THINK INDIA JOURNAL

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Comparative Studies on FDA Approved Anti-Obesity Drugs: A Review

Pooja Rani, Keerti Bhardwaj, IqbaljitKaur

Department of Pharmaceutical Sciences, School of Pharmaceutical Sciences, Lovely Professional University

Abstract

Obesity is a life cycle disorder which increasing day by day. It occurs due to accumulation of the fat in the body. Now it is known about 'New World Syndrome'. It is measure by body mass index. Body mass index (BMI) is the classification of the obesity in different parameters. If the BMI is more than 30 then person has the obesity syndrome. Obesity causes many non-communicable diseases in the person. It is more seriously disease in the public which includes many other diseases like stroke, high blood pressure, type 2 diabetes mellitus, depression, less sleep, respiratory problems, cancer. It may cause death of the person also. It causes due to genetics, environmental factors, imbalance in the diet, hormones, more sleeping, less physical activity. Then it is necessary to management of this disease. Obesity can manage by physical activity, low calorie diet, low fat diet, medication. There are so many medicines for the management for the obesity names desoxyn, Topamax, phentermine, orlistat, sibutramine, etc. many of the anti-obesity drug has banned due to their side effects on the patient. Food and drug administration (FDA) newly approved 5 anti-obesity drugs. The drug names are: Oritstat, Lorcaserin, Liraglutide, Phentermine/Topiramate, Naltrexone/Bupropion. In this review we will discuss the mechanism, effects, cost, dosage forms, the combination of the drugs and therapeutic profile of the approved drugs.

Key words: *Obesity, FDA, Lifestyle disorders, Weight management*

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Introduction

Obesity

Obesity is a health condition of excessive fat accumulation in the adipose tissue of the skin and weight gain above the bodyweight [1]. Obesity is measured by the Body Mass Index (BMI). When a BMI occurs between 25and 30 indicates that a person is carrying excess weight and if a person has BMI more than 30 then it indicates that person may have obesity disease.[2] It is caused by excessive food intake, lack of physical activities, genetic susceptibility, mental disorders.[3]Obesity is a common disease which may leads many other diseases like type 2 diabetes, cancer, stroke, high blood pressure, kidney, pregnancy problems, sleep apnea.[4]

This disease can be managed by physical activities, with healthy diet and special medication. Several diets are helpful maintaining the obesity like low carbohydrate diet.[5] There are so many anti-obesity medications for the managing the obesity like Topamax, Desoxyn, Contrave, Alipex P, Orlistat, Belviq, Lorcaserin, Phentermine, etc.[6]

WHO

It is defined as the world health organization which is a part of united nations which works on the global health issues. It works on many health issues like AIDS, family planning, maternal morbidity rates, polio eradication, childhood immunizations, smallpox.[7]

FDA

It is define as the food and drug administration which is an agency within the U.S. Department of Health and Human Services (HHS). It control the manufacturing and distribution of food, pharmaceuticals, medical devices, tobacco and other consumer products and veterinary medicine.[8]

FDA newly approved anti-obesity drugs:

- Lorcaserin (Belviq)[9]
- Orlistat (Xenical, Alli)
- Liraglutide (Saxenda)
- Bupropion/neltrexon(Contravave)
- Phentermine-Topiramate (Qsymia)

ISSN:0971-1260
Vol-22-Issue-37-December -2019

In this review we will discuss about these newly FDA approved anti-obesity drugs. There will be a discussion of efficacy, side effects, delivery system, cost effectiveness and which drug will more effective and have more bioavailability from newly approved 5 anti-obesity drugs.

Review of literature

OBESITY

Obesity is a major health problem where a accumulation of fat in the body. [1] It is harmful diseases which increases the risk of another diseases and health problems like diabetes, high blood pressure, stroke, cardiac disease, depression.[4]

It is described and measure by body mass index (BMI).[10] BMI is the body mass divided by the square of the body height. Its units are expressed by kg/m. Mass in kilograms and height in meters. If pounds and inches are used then 703 conversion factors is used.

$$\mathrm{BMI} = \frac{\mathrm{mass_{kg}}}{\mathrm{height^2_m}} = \frac{\mathrm{mass_{lb}}}{\mathrm{height^2_{in}}} \times 703$$

`BMI	**Weight status** [11]
Below 18.5	underweight
18.5-24.9	normal
25.0-29.9	overweight
30.0- and higher	obesity

Etiology

Causes

There are so many causes of obesity:

