

Pharmacologic Treatment of Adult Obesity – Is There a Magic Pill?

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Obesity is a growing public health problem, worldwide. With an increase in the prevalence of sedentary lifestyles and increased availability of inexpensive high-calorie food, it has become more difficult to maintain a healthy weight that minimizes the incidence of chronic health problems such as diabetes, hypertension, coronary artery disease and cancer. The increase in the incidence of obesity is particularly rapid in developing countries compared to developed countries. Worldwide, there are a billion people who are overweight. Out of that number, 300 million people are considered obese, with 115 million of these people living in developing countries (1-3). In the Middle East, the prevalence of obesity is rising, particularly in women. Middle Eastern women, as a whole, are more obese than women in Western countries, with a resultant increase in obesity-related health problems.

Definition

Overweight refers to a weight above the “normal” range. This is determined by calculating the body mass index (BMI, defined as the weight in kilograms divided by height in meters squared kg/m^2). Fewer health problems are seen in patients with a BMI between 19 and 25 kg/m^2 . Overweight is defined as a BMI of 25 to 29.9 kg/m^2 ; obesity as a BMI of $\geq 30 \text{ kg}/\text{m}^2$. Severe or morbid obesity is defined as a BMI $\geq 40 \text{ kg}/\text{m}^2$ (or 35 kg/m^2 in the presence of comorbidities).

Medical consequences of obesity

Obesity is associated with an increased risk of developing type 2 diabetes, hypertension, dyslipidemia, coronary artery disease, stroke, gallbladder dis-

ease, osteoarthritis, sleep apnea, and cancers of the endometrium, breast, prostate and colon. Hypertension and type 2 diabetes are the most common weight-related health conditions, with incidence increasing as obesity worsens. These chronic diseases also contribute toward the higher risk of early mortality seen in obese people. A BMI $\geq 35 \text{ kg}/\text{m}^2$ is associated with a marked increase in early mortality, though a slight increase in early mortality is seen even in people with a BMI 31-35. The association between obesity and mortality is also influenced by gender and race. For example, women and African Americans tolerate a slightly higher BMI than white males, without a significant increase in overall mortality. The health risks of obesity in people over the age of 74 are unclear; however it appears that the risk of obesity-related death probably lessens with age.

In addition to the physical consequences of obesity, people with a high BMI, especially children, tend to suffer from low self-esteem and behavior problems. Therefore, controlling weight can increase both the length and quality of an obese person's life.

Etiology of obesity

Biologic and environmental factors contribute to the development of obesity. There is a clear correlation between obesity and a caloric intake that exceeds energy expenditure. In addition, genetic traits, biologic characteristics, socioeconomic status as well as other factors that are difficult to control contribute to the development of obesity. However, studies have shown that only 30 to 70% of obesity can be explained by biological or genetic factors. The rest must take into account exogenous factors such as inactivity or excess caloric intake.

Pharmacological interventions for the treatment of adult obesity

Antiobesity drugs are a helpful adjunct to diet, exercise and behavior modification in medically supervised attempts to control the weight of patients whose BMI is greater than 30 kg/m². It is unrealistic to expect complete normalization of weight in individuals who are obese. Rather, a more realistic goal would be weight loss of 10-15% of pretreatment weight, which has been shown to significantly improve the overall health of obese individuals. In addition, patients need to be aware that obesity is a chronic disease, without a cure, and it needs to be treated as such. Once therapy ceases, patients are likely to regain any lost weight.

Prescription medications currently in widespread use for weight loss include sibutramine, orlistat, metformin, phentermine, mazindol, and diethylpropion. Fluoxetine, an antidepressant, has been evaluated for its anorectic abilities, as

well. Weight loss should exceed 2 kg during the first month of drug therapy, fall more than 5 percent below baseline by three to six months, and remain at this level for the duration of treatment, for the drug to be considered effective.

Since 1997, 5 drugs have been removed from markets around the world as a result of poorly documented efficacy and safety: fenfluramine hydrochloride, dexfenfluramine hydrochloride, and phenylpropanolamine hydrochloride worldwide, and diethylpropion hydrochloride and phentermine hydrochloride in Europe.

Fluoxetine

Fluoxetine, a selective serotonin-reuptake inhibitor (SSRI) is approved for the treatment of patients with depression and obsessive-compulsive disorder. Patients who received 60 mg of fluoxetine for 28 weeks lost more weight than those who received placebo (4). However, despite drug continuation, patients regained the weight within the next 6 months of treatment, resulting in no weight difference between the treatment groups by the end of the year-long study. Potential side effects of fluoxetine include anxiety, diarrhea, dry mouth, head ache, nausea and the serotonin syndrome (5;6).

