

Review Article

Emerging pharmacotherapy for treating obesity and associated cardiometabolic risk

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The global obesity epidemic is causing much concern among health professionals due to the major health risks associated with obesity. Excess weight, particularly abdominal obesity, elevates multiple cardiovascular and metabolic risk factors, including Type 2 diabetes, hypertension, dyslipidaemia and cardiovascular disease. Thus obesity management goals should encompass health improvement and cardiometabolic risk reduction as well as weight loss. While lifestyle and diet modification form the basis of all effective strategies for weight reduction, some individuals may need additional intervention. About one in four people with BMI >27 kg/m² (those who have weight-related morbidity and who have been unsuccessful losing weight in standard ways) may require adjunctive therapy such as pharmacotherapy, very low energy diets/meal replacements, or bariatric surgery. This review focuses on appropriate use of pharmacotherapy for obesity and cardiometabolic risk. Sibutramine and orlistat are currently available for use in Australia. Rimonabant has been approved for use in the European Union, and is being considered for regulatory approval in the USA and Australia. The efficacy and safety of these three agents are examined. In addition, several novel pharmacotherapy agents in development are discussed.

Key Words: obesity, pharmacotherapy, sibutramine, orlistat, rimonabant

Introduction

The global obesity epidemic is a well-established reality. Worldwide more than one billion adults are overweight, with at least 300 million of these being defined as obese.¹ The USA leads the way, with about two-thirds of the population being obese or overweight,² but other countries are not far behind. In Australia, the prevalence of obesity has more than doubled in the past 20 years and at least 60% of Australian adults are now overweight or obese.³ The obesity epidemic is not limited to the affluent, industrialised societies; rates of obesity are rapidly increasing in developing countries where the sheer size of the population means that numbers of obese individuals exceed even those of the West. In China, where the overall overweight and obesity prevalence is about 22.8% and 7.1% respectively, and 55.7% of the residents of Beijing are now overweight or obese; it is estimated overall that 200 million are overweight and 60 million Chinese are obese.⁴

This obesity epidemic is causing concern among health-care professionals because obesity poses a major health risk. Excess weight, particularly abdominal adiposity, elevates multiple cardiovascular and metabolic risk factors: it is associated with increased risk of Type 2 diabetes mellitus (T2DM), hypertension, dyslipidaemia and cardiovascular disease.⁵ Obesity is expected to have a catastrophic impact on health care and will increase healthcare costs in the coming decades. It has even been suggested that the obesity epidemic could reduce life expectancy in the USA during the 21st century.^{2,6}

The chronic and debilitating nature of the diseases associated with obesity (which apart from metabolic and cardiovascular disease include cancers and mechanical complications such as osteoarthritis and sleep apnoea) underlies the imperative of its prevention and treatment. Treatment may be of overweight and obesity alone, or of obesity as part of a core set of risk factors. Numerous clinical guidelines highlight the importance of addressing obesity, especially abdominal obesity, for example the clinical practice guidelines produced by the National Health and Medical Research Council of Australia⁶ and the World Health Organisation technical report.⁷ It is now accepted that a loss of 5–10% of body weight is extremely effective in reducing progression to Type 2 diabetes and improving risk factors.⁶ However, no outcome study has yet shown that this degree of weight loss, when sustained, prevents premature/excess mortality. Currently, a number of long-term studies are attempting to address this issue.

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Obesity therapy

There is a range of treatment options available for overweight and obesity, including diet and lifestyle modification, behavioural therapy, pharmacotherapy, very low calorie diets and meal replacements and bariatric surgery. No single approach will suit all overweight or obese individuals, but education and support to allow the patient to modify lifestyle and diet forms the basis of all effective strategies.⁶ This review will concentrate on the appropriate use of pharmacotherapy, particularly as there are new agents in the later stages of development and the approval process. Other strategies have been discussed in previous reviews.^{8,9}

In the past, use of obesity pharmacotherapy has been controversial and somewhat difficult. Available therapies were not ideal,⁶ and to this was added the belief or perception that losing weight or maintaining weight loss was all down to willpower and individual choice.¹⁰ This attitude still persists despite the advances in knowledge on the physiology of energy balance that show that body weight (and weight maintenance) are as powerfully defended as respiration and blood pressure.¹¹ For example a recent study showed that the lower leptin levels after weight loss may produce hunger, or drive to eat, and this may explain the propensity to regain lost weight.¹⁰ Despite this, food intake is clearly a behaviour that is in part modifiable by volition¹² and this accounts for the synergism of interventions that include behavioural therapy and pharmacotherapy in terms of amplified weight loss.^{13,14} It needs to be reemphasised that targeting obesity as a therapeutic goal is important as weight loss effectively reduces many cardiometabolic risk factors.

