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# Pharmacological treatment of obesity, food intake, and reversal of metabolic disorders

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## SUMMARY

The present paper is reviewing the current place of weight-reducing drugs in the overall management of overweight/obese subjects, especially those with metabolic disorders and type 2 diabetes. Anti-obesity agents should be carefully evaluated in long-term (1-2 years) randomized controlled trials. Recent systematic reviews and meta-analysis assessed both the safety and efficacy of the two drugs currently used in the treatment of obesity, i.e. orlistat, a gastric and pancreatic lipase inhibitor that reduces fat absorption from the gut, and sibutramine, a combined norepinephrine and serotonin reuptake inhibitor that regulates food intake. Rimonabant, a new compound acting as selective blocker of CB1 receptors of the endocannabinoid system, raises much interest as it promotes weight reduction by a central effect and also exerts peripheral effects targeting cardiometabolic risk. Special attention will be paid to beneficial metabolic effects resulting from (even moderate) weight loss and to possible additional effects beyond weight reduction.

Pharmacotherapy is defined as the treatment of undesirable or unhealthy symptoms through the use of drugs. Implicit in a review of the pharmacological treatment of obesity is the recognition of the condition of obesity as being undesirable and/or unhealthy (1). The last decade has seen not only a change in the prevalence of obesity (2), but also has highlighted the fact that obesity is a highly risky pathological condition (3,4). Obesity, especially abdominal obesity (5), is associated with various metabolic risk factors that predispose to cardiovascular disease (6,7). Numerous studies have shown that a moderate sustained weight reduction of 5-10 % initial body weight is sufficient to produce a marked improvement in metabolic disorders (8,9) and a significant reduction in the development of diseases, such as type 2 diabetes (10), presumably by reducing visceral adipose tissue to a larger extent (5).

Obesity should now be considered as a chronic disease of multifactorial etiology that is a lifelong condition for most persons (4). This chronic disease "biological" model has important implications for the treatment used. Just as in other chronic diseases, treatment must be maintained for life with lifestyle interventions combined, when necessary, with pharmaceutical approaches. Pharmacological therapy should be considered as a supplement to lifestyle intervention, which is a commonly used approach to treat the obese patient, by adherence to a specific dietary and/or physical exercise programme (11,12,). Indeed, the combination of medication and group lifestyle modification resulted in more weight loss than either medication or lifestyle intervention alone, underscoring the importance of prescribing weight-loss medications in combination with, rather than in lieu of, lifestyle modifications (13,14). Numerous clinical trials have investigated the effects of various anti-obesity approaches, but most of early studies were of limited duration, not exceeding a few months (15,16). As it is recognized that obesity is a chronic disease, only approaches able to induce long-term safe weight reduction should be considered as valuable strategies for treating obese subjects (17). That is the reason why anti-obesity drugs should first prove both efficacy and safety in 1-2 year randomized clinical trials (RCTs) before being accepted for treating obese patients (18,19).

Pharmacological therapy for the management of obesity has received great attention from clinicians and patients. However, as of 1997, 5 drugs had been removed from the U.S. and international markets because of safety concerns (fenfluramine, dexfenfluramine, and phenylpropanolamine internationally and diethylpropion and phentermine in Europe) (20-22). Current accepted pharmacotherapy treatments include two main classes of drugs : 1) drugs to suppress appetite, eg serotonin-norepinephrine re-uptake inhibitors such as sibutramine hydrochloride (23,24), and 2) drugs to change metabolism, eg a gastrointestinal lipase inhibitor that prevents absorption from the gut such as orlistat (25,26). In contrast with previous anti-obesity drugs, these two compounds have been carefully evaluated in several large placebo-controlled long-term trials in which patients were generally prescribed a modest energy deficit (around 600 kcal/day) and encouraged to increase physical activity (15-17). Clinical trials investigated body weight changes as well as, in numerous cases, ancillary markers, for instance, cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidaemia, ... All RCTs support the recommendation that drug therapy can be useful as part of a comprehensive weight loss programme in addition to diet and exercise (11,13). According to several guidelines (27-29), pharmacological therapy can be offered to obese patients who have failed to achieve their weight loss goals through diet and exercise alone. It should be considered for those with BMI > 30 kg/m² or BMI > 27 kg/m² with obesity-related risk factors or disease. It has been a research goal to develop safe and effective antiobesity drugs, analogous to what has occurred with hypertension, dyslipidaemia and diabetes (30). An emerging concept is

that the development of antiobesity agents must not only reduce fat mass (adiposity) but must also correct fat dysfunction (adiposopathy) (30, 31). To this respect, the new compound rimonabant, a specific blocker of CB1 receptors of the endocannabinoid system, may offer some advantages because of its dual effect in the central nervous system and in the periphery, especially the adipocytes and the liver (32,33).

