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Long Term Effect Of Obesity Treatment: A Review.

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ABSTRACT

Obesity is a significant issue that can lead to multiple serious diseases such as osteoarthritis, obstructive sleep apnea, gallstones, fatty liver disease, reproductive and gastrointestinal cancers, dyslipidemia, hypertension, type II diabetes, cardiac failure, CAD and stroke. When these non-pharmacological procedures are ineffective, lifestyle modification such as diet and exercise is essential for the prevention and management of obesity, pharmacotherapy may be regarded. The lifestyle and physical needs of individualized patients should be altered as the original therapy for obesity that concentrated mainly on diet and exercise. Many drugs used in obesity, including orlistat, lorcaserine, phentermine, sibutramine and rimonabant, but long-term use of above drug may cause several life-threatening side effects. Discontinuation of these anti-obesity drugs leads to weight regaining, in which the treatment will be ineffective. Due to enhanced danger of psychiatric disorders and non-fatal myocardial infarction or stroke, permits for rimonabant and sibutramine were withdrawn. Although orlistat is not as efficient in decreasing body weight as other drugs, orlistat is currently the only option available for treating obesity due to its safety for cardiovascular events and beneficial impacts on diabetic control. The aim of this study is to review the long-term effects of obesity treatment.

Keywords: Obesity, lifestyle modification, pharmacotherapy, cardiovascular events, diabetic control

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INTRODUCTION

Recently, obesity is a major problem that can leads to various severe disease such as osteoarthritis, obstructive sleep apnea, gallstones, fatty liver disease, reproductive and gastrointestinal cancers, dyslipidemia, hypertension, type II diabetes, cardiac failure, CAD, and stroke.[1] For the prevention and management of obesity lifestyle modification such as diet and exercise are important when these non-pharmacological interventions are ineffective, pharmacotherapy can be considered. When the patients having hypertension or type 2 diabetes mellitus interventions are ineffective for individuals with body mass index [BMI] ≥30 kg/m^2. Due to serious adverse effects, most of the antiobesity drugs have been withdrawn from the market.[2] Since 1980, worldwide obesity prevalence has nearly doubled. In 2008, more than 1.4 billion adults were overweight and over 500 million were obese. The global prevalence of child and adolescent obesity in 2006 using conservative definitions by WHO region varied from 3% in South-east Asia.[3]

In the 1990s, fenfluramine and dexfenfluramine were withdrawn from the market because of heart valve damage.[4] In the year of 2000, the European Medicines Agency (EMA) allowed the market withdrawal of several anti-obesity drugs, like diethylpropion, mazindol and phentermine, due to an unfavourable risk.[5] The first selective CB1 receptor blocker, rimonabant, was available in 56 countries from 2006 but was never approved by the U.S.FDA due to an increased risk of psychiatric adverse events, including depression, anxiety, and suicidal ideation. Subsequently, rimonabant was banded from the European market in the year of 2009. February 2011, the U.S. FDA rejected bupropion/naltrexone combination because of potential cardiovascular risk.[6] Individualized patients lifestyle and physical needs should be modified as the initial treatment for obesity which was majorly focused on a diet and exercise. Many drugs used in obesity, including orlistat, lorcaserine. Phentermine, Sibutramine and Rimonabant, but long-term use of above drug may cause several life-threatening side effects. Discontinuation of these anti-obesity drugs leads to weight regaining, in which the treatment will be ineffective.[7] The aim of this study is to review the long-term effects of obesity treatment.

