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AN OVERVIEW OF PHARMACOTHERAPY OF OBESITY: AN UPDATE

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ABSTRACT: Obesity is a chronic disease and a major health problem which require long term treatment in developed and affluent society of developing countries. Pharmacotherapies for obesity have to be given for a long duration with lifestyle modifications. Anti-obesity drugs acts through various targets in the body which reduce the food intake, decrease absorption and increase metabolism. Many drugs were approved and used in the past but were removed or abandoned in the later stages due to the various adverse drug reactions associated with the drugs. At present orlistat is the only approved drugs but it's also associated with steatorrhoea and other side effects. Lorcaserin and the combination of phentermine and topiramate have shown to reduce greater weight loss and fewer side effects than orlistat. There are new combinations from existing drugs are in various phase of clinical trials like bupropion/naltrexone, bupropion/zonisamide and pramlintide/metreleptin. Many single agents like tesofensine, liraglutide, cetilistat, etc are in various phases of clinical trials and have shown promise to be in the league of the present drugs with approval in future. This article aims to bring data of the present and the developing drugs from various clinical trials which hold promise to be in the market for future.

INTRODUCTION: Obesity is one of the leading causes of chronic disease in the developed countries and it's in rise in the third world too [1]. Obesity prevalence has risen dramatically and poses a great treat to patients for diabetes type 2, hypertension and other cardiovascular complications. In addition, it may elevate the risk for other diseases such as non-alcoholic fatty liver disease, osteoarthritis, sleep apnea and certain forms of cancer [2]. Obesity is classified by body mass index (BMI) which is calculated as weight in kg/height in meters squared. BMI over 25 are called overweight and BMI of over 30 represents obesity [3, 4]. On the other hand, people with increase of intra-abdominal or visceral adipose tissue are at higher risk of becoming insulin resistant or getting metabolic syndrome [4, 5, 6]. Therefore, waist circumference or waist/hip ratio is often a better indicator than BMI [7, 8]. Under diagnosis may be another reason which may increase the risk factor for cardiovascular and metabolic disorders, for example, thin person who may look thin outside but may have increase hidden fat in heart, muscle and liver are at increased risk [9] and also high level of free fatty acid in plasma [10].

BMI, waist/hip ratio and plasma free fatty acids are the indicators that should be continual monitored by the physician. It helps the physician to provide adequate drug which provide efficacy and safety. The prescribed drug should efficacious in helping losing or maintain weight loss, but if some adverse effects occur then it should be discontinued.

At present there are no drugs which can loss over 10% of total body weight so achieving a healthy body weight still remains a far reached dream. Anti-obesity drugs had a troublesome history by many failures in development and withdrawals from market due to safety profile. On the other hand, bariatric surgery is helpful for long term management of severe obesity but it is associated with surgical risks, high cost and metabolic complications. [11].

The problem of adiposity had therefore boosted to develop new single and dual-agents drugs having greater efficacy associated with a favorable safety profile and minimal side effects.

Targets in Obesity Management: Management for weight reduction in obese persons includes physical interventions along with pharmacological treatments. Lifestyle modifications significantly reduce health risks by reduction in caloric intake, increased activity, and physical exercise ("exercise pill") [12, 13, 14] even in the absence of weight reduction. Lifestyle modifications are often disappointing for long term as humans have powerful instinct for desire of food.

Human brain physiologically generates the sensation of hunger due to direct metabolic stimulation [15] and also due to regulation by central dopaminergic, opioid, serotonergic and cannabinoid system [16].

Antiobesity drugs along with lifestyle modification or alone act through five mechanisms:

1. Decreasing food consumption by appetite suppression, increasing satiety or satiation, etc
2. Interference with absorption of nutrients from gi tract or peripheral tissue.
3. Increased metabolism of nutrients by stimulating energy expenditure.
4. Reducing the inflammatory process in the adipose tissue and
5. Modulating body fat distribution [17].

However, at present scenario, pharmacotherapy along with dietary restriction and physical exercise looks more promising than given drug therapy for long term management (**Figure 1**).

