	1973	Appetite suppression Sympathomimetic	1997, valvular heart disease and pulmonary hypertension
Dexfenfluramine	1996		1997
Rimonabant	2006	Selective CB 1 (Cannabinoid Receptor Blocker	Withdrawn 2009 potential of serious psychiatric disorders
Sibutramine	1997-US	Selective combined serotonin and Noradrenaline reuptake inhibitor	2010 increase risk of heart attack and stroke

In the coming 2 and half decades, Approval of amphetamine congeners (Phenteramine), Fen-fluramine and other appetite suppressants was followed. Then in 1973 FDA raised concern, about the abusive potential of the amphetamine congeners and their transit efficacy, that has limited the indication of all antiobesity drugs to short term use (i.e. a few weeks) [7]. Drugs withdrawn were Fenfluramine and Dexfenfluramine in the year 1997, due to increased association with valvular heart disease and primary pulmonary hypertension. Sibutramine was withdrawn in the year, 2010 due to increase risk of rise in Blood pressure and heart rate. Rimonabant being cannabinoid CB 1 receptor antagonist decreases appetite and withdrawn from market in 2009 due to the risk of suicidal tendencies and mood disorders.

Currently Available Therapy: Table 2 is Orlistat, Lorcaserin, Liraglutide, Phenteramine and Topiramate Fixed Dose Combination, Bupropion and Naltrexone fixed dose combination [8].

TABLE 2: WHAT ARE THE CURRENTLY AVAILABLE ANTIOBESITY DRUGS

Drug Name	Dose	US FDA	Adverse effects
Orlistat	60-120mg TDS within or during 1hour of fat containing meals	1999	Abdominal cramps, Flatulence, liver and renal injury(rare)
Phenteramine-Topiramate (For Long Term use)	3.75mg/23mg (for 14 days) to 7.5mg/46mg once daily (for 12 weeks). Maximum dose-15mg/92mg once daily	2012	Dry mouth, anxiety, constipation, Abuse potential, Teratogenic (Topiramate)
Bupropion-Naltrexone (For Long tErm USE)	DOSE titrated with time (8mg/90mg)	2014	Vomiting, constipation, dry mouth, Tachycardia,
Liraglutide (For long term use)	0.6mg SC daily to 3mg SC daily	2014	Nausea, Diarrhoea, Hypoglycemia in Type 2 DM, delay in gastric emptying
Semaglutide	0.25mg sc once weekly to 2.4mg sc weekly	2021	Nausea, Diarrhoea, Hypoglycemia in Type 2 DM, delay in gastric emptying
Bupropion-Naltrexone (For Long term USE)	25mg Once daily to 50mg thrice a day	C-III	Not prescribed due to their adverse effects. If prescribed then only for short term <12 weeks
Phenteramine	15 to 37.5mg daily or divided twice daily	C-IV	

Orlistat was introduced in Europe and US in 1998, a synthetic derivative of Streptomyces toxytricini, for long term management of obesity, currently approved by FDA, being intestinal lipase inhibitor prevents absorption of 30% of triglycerides thus increases excretion of unabsorbed TG. The drug is to reduce weight by 5-10% than placebo in several Randomized controlled trials over 2-4 years [8, 9]. Orlistat associated with side effect of steatorrhoea, bloating, abdominal pain [10, 11]. The drug has been associated with oxalate induced acute kidney injury [12, 13, 14].The drug has an advantage over the

centrally active adrenergic and serotonergic agents as it acts peripherally and is not expected to have any cardiovascular adverse effects.

5HT2 C Receptor, distributed in the nucleus of Solitary Tract, Dorsomedial hypothalamus, Paraventricular hypothalamic nucleus and amygdale. That regulates satiety and metabolic rate, helps in inhibition of appetite and increases satiety. The well tolerated drug with rapid absorption and peak in 1.5-2 hrs, metabolized in liver and excretion in urine, associated with side effects like nausea, vomiting, headache, sinusitis and upper respiratory tract infections and having drug interactions with selective serotonin reuptake inhibitors. The drug was FDA approved in July 2012 [15]. In the year 2020, The US Food and Drug administration has asked the manufacturers to withdraw the drug from United States market, as the drug has been linked, to cause increased risk of cancer [16, 17].

