UPDATE ON PHARMACOTHERAPY FOR WEIGHT CONTROL AND OBESITY

There are serious health, economic and social consequences of obesity.

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OVERVIEW OF ECONOMIC COSTS

Estimates of the economic impact of overweight and obesity in less developed countries are not available. However, the relative costs of obesity are likely to exceed those in more affluent countries for a number of reasons. These include the accompanying rise in coronary heart disease and other non-communicable diseases, the need to import expensive technology with scarce foreign exchange and the need to provide specialist training for health care professionals. As many countries are still struggling with undernutrition and infectious disease, the escalation of obesity and related health problems creates a double economic burden. The cost of pharmacotherapy in an obese patient with 2 or more co-morbid diseases is estimated to be only Ɛ3 462 per life year gained. However, long-term sick leave taken will afford a 1.4 - 2.4-fold higher indirect cost to government and employers, and likewise the cost of disability pensions will be elevated 1.5 - 2.8-fold. Loss of productivity for obese patients will make up 7% of total loss of productivity.

RATIONALE FOR THE USE OF PHARMACOTHERAPY IN OBESITY

Pharmacological treatment of obesity can be based on at least 3 main principles. Some drugs act via appetite-regulating mechanisms in the brain. Other agents can reduce the uptake of fat, and thereby energy, from food. Drugs designed exclusively to stimulate energy expenditure in the body are also being developed, but are still largely experimental.

A growing body of evidence has eroded ingrained misconceptions about obesity that have traditionally been obstacles to the appropriate use of medication in obesity treatment. Of these paradigm shifts that have lead to the inclusion of weight loss drugs in current guidelines for obesity treatment,[1] the following are most compelling:

- understanding that obesity is a true disease with genetic determinants (not a 'character flaw')
- understanding that obesity is a major public health threat (not merely a 'cosmetic' issue)
- understanding that weight regain after stopping medications indicates that obesity is a typical chronic disease (not that drug treatment is a failure).

A genetic contribution to obesity is supported by the findings of greater similarity of body mass index (BMI) between monozygotic v. dizygotic twins and correlation of BMI with biological but not adoptive parents.[2] In addition, low metabolic rates have shown familial aggregation, greater similarity in monozygotic than dizygotic twins, and correlation with weight gain and BMI.[3]

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PRINCIPLES OF DRUGS FOR WEIGHT CONTROL (TABLE I)

While older-generation noradrenergic appetite suppressants are approved for obesity treatment in the USA and South Africa, obesity experts agree that these schedule II (e.g. amphetamine-dextroamphetamine and methamphetamine) and schedule III drugs (e.g. benzphetamine hydrochloride and phendimetrazine tartrate) have no current appropriate role in obesity treatment given the availability of newer anorectics (schedule IV) with negligible addiction or abuse liabilities.[4] In addition their side-effect profile is far more favourable and outcome-based data are available from placebo-controlled trials.

Table I. **Pharmacotherapy of agents known to produce weight loss**

Agents	Releasing agent			Reuptake inhibitor		
	5HT	NA	DA	5HT	NA	DA
Dexamphetamine		x	x			
Phentermine		x	x			
Fenfluramine	x					
Dexfenfluramine	x					
Fluoxetine				x		
Sibutramine				x	x	
Orlistat						

Among recent studies relating BMI to morbidity and mortality, there is general agreement that patients with a BMI exceeding 27 with complications, or a BMI exceeding 30 without complications, are potential candidates for weight loss drugs.[5,6] In addition, weight loss drugs should only be taken by patients who fully acknowledge obesity as a true chronic medical disease requiring nothing less than lifelong vigilance toward diet and activity patterns for sustained weight loss. Indefinite duration pharmacotherapy may be shown to be appropriate in some cases of obesity, as with other chronic diseases.

