
FOR YOUR INFORMATION



PHARMACY NEWSLETTER



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Obesity

Introduction

Obesity is a chronic, complex multifactorial disease that is increasing in incidence. The cost for the treatment and its primary comorbidities is estimated to be more than \$7 billion each year in Canada. Obesity causes many other diseases and conditions, such as; coronary artery disease, hypertension, cholelithiasis, depression, hyperlipidemia, osteoarthritis, infertility, diabetes, reflux disease and sleep apnea. It is also associated with colon, rectal, prostate, ovarian, breast and endometrial cancers. The prevalence of obesity in Canada is now 35% for men and 27% for women. Estimates of Canadian prevalence rates of childhood obesity range from 7 to 43% and is currently on the rise. Body Mass Index (BMI) is the most commonly used standard for classifying the degree of obesity. BMI is calculated by dividing the weight in kilograms by the height in meters squared ($BMI = \text{kg}/\text{m}^2$). There are several other indices used to classify obesity, including: weight-height index or ideal body weight (IBW); waist to hip ratio (W/H); waist circumference (WC). The World Health Organization classifies overweight as having a BMI 25.0 – 29.9 and obese as >30.0 .

Theories of Obesity

Obesity occurs as a result of an imbalance between energy expenditure and caloric intake, which is caused by both physiologic – genetic and environmental factors. Obesity can result from a genetic predisposition as genetic mechanisms regulate food intake, alter energy expenditure and control patterns of fat distribution. Some investigators believe that the body maintains the

metabolic rate around a specific set point. This point may be responsible for low energy output in some people. Various neurotransmitters (serotonin) and gastrointestinal peptides (cholecystokinin, enterostatin, and glucagon) may have an etiologic role in obesity. For example, serotonin suppresses hunger and food intake, while serotonin antagonists increase appetite and food intake. Hypothalamic abnormalities can cause decreased satiety or increased appetite which manifests as hyperphagia, decreased physical activity and obesity.

In our society, devices that minimize energy expenditure proliferated and manual labor has diminished. Thus energy expenditure is substantially decreased in work and leisure activities. With food readily available, this sedentary lifestyle promotes weight gain. Medications such as antipsychotics, tricyclic antidepressants, anti-epileptics, insulin, glucocorticoids, glitazones and sulfonylureas can cause weight gain. Social, cultural and ethnic factors have been associated with obesity. High fat content diets are processed more efficiently by the body and produce less satiation compared to protein and carbohydrates. Psychological factors such as emotional distress, depression and low self-esteem can also result in obesity.

Treatment of Obesity

Obesity must be recognized as a chronic condition requiring long-term therapy, support and follow-up. Although widespread prevention of obesity has been largely unsuccessful, obesity is

considered “potentially preventable”. Reduction of weight and prevention of weight gain can reduce health care costs and improve the health of obese individuals. Studies have found that a modest reduction of 5 to 10% of body weight can modify risk factors for heart disease, reduce blood pressure, improved lipid profile and decrease insulin resistance and blood glucose. One study with type 2 diabetes found that survival increased 3 to 4 months for each kilogram of weight loss.

Treatment includes counseling, caloric restriction, lifestyle changes, behavior therapy, physical activity, pharmacotherapy and surgery. Low calorie diets, aggressive exercise programs and peer group behavioral modification programs have limited short-term results and poor long-term success. Patients often revert to old behavior and regain weight. A successful weight loss program is defined as a 10% weight reduction that has been maintained for five years. The weight-loss goal and the rate of weight loss must be reasonable and achievable. Some patients should not expect to reach ideal body weight as their goal. It is essential that subsequent participation in a program to help maintain the weight loss is followed. A weight management program should have at least 30 minutes of moderately intense physical activity, 5 to 7 times per week. An individualized plan is needed to achieve this goal with emphasis on consistency and comfort initially. For example a lower level workout with several 10-minute periods of physical activity is appropriate. Treatment of an underlying condition such as depression should be considered.

