International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 13, No. 11, November 2024 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_13.11.2024.20

ORIGINAL RESEARCH

Approved Anti-Obesity Drug in India- an Updated Systematic Review

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Received date: 17 August, 2024 Revised date: 21 September, 2024 Acceptance date: 30 October, 2024

ABSTRACT

Background: In recent times, the "epidemic of obesity" arose as one of the major global health apprehensions. Since lifestyle amendments alone are often perplexing and inadequate for the maintenance of weight reduction, pharmacotherapy should be considered in an appropriate manner for obesity patients with weight-related comorbidities. Recent advances in anti-obesity medicines have enabled the eventuality of achieving clinically significant weight loss. Still, they've a high cost and may beget adverse issues depending on the existent patient. Our study also sheds light on various long term studies done in comparision of tirzepatide with other anti-obese drugs. Our review provides an overview on the currently available and FDA approved anti-obesity medications along with the only anti-obesity drug Tirzepatide, approved recently by Central Drug Standard Control in India in June 2024. Based on many studies Tirzepatide was better compared to other drugs in terms of weight reduction and maintenance of lost weight.

Key-words: Obesity, Tirzepatide, Anti-Obesity Drug, Semaglutide

Key Messages: Obesity is the 5th principal cause of mortality worldwide. Obesity causes dysregulation of complex communications between the brain and other organs, such as the gastrointestinal system, muscles, fat cells and also affects individuals quality of life. Existence of overweight or obesity hikes the risk of medical, economic and social problems. This review provides an overview on the currently available and FDA approved anti-obesity medications along with the recently approved anti-obesity drug Tirzepatide and its side effects

INTRODUCTION

Obesity is the 5th principal cause of mortality worldwide. Obesity is a routine disease concomitant with the lack of an individual's ability to accept healthy habits. Nevertheless, factors, such as genetic, environmental, behavioral (unnecessary calorie intake, stress, insomnia), and sociocultural factors, can disturb the development of excess fat in the body.[1] Even though certain risk factors are adjustable, others are difficult to control. Some exemplifications of adjustable threat factors for obesity include lifestyle and behavioral factors such as poor food habits, sleep deficit, inactive lifestyle, and inordinate weight and socioeconomic factors. Non-adaptable risk factors for obesity, on the other hand, include genetics, macrosomia at birth, gender, race, and age.[2] Extreme weight gain represents dysregulation of complex communications between the brain and other organs, such as the gastrointestinal system, muscles, and fat cells (adipose tissue). The excitatory or suppressant portion involves appetite and energy expenditure involving hormones, neurotransmitters, and genes that are caught up in the development of obesity.[3]

Existence of overweight or obesity hikes the risk of medical, economic and social problems. Excessive body weight is associated with cardiovascular disease (CVDs), stroke, type 2 diabetes mellitus (T2DM), hypertension, chronic kidney disease (CKD), gastroesophageal reflux disease (GERD), polycystic ovarian syndrome (PCOS), infertility, obstructive sleep apnea (OSA), and fatty liver disease. Modest weight loss can reduce the risk of chronic diseases.[4] The World Health Organization (WHO) customs the body mass index (BMI) to describe obesity in adults. BMI was used to classify the persons into diverse classes based on weight and height. Persons with a BMI of 25–29.9 are deliberated as overweight, while those with a BMI of 30–39.9 are well thought-out obese.[5]

Diet and exercise are recommended as the initial interventions for overweight patients; they help to lose 3–5% of their weight. The influence of diet alone on

DOI: 10.69605/ijlbpr_13.11.2024.20

weight reduction is restricted by the counter-regulatory hunger hormone, ghrelin, which brings the lost weight back to the set point. However, to have a significant impact on comorbid medical conditions, a weight loss of 5–15% is recommended.[6] Participants must combine lifestyle changes with medicines or bariatric surgery to achieve and maintain weight loss. Bariatric surgery is considered the gold standard treatment in managing obesity since it also diminishes the impact of counter-regulatory hormones such as ghrelin. Bariatric surgery helps people lose an average of 25–30% of their body; however, these procedures are underutilized because not all patients are able or willing to undergo bariatric surgery. Hence, pharmacotherapy may be a better alternative.[7]