The present review will describe and compare the effects in overweight/obese individuals of three different pharmacological approaches : orlistat, sibutramine and rimonabant (Table 1). For each drug, the mechanism of action and safety profile will be briefly presented, followed by the effects on weight loss and weight maintenance, the effects on cardiometabolic risk profile, including glucose control in patients with type 2 diabetes, and the possible weight-independent effects. Finally, as a clinical perspective, the most relevant already published or ongoing long-term clinical trial will be briefly described for each of these pharmacological compounds.

## ORLISTAT

### 1) Mechanism of action and safety profile

Orlistat is a gastric and pancreatic lipase inhibitor that blocks the absorption of about one third of the fat contained in a meal and thus promotes faecal excretion of undigested fat (25,26). The drug should be prescribed together with a low-fat diet (maximum of 30 % of total energy intake). Orlistat use frequently results in gastrointestinal adverse events including flatus, oily stools, faecal urgency or faecal incontinence, and abdominal pain, particularly among patients who do not follow the recommended low-fat diet. Daily multivitamin supplementation may be recommended to prevent the potential of impaired absorption of fat-soluble vitamins (A, D, E and K) that may theoretically occur with long-term use (22,25,26).

### 2) Effects on weight loss and weight maintenance

A recently published meta-analysis summarized the results of 29 randomized placebo-controlled studies of orlistat (usual dosage of 120 mg 3 x per day) (16). The average age of patients enrolled in these studies was 48 years. Seventy-three percent were women, and the average BMI was 36.7 kg/m². In all studies, diet was a co-intervention in all experimental arms. Thirty-nine percent of studies include educational, behavioural, or psychosocial co-interventions. Twenty-two studies were identified that reported data with 12-month outcomes. The pooled random-effects estimate of the mean weight loss for orlistat-treated patients compared with placebo recipients was 2.89 kg (95 % confidence interval or CI, 2.27 to 3.51 kg). The total weight lost in the orlistat-treated patients was 8.13 kg. However, in some studies, the dropout rate was rather high as commonly observed in long-term RCTs in obesity (15-17, 34). In a sensitivity analysis by follow-up rate, the pooled random-effects estimate of 15 studies with follow-up rates of 70 % or more was a mean weight loss of 2.83 kg (CI, 2.0 to 3.6 kg) compared with placebo. A sensitivity analysis assuming no weight loss among patients lost to follow-up yielded a mean weight loss favouring orlistat of 2.59 kg (CI, 1.90 to 3.29 kg). There was no evidence of publication bias.

A Cochrane systematic review included eleven high-quality orlistat weight loss studies over one year (four of which reported a second year maintenance phase) (34). Attrition rates averaged 33 % during the weight loss phase. Compared to placebo, orlistat-treated patients lost 2.7 kg (CI : 2.3 to 3.1 kg) or 2.9 % (CI : 2.3 to 3.4 %) more weight. The number of patients achieving ten percent or greater weight loss was 12 % (CI : 8 to 16 %) higher with orlistat than with placebo.

