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DRUG THERAPY IN OBESITY CURRENT AND EMERGING TREATMENTS

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ABSTRACT
Obesity is a growing global health problem, leading to serious conditions like numerous chronic diseases, including type 2 diabetes, cardiovascular disease, and certain cancers. While lifestyle changes like diet and exercise are important, many people need medication to help with weight loss. Currently, several drugs are approved for treating obesity, including GLP-1 receptor agonists (e.g. naltrexone-bupropion,) and combinations like phentermine-topiramate. These medications help with weight loss by reducing hunger, increasing feelings of fullness, and improving metabolism. New treatments are also being developed, such as drugs that target different hormones or gene-based therapies, offering hope for even more effective solutions. This review covers the current obesity drugs, how they work, and what new treatments might be available in the future

KEYWORDS: *Amylin mimetics, Gherlin antagonist , GLP-1 receptor agonists,Leptin analogues,obesity*

1.INTRODUCTION[1]

Obesity are defined as abnormal or excessive fat accumulation that presents a risk to health.
The condition significantly increases the risk of developing chronic diseases, such as type 2 diabetes, cardiovascular disease, and certain cancers, resulting in substantial morbidity, mortality, and economic burden.
A body mass index (BMI) over 25 is considered overweight, and over 30 is obese.
These ranges of BMI are used to describe levels of risk:
1.Overweight (not obese), if BMI is 25.0 to 29.9.
2.Class 1 (low-risk) obesity, if BMI is 30.0 to 34.9.
3.Class 2 (moderate-risk) obesity, if BMI is 35.0 to 39.9.
4.Class 3 (high-risk) obesity, if BMI is equal to or greater than 40.0.

❖ **BMI Calculate Formula**

$$BMI = \frac{\text{Weight (in kilograms)}}{\text{Height}^2 \text{ (in meters)}}$$

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Fig.1 Obesity

Obesity is the modern epidemic, generally defined as a body mass index (BMI) of 30 kg/m² or higher, though a BMI of 27.5 kg/m² or more defines obesity in Indian populations. In 2022, 70 million adults in India were living with obesity, with nearly twice as many women as men: 44 million women and 26 million men. Among children aged 19 and under, 5.2 million girls and 7.3 million boys were obese.

Obesity costs India Rs 2.8 lakh crore a year, over 1% of its GDP, according to a study. Overweight and obesity, the two common lifestyle problems affecting nearly 17% of India's population, are estimated to be costing the country $35 billion (Rs 2.8 lakh crore) annually.

The obesity rate in India has risen significantly, from 1.2% in 1990 to 9.8% in 2022 for women, and from 0.5% to 5.4% in 2022 for men. A Lancet study reveals alarming obesity rates in India, with 70% of the urban population being overweight. India ranks third globally in obesity, following the US and China.

According to a report by IMARC, a market research company, the size of the weight management market in India reached Rs 1.72 lakh crore in 2022 and is expected to grow to Rs 3.15 lakh crore by 2028.

Globally, in 2022, 1 in 8 people were living with obesity. The global adult obesity rate has more than doubled since 1990, and adolescent obesity has quadrupled. In 2022, 2.5 billion adults (18 years and older) were overweight, of which 890 million were living with obesity.

A BMI of less than 18.5 suggests underweight, between 18.5 and 24.9 suggests a healthy weight range, between 25 and 29.9 may indicate overweight, and a BMI of 30 or higher may indicate obesity.

- **MEASUREMENT OF OBESITY**

1. BMI
2. Wait Hip Ratio
3. Skin Fold Thickness
4. Air Displacement Plethysmography
5. Total Body Electrical Conductivity

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➢ TYPES OF OBESITY[4]

1. Inactivity Obesity
2. Food and Stress Obesity
3. Anxiety Obesity
4. Venous Obesity
5. Gluten Obesity
6. Atherogenic Obesity

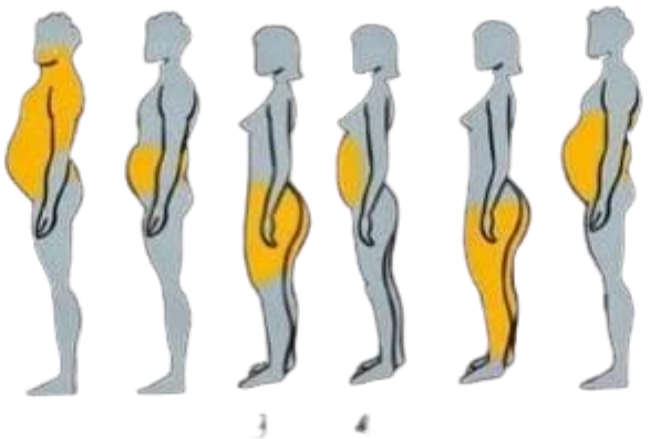

Fig.2 Types of Obesity

1. **Inactivity Obesity**
It is no secret that a lack of physical activity can cause you to become overweight. In this type of obesity, once-strong parts of the body quickly gain fat and become unhealthy.

