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Medical management of Obesity-Current status

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Pharmacotherapy can be used in conjunction with diet and physical activity to achieve and maintain a realistic degree of weight loss. Pharmacotherapy should be considered for patients with BMI greater than 27 kg/m^2 and associated obesity related complications (i.e. hypertension, CHD, hyperlipidemia, diabetes and sleep apnea) or for those with a BMI greater than 30 kg/m^2 with diagnosed complications in conjunction with diet and exercise.

Physicians are sometimes reluctant to prescribe medications for obesity, possibly because patients rapidly regain weight when treatment is discontinued. However, long-term pharmacotherapy for this chronic condition should not be dismissed. This is especially in view of the fact that the serious systemic adverse effects that have been associated with certain anti-obesity agents in the past can now be avoided with the selection of newer agents. Moreover, a landmark study by Weintraub *et al* (1) showed that appetite suppressant medication combined with diet and behaviour modification can lower body weight by as much as 10kg and maintain this weight loss for as long as 4 years. This achievement had not previously been accomplished by any method except gastric surgery. The drugs available for the treatment of obesity in the past have been outlined below.

In the 1950s and 1960s, amphetamines were the major prescription medications for weight loss (2). In the years after amphetamines were no longer approved for long-term weight loss, behavioural treatments and diet changes were used as the main strategy to achieve weight loss. No new medications were approved by the FDA for obesity treatment from 1973 to 1996 (2).

Weight loss medications again gained wide popularity in the mid 1990s with the introduction of fenfluramine and dexfenfluramine. However, these drugs were withdrawn from the market due to the continued reporting to the FDA of heart valve defects.

Currently, there are limited choices for pharmacotherapy for obesity, yet understanding of the disease and the individual neurochemical processes involved is rapidly developing. The introduction of the new agents, sibutramine, orlistat and rimonabant demonstrates that medications are evolving to treat obesity (Table-1).

Table -1 : Newer Antiobesity agents

Drug	Class	Dose
Sibutamine	Centrally acting appetite suppresent (Inhibits reputake of serotonin and nonadrenaline. This results in suppression of appetite and inducement of satiety)	Usual initial dose : 10mg OD Maximum dose : 15mg OD Patients who do not tolerate 10mg can be switched to 5mg OD
Orlistat	Lipase inhibitor (Inhibits lipase necessary for absorption of body fat)	120mg tid
Rimonabant	CB_1 receptor antagonist	5-20mg tid

A combination of drug therapy, dietary therapy and increased physical activity provides the most successful therapy for weight loss and weight maintenance.

Sibutramine:

Sibutramine blocks the presynaptic reuptake of both norepinephrine and serotonin, thereby potentiating the anorexic effect of these two neurotransmitters in the CNS. Unlike fenfluramine and dexfenfluramine, which also release serotonin from presynaptic sites, sibutramine did not cause valvular heart disease in 133 patients treated for a mean of 7.6 months (3). Sibutramine given at 2-5 times the therapeutic dose was found to lack acute abuse potential in comparison with 20mg of D-amphetamine (4).

The randomized, double-blind trial of sibutramine involved 605 obese subjects recruited from 8 European centers (5). After being treated for 6 months with a hypocaloric diet and 10 mg/d of sibutramine, 467 subjects achieving more than 5% weight loss were more randomized to 18 months of further treatment with 10-20 mg/d of sibutramine (n=352) or placebo (n=115). Forty-two percent of subjects in the sibutramine group and 50% in the placebo group dropped out. Of subjects completing the trial, 43% in the drug group as compared with 16% in the placebo group maintained 80% or more of their original weight loss. An absolute weight loss of 8.9 kg was documented from baseline. Allowing for dropouts and nonresponders, one of five subjects who received sibutramine for the entire 24 months of the study maintained 80% or more of their original weight loss.

In a number of studies lasting up to I yr, weight loss with a hypocaloric diet and 10-20 mg/d of sibutramine ranged from 4.7-7.3% of baseline or about 2-3 times that observed in placebo treated control subjects (6-9). The decline in fasting triglyceride levels ranged from 4.5-42 mg/dl (0.051-0.47 mmol/L), the increase in high-density lipoprotein cholesterol ranged from 3-9

mg/dl and changes in LDL were small and variable. Consistent side effects of sibutramine therapy included a 0.3-2.7 mmHg increase in systolic blood pressure, a 1.6-3.4 mmHg increase in diastolic blood pressure, and a 2-5 beat per minute increase in resting heart rate. Other side effects included headache, insomnia, dry mouth and constipation. One study found that the frequency of adverse events could be reduced without sacrificing efficacy if sibutramine was given intermittently as 12 wk of active drug alternating with 7 wk of placebo over a 44-wk period (10).

ORLISTAT:

Orlistat is the only approved inhibitor of the gastrointestinal lipases, predominantly pancreatic lipase, necessary for the hydrolysis of triglyceride to free fatty acids in the lumen of the gut. Because this agent can reduce the absorption of dietary fat by up to 30%, it produces weight loss comparable to or greater than that obtained by placing an individual on a fat restricted diet. Although there are no systemic side effects of orlistat due to its lack of absorption, supplementation of fat-soluble vitamins may be prudent to prevent the development of vitamin deficiency syndromes.