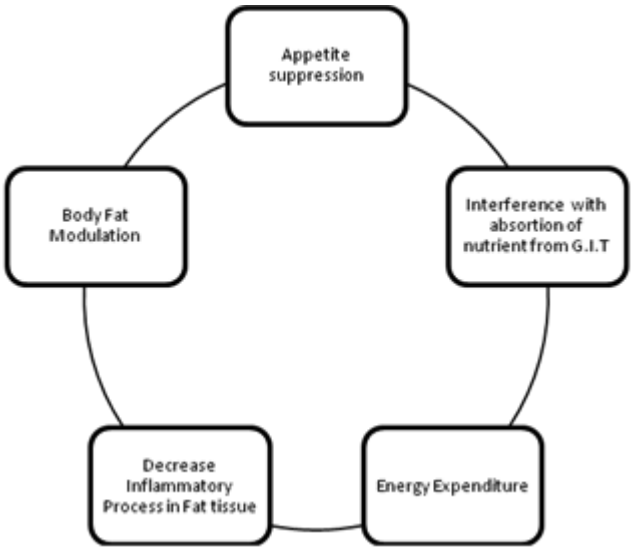

FIGURE 1: TARGETS FOR PHARMACOTHERAPY OF ANTI-OBESITY

Drugs Withdrawn: In the last eight decades, many drugs were introduced in the market for weight reduction but almost all of them were withdrawn due to various side effects (**Table 1**). The drugs used in the past mostly were appetite depressant, enhancer of metabolic rate and decrease fat absorption. In the past, drugs used include thyroid hormones, dinitrophenol, amphetamines and its analogues, phenylpropanolamine, aminorex, mazindol, fenfluramine and dexfenfluramine [18].

These drugs marketed for weight reduction were withdrawn due to serious side effects. These include mostly cardiovascular adverse effects, pulmonary hypertension, haemorrhagic stroke, neuropathy, cataracts and abuse potential [19, 20].

Fenfluramine and dexfenfluramine were suspended from the market from further use in 1997 due to increase association of valvular heart disease and primary pulmonary hypertension [21].

Phenylpropanolamine, phentermine and mazindol were withdrawn from the European market in 2000 due to unfavorable side effects [22, 23]. Rimonabant is withdrawn from the market in 2009 due to potential psychiatric side effects like suicidal tendency, mood disorder and depression [24, 25].

The most recent withdrawal is another appetite suppressant, Sibutramine in 2010 from US and European Union due to concern regarding increase in blood pressure and heart rate [26, 27, 28].

TABLE 1: ANTI-OBESITY DRUGS WITHDRAWN FROM MARKET.

Drug	Mechanism of Action	Reason for Withdrawal
Dinitrophenol	Increase metabolic rate	Neuropathy & cataracts
Amphetamines & Its analogues	Suppress appetite	Abuse potential, Cardiovascular side effects & Haemorrhagic stroke
Aminorex	Suppress appetite	Pulmonary hypertension
Fenfluramine	Suppress appetite	Cardiovascular side effects
Dexfenfluramine	Suppress appetite	Cardiovascular side effects
Sibutramine	Suppress appetite	Cardiovascular side effects
Rimonabant	Suppress appetite	Serious psychiatric disorder

Current Therapy available: The only single drug that is currently in market is Orlistat, an intestinal lipase inhibitor available over the counter in several countries. Recently USFDA approved Lorcaserin in June, 2012 and Qsymia (combination of Phentermine and Topiramate) on July 17th, 2012. Qsymia improves weight loss and helps to maintenance of weight loss with co-morbidities such as hypertension, type 2 diabetes, or dyslipidemia [29] (**Table 2**).

