EFFICACY AND SAFETY OF CURRENTLY AVAILABLE DIFFERENT ANTI-OBESITY DRUGS FOR OBESITY

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Abstract— Obesity is a chronic condition that causes morbidity and mortality around the world, and its prevalence is steadily increasing. Because obesity is a complex and heterogeneous disease influenced by numerous factors such as genetic factor, developmental factor, biochemical, and environmental factors, an obesity treatment strategy must be developed. Obesity is a key risk factor for various types of noncommunicable diseases such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, and several types of cancer. Because most individuals with obesity find it challenging to achieve and maintain long-term weight loss with lifestyle changes (e.g., diet, exercise, and behavioral treatment), Because the basal metabolic rate drops with weight loss, maintaining weight loss requires a continuous decrease in energy intake or an increase in energy expenditure. Pharmacological approaches to obesity management should be considered as a complement therapy. Currently, four medications (orlistat, naltrexone extended-release [ER]/bupropion ER, phentermine/topiramate controlled-release, and liraglutide) can be used for an extended period of time (more than 12 weeks) to assist weight loss by reducing appetite and limiting fat absorption. When compared to other antiobesity medicines, the efficacy of these four treatments for obesity is high. Pharmacotherapy for obesity should be carried out in accordance with a proper assessment of the clinical evidence and modified to individual patients, taking into account the properties of each medicine and the comorbidities associated with obesity. In this review, we explore the mechanisms of action, efficacy, and safety of these long-term anti-obesity medicines as well as the need for research on specific obesity medicine.

Index Terms— Anti-obesity, Orlistat, Obesity, Phentermine

(I) INTRODUCTION

Obesity, defined as an abnormal accumulation of body fat caused by an imbalance in energy intake and expenditure, is a major risk factor for noncommunicable diseases such as type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, and several malignancies [1,2]. Obesity was designated as a major global public health problem by the World Health Organization (WHO) in1997 [3]. For the past ten years, the prevalence of obesity has progressively increased in response to changes in dietary and physical activity patterns, most notably among adults in their twenties and thirties in South Korea. Obesity with a body mass index (BMI) of 25 kg/m2 or more was prevalent in 45.4% of adult males and 26.5% of adult women in 2018. 4.9% of women and 10.8% of men in their 20s and 30s had a BMI of 30 kg/m2, making them obese or more, which represents a sharp rise over the previous ten years [4]. The prevalence of obesity has nearly

tripled globally between 1975 and 2016, with the WHO reporting that 650 million individuals (13%) and over 1.9 billion adults (39%) who were over the age of 18 were obese in 2016 [5]. As a result, the cost of obesity to the world's socioeconomic progress and public health keeps rising.

Furthermore, undernutrition, obesity, and climate change are now acknowledged as the three main health issues facing people and the environment in the "global syndemic," which includes obesity as one of its components. However, treatment strategies for obese people are still insufficient. Given that obesity is influenced by a number of With the consideration of pharmacological therapy, an integrated and comprehensive approach based on diet, exercise, and behavioral therapy is necessary to address the complex reasons, which include genetic, physiological, behavioral, sociocultural, and environmental aspects required to help people with obesity lose enough weight. The cornerstones of managing obesity are lifestyle and behavioral changes, however in cases where lifestyle modifications areineffective or create trouble maintaining the initial weight loss, pharmaceutical therapy should be swiftly considered. Physiologically, as weight falls, the basal metabolic rate drops, therefore continuing to lose weight necessitates continuing to reduce energy intake and/or increasing energy expenditure; consequently, continuing to lose weight and keep the weight lost and maintaining the reduced weight are more difficult with only lifestyle modifications.

Anti-obesity medications are advised by the U.S. National Institutes of Health for people with BMIs of 30 or above or kg/m2. with coexisting conditions, such as dyslipidemia, diabetes, hypertension, or An apnea of sleep [7]. Anti-obesity medications should be taken into consideration for those with BMIs of ≥25 or ≥23 kg/m2 who have at least one weight-related comorbidity, according to the Asia- Pacific obesity treatment guidelines [8]. Currently, the U.S. Food and Drug Administration (FDA) has approved the following anti-obesity medications for long-term use (>12 weeks): liraglutamide, orlistat, naltrexone extended-release (ER)/bupropion ER, and phentermine/topiramate controlled-release (CR) [9]. Orlistat, naltrexone ER/bupropion ER, and liraglutide are the only medications that the European Medicines Agency has licensed for long-term usage [10]. In terms of helping people lose weight, the majority of these anti-obesity medications are only 3% to 7% effective. When lorcaserin is involved, the Based on evidence of elevated cancer risk for any specific patient category, the FDA concluded [11] that the benefits do not outweigh the risks. Utilizing a pharmaceutical approach is appropriate based on the type of obesity and related comorbidities, as well as the safety and efficacy profile of each medicine. In accordance with FDA regulations, a medication is considered an effective anti-obesity drug if, after a year of treatment, more than 35% of patients achieve 5% or greater categorical weight loss [12].