Although overweight people (body mass index, BMI, 25–30 kg/m²) are at increased risk of dyslipidaemia, hypertension and T2DM, lifestyle and diet interventions are generally considered sufficient to help reduce weight and control risk in these individuals.⁶ Such lifestyle intervention can be effective but require considerable resources to deliver.^{15–17} About 25–30% of obese people and those with a BMI >27 kg/m² may require some form of adjunctive therapy to supplement diet and lifestyle changes.⁸ Such an intervention is generally reserved for those whose health is impaired and who have been unsuccessful at losing weight in standard ways.⁶

Assessment of obesity

For years, weight alone or BMI (weight in kg/height in m²) have been used to assess obesity and overweight, but it is now recognised that body-fat distribution should be taken into account. Those with upper body or abdominal obesity are at greater risk. Such distribution may be assessed by waist-to-hip (w/h) ratios but waist circumference (WC) has been identified as the most clinically relevant measure of abdominal obesity⁶ and its response to treatment.¹⁸ Specific cut-points for the definition of obesity by BMI, and of those at increased risk by WC, have been developed, and there is continuing debate as to whether these need to be made ethnic specific.^{19,20}

Treatment goals should emphasise health improvements, not just reduced body weight and WC (BMI change is not a good measure of individual success in a programme). Success should be measured by the ability

to achieve and maintain significant weight loss (5–10% of body weight) and by the beneficial effects of weight loss on the co-morbidities of obesity, such as T2DM, hypertension and dyslipidaemia.^{6,21}

Most individuals measure the effectiveness of a weight loss programme simply in terms of weight loss in kilograms. However, waist circumference is one of the most useful clinical measures of disease risk. It is easy to determine in practice, it is obvious to the patient (change in belt size) and a reduction in WC produces a reduction in risk. Realistic goals are shown in Table 1.⁶

Table 1. Realistic goals for weight loss⁶

Duration	Weight	Waist circumference
Short term	1–4 kg/month	1–4 cm/month
Medium term	10% of initial weight	5% after 6 weeks
Long term (1–5 years)	10–20% of initial weight	<88 cm (women) <102 cm (men)

Adjunctive therapy

If patients do not achieve sufficient weight loss to meet their goals, or to control their obesity-associated co-morbidities, with a lifestyle intervention alone, then adjunctive therapy should be considered. Adjunctive therapy includes specific pharmacotherapy, very low energy diets or meal replacements, and bariatric (obesity) surgery. All are useful and effective, but in this review only pharmacotherapy will be considered.

Pharmacotherapy: When and how?

Pharmacotherapy should be considered for people who have:⁶

- a BMI of ≥ 30 kg/m², or ≥ 27 kg/m² together with other risk factors
- failed to lose weight through diet, exercise and behavioural therapy.

Pharmacotherapy is not, and should not be viewed as an 'easy option' that can replace diet and lifestyle change - all clinical studies demonstrating successful weight loss have combined pharmacotherapy with an energy-restricted diet and activity.⁶ Weight loss should be evaluated in the first six weeks to three months of therapy, as patients who experience early weight loss are more likely to obtain long-term benefit. If there is inadequate weight loss (<1.5 kg) in the first 6 weeks of therapy or if less than 5% of body weight is lost during the first 6 months, then discontinuation of pharmacotherapy should be considered.⁸

During a weight loss programme, most weight is lost over the first six months and often a plateau phase is then entered. Maintaining a steady weight is a valid goal and a major benefit in itself, since the natural history of voluntary weight loss, especially for obese people is weight regain. Clearly if pharmacotherapy has contributed to the weight loss and weight loss maintenance it should be continued. Patients do need the support of an ongoing lifestyle programme. If weight is regained, more intensive therapy needs to be started and consideration given to re-starting pharmacotherapy, if the patient has discontinued it.⁸

Current and emerging pharmacotherapies

Obesity is a chronic condition, and pharmacotherapy is only effective while it is being taken. Most clinical trials of obesity pharmacotherapy have been limited to 1 or 2 years of drug therapy (there is a single, published 4 year trial¹⁴ and other longer trials are in progress), so the effects of long term treatment are not really known. As for any other long term drug treatment, if therapy is to be continued it must be with minimal potential risks and side effects; trials in progress will help determine both effectiveness and any potential risks or problems.⁶ Still other trials will need to be performed to determine the lowest effective dose of specific obesity pharmacotherapeutic agents for long term treatment.