TABLE 2: DRUG AVAILABLE AND RECENTLY APPROVED BY US FDA

Drug	Mechanism of Action	Weight loss	Common Adverse effects
Orlistat	Decrease fat absorption	5-10 %	Steatorrhoea
Lorcaserin	Increase satiety & metabolic rate	5.8%	Nausea & Headache
Topiramate and Phentermine	Suppress appetite & decrease food craving	11% (With high dose)	Dry mouth & Constipation

ORLISTAT: Orlistat was introduced in US and Europe in 1998 and is used as over the counter drug for 60 mg tablets. It is a synthetic drug derived from natural compound lipstatin produced by the microorganism Streptomyces toxytricini [30]. It does not decrease the appetite rather than it binds with pancreatic lipase and decrease the fat absorption [31]. Since it inhibits pancreatic lipase, so it prevents lipolysis of triglyceride and result in excretion of undigested triglyceride oil [32]. It is also associated with improvement in lipid level, blood pressure and insulin resistance [33, 34].

Orlistat in the dose of 120 mg three times a day has been shown to reduce weight by 5-10% (i.e., almost 6.2 kg) than placebo in several RCTs conducted over 2-4 years [35, 36]. The most common side effects of Orlistat is steatorrhoea and others are flatulence, bloating, abdominal pain and dyspepsia. [37,38]. In May, US FDA revised the label of Orlistat with warning of severe liver injury following report of severe liver injury in US and other countries between 1999 to 2008 [39].

Phentermine and Topiramate (QSYMIA): Qsymia (combination of Phentermine and Topiramate) is the most recent addition by the pharmaceutical, Vivus in the pharmacotherapy of obesity. It is approved by US FDA on July 17th 2012.

Phentermine and topiramate are separately licensed for use in the United States. Phentermine, an analogue of amphetamine was approved in 1959 in US as an appetite suppressant in strengths ranging from 15 mg to 37.5 mg and used for short-term course (≤ 12 weeks) in some countries but the drug was withdrawn due to side effects from Europe in 2000 [23], Topiramate was approved in 1996 and is indicated for treatment of seizures (upto 400 mg/day) and for the prevention of migraine (up to 100 mg/day). It was shown to possess anti-craving and weight loss effects [40].

Phentermine on weight management is mediated by release of catecholamines which, results in reduced appetite and decreased food consumption. On the other hand, mechanism of action of topiramate on weight management is not known but most probably it effect on both appetite suppression and satiety enhancement by augmenting the activity of the neurotransmitter gamma-aminobutyrate, modulation of voltage gated ion channels, inhibition of AMPA/ kainite excitatory glutamate receptors, or inhibition of carbonic anhydrase [41].

The combination of controlled release of low dose of phentermine and topiramate (Qsymia) are available in four strength combinations are 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg and 15 mg/92 mg [29].

The 28-week EQUATE, 56-week EQUIP and CONQUER phase 3 studies showed considerable reduction of weight loss compared with single agent of the combination as well as placebo and also evaluated the safety and tolerance of this combination. A 28-week RCT using phentermine with topiramate (92 mg/15mg and 46mg/7.5mg doses) demonstrated a 9.2% and 8.5% weight loss compared to a 6.6% and 5.1% weight loss with topiramate of 92 mg and 46 mg, respectively alone. On the other hand, 6.1% and 5.5% for phentermine of 15 mg and 7.5 mg, respectively alone and 1.7% for placebo associated with low calorie diet lifestyle modification program.

A 56-week RCT (EQUIP and CONQUER) using phentermine with topiramate in low dose (3.75mg/23 mg) and high dose (15mg/92mg) causes a weight loss of 5% and 11%, respectively compared to 2% for placebo in EQUIP phase 3 clinical trials whereas in CONQUER phase 3 clinical trial with low dose and high dose causes a weight loss of 8% and 10%, respectively compared with 2% with placebo [42].

There are five safety concerns regarding the use of this combination and they are suicidality, metabolic acidosis, cognitive-related adverse events, cardiovascular risk and teratogenicity risk. The combination is contraindicated in pregnancy, glaucoma, hyperthyroidism, taken together with monoamine oxidase inhibitor within or during 14 days and known hypersensitivity or idiosyncrasy to sympathomimetic amines [29].