Combination Antiobesity Drugs: As Phenteramine being analogue of amphetamine reduces appetite and thus decreases food consumption along with topiramate affects satiety by augmenting the activity of GABA, Carbonic anhydrase inhibition and blockade of voltage dependent sodium channels. The combination has been approved by US FDA in the year 2012 [18]. The well tolerated drug is associated with side effects as insomnia, dysguesia, dizziness, paresthesia and dry mouth. A Randomised controlled trial of 56 weeks (EQUIP and CONQUER) using phenteramine +topiramate in low dose (3.75/23mg) and high dose(15/92mg) has resulted in a weight loss of 5% and 11% respectively compared to 2% for placebo [9]. The drug has been associated with adverse effects like dry mouth, constipation, paresthesia in clinical trials [18, 19].

Other fixed dose combinations Bupropion being selective dopamine and norepinephrine reuptake inhibition, Naltrexone, which is a mu-opioid receptor antagonist approved in September 2014. The randomized placebo-controlled trials, in 56 weeks study carried out in 1650 of patients, weight loss started as early as treatment given and was continuous and the continued treatment resulted in reduction of waist circumference, insulin resistance and high-density lipoprotein, Triglycerides and CRP. Recommended dose of Naltrexone 8mg/ Bupropion 90mg is recommended dose to a maximum dose of naltrexone 32mg/bupropion 360mg [20, 21].

Liraglutide this agent, is a glucagon-like peptide-1 (GLP-1) receptor analogue of the endogenous gut-derived hormone, incretin. It has the property to improve glycosylated haemoglobin concentrations, beta cell function as well as systolic blood pressure. Furthermore, the drug has been shown to facilitate weight loss in diabetic patients, but in a dose dependent manner [22]. The initial dose is 0.6mg daily for one week and then titrated at weekly intervals to 1.2, 1.8, 2.4, 3mg [23, 24]. But cases of weight regain has been reported with discontinuation of the drug. The agent has been approved as a once daily subcutaneous injection.

Semaglutide: GLP-1 agonist that has been approved for the treatment of obesity patients. The agent is administered by subcutaneous injection (2.4mg once weekly) [24]. The drug has demonstrated its efficacy in reducing weight, as well as in improving glycemia and lipids [25, 26]. In clinical trials, involving type 2 Diabetes patients, the drug has shown shown shown its efficacy in weight loss [27].

Future Aspects: Drugs like Tensofesine being novel centrally acting triple monoamine reuptake inhibitor with serotonin, dopamine and norepinephrine reuptake inhibitor, thus helps in promoting appetite suppression and increases satiety [28]. Being in phase 3 trial with 0.5 and 0.25mg and the reported side effects as dry mouth, insomnia, diarrhea and tachycardia.

Pramlintide Amylin Analogue being synthetic version of naturally occurring amylin secreted from pancreatic beta cells. The mechanism behind is not well understood but found to decrease food intake and high intensity amylin sites identified in the raphe and nucleus accumbens the regions in brain that control feeding behavior. Oxyntomodulin being having high affinity for glucagon like peptide-1 and glucagon receptor analogue and has been found to reduce weight in rodents and man. In a study, it was shown to reduce nearly 2.3 kg after 4 weeks treatment with Oxyntomodulin, as compared with placebo of weight loss of 0.5 kg [29].

Leptin being the novel target at low doses to maintain the lost weight, attained by other anorectic agents and lifestyle modifications [30, 31]. Weight loss decreases energy expenditure and reduces the tone of sympathetic nervous system and thereby reduces the circulating levels of leptin and thyroid hormones [31]. Thus weight reduction is considered to be a state of leptin deficiency [32, 33, 34]. Thus weight reduced state considered to a state of hypometabolic state, state of hyperphagia which might result in tachyphylaxis to other anorectic agents and thus weight regain. Thus, leptin mimetics and Intranasal leptin are in the stages of drug development [35, 36].

Beloranib: A novel class of the drug which is a selective methionine aminopeptidase 2 inhibitor thus reduces fat synthesis and enhances fat oxidation and lipolysis. In studies it has been found to produce weight loss by reducing hunger at a dose of 0.1-0.9mg twice weekly [37].