This indicates a statistically significant effect when compared with the placebo group. Improved cardiometabolic parameters, such as blood pressure, cholesterol levels, and glucose control, are also required by the FDA for anti-obesity medications.

Accordingly, we talk about obesity in this review. therapy plans that emphasize pharmaceutical methods and anti-obesity medications that are permitted for patients' long-term usage in relation to obesity. In this review we also discuss Efficacy and Safety of currently available different Anti-Obesity drugs for Obesity.

(II) The Effectiveness And Safety Of Currently Available Long-Term Anti-Obesity Medications For Obesity

Figure 1. summarizes the recommended methodology for the management of obesity using available long-term anti-obesity medicines. Figure 2 shows the long-term impact of four approved drugs on weight loss, cardiometabolic parameters, and safety profiles. Figure 3 summarizes a proposed method for managing obesity with long-term anti-obesity drugs.

(a) Orlistat (Xenical)

Mechanism of action

Orlistat causes weight loss by inhibiting lipases in the mucous membranes of the stomach, small intestine, and pancreas, blocking the breakdown of triglycerides into fatty acids and their absorption in the intestines [14-16]. It is the only

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available anti-obesity medication that does not influence appetite systems

.**Efficacy**

The mean weight loss from baseline was significantly greater with orlistat than with placebo after 1 year in the Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study, a longitudinal study of patients using orlistat, and the significantly greater weight loss was maintained after 4 years (5.8 kg vs. 3.0 kg). The percentage of patients who achieved at least 5% weight loss after 4 years of treatment was considerably higher in the orlistat group (52.8%) than in the placebo group (37.3%). The cumulative incidence of diabetes was 9.0% in the placebo group and 6.2% in the orlistat group at the end of the four-year research, with a risk reduction rate of 37.3%.In addition, a meta-analysis of 30 studies found that 21% More participants who use orlistat for a year achieve a 5% or more weight loss, and 12% more participants reach a 12% weight loss. Weight loss of 10% or greater than those using a placebo [18]. Orlistat reduces the intestinal absorption of 30% of triglycerides, resulting in a larger weight reduction effect than a fat-limited diet. Orlistat use also improves a variety of cardiometabolic markers, including insulin resistance, fasting plasma glucose level, low-density lipoprotein cholesterol level, and systolic and diastolic bloodpressure [16-18].

Safety

Orlistat adverse effects are mostly restricted to the intestines. Fecal incontinence, oily spotting, and fatty stool were reported by more than 20% of participants who used orlistat for two years. In one trial, 8.8% of the treatment group and 5.0% of the placebo group discontinued therapy [19,20]. Furthermore, when people with obesity who are attempting to lose weight suddenly reduce their food intake, some have severe constipation due to a lack of dietary fiber. Orlistat, in conjunction with dietary fiber supplementation, can relieve constipation through its gastrointestinal effects. Because orlistat might decrease the absorption of fat-soluble vitamins (i.e., vitamins A, D, E, and K) in individuals with chronic malabsorption syndrome or cholestasis, multivitamin supplementation may be necessary. Other potential side effects of orlistat include increased oxalic acid content in the urine, which can cause *renal stones; decreased effectiveness of cyclosporine or thyroid hormone drugs when administered simultaneously; and changes in blood clotting in patients taking* the medication due to decreased absorption of vitamin K [20,21].

However, because just a little amount of orlistat is absorbed into the body, it is considered as the safest anti-obesity medicine and the only treatment that may be used in adolescents [22]; data on the safety of orlistat in older patients is insufficient.

