Rimonabant: endocannabinoid inhibition for the metabolic syndrome

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SUMMARY

Rimonabant is the first drug to target the endocannabinoid (CB) pathway by inhibiting the actions of anandamide and 2-archidonyl-glycerol on CB1 receptors. This review gives an overview of rimonabant and the CB system and how this system relates to obesity. Rimonabant blocks the central effects of this neurotransmitter pathway involved in obesity and weight control and also blocks the direct effects of CBs on adipocyte and hepatocyte metabolism. Blockade of CB1 receptors leads to a decrease in appetite and also has direct actions in adipose tissue and the liver to improve glucose, fat and cholesterol metabolism so improving insulin resistance, triglycerides and high-density lipoprotein cholesterol (HDL-C) and in some patients, blood pressure. The Rimonabant in Obesity (RIO) trials have shown that rimonabant induces weight loss >5% in 30–40% of patients and >10% in 10–20% above both a dietary run-in and long-term hypocaloric management over a 2 year period with a low level of drug-related side effects. Rimonabant therapy is associated with an extra 8–10% increase in HDL-C and a 10–30% reduction in triglycerides and improvements in insulin resistance, glycaemic control in patients with diabetes and also adipokines and cytokines including C-reactive protein over hypocaloric diet therapy. In addition rimonabant abolishes the weight gain associated with smoking cessation and improves the chances of quitting smoking. Thus rimonabant has major effects on both the metabolic syndrome and cardiovascular risk factors thus has the potential to reduce the risks of type 2 diabetes and cardiovascular disease associated with the cardiometabolic phenotype.

Keywords: Endocannabinoid; obesity; metabolic syndrome; cardiovascular risk; smoking; addiction; treatment

What is Known About the Subject

- The prevalence of obesity is increasing rapidly.
- Current weight loss therapies have significant limitations.
- The endocannabinoid system is involved in the regulation of appetite and metabolism.

What Does This Article Add?

- The endocannabinoid system is a new target for obesity and metabolic syndrome therapies.
- Rimonabant is the first CB1 receptor blocker to reach clinical practice.
- Clinical trials in man have shown that rimonabant has consistent effects in reducing weight, abdominal obesity in patients with obesity, obesity with dyslipidaemia and obesity and concurrent type 2 diabetes.

Review Criteria

This review was compiled using data from PubMed identified using the search terms cannabinoid, endocannabinoid; drug treatment added to obesity and the drug names rimonabant and SR141716A. Additional data was sourced from conference abstracts, clinical trials databases and press releases of the American Heart and Diabetes Societies.

For the Clinic

- Rimonabant is a new anti-obesity drug acting on the endocannabinoid system.
- It delivers a consistent 5 kg of weight loss.
- It has a secondary beneficial effect on lipids, glucose and neutral effects on blood pressure.
- It has a generally good tolerability profile.
INTRODUCTION

An epidemic of obesity is occurring in the developed and developing world (1–3). As gross obesity becomes commoner, milder degrees of obesity remain unnoticed as they are the norm. It is already accepted that patients recruited for phase I drug trials in the USA should average a body mass index (BMI) of 30 kg/m². Yet the cardiometabolic consequences of mild obesity are likely to be more severe. Gross morbid obesity with its osteological and physiological problems is associated with an increased risk of mortality (4,5) and with a 9 years reduction in life expectancy (6–8). Beneficial trends have been evident for 20 years in some cardiovascular disease and diabetes risk factors including smoking, relative saturated fat intakes and cholesterol levels. However, these are counterbalanced and may be overwhelmed by adverse trends in increased carbohydrate intakes, increased food calorie densities and especially reduced exercise resulting in obesity and rises in the prevalence of obesity-associated cardiometabolic risk factors (9).

THE METABOLIC SYNDROME

Moderately overweight or obese individuals show increase in abdominal circumference which are associated with other features of the insulin resistance/metabolic syndrome (10,11). These features as universally defined includes low high-density lipoprotein cholesterol (HDL-C), high triglycerides, systolic hypertension and hyperglycaemia. Other abnormalities associated with the metabolic syndrome include increased apolipoprotein B concentrations, small dense low-density lipoprotein (LDL) particles, hyperuricaemia, non-alcoholic fatty liver disease/hepatic steatosis, elevated liver transaminases, gamma-glutamyl-transferase and microalbuminuria. The more metabolic syndrome risk factors are present in any individual the higher the risk of transition to diabetes (×20 with >4 risk factors) or cardiovascular disease (×3.5 with >4 risk factors) (12).