Other newer targets as Neuropeptide Y 5 antagonist (Velneperit), Histamine H3 receptor, Vascular endothelial growth factor, Matrix metallo-proteinase, GLP-1 receptor agonist (Efpeglenatide, Semaglutide and Liraglutide) have been investigated [37, 38].

TABLE 3: ANTIOBESITY MEDICATIONS IN PIPELINE

Drug	DOSE and Approval	Mechanism and Risks associated
Metreleptin	FDA approved in 2014, for treating generalised lipodystrophy.	Acts by binding to Leptin receptor ObR. Drug is ineffective if obesity is not resulting from leptin deficiency.
Setmelanotide	Starting dose is 1mg for adults and in children 0.5mg daily and then up titration is done by 0.5mg, every 2 weeks. (Maximum dose is 3mg)	MC4 Receptor agonist. In Phase 2 trial for Prader willi syndrome. The agent is associated with skin pigmentation, skin lesions darkening and increasing suicidal thoughts, depression
Lisdexamfetamine	FDA approved agent for binge eating disorder. Approved for >6 years of age with Attention deficient hyperactivity disorder.	The agent carries the abusive potential [40].

Certain Medications which Induce Weight gain [11]:

1. Antidepressant drugs such as monoamine oxidase inhibitors, tricyclic antidepressants (nortriptyline, amitriptyline, doxepin), paroxetine, citalopram, escitalopram, imipramine, mirtazapine.
2. Antipsychotics agents: thioridazine, olanzapine, risperidone, clozapine, quetiapine.
3. Antidiabetics: eg, insulin, sulfonylureas, thiazolidinediones, meglitinides.
4. Glucocorticoids.
5. Neurologic and mood-stabilizing agent such as lithium, carbamazepine, gabapentin, valproate.
6. Antihistamines: cyproheptadine.
7. Alpha blockers: especially terazosin.
8. Beta blockers: especially propranolol.

Complications associated with Obesity are:

1. Type 2 Diabetes mellitus,
2. Gallbladder disease,
3. Non alcoholic fatty liver disease, Gout.

Excess of body fat abecomes the source of adipocytokines and mediators of inflammation, which affects the fat as well as glucose metabolism. Obesity is linked to cause Cancer of colon, kidney, esophagus, endometrium and postmenopausal breast [37].

Obesity in Paediatric Popultaion:

FDA Approved Drugs in Paediatric Population:

Orlistat: FDA approved in >12 years of age group. The usual prescribed dose is 120mg TDS with meals. The drug is contraindicated in Cholestatsis, Pregnancy and Malabsorption.

Phenteramine: Approved in united states for a duration of upto 12 weeks. Prescribed dosage is 15mg, 30mg or 37.5mg daily [39].

Non-FDA approved drugs in Paediatrics:

Topiramate: In combination with Phenteramine in & gt; 18 years of age for obesity. Phenteramine/Topiramate extended release: FDA approved for chronic weight management in adults. A favourable treatment option in attention deficit hyperactivity disorder with obesity have been Methylphenidate (Dopamine transport and reuptake inhibitor), has been showing promising results in decreasing appetite and satiety in monogenic obesity (due to MC4R or LEPR gene mutations) [40].

Cost Effectiveness in Antiobesity Medications: The most expensive choices, which have no generic alternatives are Liraglutide and Semaglutide. The treatment of obesity is not covered by insurance, for these agents and secondly fixed dose combination of Naltrexone and Bupropion has no generic alternative and has an average cost of 365 dollars.

Phenteramine and Topiramate FDC comes in intermediate cost, phenteramine can be used alone to make it more cost effective and reduce the cost. Most affordable drug as antiobesity is Metformin, more than Orlistat [41].

