Using sibutramine to treat obesity

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Sibutramine produces significant reduction in body weight and central adiposity, and improves some cardiovascular risk factors.

Obesity has become a growing problem in Australia over the last two decades, and the prevalence is expected to increase. Obesity causes and exacerbates many chronic medical conditions, including diabetes, hypertension, dyslipidaemia, arthritis, asthma, sleep apnoea and cardiovascular disease. Patients usually seek treatment because of the perceived medical consequences, social stigma and psychological and physical discomforts. In obese people, weight loss has substantial benefits with improvements in mobility, dyspnoea, cardiovascular risk factors, confidence and psychological wellbeing.

A number of medications have been introduced over the years to treat obesity but most have been withdrawn because of side effects or lack of efficacy. There are two weight loss drugs – sibutramine (Reductil) and orlistat (Xenical) – that are currently approved for long term use. In studies, both drugs have been shown efficacious and safe over two years of treatment. This article discusses the use of sibutramine.

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How does sibutramine work?

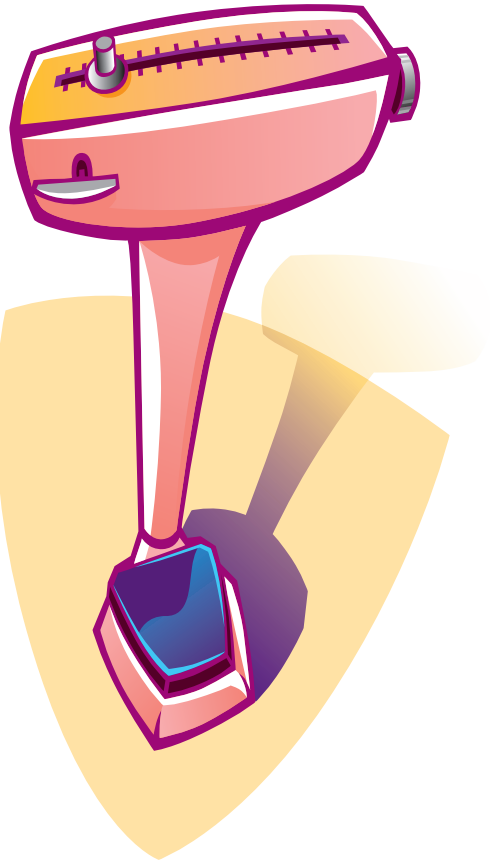
Sibutramine inhibits serotonin and noradrenaline uptake in nerve terminals. In the brain's appetite centres, this results in increased satiety. There is an earlier feeling of fullness when eating a meal and reduced snacking between meals. Sibutramine does not produce the strong anorectic effect that patients may have experienced with older appetite suppressants.

The central action also leads to increased sympathetic activity. This results in a beneficial rise in energy expenditure, but also causes an increase in heart rate and blood pressure.

Study findings

Several large studies have shown sibutramine to be effective at reducing body weight. Weight loss is seen after one to two months of treatment, with maximal loss achieved by six months and maintained for up to two years while taking the medication. The average weight loss is 4 to 6 kg. When the medication is ceased the patients slowly regain the lost weight.

In one study performed in a general practice setting, at least 10% of body weight was lost by 19% of patients treated with sibutramine 10 mg and 34% of those treated with 15 mg. In comparison, only 7% of patients using placebo lost 10% of their body weight. Nonetheless, it should be noted that 9% of sibutramine treated patients did not lose or gain weight. In two studies, sibutramine has also been shown to maintain weight loss that resulted from being on very low calorie diet.



Studies have shown consistently an improvement in central adiposity and lipid profile, and in glucose levels in diabetic subjects. However, it is important to note that sibutramine has not been shown to reduce the increased mortality associated with obesity. Effects on blood pressure have varied in different studies: from blood pressure remaining unchanged in some studies to increasing by 4 mmHg (in both systolic and diastolic measurements) in others.

Choice of patients

Patients who are suitable for treatment with sibutramine have significant obesity or obesity related comorbidity. This equates to a body mass index (BMI) of at least 35 kg/m^2, or 30 kg/m^2 when there is an obesity associated comorbidity, such as excess central adiposity, diabetes, hypertension, arthritis of weight-bearing

joints or sleep apnoea. The drug is, however, approved for use with a BMI equal to or above 27.5 kg/m^2.