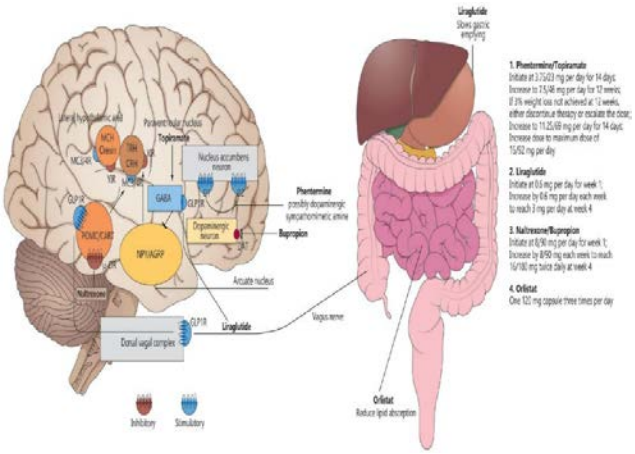

Fig. 1. Mechanism of action and dosing schedule of anti-obesity drugs. Some images were downloaded from the Smart Servier website. MCH, melanin-concentrating hormone; TRH, thyrotropin-releasing hormone; CRH, corticotropin-releasing hormone; MC3/4R, melanocortin receptor type 3/4 receptor; Y1R, Y1 receptor; GABA, gamma-aminobutyric acid; GLP1R, glucagon-like peptide 1 receptor; D1, dopamine 1 receptor; D2, dopamine 2 receptor; POMC/CART, pro-opiomelanocortin/cocaine amphetamine-related transcript (anorexigenic); μ-OR, μ-opioid receptor; NPY/AGRP, neuropeptide Y/agouti-related peptide (orexigenic); DAT, dopamine active transporter.

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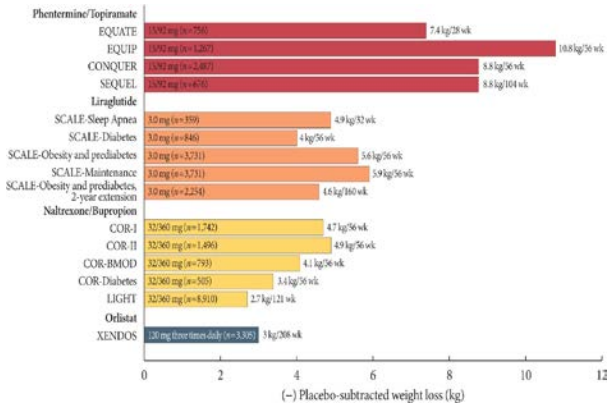

Fig. 2. The effect of currently approved long-term therapies for obesity on weight loss. EQUATE, evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults; EQUIP, controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial; CONQUER, Controlled-Release Phentermine plus Topiramate Combination in Overweight and Obese Adults; SEQUEL, 2-year Sustained Weight Loss and Metabolic Benefits with Controlled-release Phentermine/Topiramate in Obese and Overweight Adults; SCALE, Satiety and Clinical Adiposity—Liraglutide Evidence in Nondiabetic and Diabetic Individuals; COR, Contrave Obesity Research; BMOD, behavior modification; LIGHT, long-term intervention with group-wise dietary consulting supported by meal replacements maintaing weight loss in patients with concomitant obesity and knee osteoarthritis; XENDOS, Xenical in the Prevention of Diabetes in Obese Subject

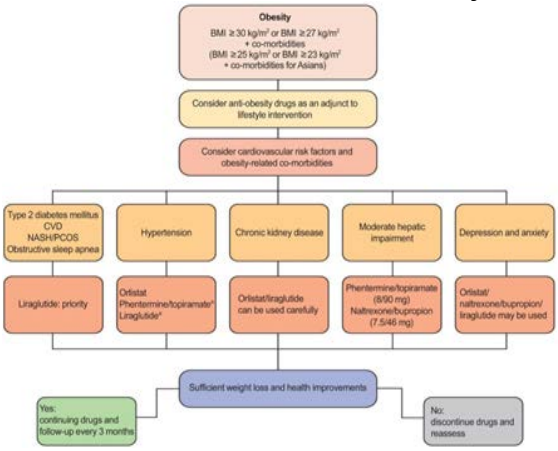

Fig. 3 Choice of anti-obesity drugs based on obesity-associated comorbidities. BMI, body mass index; CVD, cardiovascular disease; NASH, non-alcoholic steatohepatitis; PCOS, polycystic ovary syndrome. aIncrease heart rate.

(b) Naltrexone ER/bupropion ER (Contrave)

Mechanism of action

Bupropion, a norepinephrine and dopamine reuptake inhibitor, is prescribed for depression and smoking cessation treatment. It promotes pro-opiomelanocortin (POMC), a neuropeptide that lowers hunger in the hypothalamus. It also enhances dopamine activity decreased with obese patients. Bupropion reduces food intake and increases energy expenditure, leading to weight loss [23]. Naltrexone, a mu-opioid receptor antagonist, is used to treat opioid and alcohol dependency. Naltrexone reduces the appetite-enhancing effects of beta-endorphin via cannabinoid-1 receptor activation. Combining bupropion and naltrexone effectively suppresses appetite [24-26]. Endogenous opioids may block pro-opiomelanocortin POMC, which can diminish the appetite-suppressing effects of bupropion. Adding naltrexone, an opioid antagonist, can maintain bupropion's POMC activation and enhance appetite suppression (Fig. 1) [27].