A study that focused specifically on prevention of weight regain after a successful period of dieting alone showed that the use of orlistat minimizes weight readjustment and facilitates long-term improvement in obesity-related disease risk factors (35). A clinically meaningful reduction in body weight, associated with an improvement in risk factors for coronary heart disease, and the maintenance of this weight loss was achievable with orlistat treatment and dietary restriction over a period of 18 months (36). The 2-year studies which were designed to evaluate the effect of orlistat in maintaining the weight loss in the first year of treatment demonstrated significantly less weight regain with orlistat than with placebo (37-39). A retrospective analysis of pooled data from two RCTs showed that of the criteria currently suggested for assessing response to orlistat treatment, weight loss of $\geq$ 5 % at 12 weeks accurately predicts sustained improvements in weight and major risk factors at 2 years (40). Similar results in the long-term treatment of obesity with orlistat were also reported in primary care settings as compared to those of RCTs (41). Recent results obtained after a mean treatment duration of 7.1 months with orlistat in a large naturalistic postmarketing surveillance study on 11,131 women and 4,418 men followed by general practitioners in Germany were comparable with the results of placebo-controlled RCTs as far as both efficacy and safety were concerned (42). The recent Xenical Propesctive Evaluation In Real Practice Treatmen( X-PERT) study showed that orlistat was associated with weight loss, regardless of the level of dietary restriction prescribed (daily deficit of 500 or 1,000 kcal) (43). The lack of significant difference between the two groups (- 11.4 vs – 11.8 kg after one year) might be explained by insufficient compliance with the dietary regimen. Furthermore this study confirms that initial success in weight loss with orlistat predicts longer term weight loss, as it was already demonstrated whether using behavioural approach or other anti-obesity medications (44). Therefore, identifying patients who lose at least 5 % body weight after 3 months is a valuable treatment algorithm to select patients who will benefit most from orlistat treatment in combination with diet in the long term.

The prevalence of overweight and obesity in children and adolescents is increasing rapidly and, in this population, behavioural therapy alone has had limited success in providing meaningful, sustained weight reduction. A recent one-year study showed that in combination with diet, exercise, and behavioural modification, orlistat significantly improves weight management in obese adolescents compared to placebo, with a greater reduction in BMI, waist circumference and fat mass as compared to placebo (45). As in adults, mild to moderate gastrointestinal adverse effects were observed in the orlistat-treated group of obese adolescents.

**3) Effects on cardiometabolic risk profile**

Weight loss produced by orlistat therapy was consistently associated with improvements in risk factors for cardiovascular disease, including serum lipid profiles (mainly total and LDL cholesterol levels), systolic and diastolic blood pressure and fasting and post-load plasma glucose levels (39, 46-48) (Figure 1). These improvements in cardiovascular risk profile were confirmed in recent trials (49-51). Minor long-term changes in weight have beneficial effects on insulin sensitivity and beta-cell function in obese subjects (52). In a pooled analysis of 2-year clinical trials, impaired glucose tolerance and increased plasma insulin levels improved in orlistat-treated obese patients, decreasing the percentage of patients of this group who developed type 2 diabetes (53). These observations lead to the concept that orlistat may prevent type 2 diabetes in at risk obese patients (54) and lead to the initiation of the XENDOS trial (55) (see below). In addition to these classical metabolic effects, orlistat appears also to have a favourable effect on some inflammatory markers, such as TNF-alpha and interleukin-6, and has a time-dependent effect on some haemostatic factors (51).

Favourable results were especially observed in overweight/obese patients with type 2 diabetes (56). A recent Cochrane review on the use of pharmacotherapy for weight loss in adults with type 2 diabetes revealed that orlistat produced modest reductions in weight (2.0 kg; CI 1.3-2.8) at 12 to 57 weeks follow-up (57,58). The addition of orlistat also produced a moderate but significant reduction in glycated haemoglobin (HbA1c) level after one year, in diabetic patients already treated with either sulfonylurea (59), metformin (60,61), or insulin (62). A meta-analysis of these four 1-year RCTs (total of 1,475 patients) showed consistent results across the trials : pooled estimates for placebo-subtracted weight reduction was 2.64 kg (2.6 %) and the difference averaged 0.38 %; **CI XX- YY% A COMPLETER)** for $HbA_{1C}$ (57). These favourable effects on $HbA_{1c}$ levels occurred despite a decrease in dosage requirements for oral sulphonylureas, metformin or insulin in patients treated with orlistat as compared to those receiving placebo. Until now, no data are available regarding the benefits of weight loss and decreased HbA1c level associated with orlistat use on long-term diabetic vascular complications.

A systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity (63) suggested that one of the main benefits of orlistat use concerns prevention and treatment of type 2 diabetes (54). A Markov health economic model was developed to predict, over a 10-year period, the complication rates and mortality with and without a 2-year orlistat treatment, assuming a 5-year catch-up period after treatment (64). The results suggest that orlistat is cost-effective in the management of obese type 2 diabetic patients, especially in those with the presence of hypercholesterolaemia and/or hypertension. A recent study attempted to calculate the cost effectiveness (from the Swedish healthcare perspective) of orlistat plus diet for an obese and overweight population in a 1-year weight-management responder programme versus a 1-year weight-management programmed based on diet only (65). The estimates indicated that orlistat increased the number of quality-adjusted life years (QALYs) and reduced the cumulative incidence of diabetes compared with diet only. Patients starting on orlistat in addition to a dietary programme achieved an incremental cost-effectiveness ratio that was similar to many other well accepted healthcare treatment programmes, although these preliminary results should be confirmed on a longer term basis. Similarly, a Markov health economics model applied in a subgroup of patients who achieved a good weight response (defined as a weight loss of $\geq$ 5 % after 12 weeks of orlistat treatment) in 7 RCTs involving overweight and obese patients with type 2 diabetes demonstrated acceptable cost per QALY gained both in Sweden and in Switzerland (66). However, despite of these favourable reports, evidence on longer-term benefits of orlistat (> 2 years) will be of importance for future decision-making.

**4) Possible weight-independent effects**

One important question is whether orlistat may exert beneficial metabolic effects beyond weight loss (56). Interestingly, the sustained cholesterol-lowering effect of orlistat is beyond what would be expected from weight loss alone, leading to an additional reduction of total and LDL cholesterol levels by roughly 10 % (67). This additional effect may be explained by the mechanism of action of orlistat, which reduces intestinal fat absorption, and perhaps by the better compliance to a low-fat diet in order to minimize digestive side effects. A study examined weight loss-dependent and –independent effects of orlistat at 6 months, using behavioural intervention combined with randomized, double-blinded, placebo-controlled treatment with orlistat in patients with type 2 diabetes (68). Results showed that at equivalent weight loss, conjunctive use of orlistat resulted in greater improvements in free fatty acid levels and insulin sensitivity. In contrast, they were identical decreases in visceral adipose tissue, fat mass, thigh adiposity, and hepatic steatosis. Another study investigated how identical weight loss in women taking orlistat or

placebo combined with a hypocaloric diet influences body composition and insulin sensitivity (69). Insulin sensitivity improved significantly and similarly after weight loss in both orlistat and placebo groups. Intraabdominal fat and subcutaneous fat decreased significantly in both groups, but the ratio of the two decreased only in the orlistat group. Finally, in a recent small-sized placebo-controlled RCT, the orlistat group had greater changes in BMI, % body fat, waist circumference, and insulin resistance, hs-C-reactive protein (CRP), leptin and adiponectin levels after one year than the control group (70). The decrease of leptin levels and the increase of adiponectin concentrations remained significantly different between the orlistat group and the placebo group after adjusting for changes in % body fat and waist circumference, suggesting an effect of orlistat beyond weight loss. These results need confirmation by further larger studies.

**5) Long-term clinical trial**

XENDOS ("XENnical in the Prevention of Diabetes in Obese Subjects") (55) is the most important RCT performed with orlistat until now, as afar as the number of subjects enrolled (n =3277) and the duration of the trial (4 years) are concerned. It demonstrates that the beneficial effects of orlistat on body weight persisted up to 4 years (- 6.9 kg with orlistat versus – 4.1 kg with placebo; $p < 0.001$), although the difference between orlistat and placebo group tended to attenuate over time. The most striking finding of XENDOS is that such a modest difference in weight reduction was sufficient to significantly reduce the cumulative incidence of type 2 diabetes (6.2 % with orlistat *versus* 9.0 % with placebo; $p = 0.0032$; relative risk reduction of 37.3 %). The reduction in the incidence of type 2 diabetes was especially remarkable in obese patients with impaired glucose tolerance at baseline, with a reduction of conversion to diabetes after 4 years decreasing from 28.8 % in the placebo group to 18.8 % in the orlistat group ($p < 0.005$) and a number needed to treat (NNT) to avoid one event of 11 only. Significant and sustained reductions in cardiovascular risk factors such as arterial blood pressure and lipid levels (mainly total and LDL cholesterol levels) were also observed in the orlistat group as compared to the placebo group (55). XENDOS is the first study demonstrating that an antiobesity agent, like orlistat, is able to reduce the progression to diabetes in obese subjects as compared with lifestyle changes alone.