Current pharmacotherapy

Several drugs are approved for weight loss in Australia. Older drugs such as phentermine will not be considered here, since there is too small a 'modern' evidence base. Newer, approved drugs are sibutramine (Reductil[®], Abbott Laboratories) and orlistat (Xenical[®], Roche Products).

Sibutramine

Mechanism of action

Sibutramine is a selective serotonin and noradrenaline re-uptake inhibitor with both central and peripheral effects. It increases satiety, thereby acting as an appetite suppressant. It also prevents the normal fall in resting metabolic rate that occurs during weight loss.⁸

Use

Sibutramine is effective at doses ranging from 5–15 mg/day. The usual starting dose of 10 mg/day is increased to 15mg/day if a weight loss of >1.5kg is not achieved during the first 4–6 weeks of treatment.⁸ It should be used with caution in people with a history of hypertension, and is not recommended for those with coronary artery disease, arrhythmias, congestive heart failure or stroke.⁶ There is a current trial of cardiovascular outcome with weight loss induced by lifestyle programme and with sibutramine in such patients (SCOUT), and results should be available within a few years. In Australia sibutramine

is not recommended for use in conjunction with anti-depressants, both other selective serotonin re-uptake inhibitors and particularly monoamine oxidase inhibitors.⁸ Since there is a high prevalence of depression in patients presenting for treatment,²² this may limit the use of sibutramine in clinical practice.

Efficacy

Randomised controlled trials have compared sibutramine with placebo.^{6,23,24} In these trials, a greater proportion of patients in the sibutramine groups achieved weight losses of $\geq 5\%$ and $\geq 10\%$ of baseline body weight than in the placebo groups (Fig. 1). The weight loss with active treatment is about double that with lifestyle therapy alone, on average an extra 4.5 kg. Other trials have compared the combination of lifestyle therapy plus placebo with lifestyle therapy plus sibutramine in maintenance of weight loss, enrolling those patients who lost weight during either a run-in period with sibutramine or a four-week very-low energy diet.^{13,25} Sibutramine was effective both in producing weight loss and in maintaining weight loss for up to 2 years.¹³ The combination of intensive lifestyle therapy and sibutramine was more effective than either approach alone.²⁵

Sibutramine therapy improves several cardiovascular risk factors. Beneficial changes in glycaemic control (in patients with Type 2 diabetes), serum lipids, insulin, C-peptide, uric acid and waist circumference have been observed in clinical trials, and there is an important increase of more than 20% in HDL-cholesterol occurring after weight was stabilised (placebo-subtracted increase was 9% at 2 years and 4.8% at 1 year).¹³ Most of these changes were in proportion to the degree of weight lost, although the effect on HDL appeared was greater than might be expected from weight loss.¹³

Safety

Sibutramine is well tolerated and effective, but is associated with an increase in blood pressure (of 1 to 3 mm Hg) and heart rate (4 to 5 beats per minute) in some people. The most commonly-reported adverse events in clinical trials include headache, dry mouth, constipation and insomnia.⁶