ORLISTAT AND SIBUTRAMINE

Orlistat is a substance that blocks the effect of lipases, i.e. enzymes that break down the neutral fats (triglycerides) in the diet into fatty acids.[7] This reduces the uptake of fatty acids, cholesterol, and fat-soluble vitamins in the gastrointestinal tract. In 1997 it was approved by the US Food and Drug Administration (FDA). The most common side-effects of orlistat involve the gastrointestinal tract and include oily discharge from the rectum, urgency in bowel evacuation and faecal incontinence.[7] Since these side-effects are the result of greater amounts of fat in the bowel, restricting the intake of fat in the diet reduces these problems. The prevalence of side-effects decreases with continued use of orlistat. Very rare cases of elevated aminotransferases and alkaline phosphatase and occasional cases of hepatitis have been reported. Clinical trials have reported some reduction of fat-soluble vitamin levels in the blood, although usually within normal limits. No clinical cases of vitamin deficiency have been reported. The trade name of the drug is Xenical.

Sibutramine is an agent with serotonin-noradrenalin-reuptake inhibition.[8] More recently clonidine-like central effects have also been described (Fig. 1).

During the 1990s, sibutramine was evaluated in increasingly larger clinical trials and was shown to be effective in treating obesity. Since sibutramine has both noradrenergic and

Table II. **Post-marketing surveillance study on sibutramine**

BMI – mean reduction	-3.7 kg/m^2
Weight reduction > 10% – equivalent to monotherapy	S-BP↓ 7 mmHg
	D-BP↓ 0.8 mmHg
Weight loss over 12-week period	84% of patients > 5%
	50% of patients > 50%
Improvement observed in	Waist circumference
	Lipid profile
	Glucose tolerance
	Degree of concomitant medication