Patients should be prepared to take the medication for more than six months and to follow a lifestyle weight loss program at the same time – studies have shown an improved response with concurrent diet and exercise programs. Sibutramine's ability to prevent weight regain after a successful weight loss program makes it suitable to use when a patient has a past history of rapid regain after previous weight loss programs and is afraid of repeating the experience.

In practice

The usual starting dose for sibutramine is 10 mg taken in the morning. Patients should be warned not to expect an obvious anorectic effect and that the absence of this sensation does not preclude a useful response.

Before starting treatment, patients should be weighed on reliable scales and have their waist circumference measured; blood pressure should be well controlled – that is, below 140/90 mmHg. They should also be commenced on a lifestyle weight loss program that includes regular exercise and some form of diet, such as restrictive eating or a low fat diet. Review by a dietitian may be helpful.

Patients should be followed up within two weeks of starting sibutramine and then fortnightly for the first two months of treatment. The lifestyle program should be reinforced with each visit. Weight loss may be delayed for one month; however, if less than 2 kg of weight is lost after one month, the dose should be increased to 15 mg. If total weight loss is less than 2 kg after a further month, sibutramine is unlikely to produce significant weight loss and can be ceased. Patients in whom treatment is successful should continue the medication long term or as long as they can afford it.

Generally, patients' expectations of weight loss are unrealistic and not met by the medication. By reinforcing realistic treatment goals and explaining benefits of smaller degrees of weight loss, doctors may improve long term compliance.

Side effects and problems

Side effects are fairly frequent, but usually mild. The main ones are insomnia, headache, dry mouth, nasal stuffiness, nausea and constipation. They often improve with continued use or with a temporary reduction in dose from 15 to 10 mg in patients taking the higher dose.

Exacerbation of hypertension is relatively uncommon if blood pressure is well controlled before starting treatment. Blood pressure should be monitored every two weeks in the first month of treatment and after increasing the dose, and if consistently 140/90 mmHg or above, the treating doctor should consider increasing antihypertensive therapy or stopping or reducing sibutramine. Pulse rate may also increase, but this is very unlikely to be problematic.

Sibutramine should not be used in the first month after acute myocardial infarction or stroke. Use in patients with a history of arrhythmias, particularly ventricular, and in those with epilepsy should be cautious. The treating specialist's opinion should be sought prior to starting the drug. There is no evidence that sibutramine causes the cardiac valvular lesions produced by the now withdrawn appetite suppressant fenfluramine.

Interactions

Drug interactions with sibutramine are as expected from the mechanism of action. Medications that have a serotonergic or adrenergic effect or that inhibit serotonin or catecholamine uptake should be avoided because of the risk of a serotonin syndrome or excess adrenergic effect. This particularly applies to selective serotonin reuptake inhibitor (SSRI), tricyclic, tetracyclic and monoamine oxidase inhibitor (MAOI) antidepressants. A two-week wash out period is required after patients have ceased MAOIs before starting sibutramine. In practice, because sibutramine has a mild antidepressant action, it is often possible if the condition is not severe to stop an antidepressant and, after the wash out period, replace it with sibutramine only.

There is no literature on combined use with phenothiazines and newer antipsychotic medications. Hence, combination of these with sibutramine is best avoided at present.

Sibutramine is metabolised by cytochrome P450. However, other drugs that compete with or inhibit this mechanism do not seem to produce an adverse effect when used with sibutramine.

Summary

Sibutramine is the most effective weight loss medication currently available. Treatment is relatively simple, with few major side effects, and should be continued for as long as possible. Blood pressure monitoring is important, and the main drug interaction is with all types of antidepressants. MT

Further reading

1. Wadden TA, Berkowitz RI, Sarwer DB, Prus-Wisniewski R, Steinberg C. Benefits of lifestyle modification in the pharmacologic treatment of obesity: a randomized trial. Arch Int Med, 2001; 161: 218-227.

2. Smith IG, Goulder MA. Randomized placebo-controlled trial of long-term treatment with sibutramine in mild to moderate obesity. J Fam Pract, 2001; 50:505-512.

3. James WP, Astrup A, Finer N, et al. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. Lancet 2000; 356: 2119-2125.

DECLARATION OF INTEREST: Dr Marks has received honoraria for giving talks on sibutramine.