At present approved anti-obesity medications (AOM) by the United States of America (USA) Food and Drug Administration (FDA) include liraglutide (Saxenda), naltrexone-bupropion (Contrave), orlistat (Xenical), phentermine-topiramate (Qsymia), semaglutide (Wegovy), setmelanotide (IMCIVREE), and tirzepatide (Mounjaro).[8]

Nevertheless of the necessity to treat overweight, obese people, many healthcare providers remain tentative to prescribe anti-obesity medications (AOM) due to the apprehension of poor maintainable efficacy and side effects related to weight control medications. By adding to the high cost, lack of insurance coverage for AOM, and the contemplation that additional weight is a behavioral problem can make individuals unenthusiastic to use medications.[9]

Tirzepatide is the only anti-obesity drug approved by Central Drug Standard Control in India recently in June 2024. Tirzepatide is a gastric inhibitory polypeptide (GIP)/ GLP-1 binary agonist, that work centrally, in the hypothalamus to reduce food intake and possibly hike energy outlay by pacifying the GIP receptor, through chronic GIP agonism, in preclinical models. Tirzepatide also works peripherally by suspending gastric emptying.[10] So this systematic review was conducted with an aim to determine the effectiveness of Tirzepatide in reducing the body weight when compared to other drugs.

METHODOLOGY

Search process

The articles were searched from main important available databases MEDLINE, COCHRANE CENTRAL, GOOGLE SCHOLARS, EBSCO and PROQUEST.

Search strategy was based on the following key words Obesity, Tirzepatide, Anti-Obesity Drug, Semaglutide and Tirzepatide, obesity and Tirzepatide either isolated or in combination of these words according to Boolean search.A comparison of different searches was done to delete the repeated studies. Then abstracts of all available articles were examined. All studies, which appeared to meet the inclusion criteria, were obtained in the full text format and they go for validity assessment. Application of the Cochrane Collaboration tool for evaluating the risk of bias was done. Then selected articles were grouped into high risk bias and low risk bias articles.

Inclusion criteria

Type of studies: Randomized clinical trials.
Subjects: studies conducted on humans with obesity

1. Follow up time > 30 weeks.
2. Studies published up to JULY 2024.
3. Studies published in English language only.

Exclusion criteria

1. Studies published in other languages.
2. Studies with follow up less than 30 weeks

RESULTS

The initial search from all the databases (MEDLINE, COCHRANE CENTRAL, GOOGLE SCHOLARS, EBSCO and PROQUEST) resulted in 428 articles; however, 228 of these articles were excluded after reviewing the abstracts because they were duplicates and 159 articles were excluded because they were not randomized clinical trials. After analyzing the full text from 41 clinical trials, 31 were excluded because they did not fulfill all the selection criteria. Our final review included 10 articles. All of the included studies were phase 3 trials. They were all published in English and were carried out between 2021-2023.

The outcome indicators included body weight, glycosylated hemoglobin, type A1C (HbA1c). The Cochrane Collaboration bias assessment tool was used to evaluate the risk bias of the studies included by researchers independently. According to the tool the risk was categorized as “high risk” and “low risk”.

All the studies showed that Tirzepatide induced a considerable dose dependant body weight loss when compared to Placebo, 1mg Semaglutide, Degludec, Glargine and Insulin lispro. Tirzepatide showed no association with cardiovascular events. In a recent study participants withdrawing tirzepatide led to substantial regain of lost weight, whereas continued treatment maintained and augmented initial weight loss. Common adverse effects reported were transient Gastrointestinal symptoms like nausea, diarrhoea and vomiting. One of the study reported that Gastrointestinal events decreased with time.

Risk of bias of included studies: The included studies were subjected to critical analysis following the Cochrane Collaboration tool for evaluating the risk of bias, and classified 6 articles as having a low risk of bias and 4 articles as having a high risk of bias. The domain in which the trails were judged to have the high risk of bias was following

