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Review Article

Drugs and Supplements for Weight Reduction

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Abstract

Introduction: Obesity is defined as having a body mass index (BMI) greater than 30 kg per m^2. While overweight, on the other hand, is a BMI of 25 - 30 kg per m^2. Associations between overweight or obesity and morbidity and mortality were observed since the ancient history. The social stigma and the medical risk have led to cultural and professional efforts to address the problem. The US Food and Drug Administration (FDA) have approved many drugs for weight reduction. Nevertheless, alternative medication was commonly used without prescription based on worldwide cultural believes of their effects.

Aim of Work: In this review, we will discuss the most common medication and supplement used to reduce weight, proposed mechanism of action, effectiveness, and adverse effects.

Methodology: A comprehensive and systematic search was conducted regarding medication for weight reduction and commonly used alternative medicine for that purpose. PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com) were the mainly used database.

Conclusion: Orlistat is believed to yield to 5 - 10 kg weight loss. GLP-1 inhibits glucagon release and delays gastric emptying. GLP-1 receptor agonists are often used in combination with Anti-diabetic medication particularly when weight loss is desired. The FDA has recently approved lorcaserin for patient with obesity or overweight and comorbidity. Ephedra products have modest effect on weight reduction, however, due to safety concerns, experts discourage their usage. Hydroxycitric acid is another commonly used agent as alternative medication for weight reduction, evidence about its efficacy is contradictory. Most studies on green tea, l-carnitine, vitamin b5 and pyruvate were of small sample size, hence their efficacy remains questionable. Although guar gum is considered safe and well-tolerated, studies have found no effect on weight loss.

Keywords: *Primary Medication Non-Adherence (PMN); Chronic Diseases*

Introduction

Obesity is defined as having a body mass index (BMI) greater than 30 kg per m^2. While overweight, on the other hand, is a BMI of 25 - 30 kg per m^2. Since the time of Hippocrates, association between overweight or obesity and morbidity and mortality was known. Obesity is not a rare encounters; it is estimated to affect about one third of adults at the beginning of the 21st century [1]. Overweight was estimated to present in 15.5 percent of adolescents [2]. The social stigma and the medical risk have led to cultural and professional efforts to address the problem. The US Food and Drug Administration (FDA) have approved many drugs for weight reduction. Nevertheless, alternative medication was commonly used without prescription based on worldwide cultural believes of their effects. Natural Medicines Comprehensive Database has identified the presence of more than 50 types of supplements as commonly used and manufactured for weight-loss purposes [3]. Some of these herbal and supplements are more common than other and was produced by many companies [3,4]. Unfortunately, about 50 percent of these agents have not been studied in Randomized control trials in human. Moreover, the FDA laboratory test of some of these supplement has found many prescription drugs added to the commercial products. Examples include fluoxetine, furosemide, phenytoin, amphetamines, and benzodiazepines among many others.

The physicians must be aware of commonly used herbal and dietary supplements, their effectiveness and associated risks in addition to ability to prescribe adequate medication for patients requiring weight reduction. A careful consideration of risks and benefits should be taken prior to initiating medical agents for weight reduction [5-8]. It is crucial, however, to promote healthy eating, physical activity, and behavior modification as most management plans are prone to fail without that.

In this review, we will discuss most common medication and supplement used to reduce weight, proposed mechanism of action, effectiveness, and adverse effects.

Methodology

A comprehensive and systematic search was conducted regarding common drugs for weight reduction, supplement and dietary herbal believed to have efficacy, adverse event, associated risk, and contraindication. PubMed search engine and Google Scholar search were the mainly used database for search process. All relevant available and accessible articles of all types were reviewed and included. The terms used in search were: weight reduction, alternative medicine, herbal and supplements, efficacy, adverse event, and risks.