However, mild obesity and in particular central obesity carries a large excess risk of especially diabetes and also of cardiovascular disease (12). It is critical to treat this modifiable risk factor before its complications become established. The traditional therapy of diet and lifestyle is extremely successful with trials such as the diabetes prevention projects showing 40–50% reductions in new diabetes and better results than achieved with metformin therapy (13,14). However, the extent of lifestyle modification required is beyond some patients. Some people cannot do 30 min of aerobic intense exercise every day because of the osteoarthrit-itis or respiratory complications of obesity but can manage lesser degree of exercise. Others find it difficult to adhere to a −500 kcal/day diet as they have tried numerous diets and exercise programmes and only shown weight cycling and prompt regain of any lost weight and thus lost confidence in this strategy. Agents that add to even minimal lifestyle measures and help patients to attain realistic weight loss goals are thus very useful. In addition as weight is lost, features of the metabolic syndrome improve lessening the risks of complications of obesity and some weight loss drugs may have effects beyond weight reduction on these metabolic risk factors.

TREATMENT OF OBESITY

Numerous drugs can treat various aspects of the metabolic syndrome but few apart from weight loss agents have effects across the whole risk profile. Yet anti-obesity drugs have a bad reputation. They have been either been poorly effective (15) or effective at delivering weight loss but at the cost of addiction (amphetamine) or pulmonary fibrosis (dexfenfluramine). Two drugs are licensed; orlistat and sibutramine. Orlistat delivers a 10% weight reduction in 20–30% of patients and reduces the incidence of diabetes by 47% in the Xenical in prEvention of New Diabetes in Obese Subjects study (XENDOS) (16). Orlistat reduces triglycerides and blood pressure but has little effect on HDL-C (16). Unfortunately this gastric lipase inhibitor is effective only in patients consuming excess fat (many consume excess carbohydrate) and all too often is discontinued by patients because of its gastrointestinal side effects in response to fat consumption (15). It is a willpower aid: an ‘antabuse for fat’. Sibutramine is a centrally acting serotonin and noradrenaline re-uptake inhibitor (17). Sibutramine therapy induced a 10% weight loss in 20–30% of subjects with a 9% increase in HDL-C and 35% reduction in triglycerides in the Sibutramine Trial of Obesity Reduction and Maintenance (STORM) study (18). Unfortunately sibutramine causes hypertension (+4 mmHg in STORM) and tachycardia and is contraindicated in patients with established coronary heart disease. Also being a serotonin/catecholamine re-uptake inhibitor its use is contraindicated in patients receiving selective serotonin re-uptake inhibitors (SSRIs) or monoamine oxidase inhibitors (MAOIs). Both SSRIs and MAOIs are used in the treatment of depression which is often a secondary psychological complication of weight gain and may in themselves reduce weight (15). Thus, given the limitations of current therapies there has been a need for a novel approach to weight management.

THE ENDOCANNABINOIDS SYSTEM

As so often in medicine the initial breakthrough came from clinical observation which was followed by clarification of the underlying biochemical pathway. It had been noted for many years that cannabis abuse was associated with weight gain (‘the munchies’) and thirst but this was thought to be
The complexity of the system has led to it being called the endocannabinoid (CB) pathway (21,22) (Figure 1). Neurochemical studies identified specific receptors for Δ⁹-tetrahydrocannabinol in the brain and later the natural ligands for these receptors (the CBs) were identified as anandamide, mono-acyl-glycerol, 2-arachidonylglycerol and other fatty acid ethanolamides (21). Levels of CBs are regulated by fatty acid amide hydrolase (23). These compounds are unusual as they produced postsynaptically and act on presynaptic neurotransmitter release (Figure 1). CBs were shown to be related to weight sensing as anandamide concentrations were reduced when leptin was infused (24). CB receptors, as with receptors for many other psychoactive compounds, proved to be diverse both in terms of central nervous location and to exist in a number of subtypes (25). Two major CB receptor subtypes exists in man: CB1 and CB2.