Diethylpropion

Diethylpropion is indicated as a short-term adjunct to exercise, behavioral modification, and caloric reduction in the management of exogenous obesity treatment for patients desiring weight reduction who are on. It exerts its effects by stimulating the hypothalamus to release catecholamines into the central nervous system, probably via norepinephrine and dopamine metabolism. Inhibition of lipogenesis and enhancement of lipolysis may also contribute to weight loss (4).

The usual dose of diethylpropion is 75 mg daily. In placebo controlled trials, patients taking diethylpropion lost

between 1.6 and 11.5 kg more than patients taking placebo, but the efficacy in multidrug trials was no better than for other anorexiant.

Potential side effects of diethylpropion include hypertension, palpitations, tachycardia, chest pain, T-wave changes, arrhythmias, pulmonary hypertension, euphoria, nervousness, insomnia, restlessness, dizziness, anxiety, headache, agitation, confusion, mental depression and psychosis(7;8). The drug may be habit-forming.

Mazindol

Mazindol is a tricyclic anorexigenic agent unrelated to amphetamines that inhibits the reuptake of catecholamines. Mazindol suppresses food intake by inhibiting the feeding center and by stimulating the hypothalamus and causing a decrease in appetite.

Mazindol (1-3 mg daily) produced modest weight loss (0.1-7.3 kg) compared to placebo after 2-20 weeks. Efficacy was improved by combining mazindol with a very-low-calorie diet, and mazindol was shown to improve maintenance of weight loss after a very-low-calorie diet (53.3% vs.20.0%) (4;9).

Side effects of mazindol include insomnia, irritability, nausea, tremor, constipation, blurred vision and dry mouth. Mazindol may be habit-forming, as well (9).

Phentermine

Phentermine is structurally similar to dextroamphetamine, and acts by stimulating the hypothalamus and causing a decrease in appetite. It is marketed for short-term (up to 12 weeks) use as an adjunct to exercise and a hypocaloric diet in patients desiring weight loss. Its anorexiant effects are most likely mediated via norepinephrine and dopamine metabolism(10-12).

The recommended dose is 15-37.5 mg/day, before breakfast, to minimize

insomnia. In placebo-controlled trials, treatment with phentermine led to more (0.6-6.0 kg) weight loss than placebo alone (4). However, concerns about its potentially habituating properties have limited its use.

Common side effects include hypertension, palpitations, tachycardia, euphoria, insomnia, overstimulation, dizziness, dysphoria, headache and restlessness. Primary pulmonary hypertension (PPH), a rare and frequently fatal pulmonary disease, has been reported to occur in patients receiving a combination of phentermine and fenfluramine or dexfenfluramine(11;12).

Metformin

Metformin, a biguanide anti-hyperglycemic, decreases hepatic glucose production, reduces intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization(13;14). It is not metabolized, but is largely excreted, intact, in the urine. It is approved for the treatment of insulin resistance in patients with type 2 diabetes mellitus. Metformin appears to decrease caloric intake by suppressing the appetite, causing weight loss that appears to preferentially involve adipose tissue.

Metformin (850 mg twice daily) plus a low calorie diet (1200 to 1400 kcal daily) was superior to a low calorie diet alone in facilitating weight loss in obese women (15;16) (1). However, in a larger study, lifestyle intervention resulted in a weight loss of 5.6 kg, while metformin alone caused an average 2 kg weight loss over 2.8 years of treatment (1).

Most commonly reported side effects of metformin are diarrhea, nausea or vomiting, flatulence, indigestion, and abdominal discomfort that may occur in up to 50% of patients. These side effects may be caused by high intestinal drug concentrations that cause build up of lactic acid in the bowel wall. Nonetheless, only 5% of patients report discon-

tinuation of metformin due to unacceptable side effects.

Orlistat

Orlistat alters fat metabolism. It inhibits pancreatic lipases, causing an incomplete (30% lower) hydrolysis of fat and resultant increase in fat excretion. Pharmacokinetics reveal that <1% of an oral dose is absorbed, and the absorbed drug is degraded into 2 metabolites, neither of which interferes with the pharmacokinetics of digoxin, phenytoin, warfarin or glyburide. However, there is the potential for malabsorption of lipid-soluble vitamins.