2. **Food and Stress Obesity**
If you overeat, and particularly if you overindulge in unhealthy foods, you may suffer from food obesity.

Excessive sugar intake can also cause food obesity, which may lead to accumulation of fat around the middle part of the body.

3. **Anxiety Obesity**
Anxiety or depression can often lead to overeating and accumulation of fat in the body, since the body must constantly survive in fight-or-flight mode.

To treat this type of obesity, you must control your anxiety.

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4. **Venous Obesity**

Venous circulation is one obesity cause that is genetic in nature, rather than habitual in nature. This type of obesity is particularly common in pregnancy.

Exercise is the best solution for this problem.

5. **Gluten Obesity**

You are likely no stranger to the many health problems that gluten can cause. In fact, gluten can actually cause obesity.

This type of weight gain is most common in women.

6. **Atherogenic Obesity**

People whose fat tends to accumulate in the stomach area often suffer from Atherogenic obesity.

This is a particularly dangerous condition since it can affect your other organs and lead to breathing problems.

- **CAUSED BY OBESITY**

1.Types 2 Diabetes
2.Heart Disease
3.Hypertension
4.Stroke
5.Liver Disease

- **RISK FACTOR[5]**

Several Factors Are Responsible For Obesity :
1.Behavioral And Lifestyle Factors
2.Diseases
3.Mental Illness
4.Genetics

- **MANAGEMENT OF OBESITY[18]**

1.Healthy Eating
2 Exercise
3.Behavioral Changes
4.Medications
5.Bariatric Surgery
7.Monitor Progress

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2.LITERATURE SURVEY

1. Eka Molson et.al publish 1 February 2024: Obesity is a chronic disease associated with increased risk of obesity-related complications and mortality, the currently approved GLP-1 RA treatments.
2. P. Sumatran et.al 2 June 2024: The aim of this narrative review is to synthesize the available data describing the efficacy and safety of medications approved for obesity management and to provide an overview of upcoming agents in development.
3. Hae Woon et.al Jung 20 June 2024: In children and adolescents, the prevalence of overweight and obesity continues to increase, especially in classes II and III, and in younger toddlers and preschool aged children.
4. Mareana Abdel Malek et.al Published 30 May 2023: Substantial leaps have been made in the drug discovery front in tackling the growing pandemic of obesity and its metabolic co-morbidities.
5. David M. Williams et.al Published 15 April 2020: Whilst the prevalence of obesity continues to increase at an alarming rate worldwide, the personal and economic burden of obesity-related complications become severs more important.

3.AIM AND OBJECTIVE

❖ **AIM**

Drug Therapy In Obesity Current And Emerging Treatments

❖ **OBJECTIVES**

❑ Primary Objectives

1. To review the current landscape of pharmacological treatments for obesity.
2. To assess the efficacy and safety of emerging treatments.
3. To identify novel targets and mechanisms for obesity treatments.

❑ Secondary Objectives

1. To evaluate the clinical trials and regulatory approvals of current and emerging treatments.
2. To analyze the combination therapies and potential synergies.

❑ Specific Objectives

1. To examine the pharmacology and mechanisms of action of current treatments (e.g. Bupropion, phentermine-topiramate).
2. To investigate the efficacy and safety of emerging treatments (e.g., Amylin mimetics.)

4.PLAN OF WORK

Data Collection

Selection Criteria

a. Randomized controlled trials (RCTs), cohort studies, and meta-analyses focused on weight loss medications.
b. Studies that assess the impact on comorbid conditions, quality of life, and long-term weight management.
c. Pharmacokinetic and pharmacodynamic data on emerging therapies.

Data Analysis

Statistical analysis to compare the efficacy of different drugs based on weight loss outcomes (e.g., percentage of body weight lost, changes in BMI).

Safety analysis to evaluate the side effect profiles of existing and emerging treatments.
Subgroup analysis to identify which patient populations benefit the most from specific drug therapies.

