International Journal of Research and Review
Vol.7; Issue: 11; November 2020
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

A Review on Anti Obesity Drugs

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ABSTRACT

Obesity is a potentially life-threatening, chronic disease. As the most prevalent metabolic disorder affecting humans today, obesity requires multidisciplinary, long-term treatment. The worldwide prevalence of obesity has experienced a remarkably steady increase. Yet treatment is essential because obesity has been linked to the onset of many other chronic diseases, as well as higher rates of comorbidities and mortality. Weight loss of 5% to 10% of initial weight, accomplished by intense lifestyle treatment, decreases risk factors for cardiovascular disease (CVD), avoids or delays the progression of type 2 diabetes, and enhances other health effects of obesity. There is a need for adjunctive treatments that can help patients with dietary changes alone that are unable to lose or sustain adequate weight loss to improve health. With newly developed clinical guidelines, a better understanding of the biology of energy balance and patient variability in treatment response, and an increased availability of several monotherapy and combination anti-obesity medicines, we will start to better research and customize individualized treatments for the many different types of obesity.

Keywords: Obesity, Noradrenergic Activation, Gastrointestinal Lipase Inhibition, Serotonin Receptor Activation, Combination Therapy

INTRODUCTION

Obesity is a potentially life-threatening, chronic disease. As the most prevalent metabolic disorder affecting humans today, obesity requires multidisciplinary, long-term treatment[1,2]. The worldwide prevalence of obesity has experienced a remarkably steady increase. Yet treatment is essential because obesity has been linked to the onset of many other chronic diseases, as well as higher rates of comorbidities and mortality[3-5]. Despite the lack of significant long-term effectiveness, lifestyle change remains the cornerstone of obesity treatment. Pharmacotherapy is a viable treatment choice for many who don't respond to lifestyle therapy and are not candidates for weight loss surgery. Advances in understanding the processes of appetite control, nutrient sensing, and energy expenditure have not only helped shape the current drug growth, but also changed the way anti-obesity drugs are provided.[6] Obesity is a complex, highly regulated disease, with more than 150 related co morbidities, including diabetes, cardiovascular disease, non-alcoholic fatty liver disease and many types of cancer. Although many people can lose weight in the short term with lifestyle modification, few maintain their weight loss.[7] On the basis of our past understanding of obesity, drug therapy was directed either at appetite suppression or impairment of nutrient absorption, with the goal of reducing caloric intake and thus body weight. The findings were less than expected and the emergence of major adverse effects not only strengthened the idea that obesity was a voluntary or behavioural problem.

Weight loss of 5% to 10% of initial weight, accomplished by intense lifestyle treatment, decreases risk factors for cardiovascular disease (CVD), avoids or delays the progression of type 2 diabetes,

and enhances other health effects of obesity.[8] Although changes in some risk factors for CVD can be seen with sustained weight loss as low as 3%, weight loss of 5% or more is generally considered to be clinically meaningful.[9,10] Far greater weight losses lead to higher cardiovascular risk reductions. A majority of overweight patients in clinical trials lose 7% to 10% of their initial weight at 1 year with intense lifestyle therapies. Nevertheless, the outcomes of these effectiveness trials are much better than those obtained by clinicians in primary care environments, where low-intensity therapy studies have not shown mean weight loss in clinically meaningful terms. Regardless of the initial success in weight loss, it is difficult to maintain long-term weight. Weight loss can be improved but not removed with continued lifestyle therapy.[11] The need for constant vigilance in order to sustain lifestyle changes in order to regain weight in the face of biological and environmental pressures underlines the challenges facing even the most inspired patients who have accomplished weight loss. There is a need for adjunctive treatments that can help patients with dietary changes alone that are unable to lose or sustain adequate weight loss to improve health.

NORADRENERGIC ACTIVATION

Four main noradrenergic agents (phentermine, diethylpropion, phendimetrazine, benzphetamine) are FDA-approved for obesity treatment in the short term (usually 12 weeks). Both medications were prescribed for 12-week therapy and approved for obesity prior to established long-term pharmacotherapy. Therefore these drugs have outcome as compared to long term therapy.[12]

Phentermine (Adipex P) is a sympathomimetic amine which increase NE activity in hypothalamus and reduce appetite in dose range from 15-30 mg/day. The common adverse effects are dry mouth, insomnia, constipation, increased blood pressure and heart rate. Phentermine is contraindicated in patients with CAD or CVA, cardiac arrhythmia, seizures, hyperthyroidism, and uncontrolled hypertension. In phenteramine treated patients there is an increased risk of serotonin is seen therefore it should be used with caution with SSRIs.[13]

Diethylpropion is comparatively less prescribed than phenteramine even though it has a similar adverse effect and weight loss profile to phentermine. Haddock CK conducted a quantitative analysis in 2002 including 9 small studies ranging from 6 to 52 weeks found that individuals using diethylpropion (75/day) had an additional weight loss compared to placebo of 3 kg, with a mean total weight loss of 6.5 kg.[14] Phendimetrazine, is prescribed more frequently than diethylpropion for obesity treatment and have similar weight loss to other noradrenergic agents.[10] Benzphetamine is the least prescribed for obesity treatment among noradrenergic drugs and limited trial data for its safety and efficacy.[15]

GASTROINTESTINAL LIPASE INHIBITION

Orlistat (Xenical, Alli) is a gastrointestinal lipase inhibitor which, when taken three times a day during or within 1 hour after meals, leads to the excretion of about 30% of fat ingested.[16] The probable adverse effect associated with Orlistat is GI related such as flatulence, bloating, abdominal cramping which can be reduced by adding fibre rich food or supplement[17] and serious adverse effect is liver failure. Orlistat is contraindicated in liver failure and cholestasis. The fat soluble vitamins should monitor in patients taking Orlistat.