Lorcaserin: Lorcaserin is a selective agonist of 5-HT2C serotonin receptor in the brain which regulates satiety and metabolic rate. This drug has greater selectivity for 5-HT2C than 5-HT2B and 5-HT2A so the side effects of valvular heart disease and pulmonary hypertension are less compared to fenfluramine [43]. In the phase 3 clinical trial of the study BLOOM, BLOSSOM and showed a significant weight loss than placebo [44]. The other clinical trial is BLOOM-DM associated with comorbid condition of diabetes. The cumulative result from two phase 3 clinical trials, BLOOM and BLOSSOM showed a decreased of weight of 5.8% in the lorcaserin and 2.5% in the placebo from the baseline weight. About 47% with lorcaserin use versus 20-25% among placebo users ($p < 0.0001$ for both trials) achieved weight loss of ≥5% over 12 months.

It is well tolerated with a few side effects like nausea, vomiting, headache, sinusitis and upper respiratory tract infection. Cardiac valvulopathy which is more common with fenfluramine is not seen in the two trials, BLOOM and BLOSSOM except in BLOOM-DM, lorcaserin use has been associated with valvulopathy. [45]. This drug is being developed by Arena Pharmaceuticals and it recently approved by US FDA.

Drugs in Clinical Trials: Drugs approved for other indications and newer agents are under clinical evaluation as anti-obesity drugs (**Table 3**). Many drugs are abandoned from clinical trial in the various phases due to their side effects like axokine, a re-engineered human protein; taranabant, a CB1R inverse agonist and ecopipam, a selective D1/D5 antagonist. They are abandoned due to their psychiatric adverse effects. The single agents who have potential as anti-obesity drugs are as follows:

Tesofensine: Tesofensine is a dopamine, norepinephrine and serotonin reuptake inhibitor originally used for treatment of Parkinson's disease and Alzheimer's disease but it was found to cause unintentional weight loss in obese patient of neurological disorder [46]. It is being developed by Danish company Neurosearch. Tesofensine by inhibiting the three neurotransmitters helps in promoting inhibition of appetite and increase satiety. In phase 2 randomized double-blind clinical trial in 203 obese patients for 24 weeks, a dose- dependent reduction in weight is seen with tesofensine.

A weight loss of 4.5%, 9.2% and 10.6% with dose of 0.25 mg, 0.5 mg and 1 mg, respectively accompanied with light diet and physical activity. There is also reduction of triglycerides, total cholesterol, reduce insulin and HbA1C more at 0.5 mg and 1 mg [47] The weight loss seen is twice than the currently marketed drugs. The side effects observed are mostly dry mouth, insomnia, tachycardia, diarrhea, dizziness and even increase in blood pressure and heart rate (more with 1 mg) and these side effects are usually dose-dependent.

Glucagon-Like Peptide-1 Analogues:

1. **Liraglutide and Exenatide:** Liraglutide is a glucagon-like peptide-1 analogue originally developed for the treatment of type 2 diabetes (dose upto 1.8 mg/day) but causes dose-

dependent weight loss and also decreases concentration of HbA1c and improve cell function β [48]. Liraglutide and Exenatide acts on the gastrointestinal tract and the brain. They sent signals from the GI tract to the brain to increase the secretion of leptin which ultimately suppressed appetite and a delay in gastric emptying [49].

The results of a double-blind, placebo controlled 20-week trial, with open-label orlistat comparator in 564 non-diabetic individuals with a BMI between 30 and 40 kg/m^2 showed a dose-dependent reduction of weight associated with low-fat diet and physical activity and also improvement in blood pressure, fasting blood glucose and HbA1c.

With injectable doses of 1.2 mg, 1.8 mg, 2.4 mg and 3.0 mg of Liraglutide, individuals groups demonstrated a weight loss of 4.8 kg, 5.5 kg, 6.3 kg and 7.2 kg, respectively as compared with 2.8 kg with placebo and 4.1 kg with orlistat (120 mg). Individuals with higher doses (3.0 mg) showed more than 5% weight loss of the baseline as compared with orlistat and placebo (Liraglutide-76%, orlistat-44% and placebo-30%). The side effects are dose-dependent and they are mostly nausea, vomiting, insomnia, depressed mood and nervousness.