Efficacy

The Contrave Obesity Research (COR)-I experiment followed patients with obesity with a BMI of 30 to 45 kg/m2 for 56 weeks.The naltrexone ER/bupropion ER 32/360 mg group lost 6.1% of their body weight, while the naltrexone ER/bupropion ER 16/360 mg group lost 5.0% of their body weight. These results were much higher than the 1.3% drop in the placebo group. The naltrexone ER/bupropion ER 32/360 mg group had 48% weight loss, whereas the naltrexone ER/bupropion ER 16/360 mg group had 39%, significantly higher than the placebo group (17%) [28]. The COR-II study included 1,496 participants with a BMI more than 30 kg/m2 or 27 kg/m2. The combination of naltrexone ER/bupropion ER 32/360 mg resulted in a significant weight loss (-6.4% vs.-1.2%) at week 56, with a significantly higher proportion of participants achieving ≥5% weight loss (50.5% vs. 17.1%). [29].

The COR-behavior modification (BMOD) trial assessed the effectiveness and safety of naltrexone ER/bupropion ER as an addition to intense BMOD. Participants in this study were instructed to have a balanced diet of traditional foods and set personal energy intake targets depending on their beginning weight. At the end of the research, those who got naltrexone

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ER/bupropion ER 32/360 mg and BMOD lost considerably more weight than those who received placebo and BMOD (11.5% vs. 7.3%).At week 56, the naltrexone ER/bupropion ER 32/360 mg and BMOD group had a larger number of patients who lost ≥5% of their body weight compared to the placebo and BMOD groups (66.4% vs. 42.5%) [30].

In the COR-Diabetes trial, patients taking naltrexone ER/bupropion ER lost significantly more weight than those taking the placebo (5.0% vs. 1.8%). Additionally, a higher proportion of patients in the naltrexone ER/bupropion ER group lost at least 5% of their starting weight (44.5% vs. 18.9%). The combination of naltrexone ER andbupropion ER reduced HbA1c considerably (-0.6% vs. -0.1%) compared to placebo [31]. The naltrexone ER/bupropion ER 32/360 mg and BMOD groups demonstrated substantial improvements in physical function and self-esteem subscales compared to the placebo and BMOD groups (30). All COR clinical trials improved cardiometabolic indicators such as glycemic management, insulin resistance, and lipid profiles [28-32].

Safety

Nausea is a common side effect of naltrexone ER/bupropion ER, which can be severe in certain patients and lead to treatment discontinuation. Seizures occur seldom. To avoid adverse effects, it is recommended to gradually raise the dose. Naltrexone ER/bupropion ER can cause insomnia, hence starting medication in the morning is recommended. Naltrexone ER/bupropion ER should be used with caution in older individuals, and not suggested for those over 75 years old. There is limited research onits pharmacokinetics in patients with impaired liver and kidney function. Patients with impaired liver function can only take one pill per day of naltrexone ER/bupropion ER, while patients with impaired kidney function can take up to two pills per day. The medicine is not recommended for those with severe hepatic dysfunction or end-stage renal failure [33]. When taking naltrexone ER/bupropion ER, it is important to address any emotional or psychiatric issues.

In clinical trials, the naltrexone ER/bupropion ER treatment group showed lower rates of moderate melancholy mood and anxiety, which could be related to bupropion's advantages. However, the risk of suicidal ideation in adults aged 18 to 24 years taking bupropion has been reported to the FDA, and circumstances in which Adverse effects on the mental and nerve systems have been recorded. Bupropion medication raises the risk of seizures, which is further heightened by prior head trauma, excessive alcohol use, and cocaine use. Drugs that lower the seizure threshold, such as antipsychotics, antidepressants, antimalarials, tramadol, theophylline, steroids, quinolones, and sedative antihistamines, can contribute to stimulant addiction. Patients with a history of convulsive seizures or bipolar disorder should not take naltrexone/bupropion ER.

Patients with emotional or psychological illnesses should exercise caution when taking antipsychotics or antidepressants due to probable medication interactions and increased risk of seizures [33]. The LIGHT study on the cardiovascular safety of naltrexone ER/bupropion ER, a long-term intervention with group-wise dietary consulting and meal replacements to maintain weight loss in patients with obesity and knee osteoarthritis, was terminated early and did not provide conclusive results [34].