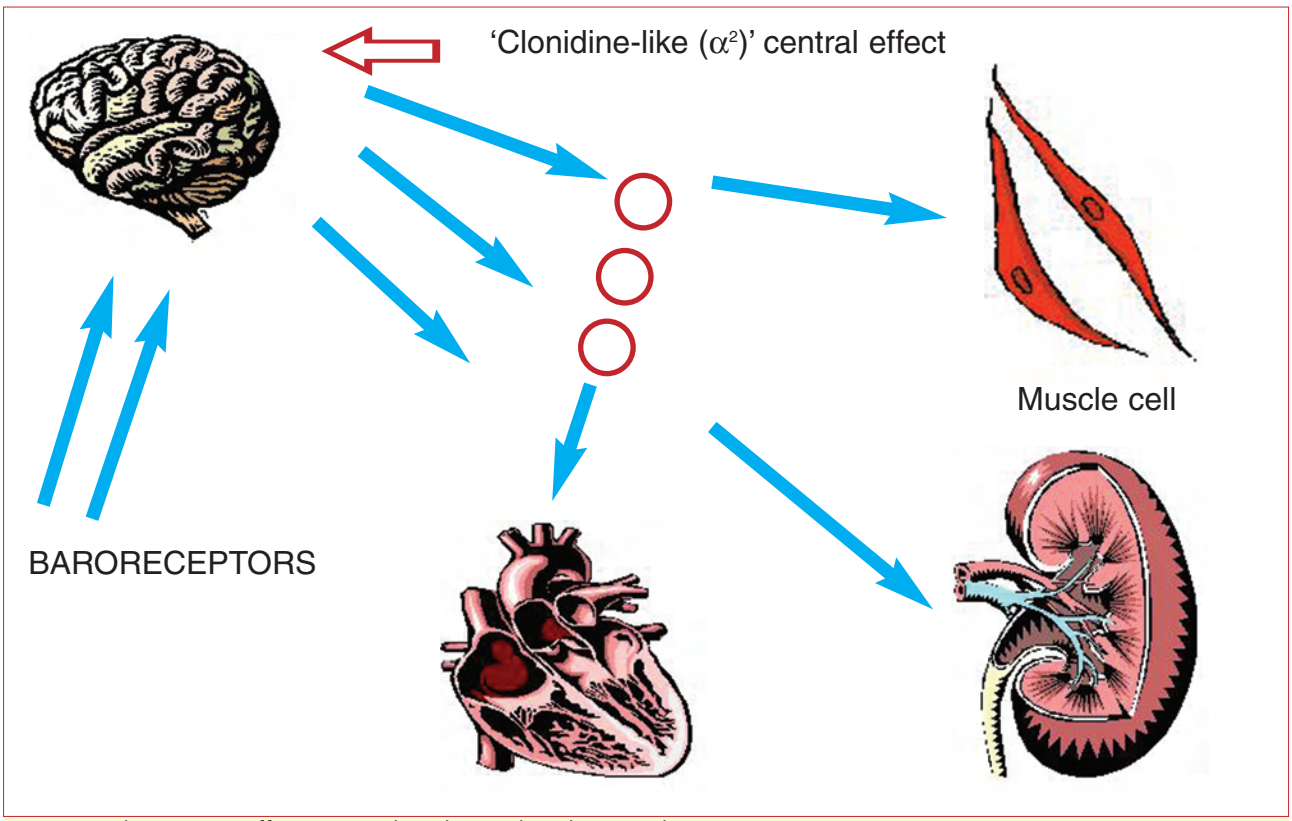


Fig. 1. Sibutramine affects central and peripheral sympathetic activity.

serotonergic effects, the cardiovascular, gastrointestinal, and central nervous side-effects of the drug can be explained completely or in part.[8] An average increase in resting systolic and diastolic blood pressure of 2 - 3 mmHg and an average increase in heart rate of 3 - 7 beats per minute have been observed.[8] Clinically significant increases in blood pressure and heart rate occur, and tend to happen during the first 4 - 12 weeks. In patients with at least a 10% weight reduction, blood pressure decreases as much after treatment with sibutramine (10 mg x 1) as after placebo. With a higher sibutramine dose (15 mg x 1), blood pressure drops less than in the placebo group. Most other side-effects occur during the first 4 weeks of the treatment and decrease in intensity and frequency with time. Side-effects include loss of appetite, constipation, mouth dryness, sleep problems, palpitations, elevated blood pressure, headache, anxiety and sweating. Sibutramine was approved in 1998 in the USA under the name Reductil. Post-marketing studies done with sibutramine had an even more favourable effect on the metabolic syndrome indices (Table II).

PHENTERMINE

This drug is available in a timed-release resin or a more quickly released hydrochloride form in various brands and generic form. In the only long-term, double-blind, placebo-controlled phentermine study, 108 obese women were assigned to receive placebo, continuous phentermine (30 mg/d of phentermine resin), or intermittent phentermine (4 weeks receiving

Table III. **Sites of CB_1 receptor and effects of CB_1 blockade**

Site of action	Mechanism(s)	Addresses
Hypothalamus/nucleus accumbens	↓ Food intake	Body weight Intra-abdominal adiposity
Adipose tissue	↑ Adiponectin ↓ Lipogenesis	Dyslipidaemia Insulin resistance
Muscle	↑ Glucose uptake	Insulin resistance
Liver	↓ Lipogenesis	Dyslipidaemia Insulin resistance
GI tract	↑ Satiety signals	Body weight Intra-abdominal adiposity

Table IV. **Cannabinoid receptor antagonist rimonabant 20 mg (1-year study)**

Weight change	-6.9 kg
Weight loss	72.9% of patients > 5% (v. 27.6%)
	44.3% of patients > 10% (v. 10.3%)
Waist circumference change	-7.1 cm
Other parameters	HDL-C ↑ 23%
	F-TG ↓ significant
	CRP ↓ significant
Metabolic syndrome	25.8% (v. 52.9%) at end of 1 year

Table V. **Long-term outcome of medical management: STORM weight loss results at 2 years**

Period of weight loss	**Outcome**
6 months	Maintained in sibutramine group
After 6 months	Weight loss 10.2 kg
At end of 2 years	Weight loss 8.7 kg
	20% increase in HDL
Control group (diet and exercise)	Weight regained
Mean difference between 2 groups at end of study	5.5 kg ($p < 0.01$)

phentermine therapy and 4 weeks not receiving phentermine therapy) for 36 weeks.[9] Weight loss was significantly greater ($p < 0.001$) in patients treated with continuous (12.2 kg) or intermittent phentermine than with placebo (4.8 kg). Adverse effects such as agitation and insomnia occurred. No other long-term, placebo-controlled data are available for phentermine.

RIMONABANT

Recent research has identified the endocannabinoid system, in particular its first selective CB_1 receptor blocker, Rimonabant, as a promising therapeutic target for the reduction of obesity and multiple cardiovascular risk factors.[10] CB_1 receptor expression is widespread (Table III), including the brain and many peripheral tissues.