## SIBUTRAMINE

**1) Mechanism of action and safety profile**

Sibutramine is a combined norepinephrine and serotonin reuptake inhibitor. At a daily dosage of 10-20 mg, it is associated with increased satiation and a resulting reduction in food intake (although some thermogenic effects may exist as well) (23). Side-effects reported with (dex)fenfluramine (a serotonin release enhancer), such as cardiac valvulopathies and primary pulmonary hypertension (20), have not been associated with sibutramine (22). However, because some patients administered sibutramine may experience moderate increases in blood pressure and heart rate, sibutramine's use is contraindicated in patients with uncontrolled hypertension, coronary heart disease, cardiac dysrythmias, congestive heart failure, or stroke (22,24,71,72).

**2) Effects on weight loss and weight maintenance**

A meta-analysis included 44 trials with sibutramine that were considered of sufficiently high quality for inclusion in the analysis (73). Included studies were RCTs that assessed sibutramine (10 mg/day to 20 mg/day),

enrolled adults 18 years of age or older (mean age range of 34 to 54 years) who had a BMI of 25 kg/m² or more. Dietary interventions were a co-intervention in nearly all primary studies, and exercise and behaviour modification were associated each interventions in about one quarter of the studies. Ultimately, 29 studies met all of the authors'inclusion criteria. Sibutramine was more effective than placebo in promoting weight loss in overweight and obese adults at all time points assessed, from 8 weeks up to 54 weeks. Among the 5 studies that assessed outcomes at 44 to 54 weeks' duration, the summary mean difference in weight loss was 4.45 kg (3.62-5.29 kg), favouring sibutramine versus placebo. Patients taking sibutramine had a 20% to 30% greater likelihood of losing at least 5 % of their body weight than did patients receiving placebo. This result was changed little by the authors'sensitivity analysis, and no evidence of publication bias was detected.

A Cochrane systematic review included five high-quality sibutramine weight loss studies over one year (three weight loss and two weight maintenance trials) (34). Attrition rates averaged 43 % during the weight loss phase. Compared to placebo, sibutramine-treated patients lost 4.3 kg (CI : 3.6 to 4.9 kg) or 4.6 % (CI : 3.8 to 5.4 %) more weight. The number of patients achieving ten percent or greater weight loss was 15 % (CI : 4 to 27 %) higher with sibutramine than with placebo.

Sibutramine was shown to facilitate long-term maintenance of weight loss after a very-low-calorie diet (74). The STORM ("Sibutramine Trial of Obesity Reduction and Maintenance") study is the longest RCT performed with sibutramine and thus provides valuable information about the role of this drug in weight maintenance (75). It recruited 605 obese patients for a 6-month period of weight loss with sibutramine (10 mg/day) and an individualised 600 kcal/day deficit; 467 (77%) patients with more than 5% weight loss were then randomly assigned 10 mg/day sibutramine (n=352) or placebo (n=115) for a further 18 months. Of the 204 sibutramine-treated individuals who completed the trial, 89 (43%) maintained 80% or more of their original weight loss, compared with only nine (16%) of the 57 individuals in the placebo group (odds ratio 4.64, $p<0.001$). Thus, this individualised management programme combining restricted diet and sibutramine achieved weight loss in almost 75% of obese patients after 6 months and sustained weight loss in around 50% of patients continuing therapy for 2 years.

A meta-analysis of eight placebo-controlled, double-blind, RCTs in a total of 1,093 obese subjects with type 2 diabetes showed significantly greater decrease in body weight (- 5.5 vs – 0.90 kg) and waist circumference (- 5.32 vs – 1.13 cm) after sibutramine treatment (n = 552) than in the placebo group (n = 541) (76). The overall effect size (standard mean difference) was 0.87 (CI 1.00 - 0.74, p = 0.0000) on weight change and 0.67 (CI 0.83-0.51; p = 0.0000) for waist circumference. A recent Cochrane review on the use of pharmacotherapy for weight loss in adults with type 2 diabetes revealed that sibutramine produced significant reductions in body weight (5.1 kg; CI 3.2-7.0) at 12 to 52 weeks follow-up (58). However, despite a clearly superior weight loss, a 12-month Finnish study showed that sibutramine 15 mg daily did not produce health-related quality of life benefits over placebo, except in diabetic subjects with particularly good weight and HbA1c responses (77).

