

Pharmacologic Therapy of Obesity

Antiobesity agents

Drugs against inflammatory cytokines

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1. SUMMARY

- Pharmacotherapy can be a helpful adjunct for the treatment of obesity in some patients. These drugs should be used only in the context of a treatment program that includes— diet, physical activity changes, and behavior therapy. If lifestyle changes do not promote weight loss after 6 months, drugs should be considered.
- Pharmacotherapy is currently limited to those patients who have a BMI ≥ 30 , or those who have a BMI ≥ 27 if concomitant obesity-related risk factors or diseases exist.
- Currently, sibutramine and orlistat are approved by the FDA for long-term use in weight loss. Sibutramine is an appetite suppressant that is proposed to work via norepinephrine and serotonergic mechanisms in the brain. Orlistat inhibits fat absorption from the intestine. Both of these drugs have side effects. Sibutramine may increase blood pressure and induce tachycardia; orlistat may reduce the absorption of fat-soluble vitamins and nutrients.

2. INTRODUCTION

- Drugs are recommended for use as an adjunct to diet and physical activity for patients with a BMI ≥ 30 Kg/m², without concomitant obesity-related risk factors or diseases, and for patients with a BMI ≥ 27 Kg/m² who have concomitant obesity-related risk factors or diseases such as hypertension, diabetes, or hyperlipidemia.
- If an individual with a BMI ≥ 27 Kg/m² meets diagnostic criteria for metabolic syndrome, then obesity pharmacotherapy may be indicated.
- Weight loss medications should not be used for cosmetic reasons.
- Weight loss using monotherapy with the drugs that are currently available is usually not $>10\%$, even with a lifestyle intervention in addition to medication..
- Not every patient responds to drug therapy. Trials have shown that initial responders tend to continue to respond, whereas initial nonresponders are less likely to respond, with an increase in dosage. If a patient does not lose 2 kilograms (4.4 lbs) in the first 4 weeks after initiating therapy, the likelihood of long-term response is very low. This may be used to guide treatment by continuing medication for the responders or by discontinuing it for the nonresponders.
- Medications cannot be expected to continue to be effective in weight loss or weight maintenance once the drug has been stopped. The use of a drug may be continued as long as it is effective and the adverse effects are manageable and not serious.
- Appropriate monitoring for side effects must be continued while drugs are part of the regimen. Patients will need to return for follow-up visits. The purpose of these visits is to monitor weight, blood pressure, and pulse, discuss side effects, conduct laboratory tests, and answer the patient's questions.
- Ephedrine plus caffeine, and fluoxetine have also been tested for weight loss but are not approved for use in the treatment of obesity. Mazindol, diethylpropion, phentermine, benzphetamine, and phendimetrazine are approved for only short-term use for the treatment of obesity. Herbal preparations are not recommended as part of a weight loss program. These preparations have unpredictable amounts of active ingredients and unpredictable, and potentially harmful, effects.

3. SIBUTRAMINE

Mode of action

- Sibutramine is a highly selective inhibitor for the reuptake at nerve endings of norepinephrine(NA) and serotonin (5-HT) and to a lesser degree, dopamine.
- Sibutramine reduces food intake by enhancing central NA and 5-HT function.
- Sibutramine promotes a feeling of having eaten enough.

Efficacy

Sibutramine has been evaluated extensively in several multicenter trials . In a 6-month dose-ranging study of 1047 patients, 67% treated with sibutramine achieved a 5% weight loss from baseline, and 35% lost 10% or more. There was a clear dose–response effect in this 24-week trial, and patients regained weight when the drug was stopped, indicating that the drug remained effective when used⁽¹⁾.

Studies in Diabetic Patients

A meta-analysis of 8 studies in diabetic patients receiving sibutramine showed that changes in body weight, waist circumference, glucose, hemoglobin A1c, triglycerides, and high-density lipoprotein (HDL)-cholesterol favored sibutramine. The mean weight loss was -5.53 ± 2.2 Kg for those treated with sibutramine and -0.90 ± 0.17 Kg for the placebo-treated patients.⁽²⁾

Other beneficial effects

- Various risk factors associated with long-term cardiovascular morbidity were reviewed including: serum total, LDL and HDL cholesterol levels, serum triglyceride levels, and change in measurement of waist circumference and waist: hip ratio. Although most of these risk factors showed changes in the direction that would be associated with improved cardiovascular risk, only some changes reached a level of statistical significance.
- In people with Type 2 diabetes the improvement in blood glucose control seen in the studies was not statistically significant when the population prescribed sibutramine was considered as a whole, although the improvement was significant for those people with Type 2 diabetes losing the most weight.