(C) Phentermine/topiramate CR (Qsymia)

Mechanism of action

Phentermine/topiramate CR is a long-lasting combination of phentermine, a short-term appetite suppressant, and topiramate, a nervous system medication. This medicine combines two drugs to reduce adverse effects and enhance efficacy, allowing for lower doses than when administered separately. Phentermine lowers hunger by boosting epinephrine production in the hypothalamus and is recommended for short-term obesity treatment. Topiramate, a gamma-aminobutyric acid agonist, glutamate antagonist, and carbonic anhydrase inhibitor, is used to treat epilepsy and migraines. Its mechanism for treating obesity is unknown (Fig. 1) [35,36]. Weight loss is achieved through improved satiety, greater energy expenditure, decreased caloric intake, and altered taste.

Efficacy

The CONQUER study was conducted on the combination of phentermine and topiramate for overweight and obese adults. The CONQUER study involved 2,487 overweight and obese patients with a BMI of 27 to 45 kg/m2 and two or

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more cardiometabolic diseases, including hypertension, dyslipidemia, prediabetes or diabetes, and abdominal obesity. Participants were divided randomly into three groups. The ratio of participants in the placebo, phentermine/topiramate CR 7.5/46.0 mg/day, and phentermine/topiramate CR 15.0/92.0 mg/day groups was 2:1:2. The treatment groups lost more weight than the placebo group (-1.4 kg vs. -8.1 kg vs. -10.2 kg) and had a higher proportion of patients who lost ≥5% of their body weight (21% vs. 62% vs. 70%) at week 56. Patients who lost at least 10% of their body weight showed similar results (7%, 37%, and 48%, respectively [37].

A randomized controlled study of phentermine/topiramate CR was conducted in persons with extreme obesity (BMI greater than 35 kg/m2). Patients were randomly assigned to one of three groups for 56 weeks: placebo, low-dose (phentermine/topiramate CR 3.75/23.0 mg), or high-dose (phentermine/topiramate CR 15.0/92.0 mg). The placebo group lost weight (1.6%) less than the low-dose (5.1%) and high-dose (10.9%) treatment groups. The treatment groups outperformed the placebo group in terms of achieving ≥5% weight loss (17.3% vs. 44.9% vs. 66.7%) [38]. The phentermine/topiramate CR group significantly improved cardiometabolic risk variables, such as waist circumference, glycemic control, and lipid profile, according to secondary endpoint analysis in clinical trials [37,38].

According to a network meta-analysis of anti-obesity medicines, phentermine/topiramate CR is the most effective for weight loss (39). After 12 weeks of usage, the FDA suggests discontinuing or increasing the medicine if weight loss is less than 3%. If a patient does not lose 5% of their body weight within 12 weeks of increasing the dose, it is recommended to progressively discontinue the medicine.

Safety

Topiramate use during pregnancy raises the chance of cleft palate in newborns. Therefore, pregnant women should undergo pregnancy testing before using phentermine. Topiramate CR is administered at the start of treatment and once a month thereafter [40]. The phentermine contraindications also apply to phentermine/topiramate CR [17,28-31,37,38,41-45]. Topiramate's inhibition of carbonic anhydrase activity can cause metabolic acidosis, hypokalemia, renal stones, angle- closure glaucoma, myopia, and anhidrosis. Monitor symptoms closely and discontinue the medicine if any appear. Topiramate should not be used with other drugs which inhibit carbonic anhydrase.

Phentermine/topiramate CR use can lead to depression, anxiety, sleep disorders, suicidal ideation, and concentration issues. If suicidal ideation or behavior is seen, the medicine should be discontinued immediately. Patients who handle dangerous machinery should use particular caution. Phentermine/topiramate CR can lead to taste abnormalities in a dose-dependent manner. When using phentermine/topiramate CR, gradually increase the dose. To avoid seizures in some individuals, it's recommended to gradually discontinue medication by taking a dose every other day for at least a week before discontinuing completely [46].

There are no large-scale investigations on the safety and efficacy of phentermine/topiramate CR in cardiovascular disease patients. However, individuals with recent cardio-cerebrovascular illness should avoid taking this medication. The FDA approved this medicine with the requirement of future follow-up studies, including an examination of long-term safety for cardiovascular disease [47]. These results will allow for a more accurate assessment of long-term safety once available. The Qsymia Cardiovascular Morbidity and Mortality study is now taking place in individuals with developed cardiovascular disease.