Pharmacotherapy

Pharmacotherapy should not be used for cosmetic purposes or when weight loss can be achieved without medication. The use of agents to reduce weight is not recommended beyond 3 months, except for sibutramine which can be given for up to 1 year. Some antiobesity agents have been associated with adverse effects including the potential for a fatal outcome. The benefits and possible risks of using these agents must be weighed where long-term use is indicated.

Previously available agents – fenfluramine, dexfenfluramine, fenfluramine-phentermine have been withdrawn recently. They were associated with cardiac valvulopathy and were taken off the market in 1997. Phenylpropanolamine (e.g. Dexatrim and other over-the-counter products) have also recently been withdrawn from the market in May 2001 due to association with haemorrhagic strokes. Antiobesity agents should not be used by pregnant or lactating women. The use of weight loss medication in children has not been studied. The simultaneous use of 2 anorexiants medications has not been approved and should be avoided in many cases as serious adverse events could result.

Phentermine, Mazindol, Diethylpropion

These agents are related to amphetamine compounds but were developed to avoid addiction. They act by suppressing appetite by activating sympathetic nervous system via central nervous system stimulation, peripheral release of catecholamines (norepinephrine and dopamine) and inhibiting neuronal reuptake of catecholamines. With these agents, weight loss is initially rapid but then plateaus. This pattern has been viewed as development of tolerance or it may reflect the limit of their therapeutic effect. Fenfluramine (now off the market) and diethylpropion have been associated with primary pulmonary hypertension (PPH). PPH is rare but serious with a 50% mortality rate. It presents as exercise intolerance, chest pain, dyspnea, syncope and lower extremity edema. The relative risk of PPH increases after more than 3 months of treatment. Other adverse effects include insomnia, nervousness, dry mouth, diarrhea, drowsiness, constipation, irritability, stomach upset, blurred vision, dizziness, chest pain, nervousness, pounding heart, breathing difficulties, mood changes and swelling. Drug interactions include high blood pressure medicines, Monamine oxidase inhibitors (MAOI) and any other weight loss drugs. Stimulant drugs such as decongestants and caffeine will increase the heart rate. Those who respond well may lose about 0.5 pounds per week. Those who do not respond in a few weeks should discontinue the drug. However, these drugs

are only indicated for short term pharmacotherapy and most patients regained weight within 2 months of discontinuing their use. See Table 1 for dosing and cost information.

Caffeine plus ephedrine, other herbal products

One such product is Metabolife: guarana (40 mg of naturally occurring caffeine) and ma huang (12 mg of naturally occurring ephedrine). Caffeine suppresses appetite centrally and ephedrine is a thermogenic agent which increases energy expenditure. However, there are no studies that support the recommendation of this combination. A randomized placebo controlled trial found no evidence that an herbal product, garcinia cambogia, promotes weight loss. As well there have been numerous reports of adverse events with the use of ephedrine-containing products such as palpitations, dizziness, gastrointestinal distress and serious outcomes such as psychosis, myocardial infarction, stroke, and death. The US FDA has advised against purchasing these products. Health Canada has recently (January 2002) requested a volunteer discontinuation and recall of products containing Ephedra/ephedrine. It also issued a warning that ephedrine containing products pose a serious risk to health.

Orlistat

Orlistat is indicated in maintenance of weight loss. It acts within the gastro-intestinal lumen to inhibit lipases, which aid in absorption of dietary fats. There have been prospective, randomized trials involving 4000 patients. The response to Orlistat was variable, ¼ to ½ of motivated patients appeared to have success with Orlistat therapy in that it prevented weight regain after dieting or it decreased weight by 5 to 10%. Diabetic patients lost 6 kg in 1 year and non-diabetics lost 8 to 10 kg in 1 year. A diet restricted to 30% of calories obtained from fat must be adhered to in order to prevent the risk of gastrointestinal side effects such as fatty diarrhea. Intestinal side effects (e.g. oily stool) will increase in intensity if the daily dietary fat allowance is exceeded. Because Orlistat interferes with absorption of fat-soluble vitamins,

(e.g. A, D, E and K) a daily multivitamin containing these nutrients is recommended. It should be taken apart from Orlistat. In studies with over 4000 patients, there were a total of 15 reports of breast cancer (12 in Orlistat group, 3 in placebo) The number of patients reporting breast cancer was small but prompted further evaluation. Re-examination of the pre-clinical data and expert reviews concluded that there was no evidence that Orlistat directly or indirectly initiates, promotes or enhances the growth of breast tumors. Side effects include fatty/oily stool, oily spotting, and intestinal gas with discharge, bowel movement urgency, poor bowel control and headaches. Drug interactions include cyclosporine, anticoagulants such as warfarin, insulin, and diabetic medicines. Orlistat must be taken with meals. If it is taken 1 hour away from meals, it will be ineffective.