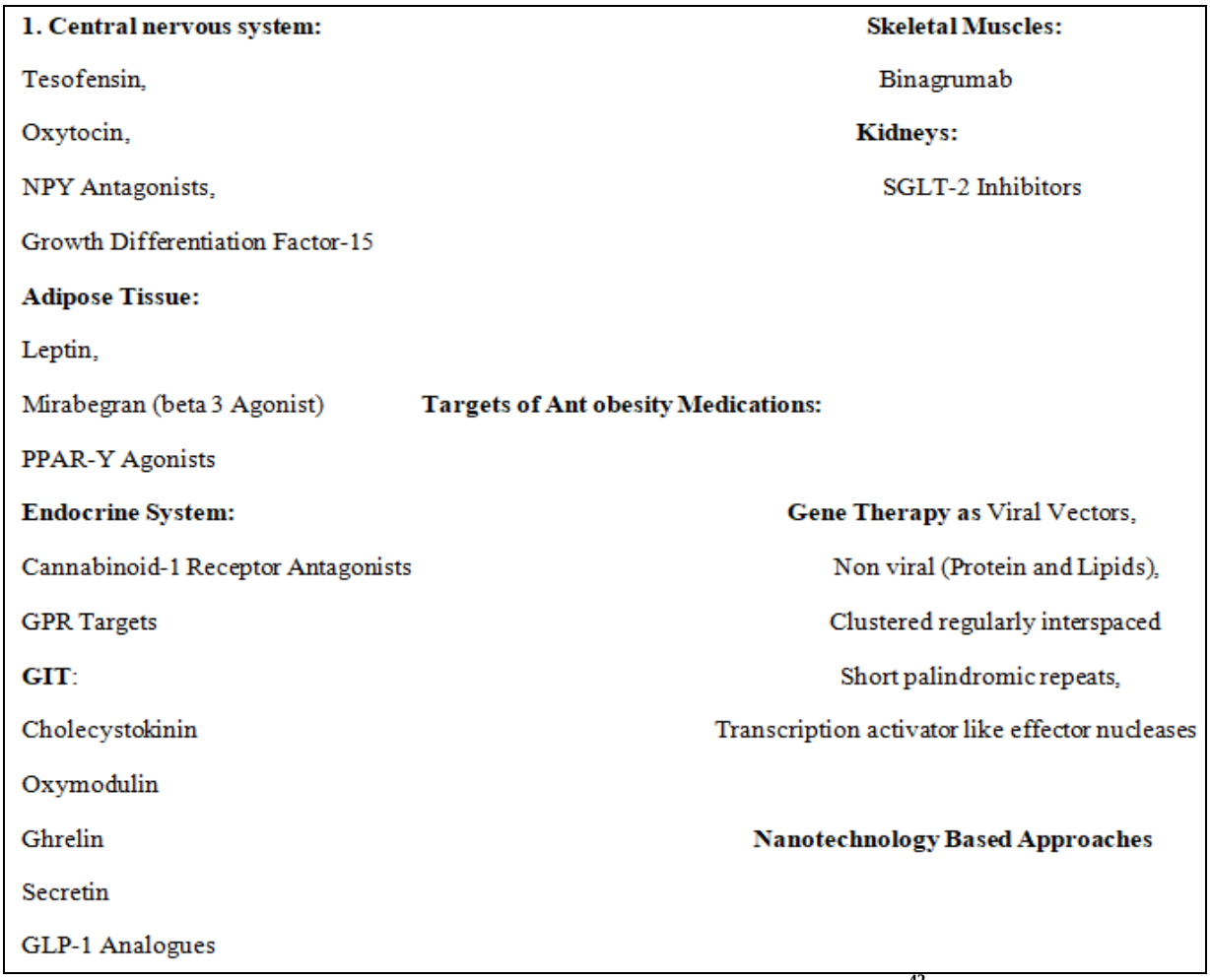

FIG. 2: TO SUMMARISE ANTIOBESITY TARGETS [42]

CONCLUSION: Obesity being a chronic disease carries many co-morbid lifestyle disorders, so the therapy has to be continued for a long duration. Pharmacotherapy of obesity with lifestyle changes (restricted diet, physical activity and behavioural modification) may promote weight loss journey. Interestigly, more than 300 loci bearing variants in general population has been found to be correlated with obesity in large scale genome wide association studies. There are many newer promising agents in pipelines, which will be helpful in reducing weight gain. Though Diet modifications, lifestyle changes play a major role in it.

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CONFLICTS OF INTEREST: None

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