Clinical trials running for 1 - 2 years (RIO programmes) enrolled over 6 600 patients, looking at benefits in weight loss, hypertension, dyslipidaemia and hyperglycaemia/diabetes. Results have been summarised in Table IV.

Approximately 50% of the improvement in insulin resistance measurements on Rimonabant is not attributable to the weight loss *per se*, but may be related to an independent increase of adiponectin levels by Rimonabant. FDA licensing for Rimonabant as a weight loss agent is currently underway and the drug has not yet been approved for use by the MCC in South Africa.

EFFECTIVENESS OF PHARMACOTHERAPY FOR WEIGHT CONTROL: REVIEW OF THE EVIDENCE

A review of the literature on studies include 9 randomised, placebo-controlled studies of orlistat and sibutramine. The 6 studies of orlistat included approximately 2 500 patients on active therapy and present results based on outcome after 1 year of treatment. On average, weight loss after 1 year was approximately 3 kg (± 5 - 6%) greater with orlistat treatment than with placebo treatment. About 20% of the patients in the studies achieved a weight loss of at least 10% of their original weight, which was twice as many as in the placebo groups (Fig. 2).[11-16] Generally a weight loss of 5% or more by 12 weeks will predict a favourable weight loss by 1 year (Fig. 2). The post-marketing X-Pert trial showed that a rapid weight loss can be achieved in the first few months.[17] In addition, Xenical produces twice the weight loss in patients with the metabolic syndrome at baseline compared with patients on placebo. More recently the XENDOS study illustrated a 52% reduction in progression to type 2 diabetes for patients on Xenical, compared with lifestyle and placebo alone.[18]

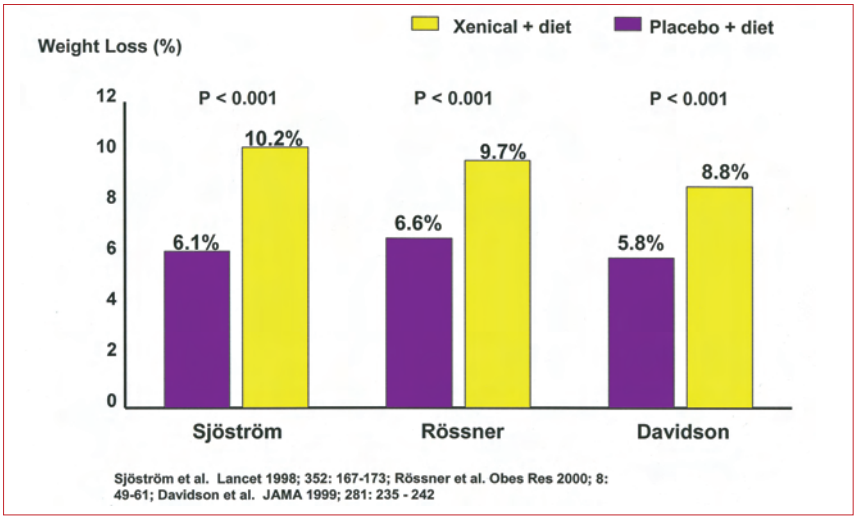
The 3 studies of sibutramine included approximately 1 400 patients on active therapy and use a somewhat different design, which renders interpretation difficult. In 2 studies, sibutramine yields weight loss which is about 4 kg greater after approximately 1 year than that in the placebo groups (Fig. 2)[19] In the largest study – Sibutramine Trial of Obesity Reduction and Maintenance (the STORM study) – weight reduction after 2 years is more than 5 kg greater in those completing the study than in the control group (Table V).[20]