It is developed by Novo Nordisk. [50]. On the other hand, Exenatide is an injectable medication approved for treatment of Type 2 diabetes that causes weight loss in some diabetic subjects. In an open-label, uncontrolled extension of three double-blind, placebo-controlled trials with exenatide in type-2 diabetes for 2 years showed a reduction of HbA1c, blood pressure and progressive reduction in weight [51]. The side effects are most commonly nausea and vomiting.

It is being developed by Amylin/Lilly/Alkermes. Since liraglutide and exenatide are injectable, Novo Nordisk to improve patient compliance is developing an oral analogue of GLP-1, NN9924. It is currently under phase 1 [52].

2. **Cetilistat**: It is the second drug after orlistat to inhibit gastrointestinal and pancreatic lipase and so reduce the absorption of triglycerides by hydrolysis [53]. In phase 2 clinical trial, the effectiveness of cetilistat is compared with orlistat. This drug is being developed by Alizyme/Takada.

   In a 12-week randomized double-blind study, 612 type 2 diabetic patients on metformin with BMI between 28 and 45 kg/m^2 were included and they were administered different doses of cetilistat (40, 80 or 120 mg three times daily), orlistat 120 mg three times a day or placebo, with meals.

   After 12 weeks, patient given cetilistat (40, 80 and 120 mg) were observed to loss 2.94%, 3.88% and 4.19%, respectively of the initial weight whereas it was 2.91% for placebo and 3.74% for 120 mg orlistat. Cetilistat with higher doses showed a comparable result with orlistat. It causes a fewer gastrointestinal side effects as compared with orlistat [54]. The present status of the molecule is not known.

3. **Oxyntomodulin (OXM):** Oxyntomodulin (OXM) is a peptide secreted from the gut postprandially that has affinity for both the glucagon-like peptide-1 receptor (GLP1R) and the glucagon receptor (GCGR). It increases insulin secretion and glucagon level that decreases food intake.

   Studies show that OXM reduces weight in rodent and human; and also act as a potent antihyperglycemic agent in rodent by this mechanism [55]. It is quite similar to GLP-1 and its peal level after subcutaneous administration is 30 min and the blood level of OXM remain for several hours.

   In a study, it was shown to reduce nearly 2.3 kg after 4 weeks treatment with OXM as compared with placebo of weight loss of 0.5 kg [56]. Thiakas who was developing the OXM analogue, TKS1225 sold the molecule to Wyeth in 2008 which in turn was acquired by Pfizer in 2010. The present status of the molecule is not known.

TABLE 3: DRUGS IN VARIOUS PHASES OF CLINICAL TRIALS WITH MECHANISM OF ACTION

Drug	Mechanism of Action	Current Status
Tesofensine	Decrease appetite, increase satiety	Phase III
Liraglutide/Exenatide	Decrease appetite, increase satiety	Phase I
Cetilistat	Decrease fat absorption	Phase III (Present Status unknown)
Oxyntomodulin	Decrease appetite	Phase I
Pramlintide	Decrease appetite, increase satiety	Phase II
TM30339	Increase satiety	Phase I/II
Obinepitide	Increase satiety	Phase I/II
BVT.5182	Decrease appetite	Phase I
PRX-0703	Decrease appetite	Phase I
Bupropion and Zonisamide	Decrease appetite & Decrease food craving	Phase II
Bupropion and Naltrexone	Decrease appetite, Increase energy expenditure	Declined by FDA, but in Phase III for for cardiac effects
Pramlintide and Metreleptin	Increase satiety and metabolism	Terminated in Phase II, due to antibody production

4. **Pramlintide:** Pramlintide is an amylin analogue originally developed for diabetes but it also shown promise in reducing weight in obese patient with type-2 diabetes. It reduced body weight by delaying gastrointestinal motility, thus enhance satiety and also reduce appetite [57, 58]. It is currently under investigation as a potential for anti-obesity drugs and completed phase 2 clinical trials under Amylin Pharmaceuticals. In a 4-month, double-blind, placebo-controlled study, 411 obese subjects were given subcutaneous injection of pramlintide in the doses of 120, 240, and 360 µg twice or thrice daily.