Studies in Hypertensive Patients

- The effects of sibutramine on blood pressure have been evaluated in a meta-analysis of 21 studies. Sibutramine produced a significant overall weight loss and significant increase in both systolic and diastolic blood pressure.
- Kim et al⁽³⁾ found the effect on systolic blood pressure to be greater with higher doses of sibutramine, in individuals weighing 92 kg or more and in younger individuals <44 years of age. Diastolic blood pressure also increased in older individuals with body weights of 92 kg.
- Taken together with the adverse effect on blood pressure seen in some individuals, these results suggest that caution should be exercised in translating the effects of weight loss

with sibutramine into a presumption of long-term improvement in cardiovascular risk or diabetic outcomes.

Limitations

- Given the lack of evidence of efficacy of sibutramine in people younger than 18 years, and the fact that obesity in children is increasing, further research on the clinical effectiveness and safety of sibutramine in this age range would be desirable.
- There is no evidence to support the co-prescribing of sibutramine with other pharmacotherapy aimed at weight reduction.
- Side Effects
 - Sibutramine's main side effects include a dry mouth, constipation, headaches, and dizziness; all may be improved by drinking more water when losing weight.
 - Poor sleep and agitation may occur early in treatment and are usually self limiting. Caution should be exercised when combining sibutramine with selective serotonin reuptake inhibitors because of potential drug interactions.
 - The noradrenergic action increases heart rate by 1-2 beats/min and attenuates the fall in blood pressure expected with weight loss. Some patients, especially if they fail to lose weight, may record a rise in their blood pressure; it is therefore essential to monitor blood pressure during the first 12 weeks of treatment.

Contraindications

- Concomitant use of MAOs and centrally- acting weight loss agents such as amphetamines.
- Drug/alcohol abuse
- Psychiatric illness:

-During premarketing testing, seizures were reported in < 0.1% of sibutramine treated patients. Sibutramine should be used cautiously in patients with a history of seizures.

It should be discontinued in any patient who develops seizures.

-Although sibutramine did not affect psychomotor or cognitive performance in healthy volunteers, any CNS active drug has the potential to impair judgment, thinking or motor skills.

- Inadequately controlled hypertension (> **140/90 mmHg**)
- Cardiovascular disease or arrhythmias
 - Sibutramine substantially increases blood pressure and/or pulse rate in some patients. Therefore, it should not be used in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke.
 - Certain centrally-acting weight loss agents that cause release of serotonin from nerve terminals have been associated with pulmonary hypertension (PPH), a rare but lethal disease. In pre-marketing clinical studies, no cases of PPH have been reported with sibutramine capsules. Because of the low incidence of this disease in the underlying population, however, it is not known whether or not Sibutramine may cause this disease.
- Hyperthyroidism
- Pheochromocytoma
- Pregnancy/lactation

- Severe hepatic or renal disease
- Age <18 years and > 65 years (no enough data)
- Narrow angle glaucoma

Dosage

Sibutramine produced a dose-related weight loss when given in the range 5-30 mg/day, with an optimal dose of 10-15 mg/day. Patients are usually started on a 10 mg dose per day.

Initiation and monitoring

- The recommended starting dose of Sibutramine is 10 mg administered once daily with or without food. If there is inadequate weight loss, the dose may be titrated after four weeks to a total of 15 mg once daily. The 5 mg dose should be reserved for patients who do not tolerate the 10 mg dose. Blood pressure and heart rate changes should be taken into account when making decisions regarding dose titration.
- Doses above 15 mg daily are not recommended. In most of the clinical trials, Sibutramine was given in the morning.
- The safety and effectiveness of MERIDIA, as demonstrated in double-blind, placebocontrolled trials, have not been determined beyond 2 years at this time.

4. ORLISTAT

Mechanism of Action

- Orlistat is a lipase inhibitor. About 30% of fat that would otherwise have been absorbed passes straight through the bowel and is excreted in the faeces. Orlistat has little effect in subjects eating a low-fat diet.
- Orlistat itself is not absorbed, except in very small quantities and thus its side effects are restricted to the gastro-intestinal tract .
- Orlistat treatment results in a dose-dependent reduction in body weight in obese subjects, with an optimal dosage regimen of 120 mg tid

Clinical Effectiveness

- In absolute terms, mean weight loss from trials shows a relatively small reduction, of some two to five kilograms per year over the weight decline with placebo.
- This has been accompanied by small but significant reductions in total cholesterol and the ratio of total cholesterol to high-density cholesterol, and in both diastolic and systolic blood pressure.
- By pooling 6 studies, Haddock et al⁽⁴⁾ estimated the weight loss in patients treated with orlistat as -7.1 kg (range: -4.0 to -10.3 kg) compared with -5.02 Kg (range:-3.0 to -6.1 Kg) for the placebo treated groups.

