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Pharmacotherapeutics efficacy in obesity treatment: A systematic review

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Abstract
Introduction: Obesity is a public health concern on a global scale, obesity can lead to significant risk of developing various comorbidities. Lifestyle interventions along with surgical and medical approaches are the primary options for obesity treatment. This systematic review aims to evaluate the efficacy and safety of pharmacological interventions for weight loss in adults with obesity.
Methods: A systematic search review was carried out from January 2018 to December 2022. The search for relevant articles was conducted through PubMed and EBSCO databases. 2290 articles were retrieved and evaluated based on the established inclusion and exclusion criteria. Among them, 362 articles were duplicates and subsequently removed. Further, 1893 articles failed to meet the inclusion criteria and were excluded from this review. Consequently, 35 articles were considered for the review.
Results: Pharmacologic interventions showed good efficacy in treating obesity. Glucagon-like peptide-1 (GLP-1) receptor agonists showed the highest efficacy. Other options including sodium glucose co-transporter (SGLT) Inhibitors, orlistat, phentermine/topiramate, metformin, tirzepatide, Gelesis100 also demonstrated efficacy to various degrees. The safety profile of these interventions was generally good with gastrointestinal symptoms being the most frequently reported adverse events in almost all the included interventions. Neurological symptoms were the most frequently reported in phentermine/topiramate.
Conclusion: This review, in agreement with prior research, indicates that medications can effectively treat obesity with a favorable safety profile. Thus, pharmacotherapy presents a promising, safe, and effective method to achieve weight loss, indicating its potential to play a significant role in the future.

Keywords: Obesity, medical management, pharmacotherapy, efficacy, review

1. Introduction
Accumulation of fat leading to health risk is referred to as overweight or obesity. Having a body mass index (BMI) higher than 25 is considered overweight, BMI above 30 is categorized as obese (World Health Organization, 2021) [31]. Several studies indicated that obesity is not a straightforward matter, but it is a multifaceted health concern that arises from gathering of personal factors (such as genetics and learned behaviors) and environmental factors (such as unhealthy eating habits prevalent in certain societies or cultures, as well as the prevalence of food deserts. (Williams *et al*., 2015) [30]. Additionally, most researchers believe that obesity is significantly influenced by lifestyle choices, such as chronic overeating and a lack of physical activity, despite being impacted by genetic and epigenetic factors) (Shaharir *et al*., 2015) [27].
Obesity is a public health concern on a global scale, obesity can lead to significant risk of developing various comorbidities such as cardiovascular disease (CVD), gastrointestinal disorders, type 2 diabetes (T2D), joint and muscular disorders, respiratory issues, and psychological complications. These conditions affects their day-to-day activities and increase their likelihood of mortality. (Fruh SM *et al*., 2017) [33]. According to World Health Organization (WHO), "650 million adults were obese in 2016 and about 13% of the world's adult population were obese in the same year" (World Health Organization, 2021) [31].
Clinical management of obesity is primarily based on comprehensive lifestyle interventions that encompass nutrition, physical activity, and behavioral therapy (Kahan, 2016) [16]. Bariatric surgery is the most effective way for the management of morbid obesity resistant to lifestyle interventions (Kahan, 2016) [16]. In the past 20 years, bariatric surgery has flourished due to the heightened awareness of its systemic benefits and the expanded utilization of laparoscopic methods, which have resulted in improved safety (Panteliou & Miras, 2017) [22].

Pharmacologic options have emerged as treatment of obesity in the last few years. Over the past 5 years, several drugs have been created with the express purpose of helping individuals to lose weight (Pilitsi *et al*., 2019) [25]. Some of these medications have already received marketing authorization, while others are still in the development phase (Pilitsi *et al*., 2019) [25]. In addition to these weight-loss drugs, other medications of promoting weight loss as a side effect (Pilitsi *et al*., 2019) [25].

Aim of this review is to:

1. Evaluate the effectiveness of pharmacotherapeutics to manage obesity in adults.
2. Assess the safety of these pharmacotherapeutics.

The objective of this review is to explore the available evidence on the efficacy and safety of different pharmacotherapeutics to manage obesity in adults. The findings of this review hope to provide valuable insights into the role of pharmacotherapeutics in the management of obesity, which could have significant implications for clinical practice and public health policy.