(d) Liraglutide (Saxenda)

Mechanism of action

Glucagon-like peptide-1 GLP-1, released by the intestines in response to carbohydrate and fats digested after a meal, lowers calorie intake by enhancing satiety [48]. Liraglutide is 97% similar to human GLP-1 but has a longer action time (49). Liraglutide suppresses appetite by directly stimulating POMC-, cocaine-, and amphetamine-regulated transcript neurons in the hypothalamus. It also indirectly inhibits neuropeptide-Y/agouti-related protein neurons that stimulate appetite, leading to weight loss. [50,51] Tide regulates glycemic control by delaying stomach emptying after meals and

balancing insulin and glucagon secretions (Fig. 1) [49].

Efficacy

The series of Satiety and Clinical Adiposity—Liraglutide SCALE trials were undertaken to assess the efficacy and safety of liraglutide 3.0 mg vs a placebo. Weight management in overweight or obese patients with or without comorbidities can be achieved through a combination of reduced-calorie diet and increased physical activity (41-43, 52). This series included two trials: the SCALE-Obesity and Prediabetes trial, which included 3,731 overweight or obese individuals without type 2 diabetes, and the SCALE-Diabetes trial, which included 846 overweight or obese adults with type 2 diabetes. (3) The SCALE Maintenance study, which included 422 overweight or obese individuals who reduced ≥5% of their original body weight with calorie restriction, and (4) the 3-year assessment of the SCALE Obesity and Prediabetes trial, which included 2,254 overweight or obese patients with prediabetes. The liraglutide group lost considerably more weight than the placebo group (SCALE-Obesity and Prediabetes,

8.4 kg vs. 2.8 kg; SCALE-Diabetes, 6.4 kg vs. 2.2 kg; and SCALE-Maintenance, 6.2% vs. 0.2%, respectively) [41-43]. The liraglutide group outperformed the placebo group in terms of weight loss, with at least 5% reduction from baseline. Liraglutide effectively achieves weight loss criteria (SCALE-Obesity and Prediabetes, 63.2% vs. 27.1%, SCALE-Diabetes, 54.3% vs. 21.4%, and SCALE-Maintenance, 50.5% vs. 21.8%) [41-43].

The SCALE Obesity and Prediabetes trial included 2,254 patients with prediabetes who were re-randomized 2:1 to either liraglutide 3.0 mg or placebo. The primary outcome was time to diabetes onset within 160 weeks. Liraglutide significantly increased the time to diabetes start by 2.7 times compared to placebo (hazard ratio, 0.21; 95% confidence range, 0.13 to 0.34; P<0.0001). At week 160, patients in the The liraglutide group dropped more weight from baseline than the placebo group (6.1% vs. 1.9%) [52].

In the SCALE-Sleep Apnea trial, 180 obese non-diabetic patients with moderate or severe obstructive sleep apnea (OSA) were randomized to liraglutide 3.0 mg or placebo. The primary endpoint was the change in the apnea-hypopnea index (AHI) after 32 weeks. At week 32, the liraglutide group had a significantly lower AHI and weight loss than the placebo group (-12.2±1.8 occurrences h-1 vs. -6.1±2.0). events (h-1) [44]. Liraglutide outperformed placebo in SCALE studies for improving glycemic control, blood pressure, lipid profiles, and health-related quality of life in overweight or obese adults (41-44, 52). Liraglutide reduces body weight in individuals by causing more fat mass loss than lean mass loss [53].

Liraglutide has been demonstrated to alleviate hepatic steatosis in patients with non-alcoholic steatohepatitis [54], and following a 26- week intervention, ovarian dysfunction was improved with 5.2 kg of weight loss in overweight women with polycystic ovary syndrome [55]. In the Gauging Responsiveness with A Verify Now assay-Impact on Thrombosis And Safety (GRAVITAS) trial, liraglutide 1.8 mg was found to significantly reduce body weight and HbA1c levels after bariatric surgery in patients with persistent or recurrent type 2 diabetes (-4.23 kg and -1.22%, respectively) compared to the placebo group (56). The FDA recommends discontinuing liraglutide if more than 4% weight loss is not achievedafter 16 weeks of use.

Safety

Liraglutide's main adverse effects include gastrointestinal symptoms like nausea, diarrhea, constipation, and vomiting. It's recommended to gradually raise the dose. Reduce the occurrence of these undesirable effects. Liraglutide's delayed stomach emptying can interfere with the effectiveness of other medications. Liraglutide can cause gallstones and, less occasionally, acute pancreatitis [57,58]. Patients with a history of pancreatitis should avoid using it. Liraglutide should not be administered in patients with a family history of medullary thyroid cancer or multiple endocrine neoplasia due to safety concerns [59-61]. Liraglutide can cause an increase in heart rate, which may require discontinuing the treatment if it persists. Liraglutide is not suggestedfor individuals above the age of 75 due to a lack of safety data [59]. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results

(LEADER) study, LEADER research examined the cardiovascular safety of liraglutide 1.8 mg in diabetic patients. The study analyzed the time to mortality for cardiovascular disease, myocardial infarction, and cerebral infarction in 9,340 diabetic patients randomized to liraglutide or placebo.