In a representative 2yr study, 1187 obese adult subjects were placed on a hypocaloric diet for 4wk (11). Of this group 892 subjects were randomized to receive placebo 3 times a day or orlistat, 120 mg 3 times a day, for 52 wk. At the end of this period, the orlistat group was again randomized to 3 times a day for an additional 52wk. During the first year, orlistat treated subjects lost more weight than placebo treated subjects (8.76 to 5.81 kg; $p < 0.001$). During the second year, subjects treated with orlistat 120mg 3 times a day regained 35.2% of lost weight; subjects treated with orlistat 60mg 3 times a day regained 51.3% of lost weight and subjects treated with placebo regained 63.4% of lost weight.

In contrast to sibutramine, orlistat causes significant reductions in total and low-density lipoprotein cholesterol and in systolic and diastolic blood pressure. Gastrointestinal side effects of orlistat, including loose stools, increased defecation, fecal urgency and oily discharge are significantly more common than observed with placebo and may lead to discontinuation of the drug. One study found that concomitant use of natural fibre (psyllium mucilloid) may reduce the incidence of these gastrointestinal side effects (12).

Because their mechanisms of action differ, it is reasonable to ask whether combined therapy with orlistat plus sibutramine might produce a greater degree of weight loss than is achievable with either agent alone. One study of 34 obese women addressed this issue (13). Subjects were treated with sibutramine for 1 yr and achieved a mean weight loss of 11.6% of initial weight. They were then randomly assigned in a double blind

fashion to 16 additional wk of treatment with either sibutramine plus placebo or sibutramine plus orlistat. The study demonstrated that addition of orlistat produced no additional weight loss during the 16wk of combined therapy. This finding suggests that weight loss with currently available agents may be limited to about 10% of starting weight. Only 20-30% of unselected individuals will come close to this degree of weight loss, body weight begins to rise again after 12-18 months of treatment. The possibility of long term failure of these agents must be borne, in mind and drug therapy should be discontinued if significant weight regain occurs.

RIMONABANT:

It is a cannabinoid receptor antagonist. Cannabinoids are well known for centuries for its appetite enhancing effect. Keeping this knowledge in mind people discovered the endo cannabinoid system. The cannabinoid (EC) system contributes to the physiological regulation of energy balance, food intake, and lipid and glucose metabolism through both central and peripheral effects. EC acts on various region of hypothalamus viz lateral hypothalamus, acute and paraventicular nucleus. At periphery EC has direct effect on fat cells through cannabinoid one (CB_1) receptor, it promotes, lipogenesis and positive energy balance. CB_1 receptor is also expressed in various other peripheral organs including autonomic nervous system, liver, muscle and gastrointestinal tract (14). Administration of the first endocannabinoid discovered, anadamide, in hypothalamus or of 2-arachidonoxyl-glycerol in the nucleus accumbens can provoke food intake in satiated rodents (15).

Rimonabant is a CB_1 receptor antagonist, it increases serotonin and dopamine levels by increasing their turn over. Centrally it blocks CB_1 receptor, inhibits orexigenic action of ghrelin and causes reduction in appetite. Peripherally, it causes lipolysis as well as increases basal metabolic rate. The effects of Rimonabant were studied in more than 1500 patients in Rimonabant in obesity Europe (RIO Europe) study (16). The results of this phase 3 study showed that weight loss at 1 year was significantly greater in patients treated with rimonabant 5mg (mean-3.4 kg, [SD 5.7]; $p=0.002$ vs placebo) and 20 mg (-6.6 kg, [7.2]; $p < 0.001$ vs placebo) compared with placebo (-1.8 kg [6.4]). Significantly more patients treated with rimonabant 20mg than placebo achieved weight loss of 5% or greater ($p < 0.001$) and 10% or greater ($p < 0.001$). Rimonabant 20mg produced significantly greater improvements than placebo in waist circumference, HDL-cholesterol, triglycerides and insulin resistance and prevalence of the metabolic syndrome. The effect of rimonabant 5 mg were of less clinical significance. Rimonabant was generally well tolerated with mild and transient side effects.

Rimonabant is prescribed in a doses of 5-20 mg/day. Common side effects are

nausea, vomiting, depression and anxiety. As seen with other antiobesity drugs, tolerance is quickly developed to its anorexic effect (16).

Many drugs are available and many more are under development for management of obesity *viz* leptin analogues, neuropeptide antagonist, amylin, melanocortin-4 receptor antagonist, and glucagon - like peptide agonists (GLP-1)

The need of new drugs arises because most of the available drugs are associated with limitations like can reduce up to 5-10% of body weight, rebound weight gain, associated side effects and lack of predictability.

In conclusion, available antiobesity drugs are effective only in presence of hypocaloric diet and physical activity. Most of the drugs can reduce up to 10% of body weight. So, quest for novel anti-obesity drug is not yet over.

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