**THE CB1 RECEPTOR**

The CB1 receptor acts through the cyclic guanosine monophosphate (GMP) cascade using G_i/o and then secondarily through voltage-gated calcium channels (L, N and P/Q subtypes) and also induces potassium currents. These actions extend to activation of focal adhesion and MAP kinases and nitric oxide synthase (24). Of the receptor types CB1 receptors were found in the hypothalamus, amygdala, basal ganglia and cerebellum (22) (Figure 1). Extensive work in animals has led to some interesting hypotheses about what this pathway is involved in. CB1 antagonist therapy in rodents is associated with reductions in hedonic (reward) behaviour (21,22,26). Thus rodents addicted to smoking (27), sugar (28), alcohol (29,30), cocaine (31) and opiates (32,33) show lower intakes of addictive compounds after treatment with CB1 antagonists. Sensations of fear (34) or pain (35) are reduced after treatment with CB1 antagonists. CB1 receptors are also involved in suppression of seizures and the pathogenesis of viral-induced dyskinesia in mice (36,37). CB1 agonists have been investigated as agents likely to reduce levodopa-induced dyskinesia (LID) in rats (38). However in primates, in both the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced model of Parkinson’s disease and in LID rimonabant monotherapy did not induce dyskinesia and indeed alleviated symptoms when added to levodopa therapy (37) emphasising the complexity and species-specificity of CB pathways.

The CB1 receptors are also located outside the central nervous system (CNS) and the central and peripheral effects of CBs can be dissociated (39). Some CB1 receptors are located in the gut and associated with its neural tissue (40) but others are found in adipose tissue, liver and muscle (Figure 2). High concentrations of CB1 receptors were found on adipocytes. In cell culture and animal models CB1 antagonists reduced adipocyte size (41), induced cell differentiation (42), altered cell surface receptor expression and reduced the secretion of adipokines such as leptin, ghrelin (GHR) and resistin while increasing secretion of adiponectin (41). Secretion of cytokines including interleukin-6 and secondarily C-reactive protein was also reduced (41,42). CB1(−/−) mice show a phenotype of thinness (orexigenic) being 30% lighter as adults because of a 15% lower food intake with possibly lesser effects in female mice (43). Their

![Figure 1](image_url)
thermogenesis and energy expenditure were normal. These mice also had defects in peripheral adipocyte function with lower lipoprotein lipase activity (43). CB1 receptors are also involved in the sterol regulatory element binding protein 1c (SREBP-1c) pathway that is involved in regulation of hypothalamic-driven feeding behaviour through fatty acid synthase (FAS) (44) and the glycolytic pathway including carnitine palmitoyltransferase-I (45–47) as well through actions on the cocaine/amphetamine-related transcript protein system (31). CB1 receptors in the liver act to increase production of very low-density lipoprotein via increases in acetyl-CoA carboxylase 1 and FAS levels driven through SREBP-1c (Figure 2). This pathway also downregulates LDL (apoE/B100) receptor in the liver through preprotein convertase subtilisin kexin-9 switching triglyceride-containing lipoproteins to peripheral muscle and adipose tissue (48). Thus CB1 antagonists were potentially useful agents for the treatment of obesity in man as this combines psychological aspects of reward with suppression of natural satiety signals including responses to adiponectin, GHR and leptin. They might also have a secondary beneficial action other behaviours associated with eating including smoking.

**CB2 AND OTHER RECEPTORS**

In contrast, the CB2 system is mostly expressed in the immune system (21) but has recently been discovered in the brain cortex and brainstem and in haemopoetic cells (49). As inflammation and immunity are closely related to atherosclerosis, the possibility exists that this CB system may also be relevant to atherosclerosis (50). Lymphocytes and macrophages which stain positively for CB2 receptors have been found in animal and human atherosclerotic plaques. As atheromatous plaques calcify it is not surprising that CB2 receptors are involved in the control of bone mass (51). In the apoE(−/−) mouse model of atherosclerosis, low dose tetrahydrocannabinol (below psychoactive doses) induced atheroma regression (52). This was associated with lower lymphocyte differentiation, lower interferon-γ production and reductions in macrophage chemoattractant protein-1 production. These effects were blocked by the CB2 antagonist SR144528. No studies have yet compared CB1 and CB2 antagonists in the same mouse models as yet or investigated the effects of CB drugs on endothelial progenitor cell release from bone marrow.