Sibutramine

Sibutramine (approved December 2000) is a centrally acting antiobesity agent. It is a serotonin and norepinephrine reuptake inhibitor that increases energy expenditure and satiety. The clinical efficacy of sibutramine has been evaluated in about 4600 worldwide. Studies found 10 to 15 mg/day with concurrent diet and lifestyle modification was superior to placebo in promoting and maintaining weight loss for 1 year. Study subjects lost between 4.8 to 6.1 kilograms. However, it has been shown that once sibutramine was stopped, patients regained weight. Responsiveness should be revealed after a 4 week trial. However, it has been found to increase heart rate by 4 or 5 beats per minute and blood pressure by 1 to 3 mm Hg. Therefore, care must be taken when using other agents that raise blood pressure. Sibutramine should not be used in patients with narrow-angle glaucoma, seizures, uncontrolled hypertension, congestive heart failure, coronary artery disease, arrhythmia or stroke. Health Canada has recently (March 2002) issued a warning that it is investigating the safety of sibutramine due to numerous adverse reactions reported (such as increased blood pressure, chest pain, stroke, eye pain and eye hemorrhage). The American Heart Association has also warned

physicians to be cautious prescribing Sibutramine due to increased heart rate and/or elevated blood pressure in some patients. Side effects include dry mouth, drowsiness, constipation, insomnia, headache, dizziness, mood/mental changes, chest pain, pounding or unusually fast heart beats, muscle pain or weakness, numbness and seizures. Drug interaction includes any anorexiants that can raise blood pressure, decongestants, dextromethorphan, antidepressants, lithium, tryptophan, meperidine, pentazocine, ketoconazole, erythromycin, and antihypertensives. A 2-week washout period is needed if a MAOI is stopped before starting Sibutramine. It should not be used in conjunction with other agents that increase serotonin (such as Fluoxetine and other SSRI's) because of the potential of inducing serotonin syndrome. The dose is 10 to 15 mg daily, doses above 15 mg daily are not recommended.

Summary

Antiobesity agents can improve weight loss, but they have been associated with adverse effects, including the potential for a fatal outcome. Where pharmacotherapy is indicated, it should be used in conjunction with a suitable weight management program. The use of phentermine, mazindol and diethylpropion beyond three months is an off-label use and may increase the risk of PPH. Orlistat has demonstrated effectiveness in motivated patients, however patients need to limit the caloric intake from fat to 30%. Sibutramine is a centrally acting agent which may be used up to one year. Patients on sibutramine should be monitored for adverse events such as increased blood pressure, increased heart rates and serotonin syndrome. Obesity is a chronic disease that is increasing at an alarming rate in Canada. Because obesity causes many other diseases and conditions, even modest reduction of 5 to 10% of body weight can have a profound effect of improving the health of overweight and obese individuals.

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TABLE 1			
ANOREXIANT MEDICATIONS			
Drug	Trade Name	Dosage	Unit Cost
Phentermine HCl	Ionamin	15 – 30 mg/d	15 mg = \$1.18/cap 30 mg = \$1.35/cap
Mazindol	Sanorex	1 – 3 mg/d	1 mg = \$0.903/tab 2 mg = \$1.65/tab
Diethylpropion HCl	Tenuate Tenuate Dospan (sustained release form)	25 mg TID 75 mg/d	25 mg = \$0.351/tab 75 mg = \$1.24/tab
Orlistat	Xenical	120 mg TID with meals	120 mg = \$1.46/cap
Sibutramine	Meridia	10 – 15 mg/d	10 mg = \$3.51/cap 15 mg = \$4.04/cap

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