According to systemic review conducted by Susan ZV proportion of treatment group achieved clinically significant weight loss that is greater than or equal to 5 percent is ranged from 35% to 73% in one year and the proportion losing at least 10 percent is ranged from 14% to 41%, in one year.[18] According to XENical in the prevention of diabetes in obese subjects

(XENDOS) data in 3305 Orlistat prescribed individuals Orlistat use decreased 2.7 Kg or about 2.4 percent of initial body weight in four years and decreasing risk of Type II DM by 9% (Placebo 6.2%).[19]

SEROTONIN RECEPTOR ACTIVATION

Lorcaserin (Belviq) – a selective serotonin (5-HT)2c receptor agonist – was approved for long-term weight loss in 2012. The approval came 15 years after the withdrawal of the nonspecific serotonin receptor agonists, fenfluramine and dexfenfluramine. Such agents are suspected of increasing the risk of serotonin-associated valvulopathy on the cardiac interstitial cells by agonizing the 5-HT2b receptor subtype.[20]

Three placebo-controlled clinical trials of lorcaserin[21] have not reported an increased risk of valvulopathy or other adverse cardiovascular events. These trials demonstrated a 3.0–3.8% placebo-subtracted weight loss with lorcaserin. The Diabetes Mellitus study of Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM-DM trial), which enrolled patients with type 2 diabetes A1C 7–10 percent, resulted in a decrease of 0.5 percent in hemoglobin A1C.[22] Caution should be used in patients with congestive heart failure and depression; in particular, those taking selective serotonin reuptake inhibitors, as there may be a small but significant risk of serotonin syndrome. High cost may be a barrier to the selection of this agent.

COMBINATION THERAPY

- **Phentermine plus Topiramate ER**

Phentermine plus topiramate - extended release (ER) is the first FDA approved combination drug for obesity, combining low-dose phentermine with an on standard dose of the antiepileptic medication topiramate-ER. The drug's effectiveness is focused on the synergistic effects of a dose of phentermine lower than recommended and topiramate's extended-release formulation.[23]

It was recommended that phentermine plus topiramate-ER be approved based mainly on 2 phase 3 clinical trials (EQUIP32 and CONQUER33). A low-intensity lifestyle plan was offered to all classes. All underwent dose titration at an allocated dose over 4 weeks, followed by treatment or placebo lasting 52 weeks. Such tests showed more than 8.5% placebo-subtracted weight loss at 1 year, with 67% and 71% of participants receiving phentermine / topiramate XR (as compared to 17% and 21% respectively in placebo group) losing more than 5% of body weight.[24]

Considering that most consumers of obesity medicines are women of reproductive age, an area of considerable concern is the potential for oral clefts in the offspring of women who become pregnant while taking topiramate (Supplement, eTable). A risk assessment and mitigation strategy was developed to minimize the likelihood of pregnancy in women with reproductive potential that includes clinical training, providing information only through certified pharmacies, and providing patient information on risks and the need for effective contraception.[25]

- **Naltrexone SR/Bupropion SR**

In September 2014, the US FDA approved the combination of naltrexone HCl and bupropion HCl (Contrave) for weight loss.[26] The drug's weight loss activity is based on the hypothalamic melanocortin system and the mesolimbic dopamine reward system combined mechanisms of action of bupropion and naltrexone. Bupropion, licensed for depression and cessation of smoking, activates hypothalamic pro-opiomelanocortin (POMC) neurons and binds melanocortin-4 receptors through alpha-melanocytestimulating hormone (a-MSH), increased energy expenditure and reduced appetite. Naltrexone is a centrally acting opioid receptor antagonist and is

approved for alcohol and opioid dependence. Although studies demonstrate mild weight loss effects with bupropion[27], naltrexone monotherapy has not been effective in treating obesity.[28] By suppressing the auto-inhibitory opioid-mediated negative feedback which suppresses POMC firing (a bupropion-stimulated compensatory effect), naltrexone improves bupropion's effectiveness, and its combined effects are additive relative to individual drug monotherapy.[29] Four 56-week randomized, placebo-controlled trials – Contrave Obesity Research (COR)-I , COR-II , COR–Behavior Modification (COR-BMOD), and COR-Diabetes (COR-D) were conducted to evaluate the efficacy of naltrexone/bupropion. Among patients without diabetes, the placebo-subtracted weight loss ranged from 4.2% among COR-BMOD to 4.8% in COR-I trials using the maximum naltrexone / bupropion SR dosage (32 mg/360 mg). The placebo-subtracted weight loss findings of 3.2% were less successful in patients with diabetes; however, there was a greater decrease in naltrexone / bupropion unit hemoglobin A1c (0.6%) relative to the placebo arm (0.1%). [30]

CONCLUSION

Obesity is known as a serious and chronic disease that requires extensive care. An advanced understanding of appetite control and energy expenditure mechanisms has led to the development of new research drugs and the recent approval of Naltrexone SR / bupropion SR, lorcaserin (Belviq), and phentermine / topiramate ER appears to be well tolerated and effective. With newly developed clinical guidelines, a better understanding of the biology of energy balance and patient variability in treatment response, and an increased availability of several monotherapy and combination anti-obesity medicines, we will start to better research and customize individualized treatments for the many different types of obesity.

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How to cite this article: Mathew J, Kandasamy K, Rajagopal S et.al. A review on anti obesity drugs. International Journal of Research and Review. 2020; 7(11): 484-488.

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