Other CB receptors including the transient receptor potential vanilloid receptors probably contribute to the hypotensive actions of cannabis acting via direct endothelial effects (53) as well as adding to the effects because of cardiac and aortic arch CB1 receptors on blood pressure in mice and man (54). These receptors may also be involved in modulating the effects of cannabinoids on glutamate transmission in the hypothalamus (53).

**CLINICAL PHARMACOLOGY OF RIMONABANT**

The first CB1 antagonist to reach clinical use is rimonabant (SR141716A). This acts a direct CB1 receptor antagonist in contrast to AM-404 that interferes with anandamide transport. Rimonabant is an active lipophilic compound best taken with food with a 1000-fold selectivity for CB1 vs. CB2 receptors. Rimonabant also binds to the vanilloid receptor involved in some neuroprotective effects of this compound (55). Its half-life varies with BMI being 6–9 days for BMI 18–28 kg/m²
and 16 days in BMI > 30 kg/m². It is metabolised by cytochrome P₄₅₀ 3A4 (CYP3A4); CYP3A4 inhibitors (ketocnazole) cause a 104% (40–197%) rise in rimonabant levels. Secondary effects on rimonabant levels are also seen with CYP2C8 inhibitors.

Rimonabant has been studied for two major indications. The major area of investigation has been the potential of the agent to induce weight loss as part of treatment of the metabolic syndrome. The other feature that has been investigated is the effectiveness of CB1 antagonists in smoking cessation.

**RIMONABANT AND SMOKING CESSATION**

Three Studies with Rimonabant And Tobacco Use (the STRATUS trials) have been performed recruiting 6500 patients in the USA and Europe and investigating the effects of rimonabant 5 mg or 20 mg against placebo on rates of smoking cessation at 10 weeks and 50 weeks in the context of detailed nurse counselling. STRATUS-US recruited 787 patients of average BMI 28 kg/m² who had not tried any other cessation agent for 3 months. Patients were encouraged to quit at 2 weeks and rates of smoking were assessed at weeks 6–10 using carbon monoxide levels (56). The quit rate was 26.7% for the 20 mg group as opposed to 16.1% in the placebo group [RR = 2.0 (1.3–3.0); p = 0.004]. The rimonabant group lost 1.1 kg in net weight while the placebo group gained 0.3 kg (p = 0.001) with the effects being seen in overweight or obese patients (2.5 kg net loss; placebo –0.4 kg). STRATUS-Europe recruited 789 patients but did not show significant differences. The combined studies remain significant (p = 0.001) for quit rates at this short end-point. STRATUS-Worldwide recruited 5055 hardened smokers (20 cigarettes/day for 25 years and >5 previous quit attempts) and followed a similar protocol but patients were re-randomised at week 11 to placebo, rimonabant 5 or 20 mg for a further year with assessment of continuing cessation rates at weeks 10–32. Loss rates from the trial were high (50%) because of protocol violations (20%); compliance with attending clinics (12%) and side effects (12%). Relapse rates were significantly decreased at 1 year in the 20 mg group and this was associated with no weight gain (41.5% vs. 32.5%; 1.49 (1.09–2.04); p = 0.005). These results though reasonable compared with bupropion therapy and nicotine replacement are less than those achieved the nicotinic α-4 receptor partial agonist varenicline (57).