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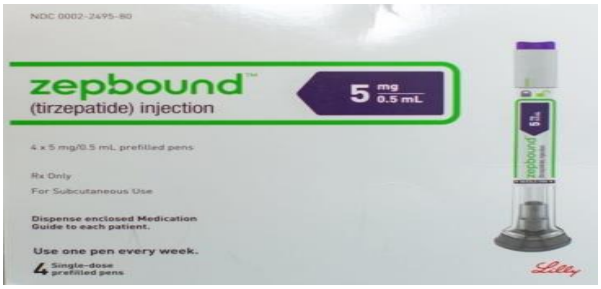
5.CURRENT AND EMERGING DRUG THERAPIES FOR OBESITY[8]:-

1. Bupropion/Naltrexone (Contrave, Mysimba)

Approved by the FDA in 2014, this combination of an opiate antagonist and a dopamine and noradrenaline reuptake inhibitor is intended for adults who are overweight or obese. It can lead to increased energy expenditure and reduced food intake.

Fig.3Bupropion/Naltrexone(Contrave,Mysimba)

2. Tirzepatide (Zepbound)



A dual agonist at GLP-1 and glucose-dependent insulinotropic peptide (GIP) receptors, this drug is administered as a weekly injection. It may reduce caloric intake, increase glucose and triglyceride uptake, and increase insulin sensitivity.

Fig.4 Tirzepatide (Zepbound)

3. Retatrutide

This drug has shown to be effective in reducing body weight and improving lipid profiles and blood pressure.

Other drugs that are currently approved for obesity treatment include: orlistat and phentermine/topiramate extended release.

Fig.5 Retatrutide

4. Orlistat

Orlistat is a selective inhibitor of pancreatic lipase, which thereby moderates the intestinal digestion and absorption of fat, approved for use both the FDA and EMA.

Fig.6 Orlistat

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Table 1 A comparison of approved weight loss therapies in obesity

Drug	Mechanism of action	Dosing	Approving bodies	Weight loss	Side effects
Naltrexone/bupropion	Dopamine and noradrenaline reuptake inhibitor (bupropion); Opioid receptor antagonist (naltrexone)	32 mg/360 mg 2 tablets Four times daily	FDA (2014) EMA (2015)	20-25% Body weight per year	Nausea/ vomiting, headache, dizziness
Tirzepatide (Zepbound)	Gastric inhibitory polypeptide) and GLP-1 (glucagon-like peptide-1) receptor agonist.	2.5 mg or 15 mg weekly	FDA (2022) EMA (2023)	12-22% Body weight per year	Nausea Vomiting Diarrhea
Retatrutide	GIP receptor agonist (gastric inhibitory peptide)	2.5mg or 5mg weekly	FDA (2022) EMA (2023)	15-20% Body weight per year	Nausea Vomiting Diarrhea
Orlistat	Pancreatic lipase inhibitor	60-120mg three times daily	FDA (1999) EMA (1998)	2.9-3.4% Body weight per year	Steatorrhea,fa ecal urgency

Compares the mechanism or action, dosing, efficacy and more common side effects of already approved drug therapies used to support weight loss in obesity.

➢ OTHER EMERGING THERAPEUTIC TARGETS[31]

1.Amylin Mimetics

Amylin is a neuroendocrine peptide co-secreted by pancreatic b-cells postprandially with insulin and acts to inhibit glucagon secretion, reduce gastric emptying and centrally induce satiety.

The amylin analogue pramlintide was licensed by the FDA in 2005 for patients with insulin-treated diabetes. Early studies reported that pramlintide use in people with insulintreated diabetes is associated with improved glycaemic control and may support weight loss by reducing food intake.

A subsequent trial in obese patients with either non-insulin treated T2D or without T2D found an additional mean weight loss of 3.7 kg versus placebo.

Co-administration of pramlintide with either the sympathomimetic sibutramine or phentermine was observed to result in 9.2 kg weight loss compared with placebo over 24 weeks,whereas pramlintide monotherapy resulted in just 1.5 kg additional weight loss.

2. Leptin Analogues

Leptin is a 167 amino acid secreted by white adipose tissue, which promotes satiety and increases energy expenditure via stimulation of hypothalamic POMC neurons and inhibition of neuropeptide Y neurons. Overfeeding and high total body fat stimulate release of leptin, whilst the fasting state and low-fat stores inhibit leptin secretion.

People with leptin gene mutations are obese secondary to pronounced hyperphagia and satiety and body weight can be regulated in people with these genetic mutations with leptin treatment.
As such,there is a good rationale for leptin analogues in the treatment of obesity.