In a recent one-year RCT (13), the combination of sibutramine and group lifestyle modification resulted in significantly more weight loss than either medication or lifestyle intervention alone supporting the concept of an integrated approach (14). Nevertheless, in a managed care setting in the US (78) and in a primary healthcare setting in Germany (79), the effectiveness and safety of sibutramine were similar to those observed in RCTs. In a GP setting following a specialist guided very-low-calorie-diet, weight loss was more effectively maintained with sibutramine in combination with a recommended diet and exercise program than with placebo over a follow-up period of 18 months (80).

One key question when prescribing sibutramine is whether the obese patient receiving the drug will benefit from it or not since large RCTs consistently showed good responders and poor responders to the pharmacological compound. Both genetic and behavioural predictors have been suggested. On the one hand, it has been showed that genotyping for the beta3 subunit gene (GNB3) C825T polymorphism is highly predictive for the identification of obese individuals who will benefit from sibutramine after 54 weeks (81). On the other hand, some psychobehavioural and nutritional characteristics (baseline BMI, depression score, restraint score and total energy intake) were used as predictors of weight loss after 12 months in response to a comprehensive weight management programme including pharmacological treatment with sibutramine (82).

Antiobesity drug therapy is not currently indicated for the treatment of adolescent obesity. However, a recent 6-month placebo-controlled RCT revealed that sibutramine plus diet and exercise induced significantly more weight loss in obese adolescents as compared to placebo (- 10.3 vs - 2.4 kg, $p<0.001$), with a good safety and tolerance profile (83).

Despite obvious statistical efficacy, neither orlistat nor sibutramine is able to induce large weight reduction in a majority of obese patients. In a pilot study designed to assess whether adding orlistat to sibutramine would induce further weight loss in patients who previously had lost weight while taking sibutamine alone (- 11.6 % of initial body weight after 1 year), no additive effects was observed after 16 weeks of combined therapy (84). Thus, combined orlistat-sibutramine therapy is not recommended for the management of obesity.

**3) Effects on cardiometabolic risk profile**

Weight reduction associated with sibutramine treatment was accompanied by significant improvement in the metabolic profile of obese subjects, with lower plasma glucose and insulin levels, and better lipid profile (74,75) (Figure 2). According to a recent review of the metabolic effects of sibutramine (85), in most trials, the drug exerted favourable effects on lipids, especially on high density lipoprotein (HDL) cholesterol and triglycerides, as well as on the total:HDL cholesterol ratio. Sibutramine also lowers serum uric acid concentrations. Furthermore, this drug seems to favourably influence adipocytokines; it reduces serum leptin and resistin levels and increases adiponectin levels (85). Nevertheless, sibutramine treatment was associated with small increases in arterial blood pressure (2-3 mm Hg) and heart rate (2-3 bpm). However, these unwanted effects were compensated by the reduction in blood pressure determined by the weight loss itself, mainly in the good responders who succeeded to lose 5% or 10 % of initial body weight (71). Combined analysis of two-placebo controlled trials demonstrated that sibutramine treatment causes no significant changes in systolic blood pressure, a slight increase in diastolic blood pressure and a slight increase in supine heart rate, as compared to placebo (86). In a direct comparative evaluation in hypertensive obese patients (87), both orlistat and sibutramine were effective on weight reduction during a 12-month treatment. While orlistat was associated to a mild reduction in blood pressure, no significant change was noticed on sibutramine, which was not associated to any cardiovascular effect and was better tolerated than orlistat. In a meta-analysis of 21 placebo-controlled, double-blind, RCTs of sibutramine, the effect size (standardized difference of follow-up minus baseline changes between the treatment and the control groups) of sibutramine on weight change was -1.00 (-1.17 to -0.84), whereas the effect sizes on systolic and diastolic blood pressure changes were 0.16 (0.08 to 0.24) and 0.26 (0.18 to 0.33), respectively (15). By subgroup analysis, the effect sizes on weight loss were significantly larger when the dosage was $\geq$ 15 mg per day. The conclusion is that sibutramine treatment is unlikely to elicit a critical increase in blood pressure even in hypertensive patients. However, blood pressure and heart rate should be monitored closely. In

patients who experience a clinically significant and sustained increase in blood pressure, the drug should probably be discontinued. According to the systematic review of Arterburn et al (73) there is insufficient evidence to accurately determine the long-term risk-benefit profile for sibutramine. This lack of evidence leads to the initiation of the SCOUT study (seen below).