**RIMONABANT IN OBESITY STUDIES**

The other major trials with Rimonabant in Obesity (RIO) series have investigated its effects in primary prevention patients with BMI 27 kg/m² with cardiovascular risk factors or >30 kg/m² without all prescribed a –600 kCal/day diet. These trials have recruited populations in the USA and Canada [RIO-North America (RIO-NA)] (58), Europe (RIO-Eur) (59), patients with dyslipidaemia (RIO-Lipids) (60) and type 2 diabetes (RIO-Diabetes) (61) and compared placebo, 5 mg and 20 mg for up to 2 years. RIO-NA (58) examined the effects of 1 year’s treatment on weight loss in 3040 patients and secondarily after re-randomisation the effects of drug withdrawal on weight regain in 1557. In the initial run-in phase patients lost 1.9 kg in weight and their HDL-C reduced by 5.8% and triglycerides by 1.2%. At randomisation baseline patients weighed 105 kg had a BMI of 38 kg/m² and a waist circumference of 108 cm. At 1 year the 20 mg group lost a net 4.8 kg (placebo –1.6 kg) and those continuing this increased by a further 1.1 kg. Those receiving placebo after rimonabant regressed to a 0.9 kg benefit over placebo (–2.3 kg). Greater than 5% weight loss was achieved in 39.7 vs. 19.7% (p = 0.001) and >10% in 16.5% vs. 8.3% (p = 0.001). RIO-Eur (59) recruited 1507 similar patients and followed the effects of rimonabant 20 mg for 2 years. Starting at BMI 36 kg/m² and 108 cm waist circumference a net weight los of 4.8 kg was achieved at 1 year against placebo (–1.8 kg). Rates of >5% weight loss were 50.9% vs. 19.2% (p = 0.001) and >10% were 27.4% vs. 7.3% (p = 0.001). Lipids changed predictably with increases in HDL-C with diet of 12% but little change in triglycerides (–0.5%). The extra effect of rimonabant on HDL-C was 7.8% (0.11 mmol/l) and 11.2% on triglycerides. Regression analysis of lipid changes against weight suggested that this accounted for only 50% of the effect of rimonabant. These differentials were maintained at 2 years (3.3 kg net loss over 1.2 kg in the placebo group). The incidence of the metabolic syndrome fell from 42% to 19.6%.

RIO-Lipids (60) recruited 1063 patients with a BMI 27–40 kg/m² and dyslipidaemia defined as triglycerides 1.70–6.90 mmol/l or a total: HDL-cholesterol ratio >4.5 in women and >5 in men. During the run-in phase patients lost 2 kg in weight and a further net 6.3 kg (placebo 2.3 kg) with rimonabant therapy. Patients recruited had an average BMI of 34 kg/m², waist circumference of 105 cm, triglycerides of 2.26 mmol/l and HDL-C 1.15 mmol/l. Waist circumference fell by 5.8 cm and this was associated a 11.2% net increase in HDL-C (placebo 12.2%), a 12.2% reduction in triglycerides (placebo –3.6%) and a 4 nm (placebo 1 nm) increase in average LDL particle size and a 5.2% reduction in small dense particle number (placebo 0.4%). Blood pressure was reduced in patients with hypertension by a net 5.9/3.9 mmHg (placebo 7.2/2.4 mmHg). Using the National Cholesterol Education Program adult treatment panel 3 criteria the prevalence of metabolic syndrome was reduced from 50% to 25.8%. In parallel with these effects C-reactive protein levels fell by a net 0.6 mg/dl while adiponectin levels rose by a net 27% compared with a 14% rise in the
placebo group. Safety was similar to other studies with increase in depression (2.9% vs. 0.6%), anxiety (1.7% vs. 0.6%) and nausea (1.2% vs. 0%).

RIO-Diabetes (61) recruited 1045 patients on sulphonylurea (35%) or metformin therapy (65%) and BMI 27–40 kg/m². All had hypertension with 65% having a blood pressure >140/80 mmHg. All were centrally obese (waist 110 cm) with a BMI of 34 kg/m² and moderate glycaemic control (HbA1c 7.5%). After 1 year rimonabant resulted in a 3.9 kg net weight loss (placebo 1.4 kg) with 16% losing more than 10% of body mass (placebo 2%). Glycaemic control improved by a net 0.7% (placebo +0.1%) in all patients irrespective of hypoglycaemic therapy 43% as opposed to 23% (p < 0.001) achieved an HbA1c < 6.5%. This was associated with an 8.3% net rise in HDL-C (placebo 7.1%) and a 16.4% net reduction in triglycerides (placebo +7.3%). No change was seen in LDL-C. Prevalence of the metabolic syndrome was reduced by a net 12.3% (placebo 7.6%) (p = 0.007).