3.Ghrelin Vaccines and Antagonists

Ghrelin is the only known orexigenic peptide hormone and is secreted by the stomach and proximal small intestine. Conversely to the hormone leptin, ghrelin stimulates neuropeptide Y neurons and inhibits hypothalamic POMC neurons .
As ghrelin induces hunger,inhibition of the ghrelin receptor represents an attractive therapeutic target in obesity.
Ghrelin receptor antagonists and vaccines have shown promise with reduced food intake and body weight in pre-clinical studies.

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6.EVALUATION TESTS[21]

1.Bupropion/Naltrexone (Contrave, Mysimba)

Fig.7 Bupropion/Naltrexone (Contrave, Mysimba)

Bupropion Tablet Evaluation Test

1. **Physical Appearance**
- **Shape, size, and color:** Check if the tablet looks as described (e.g., round, white, imprinted).
- **Surface quality:** Ensure tablets are smooth and free from cracks or chips.

2. **Weight Uniformity**
- **Test:** Weigh a sample of 20 tablets.
- **Pass Criteria:** The weight of each tablet should be close to the average (within ±5% of the average weight).

3. **Hardness Test**
- **Test:** Measure how hard it is to crush the tablet.
- **Pass Criteria:** The tablet should have enough strength to resist breaking, typically **4-8 kg**.

4. **Friability Test**
- **Test:** Tumble a sample of tablets to check if they break easily.
- **Pass Criteria:** Tablets should not lose more than **1%** of their weight.

5. **Disintegration Test**
- **Test:** Place tablets in water and see how long it takes for them to break apart.
- **Pass Criteria:** Tablets should disintegrate within **15-30 minutes**.

6. **Dissolution Test**
- **Test:** Measure how quickly the active ingredient (Bupropion) is released into a solution (mimicking stomach conditions).
- **Pass Criteria: >80%** of the drug should dissolve within **30 minutes**.

7. **Content Uniformity**
- **Test:** Check if each tablet contains the correct amount of Bupropion.
- **Pass Criteria:** The amount of Bupropion should be between **90-110%** of the stated dose.

8. **Stability Testing**
- **Test:** Store the tablets at different temperatures and check if they stay effective over time.
- **Pass Criteria:** The tablets should remain stable and not degrade significantly over their shelf life.

9. **Side Effects (Patient Monitoring*)***
- **Test:** Monitor patients for any unwanted effects (e.g., insomnia, dry mouth).
- **Pass Criteria:** Side effects should be manageable and not severe in most patients

➢ Sure! Here's a **simplified evaluation test** for **Bupropion tablets** in a pharmaceutical context. This focuses on basic quality control and performance tests to ensure the tablet is safe and effective:

➢ COMBINATION WITH MEDICATION[12]

A treatment plan for obesity typically includes a combination of diet, exercise, and lifestyle changes:-

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1. DIET

Fig.8 Diet

Reduce the number of calories you consume each day. A low-calorie diet can involve reducing your daily caloric intake by 500–1000 kcal/day. You can also try eating more slowly and being mindful of what and when you eat.

2. EXERCISE

Fig.9 Exercise

Get at least 150 minutes a week of moderate-intensity physical activity. This could include activities like walking, jogging, swimming, or tennis**.**

3. EVERYONE CAN TAKE STEPS TO:

A. Eat healthy foods and drink healthy beverages.
B. Get the recommended amount of physical activity.
C. Get enough sleep.
D. Manage stress.
E. Talk to your health care provider about whether weight is a health concern.

Your plan will likely include reducing the number of calories you eat each day, getting more physical activity, and adopting lifelong healthy lifestyle changes. The goal of your treatment plan is to reduce your risk of obesity-related complications and improve your quality of life.

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7. SCOPE OF THE STUDY

This review covers the current and emerging drug treatments for obesity. It looks at the medications that are already approved, such as GLP-1 receptor agonists (like bupropion-naltrexone) and combinations like prevention, focusing on how they help with weight loss and improve metabolic health. It also discusses new treatments being developed, including drugs that target different hormones or genes, offering hope for more effective solutions. The review aims to explain how these treatments work, their benefits, and their potential for helping people who struggle with obesity, especially those who haven't had success with diet and exercise alone. It also considers safety and how different therapies might work together in the future.

8.CONCLUSION

- The obesity pandemic continues to grow at an alarming rate. Because lifestyle modifications have been limited in their success in weight loss maintenance, pharmacotherapy plays an important role in achieving clinically significant weight loss and preventing the development or exacerbation of comorbid conditions.
- Obesity is a chronic, relapsing, multifactorial disease, which has become a serious threat to public health globally, and is associated with a higher incidence of a number of diseases, including CVD, T2DM and cancer.

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