- High calories
- Lack of physical activity
- Poor diet
- Genetics
- Medical reasons
- Aggressiveness
- Smoking
- Environmental
- Sedentary life style [12]

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Health risk of obesity

- High blood pressure
- Increase level of cholesterol
- Diabetes
- Cancer [14]
- Increase heart disease
- Stroke
- Renal disease
- Sleep apnea
- Menstrual irregularities
- Physiological burden
- Gallbladder [15]

Pathophysiology of obesity

Increasing in the volume of skeleton muscles, liver and other body organs and tissues occur due to excess secretion of lipids, mainly triglycerides with conjugation the adipose tissues. If obese person or overweight person compared with the normal person they have large mas, large fat with cardiac output, hypertension, great pancreatic mass. [16] When glucose load increases and insulin secretion is in fasting state then BMI increases. When person get obese then large amount of the lipids in the tissues distributes in the different compartments of the body. Most of the lipid stored in the subcutaneous adipose tissues with different anatomical sites with different physiological and metabolic pathways. [17]

In the subcutaneous tissues there are white adipocytes, brown adipocytes and beige adipocytes.

White adipocytes: It stores the high level of triglycerides and large amounts of intracellular droplets. [18]

Brown adipocytes: It has the multiple lipid droplets, uncoupling protein 1- containing mitochondria which activates the heat through sympathomimetic nervous system. [18]

Beige adipocytes: It contains the multiple lipid droplets, uncoupling protein 1- containing mitochondria and progenitor cellular region. It is also known as 'brite' (brown and white adipocytes). [18]

In blood pressure: hypertension occurs with the renal compression in the obese person when adipose tissues cover or surrounds the kidney. [19]

Sleep apnea: In obesity the pharyngeal soft tissues increase and it blocks to the airways during the sleeping. [19]

Osteoarthritis: When mechanical load occurs on the joints due to the excess adiposity cause the osteoarthritis. [20]

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Gastroesophageal reflux disease: When intraabdominal pressure occurs or increase then it causes the gastroesophageal disease. [21]

Management of obesity

Dietary modifications

Patient should follow the health balanced diet. Patient should increase vegetables and fruits intake, healthier snakes with decreasing the drinks with high sugar content, fruit juices, soft drinks. [22]

Low fat diets

Low fat diets helps in the weight loss and obesity. Fat diet should be in limited which helps to reduce the energy intake in the body to the tissues. [23]

Low calories diet

Low calorie diet helps to reduce weight until 8% total of the body mass. Patient should take less calorie food. It also helps in the control of diabetes. [24]

Physical activity

It is important obesity management factor which helps to reduce body quickly than other management factors. It also decreases the risk of heart disease, high blood pressure. [25]

Behavioral modification

It includes the social support, self-monitoring, Stress management. Behavioural treatment helps to the patient weight loss and helps in the identification of patterns like physical activities, eating and thinking habits. [26]

Pharmacological management

Most of the modifications of lifestyle help to the obesity patient in management of obesity. Drugs of obesity should use with diet modifications, physical activity.[27]

Drugs considered for anti-obesity action[29]

Class of the drugs	**Example**
Lipase inhibitor	Orlistat, cetilistat
Serotonergic agents	Non selective: Fenfluramine, Dexfenfluramine. Selective: lorcaserine
CB1receptor antagonist	Rimonobant, taranabant, otenabant, surnibant, ibipinabant
Centrally acting	NE release/ NE reuptake inhibitor:

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Sympathomimetic (Amphetamine derivatives)	Phentermine, diethylpropion, desoxyephedrine NE & 5HT reuptake inhibitor: sibutramine

Banned drugs of obesity:

SIBUTRAMINE: This anti-obesity drughas banned before the past two years. It is majorly used in the diabetes and obesity disease. It's manufacturing and sales is bane due to its side effects and including heart attacks in consumers. The combination and related various brands related to sibutramine are also banned by the Indian government. [30]

RIMONABENT: This drug is banned by food and drug administration (FDA). It is banned due to its serious psychiatric side effects and it includes suicidal tendencies among the consumers. This drug is also known with names like silmona, acopmolia, monaslim, bethin. [31]

FDA newly approved 5 anti-obesity drugs

Food and drug administration (FDA) is a United State agency which is the department of human health services. This agency ensures the quality, safety, efficacy, purity, sales of the food and drugs in the united states. [36]

Obesity is a health disorder and it has a challenging treatment. There are many drugs have been banned in the market due to their side effects. After few years interruption the FDA agency approved new anti-obesity drugs. [37]

Approved anti-obesity drugs:

- Orlistat
- Lorcaserine
- Liraglutide
- Phentermine/topiramate (Qsymia)
- Naltrexon/bupropion (Contravave)

ORLISTAT

In 1990; It was initially approved and It was the only approved anti-obesity drug by FDA until 2012. Since it has available non-prescription drug in U.S.A in 2007.