This review questions are:

1. What are the effects of different weight losing pharmacotherapeutics on patients with obesity?
2. Are pharmacotherapeutics effective in the management of adults obesity?

2. Methodology

PRISMA guidelines were used to ensure transparent and complete reporting (Page *et al*., 2021). The research protocol was not registered or published prior to the review.

2.1 Search Strategy

The search was carried out from January 2018 to December 2022. The search for relevant articles was conducted through PubMed and EBSCO. By using (PICO) framework to create a search syntax (Aslam & Emmanuel, 2010) [3], application of the PICO framework is summarized in Table 1 below:

Table 1: PICO concepts

PICO	Population	Intervention	Control	Outcome
Representation	Obese patients	Medical Management	Not applicable	Efficacy, saftey

The keywords used to search articles for this systematic review are presented in Table 2 below.

Table 2: Keywords

Keywords	Obese patients OR Overweight OR Excessive weight OR Excessive body weight OR Increased BMI OR obese OR adiposity "Overweight" OR "Adiposity" OR "Obesity"	Medical management OR Medical treatment OR Medical therapy OR Drug therapy OR Non-surgical treatment OR Non-surgical therapy OR Medical intervention OR Pharmaceutical intervention OR GLP-1 agonists OR GLP-1 receptor agonists OR Glucagon-like 1 agonists OR Glucagon-like receptor agonists OR semaglutide, liraglutide "Drug Therapy" OR "drug therapy" OR "Early Medical Intervention" OR "Practice Management, Medical" OR "Medical Futility" OR "Practice Management" OR "Patient Care Management" OR "Drug Therapy, Combination"	Efficacy OR Adequacy OR Competence OR Effectiveness OR Potency OR Advantage OR Usefulness OR Efficiency OR Capability OR Reliability "Efficiency" OR "Collective Efficacy" OR "Clinical Competence" OR "Cost-Effectiveness Analysis" OR "Treatment Outcome"

2.2 Inclusion and exclusion criteria

Presented in Table 3. Peer-reviewed articles dated from 2018-2022 were included.

Table 3: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Obese patients	Normal weight individuals
Adults	Diabetic obese patients
Pharmaceutical intervention	Pediatric population
Papers written in English	Herbal intervention
Papers translated to English	Lifestyle intervention
	Papers in any language other than English

2.3 Selection procedure

The screening process involved three phases. In phase one, the titles and abstracts of the publications found during the search were screened.

During phase two, the full texts of the relevant publications were evaluated. However, some of the publications were not available in their entirety, so the authors of these articles were contacted to obtain complete copies of their works. A few authors responded to the request. In phase three, the reference lists of the publications selected in phase two were screened and examined to confirm that no relevant articles were overlooked.

3. Results

A total of 2290 articles were obtained and were then assessed based on the inclusion and exclusion criteria. Of these articles, 362 articles were removed as duplications. 1893 articles were filtered out as they did not meet the inclusion criteria for this review. Therefore, 35 articles were accepted for the review. Figure 1 shows how the selected articles were obtained. Appendix A shows the list of selected articles.