The effects of sibutramine on cardiovascular risk factors have been carefully assessed in patients with type 2 diabetes, a metabolic disorder considered as a coronary heart disease equivalent. Two recent meta-analysis compared the effects of sibutramine with those of other anti-obesity drugs in obese type 2 diabetic patients (57,58). None of the 4 sibutramine trials performed in the diabetic population lasted more than 26 weeks and the total number of patients included only 460 patients. Pooled estimates for placebo-subtracted weight reduction averaged 4.49 kg (3.3 %) while it averaged 0.68 % for $HbA_{1c}$ decrease, but with a significant heterogeneity. However, when the Authors of the meta-analysis excluded one outlier study, the pooled effect was a reduction in weight of only 2.5 kg (95% CI, 1.8-3.2 kg) and in $HbA_{1c}$ of only 0.2 % (95% CI, -0.1-0.4%) (400 patients evaluated) (57). According to a meta-analysis of 8 placebo-controlled, double-blind, randomized clinical trials (76), fasting blood glucose and $HbA_{1c}$ significantly decreased after sibutramine treatment. The overall effect size on $HbA_{1c}$ was – 0.28 % (CI 0.13-0.42; p = 0.0002) again with some heterogeneity among the studies. Treatment benefits were seen in plasma triglycerides and HDL, without significant variation in serum total and LDL cholesterol. The overall effect size on triglycerides was – 0.24 (CI 0.09 - 0.39; p = 0.0024) and 0.20 (CI 0.05 - 0.35; p = 0.0087) for HDL cholesterol. No differences in systolic blood pressure between sibutramine and the placebo groups were seen, while recording of diastolic blood pressure and heart rate showed that sibutramine produced a small increase relative to placebo. In obese patients with type 2 diabetes, a decrease in HbA1c combined with significant weight loss was shown to be associated with many health-related quality of life benefits (77). A comparative randomized double-blind trial performed in type 2 diabetic obese patients showed that both orlistat and sibutramine were effective on anthropometric variables and on metabolic pattern (including $HbA_{1c}$ reduction) during a 12-month treatment (88).

A model estimates the costs and quality of life benefits associated with weight loss itself and the reduced incidence of coronary heart disease and diabetes in the healthy "obese" (89). The analysis of 2 randomized controlled trials over 12 months concluded that sibutramine is a cost-effective treatment for obesity when combined with diet and lifestyle advice.

**4) Possible weight-independent effects**

Most beneficial effects observed with sibutramine appear to result from the drug-induced weight loss. However, in the STORM trial, sibutramine treatment was associated with an impressive increase in HDL cholesterol levels : overall increases were 20.7% with sibutramine versus 11.7% with placebo ($p<0.001$) (75). It was concluded that changes in concentrations of HDL cholesterol, VLDL cholesterol, and triglycerides, but not LDL cholesterol, exceed those expected either from weight loss alone or when induced by other selective therapies for low concentrations of HDL cholesterol relating to coronary heart disease. The precise mechanism explaining such high increase in HDL cholesterol with sibutramine treatment remains unclear.

Sibutramine may help improve glucose control because it is conductive to weight loss but does not seem to exert glucose-lowering effects per se (56). In fact,the improvement in blood glucose control observed with sibutramine in obese patients with type 2 diabetes is generally less impressive in terms of reduction in $HbA_{1c}$ levels as compared with other trials performed with orlistat, despite a trend for a greater weight loss with sibutramine than with orlistat

(56) These differences may result from intrinsic beneficial effects of orlistat on insulin sensitivity beyond weight loss (see above) and/or from deleterious direct effects of sibutramine on insulin sensitivity, possibly via activation of sympathetic nervous system evidenced by heart rate increase. For the same reason, and as previously discussed, sibutramine treatment could somewhat dampen the classically observed reduction in arterial blood pressure resulting from weight loss (71,72,86,87).