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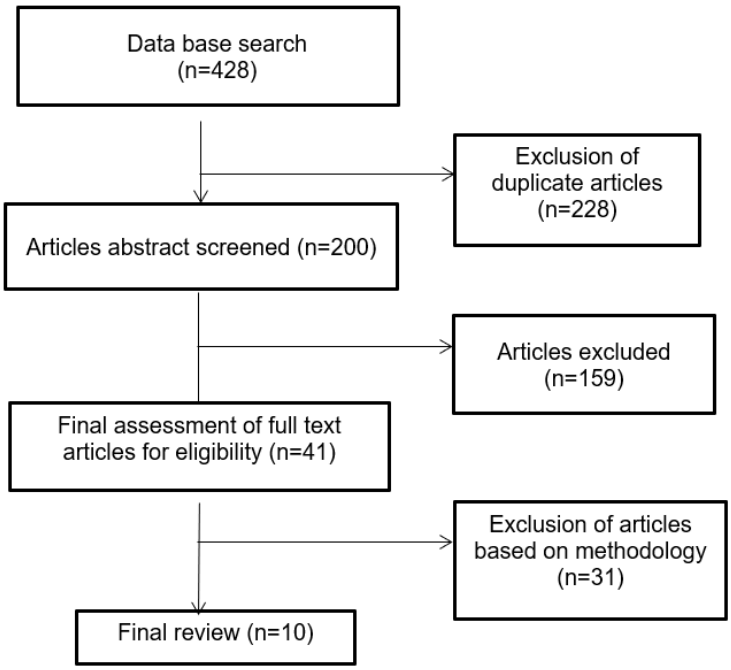

Figure 1: Flow chart showing analysis of articles

Table 1: Demographic and clinical characteristics of included studies

Study type	Author &year	Intervention		Control	Study period	Study population	Study design	Site of study	Outcome	Adverse effects
		Tirzepatide								
SURPASS 1	Rosenstock J et al[11]., 2021	5mg	121	Placebo 115	40 weeks	Patients aged above 18 years with Type 2 diabetes and BMI≥23kg/m^2	Phase 3 trial	52 centers in India, Japan, USA and Mexico	Tirzepatide induced a dose dependant body weight loss ranging from 7.0 kgs to 9.5 kgs.	Diarrhea, Nausea and Vomiting.
		10 mg	121							
		15 mg	121							
SURPASS 2	Frias JP et al[12]., 2021	5mg	470	1mg Semaglutide 469	40 weeks	1,879 participants with Type 2 diabetes and BMI≥23kg/m^2	Phase 3 trial	128 sites in 8 countries	The drop in weight was 6.7% for semaglutide, while it was 8.5, 11.0 and 13.0% in each of Tirzepatide doses.	Nausea, Vomiting and Diarrhoea.
		10 mg	469							
		15 mg	469							
SURPASS 3	Ludvik B et al[13]., 2021	5mg	358	Degludec 360	52 weeks	1,437 participants with Type 2 diabetes and BMI≥25kg/m^2	Phase 3 trial	122 sites in 13 countries	Tirzepatide induced a dose dependant body weight loss ranging from 7.9 kgs to 12.9 kgs.	Gastrointestinal events decreased with time.
		10 mg	360							
		15 mg	359							
SURPASS 4	Prato S et al[14]., 2021	5mg	329	Glar	52	1,995 participants with	Pha	187 sites in 14	Tirzepatide demonstrated a greater decrease in	Nausea, Decreased apetite and