Medication for weight reduction by mechanism

Drugs that alter fat digestion and absorption

This category of drugs include includes orlistat. Orlistat is believed to modulate fat digestion through its action on inhibiting pancreatic lipases. Lipases enzymes hydrolyze fats to facilitate absorption, hence, inhibiting them will lead to excessive fat excretion in feces. Normally, daily diet contains about 30 percent fat, orlistat inhibits the absorption of 25 - 30 percent of calories ingested as fat. The Role and effectiveness of orlistat in weight reduction has been examined in several randomized trials and meta-analyses [9-15]. One meta-analysis of 12 randomized trials comparing orlistat plus a behavioral intervention with placebo plus behavioral intervention has found 5 - 10 kg loss in intervention group versus 3 kg in the control group [16]. The weight loss was maintained up to 2.5 years of treatment. In one of the longest large trials, researchers randomized 3304 patients to orlistat or placebo [9]. Orlistat group have lost 11 percent of baseline weight in the first year compared with only 6% in placebo group. Over the next 3 years follow-up period, a small regain in weight occurs, yet the orlistat-treated patients were 6.9 percent below baseline compared with 4.1 percent for control.

Additional benefits of orlistat is more reduction of glycated hemoglobin (A1C) than placebo [13-15]. Nevertheless, orlistat leads to improvement in systolic and diastolic blood pressure in hypertensive patients. This is shown in a meta-analysis and could be explained by weight loss effects on blood pressure [17]. In addition, it is suggested that orlistat plays additional role in reducing lipid profile, the effect

is beyond expected from weight reduction alone [12]. This includes serum total, low-density lipoprotein (LDL), and cholesterol concentrations [18]. Some experts believes the mechanism is probably related to fecal fat loss. The drug is contraindicated in pregnancy, cholestasis, and chronic malabsorption. In addition, fat soluble vitamins are prone to malabsorption, hence vitamins supplement is advised [19].

GLP-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) are known to stimulate glucose-dependent insulin secretion. GLP-1 also inhibits glucagon release and delays gastric emptying. GLP-1 receptor agonists are often used in combination with Anti-diabetic medication particularly when weight loss is desired. Liraglutide is manufactured human GLP-1 and it could be used by overweight and obese patients for weight loss purposes. Experts recommend the use of Liraglutide in obese patients with type 2 diabetes where its side effects, need for injections, and cost are justifiable by improve glycaemia in addition to weight loss.

In one trial on diabetic patients, the use of liraglutide was associated with 2 - 4 Kg reduction in weight when compared with placebo or other anti-diabetic medication as glimepiride. Many studies have examined its efficacy in weight reduction in healthy individuals. In one trial comparing 4 doses of liraglutide, orlistat, and placebo has found linear association between the daily dose of liraglutide and weight loss; the range was 4.8 - 7.2 kg [20]. Interestingly, higher doses of liraglutide led to more weight reduction than orlistat. Longer follow-up yield similar results [21]. Additional improvement in cardio-metabolic risk factors, glycated hemoglobin (A1C), and quality of life were observed in obese patients with dyslipidemia and/or hypertension [22]. Liraglutide is known reduce the risk of major cardiovascular events in type 2 diabetic patients and preexisting cardiovascular disease [23]. There is no studies about cardiovascular outcomes of liraglutide in obese patients without diabetes.

The drugs may commonly cause nausea and vomiting. Higher dose was associated with a higher percent of gastrointestinal side effects [20,22,24]. Liraglutide side effects on gastrointestinal may partially explain its role in weight reduction either directly or through suppression of appetite. Other side effects include diarrhea and hypoglycemia. Pancreatitis, gallbladder disease, and renal impairment are less commonly seen serious side effects [22].