   The study was extended to 8-month single-blind extension. At month 4, mean weight loss with pramlintide ranges from 3.8 kg to 6.1 kg as compared with placebo (weight loss is 2.8 kg). After 1 year, weight loss from seen in fourth month was maintain except in 120 µg twice daily and placebo. It decreases initial weight as well as help in maintenance of weight loss for long term. Nausea was the common side effects seen in the study [59].

5. **Pancreatic Polypeptide Analogues:** Pancreatic polypeptide is a 36-amino acid peptide, secreted by pancreas and to lesser extent by colon. It plasma level rises after ingestion of food and maintain the plasma level upto 6 hours. This shows it acts by inducing satiety and has high affinity for Y4 receptors followed by Y1 and Y5 in brainstem and hypothalamus [56]. A Danish company, 7TM is developing two synthetic PP analogues named TM30339 which act at neuropeptide Y4 agonist and another molecule, Obinepitide which acts through both neuropeptide Y2 and Y4 receptor agonist. TM30339 shown a good safety and demonstrate weight loss and currently in phase I/II. On the other hand, Obinepitide has a greater weight reducing effect and after a single subcutaneous dose, it inhibit food intake for 9 hours. It is currently in phase I/II [60, 61].

6. **5-HT6 Agonists:** 5-HT6 receptors are widely distributed within the Central nervous system and have potential for suppressing appetitive and weight loss. In the preclinical studies, Biovitrum's BVT.5182 is a 5-HT6 receptor antagonist causes a significant weight loss in rat and mouse models of obesity. PRX-07034 from Epix Pharmaceuticals also successfully reduces food intake and body weight in rats [62]. Both the molecules are in Phase 1 clinical trial and have a great potential as an anti-obesity drug in the future [63].

Monotherapies are always used as pharmacotherapy for obesity but often have the problem of counter-regulation. There are multiple mechanisms involved in appetite regulation and energy homeostasis [64]. Polytherapies are therefore designed to target the multiple steps involved in

the regulation of food intake and energy expenditure. That will help to reduce body weight and decrease the risk factors associated with it. Polytherapy will help the drugs in the combination to have synergistic effect, lower doses and also side effects will be less than the individual drugs [65]. The combinations currently under clinical trial as follows:

7. **Bupropion plus Zonisamide:** Bupropion is an antidepressant which acts by inhibiting uptake of norepinephrine and dopamine and thus increases the level of dopamine in brain which helps to regulate appetite and decreased food cravings [66]. On the other hand, zonisamide is an anticonvulsant drug which decreases appetite most probably by GABA, serotonin and dopamine. It also inhibits carbonic anhydrase activity which may change the perception of taste [67]. This drug is being developed by Orixegen as a combination drug named Empatic.

   In the phase 2 clinical trial, different doses of zonisamide (120 mg to 360 mg) is combine with bupropion 360 mg were tried for 24 week duration and it was found that weight loss of 7.5% seen with combination of zonisamide 320 mg and bupropion 320 mg, 6.1% with combination of zonisamide 320 mg and bupropion 320 mg and 1.4% with placebo. The weight loss for more than 5% is 47% and 60% respectively leaving the placebo. Common side effects seen with combination are insomnia, headache and nausea [68]. The combination is anticipated to move to phase 3 clinical trials.

8. **Bupropion plus Naltrexone:** Bupropion and naltrexone is the third combination consisting of existing drugs. The combination is being developed by Orixegen as Contrave. Bupropion increased levels of dopamine and norepinephrine which stimulates the neural activity of proopiomelanocortin (POMC). POMC then produce α-melanocyte (α-MSH) and β -endorphin. α-MSH leads to activation of the Melanocortin 4 Receptor (MC4R) which leads to increased energy expenditure and decreased appetite but β –endorphin causes autoinibition mechanism of POMC which may increase food intake.

   By inhibiting opioid receptors, naltrexone causes release of POMC by inhibiting β-endorphin and thus enhances synergistic effect with bupropion [69, 70]. Naltrexone sustained release (SR)/bupropion SR (Contrave) used for the treatment of obesity consist of naltrexone SR 32 mg and bupropion SR 360 mg.