Orlistat in diabetic patients

- Finer et al⁽⁵⁾ compared orlistat with placebo, all risk factors for coronary heart disease improved and 37% fewer patients developed diabetes over four years.
- Reduced intestinal fat absorption may have direct effects on improving lipids and insulin sensitivity. Patients with diabetes treated with orlistat, 120 mg 3 times daily for 1 year,

lost more weight than the placebo treated group. The subjects with diabetes also showed a significantly greater decrease in hemoglobin A1c levels.⁽⁶⁾

- The XENDOS (Xenical in the prevention of Diabetes in Obese Subjects trial) was a randomised, double-blind, placebo-controlled, prospective, multicentre trial investigating whether orlistat 120 mg tid combined with hypocaloric diet and moderate physical exercise can reduce the incidence of type 2 diabetes in obese subjects over a period of 4 years. Weight loss was greater in the orlistat group (– 6.9 kg; n = 1 640) than in the placebo group (– 4.1 kg; n = 1 637; p <0.001). Such a difference in weight reduction was sufficient to significantly reduce the cumulative incidence of type 2 diabetes (6.2% versus 9.0%; p = 0.0032; relative risk reduction of 37.3%). The difference was especially remarkable in obese patients with impaired glucose tolerance, with a reduction of conversion to diabetes from 28.8% in the placebo group to 18.8% in the orlistat group
- Significant and sustained reductions in cardiovascular risk factors such as arterial blood pressure and lipid levels were also observed in the orlistat group as compared to the placebo group.⁽⁷⁾

Limitations

- Orlistat itself is not absorbed, except in very small quantities and thus its side effects are restricted to the gastro-intestinal tract.
- Orlistat can cause ‘fatty stools’, urgency and increased frequency of defecation often with anal leakage or oily spotting.
- Orlistat can cause small but significant decreases in absorption of fat-soluble vitamins. Levels usually remain within the normal range, but a few patients may need vitamin supplementation. Because it is impossible to tell which patients need vitamins, it is wise to provide a multivitamin routinely with instructions to take it before bedtime.
- Orlistat does not seem to affect the absorption of other drugs, except cyclosporin.
- The Food and Drug Administration (FDA) approved orlistat capsules as an over-the-counter (OTC) weight loss aid for overweight adults.

Contraindications

- Orlistat is contraindicated in patients with chronic malabsorption syndrome or cholestasis, and in patients with known hypersensitivity to orlistat or to any component of this product.
- Pregnancy : Category B. There are no adequate and well-controlled studies of XENICAL in pregnant women. Because animal reproductive studies are not always predictive of human response, orlistat is not recommended for use during pregnancy.
- Lactation: It is not known if orlistat is secreted in human milk. Therefore, orlistat should not be taken by nursing women.

Dosage

There is a dose response to orlistat. The maximal weight loss is achieved between 6 and 9 months. The maximum weight reduction is attainable with 120 mg tds. The 30 and 60 mg doses were less effective.

Initiation and monitoring

- The recommended dose of orlistat is one 120-mg capsule three times a day with each main meal containing fat (during or up to 1 hour after the meal).
- The patient should be on a nutritionally balanced, reduced-calorie diet that contains approximately 30% of calories from fat. The daily intake of fat, carbohydrate, and protein should be distributed over three main meals. If a meal is occasionally missed or contains no fat, the dose of orlistat can be omitted.
- Because orlistat has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene, patients should be counseled to take a multivitamin containing fat-soluble vitamins to ensure adequate nutrition. The supplement should be taken at least 2 hours before or after the administration of orlistat, such as at bedtime.
- Doses above 120 mg three times a day have not been shown to provide additional benefit.
- Based on fecal fat measurements, the effect of orlistat is seen as soon as 24 to 48 hours after dosing. Upon discontinuation of therapy, fecal fat content usually returns to pretreatment levels within 48 to 72 hours.
- The safety and effectiveness of orlistat beyond 4 years have not been determined at this time.

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