Therapeutic profile of the drug:

Molecular formula	495.73 g/mol[38]
Chemical formula	C_{29} H_{55} NO_5[39]
IUPAC name	N-Formyl-L-leucine (1S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester[40]

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Synonym	Alli, Xenical
Oral absorption	It has systemic absorption is minimal, drug is not needed for activity.
Pharmacology	It is a lipase inhibitor which manage the obesity by inhibiting the absorption of dietary fat
Protein binding	99%
Route of elimination	Fecal excretion [41]
Metabolism	Metabolized in the gastrointestinal wall with inactive metabolites
Half life	1 to 2 hours [42]

Dosage form: tablet, capsules

Bioavailability: less than 1%

Adverse effect: abdominal pain, Urgent bowl movement, flatulence[44]

2.3.2 LIRAGLUTIDE

It is approved in the Europe state in 2009 and in United State it is approved in 2010.This medicine is used to treat the diabetes mellitus 2 and obesity. It is soled in the market under the name brand called Victoza. This drug given subcutaneously under the skin.[45]

Molecular weight	3751.2 D [46]
Chemical formula	$C_{172}H_{265}N43O_{51}$
Synonym	Liraglutide, liraglutidum, xultophy[47]
Oral absorption	After subcutaneous injection it's bioavailaility is in the body near to 55%
Pharmacology	It is an agonist of glucagon like peptide-1, it coupled with adenylatecyclase, Camp stimulate the insulin secretions and inhibit the release of glucagon. [48]
Route of administration	5% excreted by feces 6% excreted by urine [49]

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Metabolism	Slowly metabolized by dipeptidyl peptidase-4 and neutral endopeptidase to different polypeptide. It may be metabolized to carbon dioxide and water. [50]
Half life	13 hours
Protein binding	>98%
Adverse effect	Headache, dizziness, nausea, [51] vomiting, indigestion, Upset stomach

Dosage form: injection (subcutaneous), Solution form [52]

Bioavailability: 55%[53]

2.3.3LORCASERIN

This drug is currently marketed with the name of the brand **Belviq**. It is use long term for the treat obesity. [56]Sometimes this drug is used to obesity that related to high blood pressure, cholesterol, diabetes.

Molecular weight	195.69 g/mol
Chemical formula	$C_{11}H_{14}ClN$
Synonym	Lorqess
Oral absorption	Peak plasma concentration is about 1.5-2 hours [57]
Pharmacology	Exactly mechanism of action is not known but it is believed that it decreases food consumption and activating the 5-HT2C receptor anorexigenic (POMC) po-opiomelanocortin neurons located in the hypothalamus. [58]
Pharmacodynamics	It reduces the weight within 12 weeks when taken with balanced food consumption [59]
Route of elimination	Mostly eliminated through urine (92.3%) and through feces (2.2%)
Metabolism	It has the hepatic metabolism which produce inactive componds[58]
Half life	approximately 11 hours

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Protein binding	Approximately 70% [60]
Adverse effects	Headache, nausea, cold body pain, Seizures, bloody urine [61]

Dosage form: Tablet, film coated [63]

Bioavailability: Not determined

Phentermine/Topiramate Combination (Qsymia)

Phentermine: It was approved by FDA in 1959 for short term management of anti-obesity.

It is a combination of fenfluramine and dexfenfluramine. This drug is chemically belong to amphetamine. [64]

Molecular weight	Hydrochloride salt (185.7) free base (149.2) [64]
Chemical formula	$C_{10}H_{15}N$ [64]
Synonym	Fentermina Phentermine resin
Oral absorption	It shows dose dependent pharmacokinetics. maximal concentration achieved after 6 hours when administered the drug. [65]
Pharmacology	This drug release dopamine and serotonine. It triggers the release of monoamine and help to reduction of hunger perception. [65]
Route of elimination	Mainly excreted through urine about 70-80%
Metabolism	It has a conjugation of N- hydroxylation, P-hydroxylation and N- oxidation. N- oxidized and N- hydroxylated show its 5% metabolism. [66]
Half life	Approximately 20 hours but if there is acidic urine then 7-8hours
Protein binding	17.5%[67]
Adverse effect	Chest pain, decrease ability of exercise, Dizziness, numbness, swallowing in the feet [68]

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Dosage forms: Tablet, capsules

Bioavailability: Consumption of high fat meal does not affectes the bioavailability[69]

Topiramate:

It is present in the market with the brand name **Topamax**. It is used for migrains, epilepsy and also used for alcohol dependence.[70] It is also used for the treatment of mood disorders.