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		10 mg	328	gine 1000	weeks	Type 2 diabetes and BMI≥25kg/m^2	se 3 trial	countries on 5 continents	HbA1c . No association of tirzepatide treatment with cardiovascular risk was observed.	Vomiting
		15 mg	338							
SURPASS 5	Dahl D et al[15]., 2022	5mg	116	Placebo 120	40 weeks	475 participants with Type 2 diabetes and BMI≥23kg/m^2	Phase 3 trial	45 sites in 8 countries	Tirzepatide induced a dose dependant body weight loss ranging from 5.4 kgs to 8.8 kgs.	Diarrhea, Nausea
		10 mg	119							
		15 mg	120							
SURPASS 6	Rosenstock J et al[16]., 2023	5mg	243	Insulin lispro 708	52 weeks + 4 weeks safety follow up	Adults aged ≥ 18 years with Type 2 diabetes and BMI≥23-45kg/m^2	Phase 3 trial	135 sites in 15 countries	Tirzepatide induced a dose dependant body weight loss ranging from 6.7 kgs to 11 kgs.	Mild to Moderate gastrointestinal events.
		10 mg	238							
		15 mg	236							
SUMOUNT 1	Jastreboff AM et al[17]., 2022	5mg	630	Placebo 643	72 weeks + 4 weeks safety follow up	Adults ≥ 18 years with BMI≥27kg/m^2 or with weight related complications.	Phase 3 trial	119 sites in 9 countries	Waist circumference was reduced by 14.0 cm with 5 mg of Tirzepatide, 17.7 cm with 10 mg dose, 18.5 cm with 15 mg dose, and by 4.0 cm in the placebo group	Mild to Moderate gastrointestinal symptoms.
		10 mg	636							
		15 mg	630							
SUMOUNT 2	Garvey WT et al[18]., 2023	10 mg	312	Placebo 315	72 weeks	Adults ≥ 18 years with BMI≥27kg/m^2& HbA1c of 7-10%	Phase 3 trial	7 countries	This therapy with once-weekly tirzepatide 10 mg and 15 mg provided substantial and clinically meaningful reduction in bodyweight.	Diarrhea, Nausea and Vomiting.
		15 mg	311							
SUMOUNT 3	Wadden TA et al[19]., 2023	10 mg or 15 mg	287	Placebo 292	84 weeks	Adults with BMI≥27kg/m^2&Atleast one obesity related complication	Phase 3 trial	62 research centers in USA, Argentina, Brazil	Tirzepatide provided substantial additional reduction in body weight in 87.5% participants who had achieved ≥5.0% weight reduction with intensive lifestyle intervention.	Mild to Moderate gastrointestinal symptoms.
SUMOUNT 4	Arrone LJ et al[20]., 2023	10 mg or 15 mg	335	Placebo 335	88 weeks	Adults with BMI≥27kg/m^2&Atleast one weight related	Phase 3 trial	70 sites in 4 countries	The overall weight reduction was 25.3% for tirzepatide and 9.9% for placebo. In study participants withdrawing tirzepatide led to	Diarrhea, Nausea and Vomiting.

DOI: 10.69605/ijlbpr_13.11.2024.20

						complication excluding diabetes			substantial regain of lost weight, whereas continued treatment maintained and augmented initial weight loss.	

Table 2: Categorization of included studies into high and low risk of bias

Author &year	Randomization	Concealment of randomization	Blinding	Proper reporting of dropouts	Free of bias for selective outcomes	Free of other source of bias
Rosenstock J et al., 2021 SURPASS 1	Yes	Yes	Yes	Yes	Yes	---
Frias JP et al., 2021 SURPASS 2	Yes	---	Yes	Yes	Yes	---
Ludvik B et al., 2021 SURPASS 3	Yes	Yes	No	No	Yes	---
Prato S et al., 2021 SURPASS 4	Yes	Yes	No	Yes	Yes	---
Dahl D et al., 2022 SURPASS 5	Yes	Yes	Yes	Yes	Yes	---
Rosenstock J et al., 2023 SURPASS 6	Yes	Yes	No	Yes	Yes	---
Jastreboff AM et al., 2022 SURMOUNT 1	Yes	Yes	Yes	Yes	Yes	---
Garvey WT et al., 2023 SURMOUNT 2	Yes	Yes	Yes	Yes	Yes	---
Wadden TA et al., 2023 SURMOUNT 3	Yes	Yes	Yes	Yes	Yes	---
Arrone LJ et al., 2023 SURMOUNT 4	Yes	Yes	Yes	Yes	Yes	---

Table 3: Studies having high risk of bias

Improper randomization	1 Study (Frias JP et al.,2021)
Improper blinding	3 Studies(Ludvik B et al., 2021; Prato S et al., 2021; Rosenstock J et al., 2023)
Improper blinding and Improper reporting of dropouts	1 Study(Ludvik B et al.,2021)

DISCUSSION

Tirzepatide is a gastric inhibitory polypeptide (GIP)/ GLP-1 binary agonist, that work centrally, in the hypothalamus to reduce food intake and possibly hike energy outlay. Tirzepatide also works peripherally by suspending gastric emptying. The findings of our study suggested that as Tirzepatide dose increased from 5mg, 10mg, 15mg the effectiveness of weight loss also increased. The effectiveness of Tirzepatide in reducing weight was superior to other drugs. But mild to moderate Gastrointestinal symptoms were present which were dose dependant and subsequently subsided.