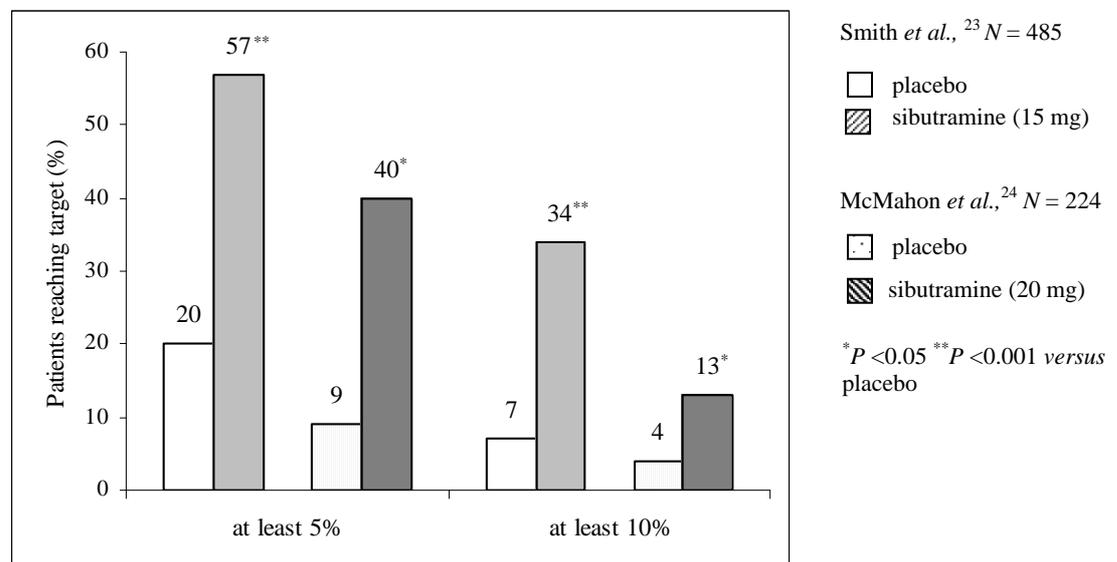


Figure 1. Proportion of patients achieving a weight loss of $\geq 5\%$ or $\geq 10\%$ of body weight with sibutramine versus placebo

Orlistat

Mechanism of action

Orlistat acts by inhibiting gastrointestinal lipases, which then are unable to breakdown dietary triglycerides. Fat absorption is reduced by about 30%, and non-digested fat is passed out with the faeces.²⁶

Use

Orlistat is typically taken in doses of 120 mg three times daily before meals. It is important that dietary fat intake is restricted to <20 g per meal, to minimize gastrointestinal effects (see safety).^{6,8}

Efficacy

Orlistat combined with a low-energy, low-fat diet induces a mean weight loss of about 8.5 kg (8.5% body weight) after one or two years of treatment. In placebo-treated patients there is a loss of some 5.5 kg, giving those treated with orlistat an average additional weight loss of 3 kg.^{6,27} Compared with placebo, orlistat improves weight maintenance when patients switch from a low-energy to normal energy (weight maintenance) diet, and this effect continues for up to 4 years, although over that time a small increase in weight is observed in both placebo and active treatment groups.^{6,27} However, there is quite good weight loss with persisting beneficial changes in lipids, blood pressure, diabetes control and weight and WC.

Orlistat has been shown to decrease total and LDL-cholesterol relative to placebo due to its specific mode of action,⁶ and there is a small rise in HDL-cholesterol. In the four-year XENDOS study, orlistat significantly reduced the incidence of Type 2 diabetes among obese patients with impaired glucose tolerance (Fig. 2).¹⁴ Orlistat appeared to improve LDL-cholesterol¹⁴ and insulin resistance²⁸ to a greater degree than would be expected from weight loss alone. When those with equal weight losses (produced by a weight programme alone or by orlistat plus such a programme) were considered, those treated with orlistat had less insulin resistance because of the effect of orlistat in reducing fat absorption.²⁸

Safety

Orlistat is associated with gastrointestinal adverse effects including steatorrhoea, bloating, flatulence, faecal urgency and leakage, all of which may be reduced if patients adhere to a low fat diet. However these unpleasant side effects can be considered a "learning experience" and may encourage dietary adherence.^{6,8,27} Gastrointestinal adverse events were more common during the first year (91%) than the fourth year (36%) of orlistat therapy.¹⁴ Absorption of fat soluble vitamins is reduced with orlistat though the serum levels remain in the normal range, but vitamin supplementation may be required with long courses of treatment (>1 year).⁶ Orlistat has a good safety profile and is now available "over the counter" in Australian pharmacies. These medications are available - what about even newer agents?

Rimonabant

Rimonabant (Acomplia[®], sanofi-aventis) has recently been approved for use in the European Union as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30 kg/m²) or overweight patients (BMI ≥ 27 kg/m²) with associated risk factors such as Type 2 diabetes or dyslipidaemia. It is also being considered for regulatory approval in the USA and Australia.