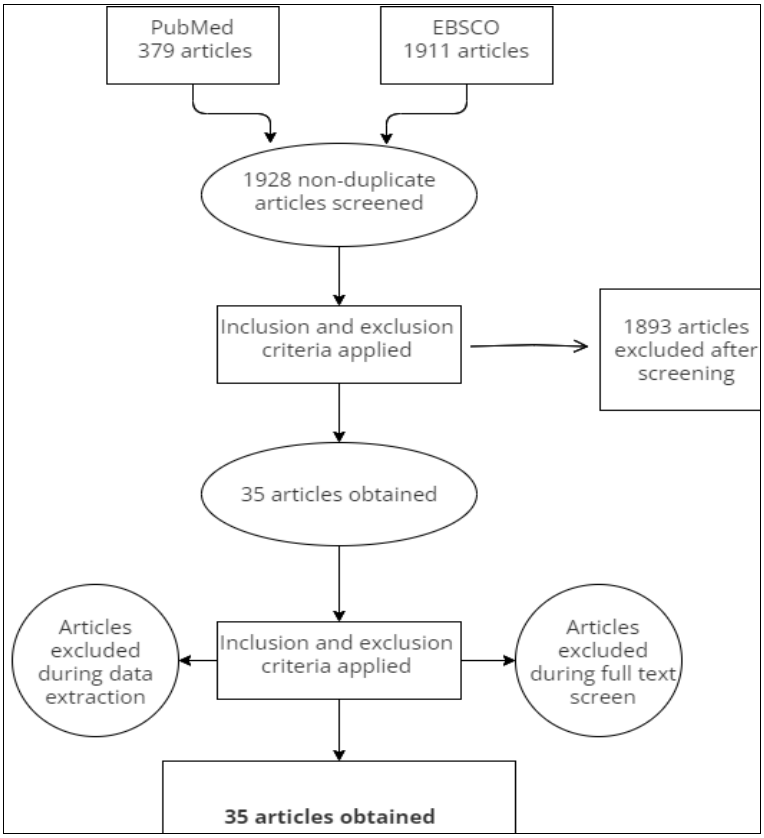

Fig 1: Flow diagram

3.1. General characteristics of the publications

Table 4 below represents a general description of the selected publications.

Table 4: General characteristics of the publications

Classification	Subcategory	N (%) *	Reference index
Study type	Meta-analysis	25.71	1, 6, 8, 11, 17, 23, 26, 28, 32
	RCT	34.28	2, 3, 4, 5, 7, 9, 12, 13, 20, 27, 29, 31
	Randomized trial	08.57	14, 18, 22
	Cohort study	08.57	10, 15, 16
	Review	22.86	19, 21, 24, 25, 30, 33, 34, 35
Year of publication	2018	08.57	4, 8, 27
	2019	25.71	1, 13, 15, 23, 24, 25, 29, 32, 33
	2020	17.14	6, 7, 14, 20, 30, 31
	2021	17.14	2, 17, 18, 21, 22, 34
	2022	31.43	3, 5, 9, 10, 11, 12, 16, 19, 26, 28, 35
Type of drug therapy	GLP-1 agonist-containing therapy	60.0	1, 2, 3, 5, 10, 11, 12, 13, 14, 15, 16, 18, 19, 20, 21, 24, 26, 33, 34, 35
	SGLT inhibitor-containing therapy	08.57	7, 17, 28
	Other drugs	34.28	4, 6, 8, 18, 22, 23, 25, 27, 29, 30, 31, 32

* Percentage of the total reviewed publications

3.2 Overall evidence

3.2.1 Weight loss: This review included 35 clinical Trials, reviews, and meta-analyses investigating the effects of therapeutics on body weight, all the included studies showed efficacy of pharmacotherputics over placebo.

Glucagon-like peptide 1(GLP-1) receptor agonists

GLP-1 agonists has significant effect on weight reduction. Semaglutide 2.4 mg has shown statistically significant weight reduction over placebo after 104 weeks (–16.7% (0.9) with semaglutide and –0.6% (0.9) for placebo) (Garvey *et al*., 2022) [8]. Once-weekly subcutaneous semaglutide has also been shown to be superior to once-daily subcutaneous liraglutide in a statistically significant manner. The study results indicate that there was a significant difference in mean weight change from baseline between semaglutide and liraglutide. Specifically, the mean weight change from baseline was -15.8% with semaglutide, whereas it was -6.4% with liraglutide (Rubino *et al*., 2022) [26]. Subcutaneous 3.0 mg Liraglutide also demonstrated a significant weight reduction for patients with overweight or obesity with or without type 2 diabetes mellitus (Konwar *et al*., 2022) [17].

GLP-1 and glucagon receptor dual agonist demonstrated efficacy in early phase clinical trials (Asano *et al*., 2021; Di Prospero *et al*., 2021; Ji *et al*., 2021, 2022) [2, 7, 14, 15].