**THE SAFETY PROFILE OF RIMONABANT**

The safety profile of rimonabant in the RIO programme has been good. Though side effects are commonly reported in these trials (80%) detailed analysis only reveals a few specific signals (Table 1). Nausea was seen in 12.9% vs. 3.4%; dizziness in 8.7% vs. 4.9% and diarrhoea in 7.2% vs. 3.0%. In patients with diabetes hypoglycaemia was reported in 3.4% vs. 1.7%. Most of these side effects were considered mild. Only psychiatric disturbance comprising anxiety and depression was clearly associated with rimonabant therapy (1.5% vs. 0.3%; number need to harm = 85). Among the serious side effects reported in the pooled programme 5.6% vs. 4.1% of patients indicated an excess of anxiety disorders. Discontinuation rates at 1 year were doubled with rimonabant therapy (13.6% vs. 7.7%) caused by depression and anxiety (6.7% vs. 3.2%), headaches and dizziness (2.1% vs. 1.1%) and nausea (2.3% vs. 0.4%). At 2 years data were similar with an excess of psychiatric disturbance (8.8% vs. 5.9%) and nausea (3.8% vs. 1.0%). These discontinuations were assessed clinically as there was no change in the Hospital Anxiety and Disease Scores (62). It is too early to say what other rare side effects may be discovered with rimonabant though already there have been a case report of multiple sclerosis (63) but this may have been because of chance. Currently the side effect profile of rimonabant follows from predictions of its mechanism of action. Thus mood disturbance and effects on gastrointestinal motility are predictable given the actions of CB1 receptors.

**COMPARISON WITH OTHER AGENTS**

Rimonabant is a new agent and thus long-term safety data applicable to rare side effects is not yet available. However, it is possible to compare rimonabant with the other drugs used to treat obesity (15,17) (Table 2). Orlistat is well established as a weight loss agent and is considered pharmacologically safe enough that in the USA it may become available over-the-counter. However, in clinical practice a meta-analysis of 29 orlistat studies showed a 2.89 kg (2.27–3.51) weight loss in patients with an initial BMI of 36.7 kg/m² (15). Orlistat therapy was associated with a 3.4-fold increase in diarrhoea,

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Reductions in cardiovascular risk factors in the Rimonabant in Obesity trial programme</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial</strong></td>
<td><strong>Dose (mg)</strong></td>
</tr>
<tr>
<td>North America</td>
<td></td>
</tr>
<tr>
<td>n = 1222</td>
<td>20</td>
</tr>
<tr>
<td>n = 607</td>
<td>0</td>
</tr>
<tr>
<td>Δ</td>
<td>5.8</td>
</tr>
<tr>
<td>Europe</td>
<td></td>
</tr>
<tr>
<td>n = 599</td>
<td>20</td>
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<td>0</td>
</tr>
<tr>
<td>Δ</td>
<td>4.8</td>
</tr>
<tr>
<td>Lipid</td>
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</tr>
<tr>
<td>n = 346</td>
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</tr>
<tr>
<td>n = 342</td>
<td>0</td>
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<tr>
<td>Δ</td>
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<tr>
<td>Diabetes</td>
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<tr>
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</tr>
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<td>n = 339</td>
<td>0</td>
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<td>Δ</td>
<td>4.0</td>
</tr>
<tr>
<td>Weighted change</td>
<td>5.4</td>
</tr>
</tbody>
</table>

BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.
Table 2 Effects of different cardiovascular therapies on features of the metabolic syndrome and end-point trial evidence of effects in prevention of diabetes and cardiovascular disease