Mechanism of action

The endocannabinoid (EC) system plays a role in regulating metabolism and body composition. Activation of cannabinoid-1 (CB₁) receptors by endogenous ligands (endocannabinoids) enhances the central orexigenic drive (stimulating appetite) and alters glucose and lipid metabolism.²⁹ CB₁ receptors are found in several sites including the brain, liver, muscle and gut.²⁹ Rimonabant is the first selective CB₁ receptor blocker, and is thought to act by decreasing the overactivity of the EC system which is present in obesity.³⁰ In pre-clinical trials, rimonabant decreased the body weight of diet-induced obese mice by 20% and depleted fat stores by 50%. Plasma glucose and insulin levels were lowered, and both insulin resistance

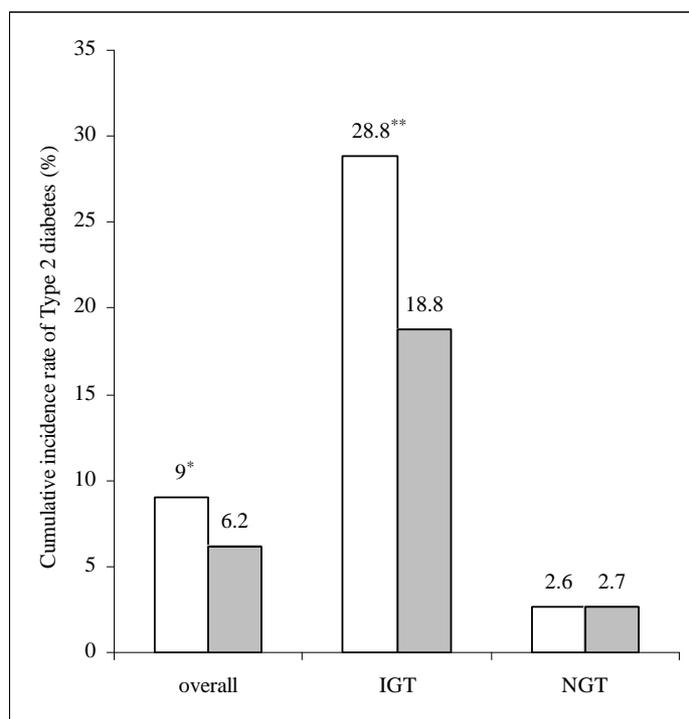


Figure 2: Incidence of Type 2 diabetes in obese patients randomised to lifestyle changes plus either orlistat or placebo for 4 years¹⁴

□ placebo

▨ orlistat

Overall: $N = 3277$; * $P = 0.0032$ versus placebo

IGT: impaired glucose tolerance; $N = 694$;

** $P = 0.0024$ versus placebo

NGT: normal glucose tolerance; $N = 2583$;

$P =$ not significant

and pro-inflammatory cytokine levels were reduced.²⁹

Efficacy

Rimonabant effectively reduces both weight and waist (there have been 4 major trials in over 6,600 patients to date and the results are similar in each).^{30–33} Significantly more subjects taking rimonabant (20mg) achieved a weight loss of $\geq 5\%$ and $\geq 10\%$ than those on placebo ($P < 0.001$), both groups having been treated with a lifestyle intervention (Fig. 3). The decrease in waist circumference was approximately 1cm for each kilogram lost. Rimonabant therapy reduced serum triglycerides, fasting insulin, and C-reactive protein levels,^{30–32} and, importantly, HDL cholesterol levels increased by up to 27% after one year³¹ (placebo subtracted increase approximately 9%^{30–32}). In those with Type 2 diabetes, glycaemic control improved with rimonabant therapy.^{29,33} When the ATPIII definition for the metabolic syndrome was used, the proportion of patients in which this syndrome improved or disappeared was greater following treatment with rimonabant than in the placebo group.^{30–32}

Rimonabant appeared to improve some cardiometabolic parameters to a greater degree than would be attributed to weight loss alone. Specifically, there were increases in HDL-cholesterol and adiponectin, and falls in triglycerides and HbA_{1c} that were up to 50% greater than would be expected just from weight loss alone.^{30–33} This may reflect the metabolic action of rimonabant in peripheral tissues.³⁴ A trial of cardiovascular outcomes with rimonabant (CRESCENDO) has recently commenced and will follow patients for over 4 years.

Safety

Rimonabant treatment for up to 2 years was well tolerated, with adverse events reported in the 4 major clinical trials being mostly mild to moderate and transient.^{30,31} The most common adverse event associated with rimonabant was mild nausea.^{29–32} Other adverse events reported include diarrhoea, dizziness and less frequently mood disorders. One potential concern was the possibility of mood

alterations with this new class of agents. Withdrawals from trials due to depression and anxiety were more frequent among rimonabant-treated patients, but there were no differences between rimonabant and placebo groups in the anxiety or depression subscales of the Hospital Anxiety and Depression scale.^{30,31}

Agents in development

There are a number of pharmacotherapies currently in clinical development for obesity and associated risk factors.³⁵ Some of these are in existing drug classes (e.g. lipase inhibitors, CB₁-receptor blockers). Some information on drugs in new pharmacological categories is given below, although information on such drugs is limited.