Studies done by Bhagavathula et al[21]., and Karagiannis et al[22]., revealed that there was no difference in incidence of serious adverse events between any of the tirzepatide doses and any comparator and also observed that adverse events

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were lower with tirzepatide in any dose than with basal insulin. But a study done by Kadowaki T et al[23]., reported that the incidence of gastrointestinal bleeding occurred frequently between 0-4 weeks after the first dose of Tirzepatide and was found to be higher for the 15 mg tirzepatide group.

Tirzepatide significantly reduced the HbA1c levels of patients in all the dosages (5mg,10mg,15mg) compared to Placebo, 1mg Semaglutide, Degludec, Glargine and Insulin lispro. Similarly significant reduction of HbA1c levels were observed with Tirzepatide in studies done by Bhagavathula et al[21]., and Guan R et al[24].

Nicholls SJ et al[25] and his colleagues conducted a randomized, double-blind, active-controlled CV outcomes trial. This study was conducted with an aim to Compare the tirzepatide and dulaglutide on major adverse cardiovascular events in participants with type 2 diabetes and atherosclerotic cardiovascular disease. Participants with type 2 diabetes aged ≥ 40 years, with atherosclerotic CV disease, HbA1c ≥ 7% to ≤ 10.5%, and body mass index ≥ 25 kg/m^2 were randomized 1:1 to weekly once SC injection of either tirzepatide up to 15 mg or dulaglutide 1.5 mg. The primary outcome was time of first occurrence of any major adverse cardiovascular event (MACE), defined as CV death, myocardial infarction, or stroke. The trial was event-driven and planned to continue until ≥1,615 participants experience an adjudication-confirmed component of MACE. The primary analysis is non-inferiority for time to first MACE of tirzepatide vs dulaglutide by demonstrating an upper confidence limit <1.05, which will also confirm superiority of tirzepatide vs a placebo, and also to conclude if tirzepatide produces a greater Cardiovascular benefit than dulaglutide (superiority analysis). In 2 years, 640 sites in 30 countries across all world regions and 13,299 people were randomized. The mean age of randomized participants at baseline was 64.1 years, diabetes duration 14.7 years, HbA1c 8.4%, and BMI 32.6 kg/m^2. 19.1% of participants had a prior stroke and 25.3% had peripheral artery disease. This trial is fully recruited and ongoing. SURPASS-CVOT will make available definitive evidence as to the Cardiovascular (CV) safety and efficacy of tirzepatide as compared with dulaglutide, which has established CV benefit.

Yu Y et al[26] and his colleagues conducted a meta-analysis and trial sequential analysis on Optimal dose of tirzepatide for type 2 diabetes mellitus. This recent trial sequential analysis exploring the optimal dose of tirzepatide in patients with DM, showed a dose dependent effect on glycemic control and weight reduction, without a significant hike in the rate of adverse effects in higher doses.

Tirzepatide, marketed under the brand name Mounjaro for diabetes treatment, is expected to cost around ₹80,000 per month in India. This translates to approximately ₹20,000 per weekly dose. While this medication offers significant benefits for managing diabetes and potentially aiding in weight loss, its high cost might limit accessibility for many people. Sun pharma and Dr. Reddys labs are trying to reduce the burden of tirzepatide cost by manufacturing in India.[27,28]

To conclude continuous use of Tirzeptide will maintain and augment weight reduction with less adverse effects compared to other anti-obesity medication. All the included studies involved patients with either obesity along with Type 2 diabetes and one or more complications of obesity or obesity and one or more complication of obesity excluding diabetes. Studies involving only obesity patients without systemic complications are recommended to evaluate the effectiveness of Tirzepatide in reducing body weight.

CONCLUSION

Tirzepatide decreased body weight in Type2 diabetes and obesity patients, and can be considered a potential therapeutic drug for weight-loss. Dose dependant mild to moderate Gastrointestinal symptoms were witnessed. Continued treatment with Tirzepatide maintained and augmented initial weight loss. Tirzepatide also demonstrated a greater decrease in HbA1c and no association of tirzepatide treatment with cardiovascular risk was observed. But in present scenario the major constraint for continuous use of tirzeptide is its cost which gives a weekly burden of rupees 20,000 for a person.

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