Over a 3.8-year follow-up period, the liraglutide group had a significantly lower incidence of the primary composite outcome, such as death from cardiovascular disease, non-fatal myocardial infarction, and non-fatal cerebral infarction than in the placebo group (13% vs. 14.9%) [62]. However, there is no scientific evidence supporting the safety and efficacy of liraglutide 3.0 mg in cardiovascular disease.

(III) Comparison Of Available Anti-Obesity Drugs For Long-Term Obesity Management

Based on the findings of a systematic literature review and A meta-analysis of 28 randomized clinical studies involving 29,018 subjects found that all agents resulted in significantly greater weight loss than the placebo after one year. Phentermine/topiramate CR, liraglutide, naltrexone ER/bupropion ER, and orlistat all reduced weight by 8.8, 5.3, 4.9, and 2.6 kg, respectively, compared to the baseline. Phentermine/topiramate CR has a significantly larger proportion of patients losing at least 5% of their body weight compared to orlistat, naltrexone ER/bupropion ER, and liraglutide. Moreover, the proportion of individuals who dropped 10% of their weight after one year of treatment varies between phentermine/topiramate CR (54%), liraglutide (34%), and naltrexone ER/bupropion ER (30%). and orlistat (20%) groupings. Patients are more likely to discontinue liraglutide for adverse effects, followed by naltrexone ER/bupropion ER [39]. Phentermine/topiramate CR is the most effective and well-tolerated medicine, while naltrexone ER/bupropion ER and liraglutide have intermediate efficacy. Orlistat has the fewest side effects [63]. However, there are no direct comparisons between these anti-obesity medicines, and the inclusion criteria, lifestyle, and interventions vary across research. Therefore, we should take these findings with caution.

(IV) Effects Of Anti-Obesity Drugs On Eating Behaviour And Neural Activity

For appropriate treatment for obesity in adults, it is critical to address behavioral factors linked with obesity. In a crossover intervention study, functional magnetic resonance imaging (fMRI) data indicated that liraglutide (1.8 mg for 10) Viewing photographs of food and high-calorie food during fasting and postprandial phases reduces central nervous system activity in the insula and putamen compared to insulin (64). Liraglutide(3.0 mg for 5 weeks) improves satiety and fullness, decreases hunger, and reduces prospective food consumption compared to a placebo [65]. The COR-BMOD experiment found that the naltrexone ER/bupropion ER group outperformed the placebo group in controlling their eating habits significantly.

Furthermore, fMRI research suggests that naltrexone/bupropion treatment can improve eating behavior control [66]. There is limited clinical research available on the impact of phentermine/topiramate ER on eating behaviors.

(V) Considerations For Anti-Obesity Drug Use In Depression And Anxiety

The recommended medicine for individuals with obesity and associated mood disorders is naltrexone ER/bupropion ER, as there is no significant difference in the incidence of depression or anxiety compared to the placebo group. Use naltrexone ER/bupropion ER with caution in patients taking antidepressants. Although liraglutide has no impact at a low dose, but with a high The dose causes mood problems to worsen slightly. For patients using antidepressants, liraglutide should be investigated first due to its low interaction with these medications. Patients with mood disorders should avoid taking phentermine/topiramate CR, as it can cause mood issues. Sleep disturbances have been documented in a substantial proportion of patients taking naltrexone ER/bupropion ER. It is important to monitor the treatment of current sleep disorders and prevent the development of new ones. Phentermine/topiramate CR is not recommended for people with sleep difficulties [67,68].

(VI) Emerging Drug Therapies In Obesity

(a) Setmelanotide

Setmelanotide, a synthetic melanocortin 4 receptor (MC4R) agonist, specifically activates MC4Rs in the paraventricular nucleus of the