Serotonin agonists

Recently, the FDA approved the drug lorcaserin for patient with obesity or overweight and at least one medical comorbidity, such as type 2 diabetes, hypertension, high cholesterol, or sleep apnea [25,26]. Lorcaserin is suggested to have similar efficacy and fewer adverse effects than orlistat. Long term data about safety and efficacy are scant. The mechanism of action is believed to be through reduction in food intake caused by serotonin. Lorcaserin is a selective agonist of the serotonin 2C receptor that leads to reduce appetite and subsequently body weight [27-29]. The efficacy of lorcaserin in weight loss appears to be similar to orlistat (3 to 4 kg mean difference compared with placebo). Most trials that examined lorcaserin showed high loss of follow-up that ranged between 35 to 50 percent. In addition, fewer than 50 percent of patients taking lorcaserin lost 5 percent or more of their baseline body weight [27,28,30,31].

A large randomized trial on 12,000 overweight or obese patients, followed for more than 3 years, compared lorcaserin with placebo to determine the safety of the drug on cardiovascular [30]. The study has concluded that lorcaserin was not incriminated in increasing the risk of cardiovascular events. In the first year, more patients on lorcaserin lost at least 5 - 10 percent of their body weight than placebo. The difference in weight loss between the two groups narrowed after one year but remained significant. Lorcaserin has additional desired effects such as on glucose control, kidney function, and possibly blood pressure and low-density lipoprotein (LDL) cholesterol. In one trial, lorcaserin was associated with fewer incidence of new-onset diabetes among prediabetes patients; lowered glycated hemoglobin (A1C) by 1.0 percentage was seen with 10 mg of lorcaserin in another [30,31]. Nevertheless, 10 mg of lorcaserin was associated with lower risk and slower progression of kidney disease in obese patients with atherosclerotic cardiovascular disease or multiple cardiovascular risk factors [32]. Some trials showed beneficial effects of lorcaserin on blood pressure [27,30] but other trials did not yield such effects [28,31].

Lorcaserin is well-tolerated with mild adverse effects. Reported adverse effects include headache, upper respiratory infections, nasopharyngitis, dizziness, and nausea; all these effects appeared in less than 20 percent of patients [27,31]. In patients with type 2 diabetes on oral anti-diabetic or insulin, lorcaserin may increase the risk of hypoglycemia. Hence the modifying the dose of diabetes medications should be considered [30,31].

Lorcaserin is contraindicated in patients with creatinine clearance (CrCl) less than 30 mL/min and during pregnancy. In addition, lorcaserin should not be used with other serotonergic drugs as SSRIs, bupropion, tricyclic antidepressants, and MAO inhibitors because of the theoretical potential for serotonin syndrome.

Alternative medicine for weight reduction classified by mechanism

Increase energy expenditure

Plant derivatives ephedra and ephedra alkaloid (Chinese Ma huang) are known supplement for weight reduction that are native to china. These derivatives are molecularly similar to sympathomimetic amine ephedrine; known to prolong duration of action, increase peripheral actions, and decrease central actions of adrenergic receptors. Similar component are found in bitter orange and country mallow. Ephedra products are commonly used in combination with caffeine or its botanical sources [33]. In one recent meta-analysis of randomized trials, weight reduction by 0.9 kg per month was observed with ephedra supplements compared with placebo. Yet, long follow-up data for more than 6 months are scarce. Adverse effects from trials of ephedra showed two to three fold increases in the risk of cardiovascular, psychiatric, autonomic, and gastrointestinal symptoms [34]. Other undesired effects as episodes of arrhythmias, hypertension, MI and stroke, and seizures were reported to FDA [35]. Ten events led to death and 13 yielded permanent disability. Among these reports, nine cases occurred despite the recommended dosages of ephedra without significant preexisting cardiovascular risk factors [35]. Although ephedra products comprised less than 1 percent of supplement in 2001, more than 60 percent of herbal adverse events reported to U.S. Poison Control Centers during the same year were due to ephedra products [36]. Hence, in spite of their modest effect, the FDA banned their sale in 2004 and experts discourage their usage [37].