In randomized, placebo-controlled trials, orlistat (60 or 120 mg before each of 3 meals) was prescribed along with a hypocaloric diet containing 30% fat. In the first year of treatment, patients taking orlistat lost, on average, 8.5-10.2% of their body weight, compared to 5.5-6.6% with placebo. When assessing weight loss maintenance, the patients taking orlistat regained less weight than those taking placebo (32 vs. 56%, respectively) (17).

The attrition rate with orlistat was approximately 33%. The major side effects were intestinal borborygmi, cramps, flatus, fecal incontinence and oily spotting, occurring in 15-30%. The side effects frequently subsided after the first several weeks of treatment. Vitamin supplementation, especially with the fat-soluble vitamins A, D, E and beta-carotene, is recommended.

Sibutramine

Introduced in 1997, sibutramine hydrochloride is a relatively new agent for weight loss that has a novel mechanism of action - it is a norepinephrine and serotonin reuptake inhibitor that may also stimulate thermogenesis. It is designed to help people who are obese (body mass index [BMI] > 30) lose weight. In some circumstances, it may be prescribed for people with BMIs of

27-30 when they have other conditions (such as diabetes or sleep apnea) that are aggravated by being overweight. Sibutramine is licensed worldwide for use at 10 to 15 mg/d, at which doses it has been shown to promote modest weight loss when combined with a sensible calorie-controlled weight-loss diet and a regular program of physical exercise (18;19).

Sibutramine acts on serotonin levels in the brain to reduce hunger and provide a feeling of fullness. It exerts its pharmacological actions predominantly via its secondary (M1) and primary (M2) amine metabolites. The parent compound sibutramine is a potent inhibitor of serotonin (5- hydroxytryptamine, 5-HT) and norepinephrine reuptake in vivo but not in vitro. However, metabolites M1 and M 2 inhibit the reuptake of these neurotransmitters both in vitro and in vivo. In human brain tissue M1 and M 2 also inhibit dopamine reuptake in vitro. As with all sympathomimetic agents, sibutramine is felt to reduce food intake by causing early satiety (21). Clinical trials of sibutramine have not detected an increase in heart or lung problems (which were seen with dexphenfluramine and fenfluramine). The European Committee for Proprietary Medicinal Products and the Health Sciences Authority (United Kingdom) conducted independent reviews of sibutramine and concluded that the risk-benefit profile remains positive (20).

All studies indicate that sibutramine works best when combined with behavior and dietary modification as well as an increase in physical activity. A review of published placebo-controlled trials reveals that, on average, patients lost 4.3 kg (4.6%) more with sibutramine than with placebo (22). In a maintenance study, after 2 years of treatment, patients taking sibutramine kept off more weight (4 kg) than those receiving placebo (19). When compared to orlistat and metformin, another study reported an average weight loss of 13.4 kg for sibutramine, 8 kg for orlistat and 9 kg for

metformin (20). Despite a 43% overall attrition rate, most studies reported significant side effects in only 7-20% of patients. The side effects included an average 0.8 mmHg rise in systolic blood pressure, a 0.7-3.3 mmHg rise in diastolic blood pressure and a 4-6 beats per minute increase in pulse rate, as well as occasional insomnia, nausea, constipation and dry mouth. Because of the mild overall elevation in blood pressure, the use of sibutramine is not recommended in patients with uncontrolled blood pressure, though many patients do report a lowering of their mean blood pressure as weight loss progresses.

Conclusions

Obesity is a chronic disease that requires long-term treatment. Treatment, once

initiated and found to be effective, should be continued indefinitely. Effective treatments include behavioral modification, dietary modification and drug therapy, with the combination being more effective than either treatment alone. Available prescription medications for the control of obesity appear to have similar efficacy, with sibutramine having most data in successful weight loss and maintenance. The most significant predictor of successful weight loss is the amount of weight lost in the first several weeks of treatment. Therefore, choice of medical therapy for obesity needs to take into account the possible short-term and long-term side effects of the medications and compare them to the potential improvements in obesity-related diseases. Guidelines suggest that nonpharmacologic therapies should be

tried for 6 months. If weight loss is less than 0.45 kilograms per month, medications for the treatment of obesity may be considered. With the understanding that treatment of any chronic illness requires great commitment on the part of the patient and the physician, combination of medication and life style modification may offer patients the best chance of success in treating this life-threatening disease.

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