hypothalamus to regulate hunger [69]. The MC4R neuronal circuit in the hypothalamus influences food consumption behavior [70]. Accumulation of fatty acids in adipocytes triggers the secretion of leptin, a hormone that promotes satisfaction. Leptin enters the hypothalamus through the bloodstream and binds to the leptin receptor (LEPR) in neurons. Binding with leptin activates the LEPR signaling pathway, converting POMC to α-MSH (also known as alpha-melanotropin). α-MSH released to other neurons activates the MC4R signaling pathway, leading to a sense of fullness. α-MSH secretion activates the MC4R signaling pathway, leading to increased satiety and decreased food consumption. Defects in the LEPR and POMC genes, implicated in the upstream pathways of MC4R-related brain circuits, can lead to insatiable appetite. Setmelanotide's unique method of action can overcome genetic defects that arise upstream in this pathway in persons with obesity caused by rare genetic diseases. Setmelanotide has been demonstrated to lower body weight and hunger in individuals with obesity due to POMC or LEPR deficit in phase 2 studies [71,72]. It is currently being studied in phase 3 trials in subjects with POMC and LERP deficiency (NCT03287960 and NCT02896192). A recent phase 3 research found that setmelanotide medication significantly reduced body weight and hunger in persons with Bardet-Biedl syndrome after one year of treatment [73]. Adverse reactions of setmelanotide treatment include injection site reactions, nausea, vomiting, and hyperpigmentation. Setmelanotide has no reported serious adverse reactions or cardiovascular side effects.

(b) Tesofensine

Tesofensine prevents the synaptic reuptake of serotonin, noradrenaline, and dopamine. Initially designed as a treatment for Alzheimer's and Parkinson's disease, it failed to provide sufficient results. Clinical trials on obesity were done following reports of weight loss as a secondary effect. Tesofensine has been shown to reduce food cravings, consumption, and obesity [74]. A short clinical research with 161 participants found that either 0.5 or 1.0 mg of tesofensine for 24 weeks reduced weight by 11.3 and 12.8 kg, respectively. Tesofensine may have twice the weight-loss effect of other medicines, since the placebo group lost 2.2 kg [74]. Tesofensine can reduce weight by increasing fatty acid oxidation rate [75]. Tesofensine improves waist circumference, insulin resistance, adiponectin, lipid profiles, and glycemic management. Tesofensine can cause side effects such as dry mouth, sleeplessness, constipation, nausea, and elevated heart rate. High doses of tesofensine have been linked to an increase in blood pressure. Therefore, a large-scale clinical investigation is necessary to prove its safety. Additionally, phase 3 trials are currently underway [76]. Clinical trials are examining many treatment options for obesity, such as cannabinoid type 1 receptor blockers, amylin mimetics, peptide YY, neuropeptide Y inhibitors, fibroblast growth factor 21 analogs, and vaccines [36]. A combination of these medicines may improve physiological aspects related to body weight maintenance.

(VII) Future Perspectives: Personalized Medicine In Obesity

Obesity phenotypes vary based on genetic, biochemical, environmental, and behavioural factors, influencing medication response in clinical practice. Although anti- obesity drug therapy has evolved, there are no recommendations on which patients are more effective in terms of good and poor responders. This indicates the need for personalized medicine in this field. Pharmacometabolomic research, such as metabolicand genetic profiling, is not effective in identifying therapeutic gene clusters that differentiate early responders from non-responders to anti-obesity medicines. The Identifying response patterns to anti-obesity medicines can enhance their efficacy and prepare the way for specific obesity treatment. Pharmacogenetic and mechanistic studies may confirm the effects of drugs on feeding behavior and reward processing, allowing for better characterization of successful anti-obesity treatments [77].

(VIII) Conclusions

Obesity, a chronic condition with high morbidity and mortality rates, is a substantial public health problem. There are four anti-obesity medications available for long-term use. The possible weight loss effects of these four anti-obesity medicines are ranked below: Phentermine/topiramate CR

leads to liraglutide 3.0 mg, followed by naltrexone ER/bupropion ER and orlistat. Orlistat is easier to administer and tolerate, but its weight loss potential is lower than other approved anti-obesity medicines. Orlistat has a higher rate of non-responders compared to other medicines, and its cardiovascular safety remains unknown. Phentermine/topiramate CR is the most effective weight loss medication, but its potential for neuropsychiatric side effects needs careful monitoring. Topiramate's fetal toxicity limits its usage in women of reproductive age and require risk evaluation. Naltrexone ER/bupropion ER and liraglutide have a moderate effect on weight loss. The cardiovascular safety of naltrexone ER/bupropion ER is unknown due to the early unblinding of the sole relevant outcome trial. The LEADER trial, which included patients with type 2 diabetes and high cardiovascular risk, found that liraglutide 1.8 mg significantly reduced cardiovascular outcomes. Although there is no clear evidence to support the safety and efficacy of liraglutide 3.0 mg on cardiovascular disease, it is the preferred medication for people with obesity and type 2 diabetes. To optimize drug selection and treatment algorithms, it's important to classify patients based on their specific responses to anti-obesity medications.

(IX) Conflicts of Interest

No conflict of interest.

(X) Acknowledgments

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