Orlistat

Orlistat is a potent and reversible gastrointestinal lipase inhibitor preventing dietary fat absorption by 30% by inhibiting pancreatic and gastric lipase. Orlistat was approved in 1998 and is currently the only available drug for the long-term management of obesity. The prescribed dose was 120 mg capsule thrice daily, and a half dose (60 mg) available over-the-counter medicine in some countries. The beneficial effect on body weight is sufficient to improve several cardiometabolic parameters, including waist circumference, blood pressure, blood glucose levels, and lipid profiles.[8] Orlistat common side effects was found to be influenza, hypoglycemia, upper respiratory infection, oily spotting from the rectum, flatus with discharge, fecal urgency, fatty or oily stools, flatulence, liquid stools, oily evacuation and increased defecation. These symptoms generally occur at the beginning of treatment, and go away after some time.[9]

Long term effect: Orlistat was contraindicated for the patients having hypersensitive to orlistat or any of the other ingredients. Patient with long-term malabsorption disease and cholestasis should not use this medication. It was also contraindicated in women with breast-feeding. Long term use may leads to severe liver injury however, there is no scientific evidence with altered liver function or liver injury.[9] Douglas et al. published a clinical series study with nearly 100,000 patients in UK and found an increased liver injury immediately throughout orlistat prescription.[10] Evidence suggests that Vitamins A, D, E, K and other fat soluble vitamins decrease their absorption.[11] Thus, the supplementation of diet with concomitant multivitamins and beta-carotene is advised for individuals taking orlistat. It has been reported that INR must be monitored closely as concominant use of orlistat along with vitamin k enhances the effect of warfarin.[12] Unabsorbed dietary fat due to orlistat can also bind dietary calcium, leading to some potential concerns. Calcium malabsorption may also lead to bone alterations, but major studies have not shown any significant alterations.[13]

Lorcaserin

Lorcaserin is a selective serotonin receptor (5-HT2C) agonist. Serotonergic drugs have already been used for the management of obesity.[14] The 5HT2 receptor family, is basically composed of 5HT2-a, 5HT2-b and 5HT2-c receptors. The main effect of serotonin is mediated by 5HT2-c, which is present mainly in the

hypothalamus, whereas 5HT2-a is mostly present at the cerebral cortex and 5HT2-b in cardiac valves.[15] Lorcaserin is leading to increased consequently weight loss and hypothetically free of the fenfluramine valvular health risk.[16] Apparently, increased energy expenditure, is observed with other serotonin agonist agents, but it does not occur with lorcaserin. Previous study proved that lorcaserin is safe drug when administered at the dose of 10 mg two times a day.[17] The main side effects of lorcaserin are upper respiratory infections, headache, dizziness, nasopharyngitis and nausea, and the difference between groups for headache and dizziness was less evident after a year of treatment.[18]

Long term effect: Long term use of lorcaserin can leads to valvulopathy, disease or disorder of the valves of the heart. Valvulopathy is a danger with prior weight loss drugs, but it was not shown with lorcaserin; however, this drug was not assessed in patients with important valvulopathy or congestive heart failure. Its long-term impacts are uncertain, as it was not studied for more than two years.[19]

Phentermine

In 1959, US FDA approved Phentermine which was the mainly prescribed as appetite suppressant drug.[20,21] Phentermine is an amphetamine analog stimulant approved for not long-term use, because clinical trials showed increased tolerance and dependency from its prolonged use.[22] This drug acts as sympathomimetic agents; the mechanism of action includes an increase in CNS dopamine and norepinephrine (both catecholamines), and serotonin (an indolamine) activity, resulting in appetite suppression. As stimulants, it also increased pulse rate and blood pressure.[23]

Phentermine resin formulations allow for a slower gastrointestinal release after ingestion. Phentermine resin administration often starts with a dose of 15 mg, titrated to 30 mg / day if necessary. Phentermine hydrochloride (HCl) was created in the 1970s, with doses varying from 8 to 37.5 mg, usually equal to 6.4-30 mg of phentermine resin. The phentermine HCl salt easily dissociates in the GI tract, resulting in immediate release of phentermine drug; phentermine HCl is absorbed from the gastrointestinal tract approximately three times faster than phentermine resin. Theoretically, phentermine HCl has a more intense impact on the suppression of appetite compared to phentermine resin, but for a shorter period of time.[24] Phentermine is contraindicated in patients with hypertension of the pulmonary artery, serious arterial hypertension, present or past history of cardiovascular or cerebrovascular disease or psychiatric disorders including anorexia and depression; it is also contraindicated in patients with drug abuse or known alcoholism. Phentermine is contraindicated with any other central anorectic agent owing to the enhanced danger of possibly deadly pulmonary artery hypertension.[25]