   The combination had been tested in four randomized, double-blind, placebo-controlled, phase III trials namely COR-I, COR-II, COR-BMOD and COR-Diabetes [71] COR Diabetes was a 56-week RCT of 505 obese patients with type 2 diabetes were randomized and given naltrexone 32mg SR/bupropion 360 mg SR or placebo.

   The combination causes weight loss of 5.0% as compared with placebo of 1.8% at 56 weeks. In this phase 3 trial, 44.5% of patients achieved weight loss of ≥ 5% compared to 18.9% on placebo. It also causes improvement in HbA1C and other glycemic factors. In other trial, it causes reduction of weight loss in addition to improvement of depression disorders because of central effects. In COR-I, SR naltrexone of 16 and 32 mg/day were combining with bupropion SR of 360 mg/day, twice a day and tried in 1742 healthy, nondiabetic, obese patients. After 56 week study weight loss of 3.7% and 4.8% were seen in NB16 and NB 32, respectively.

   On the other hand in COR-II, combination of 32 mg/day of naltrexone SR and 360 mg/day of bupropion SR were tried in 1001 healthy, nondiabetic, obese patients. The weight loss seen is 5.2 %. Patient of more than ≥ 5 % weight loss in both studies are 48% and 56% respectively. Nausea is the most common side effects in these studies; others are constipation, vomiting, headache and dry mouth [72].

   Although approved by FDA, it was temporally rejected by the FDA in 2011 due to cardiovascular risk concerns so demanded more cardiovascular safety data for its commercialization. [73] Currently recruitment phase is in process for phase 3 clinical trials to prove its efficacy in cardiovascular outcomes (The Light Study) [74].

9. **Pramlintide and Metreleptin:** Amylin is a peptide hormone which binds to receptors in the hindbrain and increase satiety and decreased food intake. On the other hand, leptin is a neurohormone which binds to receptors in the hypothalamus and regulates energy homeostasis. Therefore, pramlintide, an amylin is combined with metreleptin, a recombinant methyl human leptin for greater weight loss than either drug alone [75]. In the preclinical studies, the combination of pramlintide and metreleptin showed synergistic effects on the drugs in reducing weight as well as reducing craving for food [76].

   In a clinical trail, 177 obese patients were tried with subcutaneous doses of single as well as combination of pramlintide and metreleptin. The study was for 24 weeks with doses of 5 mg of metreleptin twice a day, 360 µg of pramlintide twice a day and combination of pramlintide/metreleptin of dose 360 µg and 5 mg, respectively twice a day. At the end of the study weight loss was significant in combination than the single agents.

   The weight loss seen was 12.7% with the combination, 8.4% with pramlintide and 8.2% with metreleptin. Most common side effects seen in the study are nausea and pain at the injection site [75]. The combination is being developed by Amylin but the programme was terminated in phase 2 trials in 2011 due to the formation of antibody [63].

CONCLUSION: Obesity is a chronic disease with many co-morbid lifestyle disorders so the therapy has to be continued for long duration. Pharmacotherapy of obesity with lifestyle changes (restricted diet, physical activity and behavioural modifications) may promote weight loss. Successful weight loss can be done by decrease food intake, depressing appetite, decrease absorption of nutrient and energy expenditure.

There are many single and dual agents which are in various phases of clinical trials and in future, with their approval may widen the pharmacotherapy of obesity. Several new compounds are currently in late stage testing and are poised to take their place alongside the ranks of the currently approved antiobesity drugs.

Orlistat is the only drug available in the market but with the approval of lorcaserin and combination of phentermine and topiramate by US FDA have added more promise in the field of obesity. One of the barriers in the therapy of obesity is that if the drug is discontinued then patient may regain weight and there is always safety concern associated with the drug.

Many drugs introduced in the market having potential as anti-obesity but were withdrawn from the market after post-marketing surveillance as they have health hazards affecting different system of the body, mostly central nervous system and cardiovascular system. The combination therapies bupropion with naltrexone and bupropion with zonisamide have great potential for effective weight loss.

Thus, to meet the demand for effective antiobesity pharmaceutical agents, many companies are currently developing novel drugs with emphasis on weight loss and decrease adverse effects.

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