Molecular weight	339.36 g/mol[71]
Chemical formula	$C_{12}H_{21}NO_8S$[72]
Synonym	Tipiramate, tipiramato Topiramato[73]
Oral absorption	Drug absorbed rapidly. The administration of the meal changes the absorption rate.[74]
Pharmacology	It has different mechanism of action includes GABA receptor, glutamate receptors, voltage dependent sodium channel. It decreases the glutamate activity in AMPA and also reduce the dopaminergic activity.[74]
Route of elimination	Its elimination with renal clearance. 80% of the drug unchanged in the urine.[75]
Metabolism	When drug administered the metabolism of topiramate acts only 20%. Hydroxylation, Glucuronidation and hydrolysis are characterized the restricted metabolites which produces other metabolites.[76]
Half life	19-23 hours.
Protein binding	About 15% [74]
Adverse effect	Anxiety, diarrhea, diplopia, nervousness, Memory impairment, lack of concentration.[77]

Dosage form: Tablet, capsule

Bioavailability: 81-90%

Mechanism of action of topiramate/ phentermine: decrease Appetite and increase Leptin[79]

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Side effect of the combination: Dry mouth, Constipation, paraesthesia, heart attack.

According to Australian experiment the Topiramate and phentermine combination was not tolerated by the several patients because of their adverse effects. [79]

Naltrexon/bupropion (Contravave)

This combination is managed the obesity or overweight with the obesity related problems like high blood pressure, stroke, cholesterol. [80]

Naltrexon:

This drug is in the market under the name of ReVia and vivitrol. It is used for the alcohol or opioid dependence. This drug is related to methylnaltrexone. [81]

Molecular weight	377.86 g/mol
Chemical formula	C20H23NO4•HCl [82]
Synonym	Naltrexone Naltrexonum
Oral absorption	Well absorbed orally. [83]
Pharmacology	It is opiate antagonist, not agonist. It binds compitatively with m, k receptors in CNS and blocks the endogenous opiods. [84]
Route of elimination	Through kidney 53-79%, through urine 2%
Metabolism	When taken orally it undergoes to the biotransformation and metabolized with 6 beta- naltrexone. [85]
Half life	4hours of naltrexone and 13 hours of metabolite 6 beta-naltrexon. [85]
Protein binding	21% binds with plasma protein
Adverse effects	Weakness, tiredness, Insomnia, joint aches, Restless, nervousness [86]

Dosage form: Tablet

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Bioavailability: 5-40%

Bupropion:

It is present in the market name under wellburtin and zyban. It is used for depressive disorder and stop smoking.

Molecular formula	239.74 g/mol[87]
Chemical structure	$C_{13}H_{18}ClNO$[88]
Synonym	Amfebutamone
Orally absorption	Immediate release formulation= absorption taking 2 hours Sustain release taking 12 hours Extended release taking 5 hours [89]
Pharmacology	It inhibit the enzymes which uptake the neurotransmitter of norepinephrine/dopamine and binds the norepinephrine transmitter and dopamine transmitter. [90]
Metabolism	It metabolized in the humans with three metabolites: hydroxybupropion, theohydrobupropion, Erythrohydrobupropion[89]
Route of elimination	Elimination through urine metabolites
Half life	24 hours
Protein binding	84%
Adverse effects	Headache, constipation Dizziness, confusion, Tachycardia. [90]

Dosage form: Tablet

Naltrexon/Bupropion mechanism: mechanism of this combination is not properly known but in CNS pathway regulate the food intake and target the hypothalmusmelanocortin system and mesolimbic reward system. This combination targets these systems. Bupropion stimulates the POMC (pro-opiomelanocor) neurons and naltrexone blocks the autoinhibitory feedback for reducing the weight. [91]

ISSN:0971-1260
Vol-22-Issue-37-December -2019

This combination is beneficial for long term treatment of obesity.[91]

Conclusion:

Obesity is a most serious disease which includes many other non-communicable diseases. It is complicated disease and it is a challenge for the practitioners to treat this obesity. From this review we observe that all of the 5 approved anti-obesity drugs the Liraglutide has better bioavailability and in combination the naltrexone/ bupropion is better for obesity treatment.