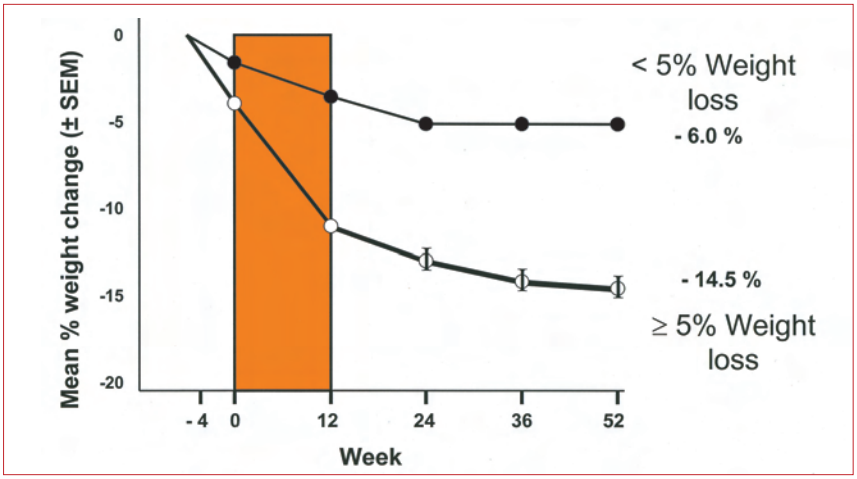
The proportion of patients who lost at least 10% of their original weight was approximately twice as high in the sibutramine groups as that in the control groups, namely 31% v. 8%. A subgroup of patients in the STORM study showed a 30.6% increase in HDL-cholesterol compared with the 6% increase in patients on gemfibrozil. Although sibutramine has not yet been licensed for use in children or adolescents, data on file indicate that a 3.4 BMI (± 12 kg) weight loss is achievable in the youngsters within 12 months. In addition, diabetic patients, regardless of mode of therapy, stand to lose around 7% over 52 weeks on sibutramine treatment.

CONCLUSIONS

The health risk related to obesity can be reduced effectively through correct management. Patients failing repeated attempts at behaviour modification therapy should be placed on pharmacotherapy. Selected patients will be eligible for bariatric surgery. An increased understanding of the reasons for obesity and the difficulties in treating it may help to reduce the prejudice against people with obesity among health professionals and society at large.

References available on request.





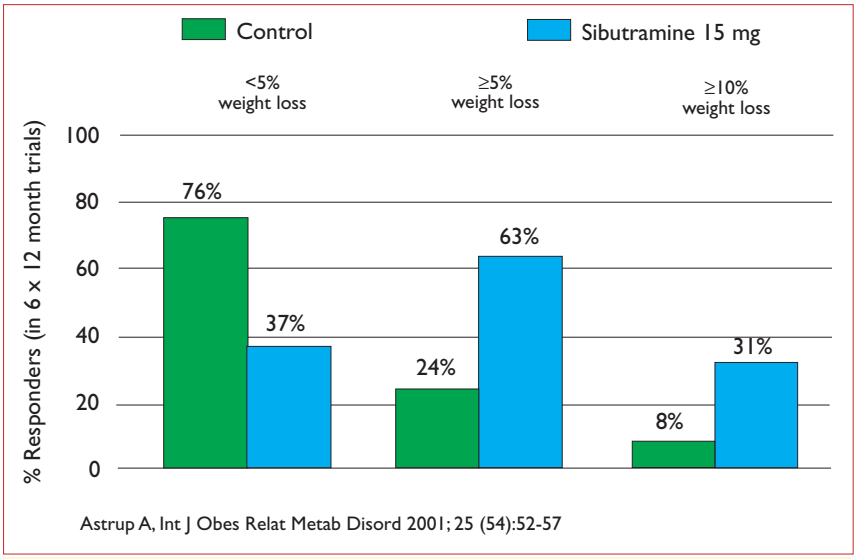


Fig. 2. Effectiveness of pharmacotherapy.[11,15,16]

IN A NUTSHELL

Recent paradigm shifts in the understanding of obesity have led to the inclusion of weight loss drugs for treatment. These include a recognition that obesity is a true disease with genetic determinants (not a 'character flaw'), that it is a major public health threat, and that weight regain occurs after discontinuation of weight loss medication.

Pharmacological treatment of obesity is based on three possible principles: reduced food intake via appetite-regulating mechanisms in the brain, reduced gut absorption of dietary fat, and increased energy expenditure.

There is increasing evidence that obesity is a chronic disease, and as such, long-term pharmacotherapy may be safe and appropriate for some individuals.