Sodium-glucose cotransporter (SGLT) inhibitors

SGLT inhibitors work by inhibiting the action of the SGLT protein in the kidneys, which is responsible for reabsorbing glucose from the urine and returning it to the bloodstream (Hsia *et al*., 2016) [10]. In addition to their glucose-lowering effects, SGLT-2 inhibitors have also been shown to have additional benefits, such as promoting weight loss and

reducing blood pressure (Pereira & Eriksson, 2019) [24].
Licogliflozin, an SGLT 1 and 2 Inhibitor demonstrated efficacy in clinical trials. After 24 weeks of treatment, there were small yet statistically significant differences in waist circumference observed between the study groups (Bays *et al*., 2020) [4]. 2 meta-analyses have found that SGLT-2 inhibitors reduced weight in obese nondiabetic patients (Shi *et al*., 2022; Zheng *et al*., 2021) [28, 32].

Other drugs
Orlistat, a lipase inhibitor, showed efficacy on reducing visceral fat over a placebo [The mean percentage change (with standard error [SE]) in weight was -13.50 ± 1.52% for the orlistat group and -5.45 ± 1.50% for the placebo group (Shirai *et al*., 2019) [29]. Phentermine/topiramate also showed significant benefit in terms of reducing body weight, and the effectiveness is closely linked to the dosage (Lei *et al*., 2021a) [18].
Metformin has been found to be effective in decreasing body weight in individuals with simple obesity, and it does not cause hypoglycemia as an adverse event (Ning *et al*., 2018) [20]. The results of one study showed that both 0 mg and 15 mg doses of tirzepatide administered once weekly led to significant and lasting reductions in body weight (Jastreboff *et al*., 2022) [12].
Gelesis100, a novel nonsystemic oral hydrogel, demonstrated greater weight loss over placebo (6.4% vs. 4.4%, P = 0.0007) (Greenway *et al*., 2019) [9].

3.2.2 Adverse events
The safety profile was reasonable in almost all the included drugs in this review with gastrointestinal-related symptoms being the most frequent. The most reported adverse events associated with semaglutide were gastrointestinal disorders, specifically nausea, diarrhea, vomiting, and constipation. (Garvey *et al*., 2022) [8].
Gastrointestinal disorders that included defecation-related symptoms were also the most frequent adverse event in orlistat (Shirai *et al*., 2019) [29]. Gastrointestinal symptoms were also reported as the most frequent adverse events in licogliflozin and tirzepatide and gelesis100 (Bays *et al*., 2020; Greenway *et al*., 2019; Jastreboff *et al*., 2022) [4, 9, 12].
The most frequently reported adverse events of phentermine/topiramate were neurological symptoms, such as dysgeusia (altered taste), paresthesia (tingling or prickling sensation), dry mouth, attention disturbance, and irritability (Lei *et al*., 2021b) [19].