<table>
<thead>
<tr>
<th>Drug/treatment group</th>
<th>Component of the metabolic syndrome reduction (%)</th>
<th>DM risk reduction (%)</th>
<th>CVD risk reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight/ waist</td>
<td>HDL-C</td>
<td>TG</td>
</tr>
<tr>
<td>Lifestyle (4 years) (13)</td>
<td>6–8</td>
<td>+16</td>
<td>34</td>
</tr>
<tr>
<td>Metformin (4 years) (13)</td>
<td>0–3</td>
<td>+15</td>
<td>15</td>
</tr>
<tr>
<td>TZD (4 years) (67)</td>
<td>+4</td>
<td>+9</td>
<td>12</td>
</tr>
<tr>
<td>Statin (5.5 years) (68)</td>
<td>0</td>
<td>0 to +15</td>
<td>15–25</td>
</tr>
<tr>
<td>Fibrate (6 years) (69)</td>
<td>0–5</td>
<td>+2 to +16</td>
<td>15–24</td>
</tr>
<tr>
<td>Niacin (6 years) (69)</td>
<td>1</td>
<td>+10 to +25</td>
<td>15–35</td>
</tr>
<tr>
<td>Orlistat (4 years) (16)</td>
<td>3</td>
<td>+3</td>
<td>1</td>
</tr>
<tr>
<td>Sibutramine (2 years) (18)</td>
<td>10</td>
<td>+9</td>
<td>25</td>
</tr>
<tr>
<td>Sibutramine (2 years) (64)</td>
<td>4.4</td>
<td>+3.5</td>
<td>2</td>
</tr>
<tr>
<td>Rimonabant (2 years) (58–60)</td>
<td>4–8</td>
<td>+9 to +11</td>
<td>9–29</td>
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<tr>
<td>Bariatric surgery (10 years) (70)</td>
<td>13–25</td>
<td>+20 to +47</td>
<td>15–28</td>
</tr>
</tbody>
</table>

*Largest increases seen with immediate-release preparations. CVD, cardiovascular disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides; TZD, thiazolidinedione. Abbreviations: United Kingdom Prospective Diabetes Study (UKPDS).

The clinical trial data for rimonabant shows superior weight loss (5.4 kg) compared with orlistat (2.85 kg) and sibutramine (4.85 kg) in clinical trials allied with a wider degree of benefit on cardiovascular risk factors. Compliance in all the obesity trials is about 70% and side effects are generally seen in 10–30%. The side effect profile of rimonabant is better than that of orlistat where gastrointestinal side effects occur in 20–30% and similar to sibutramine where compliance and side effect rates are similar but the drug is contraindicated in significant groups of patients (secondary prevention and hypertension). No data exists as yet for rimonabant in combination with other obesity medications. Given the profoundly different mechanism of action of rimonabant it is a good alternative where other anti-obesity medications have not been tolerated or are contraindicated. As it has beneficial action on lipid profiles that are not seen with orlistat, it may be superior to this agent in patients with notable dyslipidaemia as well as obesity and insulin resistance and also has beneficial effects in helping increase rates of cessation of smoking. The long-term benefits of rimonabant will be confirmed in studies looking directly at its effects on the progression of atherosclerosis by intravascular ultrasound and in a cardiovascular end-point trial (the Comprehensive Rimonabant Evaluation Study of Cardiovascular End-points and Outcomes (66) trial) where rate of progression to diabetes is a secondary end-point.

**CONCLUSIONS**

Rimonabant is the first drug to target the CB pathway. This drug blocks both the central effects of this neurotransmitter pathway involved in obesity and weight control. It also has direct actions in adipose tissue and the liver to improve glucose, fat and cholesterol metabolism so improving insulin...
resistance, triglycerides and HDL-C and in some patients, blood pressure. Thus this drug has the potential to have major effects on both the metabolic syndrome and thus reduce the risks of type 2 diabetes and cardiovascular disease associated with the cardiometabolic phenotype.

ACKNOWLEDGEMENTS

Dr Wierzbicki has received honoraria for lectures and advisory boards as well as travel and research grants from AstraZeneca, Bristol-Myers-Squibb, GlaxoSmithKline, Merck kGA, Merck, Sharp & Dohme, Novartis, Pfizer, Sanofi-Aventis, Schering-Plough, Solvay-Fournier and Takeda.

DISCLOSURES

Dr Wierzbicki has received honoraria for lectures and advisory boards as well as travel and research grants from AstraZeneca, Bristol-Myers-Squibb, GlaxoSmithKline, Merck kGA, Merck, Sharp & Dohme, Novartis, Pfizer, Sanofi-Aventis, Schering-Plough, Solvay-Fournier and Takeda.

High relevance: advisory boards for Sanofi-Aventis on rimonabant.

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*Paper received July 2006, accepted September 2006*