Glucagon-like peptide-1 (GLP-1) based drugs

The antidiabetic drug exenatide, and other related compounds, such as exenatide-LAR, PC-DAC:Exendin-4 and liraglutide, are incretin-mimetics that exhibit glucoregulatory activities similar to the endogenous hormone GLP-1.^{35,36} They are approved (or are in development) for glycaemic control in people with Type 2 diabetes. They are given by injection currently, and appear to be very effective. People with diabetes who participated in clinical trials with these compounds demonstrated a weight loss, in addition to much improved glycaemic control.³⁶

Pramlintide

The amylin analogue pramlintide is currently FDA-approved for use in people with Type 1 or Type 2 diabetes who cannot achieve glycaemic control with intensive insulin therapy. Clinical trials with pramlintide demonstrated a weight loss in patients with Type 2 diabetes,^{37,38} and one study indicated enhanced satiety and reduced food intake may account for these effects.³⁸

APD-356

APD-356 is a selective 5-HT_{2c} agonist which is thought to act by reducing food intake. Phase I and II clinical trial data suggest that the drug is well tolerated and leads to weight reduction.³⁵

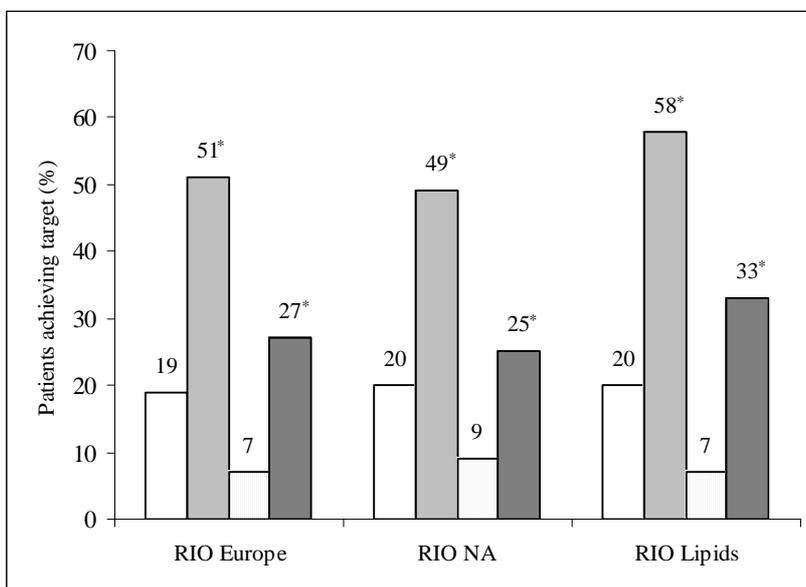


Figure 3. Patients achieving weight loss of $\geq 5\%$ or $\geq 10\%$ of body weight after 1 year treatment with rimonabant 20 mg (intent-to-treat population)^{30–32}

- placebo patients achieving $\geq 5\%$ weight loss
- ▨ rimonabant patients achieving $\geq 5\%$ weight loss
- ▤ placebo patients achieving $\geq 10\%$ weight loss
- ▩ rimonabant patients achieving $\geq 10\%$ weight loss

* $P < 0.001$ versus placebo

RIO Europe: Rimonabant In Obesity European study;³¹

rimonabant (20 mg) $N = 599$, placebo $N = 305$

RIO NA: Rimonabant In Obesity North American

study;³⁰ rimonabant (20 mg) $N = 1219$, placebo $N = 607$

RIO Lipids: Rimonabant In Obesity study in obese people with dyslipidaemia;³² rimonabant (20 mg)

$N = 346$, placebo $N = 342$

AOD-9604

AOD-9604 is a novel anti-obesity drug, a synthetic growth hormone fragment that is thought to stimulate fat metabolism by selectively mimicking the activity of growth hormone on adipose tissue and increasing lipolysis. In preclinical trials weight gain was inhibited in obese rodents, an effect thought to be associated with an increase in fat breakdown and decrease in fat storage. A Phase IIB clinical trial conducted in five centres across Australia demonstrated significantly greater weight loss with AOD-9604 (1–30 mg) than with placebo; the effect was most marked at the lowest dose of the range trialed.³⁵