4. Discussion
Obesity management is multifaceted process that requires a complex approach; the management of obesity includes lifestyle interventions, surgical approaches, and medical approaches among other options. The aim of this review is to evaluate the efficacy of pharmacotherapeutics in reducing weight in adults with obesity and to assess the safety of these agents.
This review demonstrated that all the pharmacologic agents included have efficacy in achieving weight loss in obese patients to varying degrees. Glucagon-like peptide 1(GLP-1) receptor agonists including semaglutide and liraglutide have been shown to be the most effective in reducing body weight. Previous research has indicated the good efficacy of these agents in the management of obesity, Mojca *et al*. Reported that the mean weight loss difference observed in patients without diabetes who received GLP-1 receptor agonists as a supplement to lifestyle intervention was 6.1% to 17.4% compared to those who received a placebo (Jensterle *et al*., 2022) [13].
To a lesser extent, other pharmacologic agents including SGLT inhibitors, orlistat, metformin, phentermine/ topiramate, tirzepatide, Gelesis100 were also shown to be effective in weight management.
SGLT inhibitors revealed an acceptable effect on body weight in this review. SGLT inhibitors effects on weight and other metabolic parameters have been described extensively in the literature; however, previous research into the weight loss benefits of the SGLT2 inhibitor in non-diabetic individuals has been significantly restricted in terms of participant numbers and treatment plans (Ard *et al*., 2021) [1]. According to one meta-analysis, SGLT2 inhibitors resulted in a significant reduction in body weight among obese patients without diabetes, despite the weight loss effect being mild (Cho *et al*., 2021) [6]. Metformin has also shown a mild efficacy in reducing body weight in non-diabetic adults. The novel antidiabetic agent tirzepatide, which is dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) receptor agonist, has also shown to be effective in chronic weight management. The data available for the efficacity and safety of tirzepatide is very limited as this drug is the first of its class in the market (Chavda *et al*., 2022) [5].
Orlistat, a lipase inhibitor, revealed a significant effect on body weight. Orlistat has relatively sufficient data in the literature that support its efficacy. For example, Jain *et al*. reported that orlistat is a well-tolerated and effective medication for treating obesity. It can be used in conjunction with lifestyle changes to attain and sustain a healthy weight (Jain *et al*., 2011) [11] and Phentermine /topiramate showed modest reduction in body weight; however, increased neurologic sides effects and lack of sufficient safety data remain an obstacle in evaluating the usefulness of this drug in weight management (Lei *et al*., 2021b) [19].
Gelesis100 is a novel oral hydrogel that showed mild efficacy in weight reduction with an excellent safety profile (Greenway *et al*., 2019) [9].
The results showed that the safety profile of anti-obesity medications was quite good with gastrointestinal symptoms being the most frequently reported in the agents included. Patel *et al*. reported that most of the new generation anti-obesity medications exhibit promising tolerability profiles (Patel & Stanford, 2018) [23]. Phentermine/topiramate was an exception with neurological symptoms were the most reported side effect, limiting the usefulness of this drug in treating obesity (Lei *et al*., 2021b) [19].
This review demonstrated that anti-obesity drugs have a relatively high efficacy in weight management with a good safety profile. These findings provide strong evidence that pharmacologic management of obesity can be effective in achieving weight loss and highlight the potential importance of these agents in treating obesity, these findings provide valuable insights about the pharmacologic treatment of obesity that add to the existing literature Click here to enter text.
However, it is important to interpret these results with caution due to some limitations. First. The included studies were limited to publications written in English and available in full-text format. Second, the studies that were incorporated in this review only include adult population, which may be not applicable to other populations, for example, pediatric population. Third, the studies included in this review may vary in terms of their designs, and outcome measures.

5. Conclusion
Along with previous research, this review suggests that medications are effective in the treatment of obesity and are relatively well tolerated with a favorable safety profile. GLP-1 agonists in particular have the highest efficacy. These findings suggest that pharmacotherapy offers a safe and effective way to achieve weight reduction and holds a great promise to carry a greater significance in the future.

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Author's Contribution
Not available

Conflict of Interest
Not available

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Not available

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Appendix A: List of selected articles for review

S. No	Author	Year	Type of Study
1.	Zhang P, *et al.*	2019	Systematic review (SR) and meta-analysis (MA)
2.	Ji L, *et al.*	2021	Randomized Controlled Trial (RCT)
3.	Garvey WT, *et al.*	2022	RCT
4.	Shirai K, *et al.*	2018	RCT
5.	Ji L, *et al.*	2022	RCT
6.	Lei XG, *et al.*	2020	SR and MA
7.	Bays HE, *et al.*	2020	RCT
8.	Ning HH, *et al.*	2018	MA
9.	Jastreboff A, M *et al.*	2022	RCT
10.	Kim N, *et al.*	2022	Cohort Study (CS)
11.	Anam M, *et al.*	2022	SR
12.	Rubino DM	2022	RCT
13.	Tronieri JS, *et al.*	2019	RCT
14.	Chou CA & Chuang SF	2020	Randomized trial (RT)
15.	Martínez G, *et al.*	2019	CS
16.	Ghusn W, *et al.*	2022	CS
17.	Zheng H, *et al.*	2021	SR and MA
18.	Asano M, *et al.*	2021	RT
19.	Alorfi NM & Algarni AS	2022	Review
20.	Alba M, *et al.*	2020	RCT
21.	Phillips A & Clements JN	2021	Review
22.	GaoL, Hong Huang, *et al.*	2021	RT
23.	Singh AK & Singh R	2019	SR & MA
24.	Lin CH, *et al.*	2019	Review
25.	Tchang BG, *et al.*	2019	Review
26.	Konwar M, *et al.*	2022	SR & MA
27.	Greenway FL, *et al.*	2018	RCT
28.	Shi Y, *et al.*	2022	MA
29.	Uebelhack R, *et al.*	2019	RCT
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