Increase fat oxidation or reduce fat synthesis

Another widely used alternative products for weight reduction is hydroxycitric acid (HCA). HCA is derived from Indian Malabar tamarind tropical fruit. The proposed mechanism of action is through mitochondrial citrate lyase inhibition that leads to decrease production of acetyl coenzyme A production and subsequently fatty acid synthesis [38]. In one RCT comparing HCA with placebo for 12 weeks duration in mildly overweight women, about 1.3 kg greater weight loss was observed in 750 mg daily group [34]. Oppositely, another randomized trial found no difference between HCA and placebo in patients with higher BMI [35]. Experts believe that HCA carries no risks, yet the evidence for efficacy is contradictory.

Conjugated linoleic acid (CLA) is a group of trans-fatty acids. Studies on mice yielded reduction in fat deposition, possibly by increasing fat oxidation and inhibiting triglyceride uptake in adipose tissue [39]. A three-month trial on 60 patients has found no effects of CLA on BMI. Mild to moderate gastrointestinal symptoms were reported [40]. Hence, data supporting the efficacy of CLA for weight reduction in human are absent.

Other examples of these category of supplements include green tea, l-carnitine, vitamin b5, and pyruvate. Unfortunately, most studies on these products were of small sample size. One study has found fat oxidation and thermogenesis effect of green tea in 10 individuals, however, the study was not designed to assess weight loss [41]. Licorice is believed to have effect on body fat mass without BMI changes in 15 persons of normal weight [42]. Adverse effects of licorice include hypertension, pseudoaldosteronism, and hypokalemia [43]. Six gram of pyruvate daily for 6 weeks was associated with 1.2 kg weight reduction compared with placebo [44]. No randomized trials on human support the claims of weight loss caused by vitamin B5 nor L-carnitine [45].

Increase satiety

Soluble fibers is believed to absorb water in the GIT causing increased satiety and lower caloric intake. In addition, fiber consumption may improve diabetes and dyslipidemia commonly seen in obese patients. Accordingly, many weight-loss products are used based on this theoretical believe. Examples include Indian guar gum, glucomannan, and psyllium products. One meta-analysis of 11 randomized trials comparing the efficacy of guar gum in weight loss with placebo found no benefit [46]. Yet, guar gum is considered safe and well-tolerated. Regarding the usage of glucomannan in 3 to 4g daily, three trials suggest modest effect on weight reduction with mild adverse events [47-49]. However, all these trials were of small sample and had methodologic limitations. Psyllium derivatives are purported to improved glucose and lipid parameters compared with placebo in one study including 125 overweight patients with type 2 diabetes; yet, no effects of weight reduction was observed in this study [50].

Conclusion

Obesity is defined as having a body mass index (BMI) greater than 30 kg per m2. While overweight, on the other hand, is a BMI of 25 - 30 kg per m^2. Associations between overweight or obesity and morbidity and mortality were observed since the time of Hippocrates. The US Food and Drug Administration (FDA) have approved many drugs for weight reduction. Natural Medicines Comprehensive Database has identified the presence of more than 50 types of supplements as commonly used and manufactured for weight-loss purposes.

Orlistat is believed to modulate fat digestion through its action on inhibiting pancreatic lipases. Studies have estimated 5 - 10 kg weight loss of orlistat. GLP-1 also inhibits glucagon release and delays gastric emptying. GLP-1 receptor agonists are often used in combination with Anti-diabetic medication particularly when weight loss is desired. The FDA has recently approved lorcaserin for patient with obesity or overweight and at least one medical comorbidity, such as type 2 diabetes, hypertension, high cholesterol, or sleep apnea. Lorcaserin is suggested to have similar efficacy and fewer adverse effects than orlistat.

Plant derivatives ephedra and ephedra alkaloid are known supplement for weight reduction that are native to china. These products have modest effect, however, due to safety concerns, the FDA banned their sale in 2004 and experts discourage their usage. Hydroxycitric acid is another commonly used agent as alternative medication for weight reduction, its efficacy is contradictory. Most studies on green tea, l-carnitine, vitamin b5, and pyruvate were of small sample size, hence their efficacy remains questionable. Although guar gum is considered safe and well-tolerated, studies have found no effect on weight loss.

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