Long term effect*:* Kristina H. Lewis et.al conducted a study on Safety and Effectiveness of Long-Term Phentermine Use: Clinical Outcomes from an Electronic Health Record Cohort suggest that use of phentermaine monotherapy on long term use showed greater weight loss without any increased risk of incident CVD or death.[26]

Sibutramine

Sibutramine is a norepinephrine and serotonin reuptake inhibitor. The hepatic cytochrome P450 system quickly metabolizes sibutramine, producing two pharmacologically active metabolites that influence both food intake and energy costs.[27] Sibutramine was comparatively well tolerated as only constipation, headache, dry mouth and insomnia were prevalent side effects.[28]

Long term effect: It has been shown that the long-term impact of therapy with sibutramine increases the risk of non-fatal myocardial infarction and non-fatal stroke, but not of cardiovascular suicide or death from any cause in patients with pre-existing cardiovascular diseases. The U.S. FDA initially allowed sibutramine to be available and reviewed its potential benefits and risks, but asked for stronger warnings on the product labels. People with a history of stroke or heart attacks and uncontrolled high blood pressure do not use the alert suggested sibutramine.[29,30]

Rimonabant

Rimonabant is a cannabinoid receptor antagonist; it functions by blocking a particular receptor type called CB1 receptors contained in the nervous system and is component of the system used by the body to

regulate the consumption of food. The endogenous cannabinoid system governs elements of food intake and energy balance, rimonabant can assist patients to decrease food intake and lose weight by blocking receptors.[31] The most common side effects were infections (nasopharyngitis, influenza), gastrointestinal disorders (nausea), musculoskeletal and connective tissue disorders (back pain, arthralgia), nervous system disorders (headache, dizziness), and psychiatric disorders (anxiety, depressed mood disorders, and disturbances).[32] In 2007, the cannabinoid receptor antagonist rimonabant was withdrawn by the FDA from the European market because of an increased risk of depression, anxiety and suicidal ideation.[33]

Long term effect: In lipid and glycaemic factors, rimonabant treatment was correlated with important improvements. While improvements in HDL-C and triglyceride concentrations were noted in conjunction with a higher decrease in BW during year 1, such changes in the 20 mg rimonabant group continued during year 2 when BW was nearly stable.[34] The 2-year information from RIO-Europe proved a rimonabant safety and tolerability profile consistent with that reported during the study's first year. Treatment with rimonabant was generally well tolerated; the most common adverse events in rimonabant 20 mg patients were mild to moderate in intensity and transient in nature. A recent meta-analysis considering the four RIO clinical trials (1 year data) reported an overall increased risk of depression (OR: 2.51; 95% CI 1.23 –5.12), which was, however, lower in RIO-Europe (OR: 1.25; 95% CI 0.55 –3.13). It should be noted that 'depression' actually corresponds to 'depressed mood disorders and disturbances'. During the first year, the surveys verified this information, but showed that the incidence of depressed mood disorders and disturbances during year 2 was small and nearly comparable between placebo and 20 mg rimonabant. Moreover, although with rimonabant the rate of withdrawals due to negative psychiatric occurrences was slightly greater than with 2-year therapy.[35]

CONCLUSION

Obesity was one of the major health issues facing now a days. Lifestyle modification are the best choice for the prevention and treatment. Medication offers possible adjunct, but their effect is modest, through limiting side effects. The weight loss only lasts as long as the drug is taken, as the weight is recovered once the treatment is stopped. Due to enhanced danger of psychiatric disorders and non-fatal myocardial infarction or stroke, permits for rimonabant and sibutramine were withdrawn. Although orlistat is not as efficient in decreasing body weight as other drugs, orlistat is currently the only option available for treating obesity due to its safety for cardiovascular events and beneficial impacts on diabetic control, it is currently the only option for treating obesity.

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