Discussion

What is now evident is that moderate weight loss can be achieved and maintained for up to at least 4 years. This duration of weight loss has significant effects on obesity-associated diseases such as diabetes, and on metabolic and cardiovascular risk. These maintained beneficial changes can be brought about by a therapeutic programme which includes a mildly hypocaloric diet, increased activity, behaviour modification and specific obesity pharmacotherapy. This simple finding needs to be emphasised, as many in the health system need to realise what has already been, and can be, done in weight loss and maintenance.

The hypothesis that abdominal adiposity, rather than the absolute amount of fat, underlies the increased risk of Type 2 diabetes and cardiovascular disease was first advanced almost 50 years ago by Jean Vague,³⁹ and is now supported by growing evidence.^{5,40} Intra-abdominal adipose tissue is an active endocrine organ that secretes biologically-active substances (adipokines). Secretion of pro-inflammatory, pro-atherogenic adipokines, such as interleukin-6, tumour necrosis factor- α , plasminogen activator inhibitor-1 and C-reactive protein all increase with increased abdominal obesity, whereas secretion of adiponectin, an apparently cardioprotective adipokine, is reduced in abdominally obese individuals.⁴⁰ There are other possible factors which also change with abdominal adiposity. For example, decreased release of fatty acids from visceral fat depots with consequent reduced portal vein concentrations and exposure of hepatocytes to fatty acids, may directly decrease insulin resistance.

One main clinical goal in obesity management (as well as the obvious weight reduction which may have mechanical benefits and improve psychosocial factors) is the reduction of cardiovascular and metabolic risk. Therefore obesity management should target abdominal obesity and its associated cardiometabolic risk parameters.

Pharmacotherapy for obesity is often regarded as a last resort. However, it is interesting to note that, although management guidelines for individual risk factors such as hypertension and dyslipidaemia recommend diet and lifestyle changes as the first option, prescription of anti-hypertensive or lipid-lowering medication is common because lifestyle measures are frequently unsuccessful. With the development of new, effective drugs, pharmacotherapy for the cardiometabolic risk associated with obesity may, in the future, be considered in the same light. Additionally, two factors need to be emphasised. The first is the role of pharmacotherapy in weight loss main-

tenance, a concept rather like the long-term control of hypertension. Secondly, the absolute necessity for diet, activity and behaviour change (a "lifestyle programme") to underpin abdominal fat loss, weight loss and maintenance cannot be over-emphasised.

Summary

Moderate weight loss, and reduction in abdominal obesity, can be achieved and maintained with the new pharmacotherapies plus a lifestyle programme. This has beneficial effects on metabolic disease and cardiovascular risk factors, as well as mobility and self esteem in the obese individual. The emerging pharmacotherapy with rimona-bant holds additional promise, with effects that appear independent of weight loss, and it is hoped that with such specific treatment, more individuals will achieve and maintain their weight goals and improve their cardio-metabolic risk.

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Review Article

Emerging pharmacotherapy for treating obesity and associated cardiometabolic risk

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新興的肥胖藥物療法及相關的心臟代謝危險

由於主要的健康風險與肥胖有關，引起健康專業人員對全球的肥胖情疫的關注。過重、尤其是腹部肥胖，提高了多重的心血管與代謝的危險因子，包括第二型糖尿病、高血壓、血脂異常及心血管疾病。因此肥胖管理的目標應該要包含促進健康、降低心臟代謝危險以及減重。儘管改變生活型態與飲食是所有有效減重的策略的基礎，還是有些人可能需要額外的介入。在 BMI>27 kg/m²的人當中，有四分之一的人（有與體重相關的疾病而且採用標準方法無法成功減輕體重）可能需要附屬的治療，例如：藥物治療、極低熱量飲食/代餐或是手術。本文評述重點為適當的藥物治療肥胖及心臟代謝危險性。Sibutramine及Orlistat目前在澳洲已經可以使用。Rimonabant已經被歐盟通過使用，在美國及澳洲可能被有條件的通過。這三個藥劑的功効及安全性已被評估過。另外，本文還會討論幾個正在開發的新藥。

關鍵詞：肥胖、藥物治療、sibutramine、orlistat、rimonabant