**5) Long-term clinical trial**

There is no direct evidence that sibutramine reduces obesity-associated morbidity or mortality (90). A long-term large-scale prospective trial (« Sibutramine Cardiovascular and Diabetes Outcome Study » or SCOUT) has been designed to determine whether weight management with a novel lifestyle intervention plus either sibutramine (10-15 mg/day) or placebo in cardiovascular high-risk overweight and obese patients can impact upon cardiovascular endpoints (91). To be eligible for inclusion, patients must have experienced a cardiovascular event or have diagnosed type 2 diabetes and another cardiovascular risk factor. The primary endpoint of the trial will include a composite of myocardial infarction, stroke, resuscitated cardiac arrest, and cardiovascular death. The event-driven study will involve almost 9,000 patients in 16 countries who will be followed for at least 3 years. Results are not expected before 2008-2009. The Executive Steering Committee is confident that SCOUT will be able to provide the evidence needed to transform the clinical management of overweight and obesity in high-risk cardiovascular patients (91).

**RIMONABANT**

**1) Mechanism of action and safety profile**

Rimonabant acts as a specific blocker of the CB1 receptors of the newly discovered endocannabinoid (EC) system (32,92). This system contributes to the physiological regulation of energy balance and lipid and glucose metabolism through central and peripheral effects (33,93). EC system consists of endogenous ligands and G-protein-coupled $CB_1$ receptors, located in several brain areas and in a variety of peripheral tissues including adipose tissue, the liver and the gastrointestinal tract. Preclinical studies in $CB_1$ receptor knockout mice which are resistant to diet-induced obesity, support the role of the $CB_1$ receptor in central and peripheral regulation of body weight. Treatment with the selective $CB_1$ receptor blocker rimonabant produces weight loss and improves metabolic abnormalities in rodents. Evidence also exists for an enhancement of energy expenditure after blockade of CB1 receptors. These animal studies open new perspectives for the management of overweight/obese human subjects (33,92,93). Double-blind short-term phase II clinical trials confirmed that rimonabant reduces hunger, caloric and fat intake over a 7-day period and that it promotes weight loss as compared to placebo over a 4-month period (32). Most frequently reported side-effects in humans included digestive symptoms (nausea and rarely vomiting) and complaints dealing with the central nervous system (anxiety, depressed mood), which were generally mild to moderate and transient.

**2) Effects on weight loss and weight maintenance**

The RIO (Rimonabant in Obesity and related disorders) programme comprises four large-scale clinical trials assessing both the efficacy and safety of rimonabant (5 or 20 mg per day versus placebo) in more than 6,600 overweight/obese individuals (94). RIO-Europe (95) and RIO-North America (96) were performed in overweight/obese patients without specific comorbidities (type 2 diabetes was excluded) and lasted 2 years. RIO-Lipids (97) and RIO-Diabetes (98) were one-year trials investigating overweight/obese patients with either untreated dyslipidaemia or type 2 diabetes treated with monotherapy by metformin or sulfonylurea, respectively. What is remarkable is the consistency between results throughout all these four studies. Although rimonabant 5 mg exerted only modest effects, rimonabant 20 mg combined with diet therapy was associated with a significantly greater weight loss (- 3.9 to – 5.4 kg; $p < 0.001$) and a greater reduction in waist circumference (- 3.3 to – 4.7 cm; $p < 0.001$) as compared to placebo. After one year, two to threefold more patients achieved a weight reduction $\geq 5$ % or $\geq 10$ % of initial body weight in the rimonabant 20 mg group as compared to the placebo group. The two 2-year trials demonstrated that these favourable effects on body weight and waist circumference were maintained during the second year of treatment, whereas patients who were re-randomized towards placebo after one year regained weight in the RIO-North America trial (96).

**3) Effects on cardiometabolic risk profile**

Rimonabant has shown significant and sustained efficacy in the management of multiple cardiovascular risk factors such as abdominal obesity, insulin resistance, glucose tolerance, and atherogenic dyslipidemia in non-diabetic populations in the RIO-North America, RIO-Europe and RIO-Lipids trials (Figure 3). The most impressive data concerned a significant rise in HDL cholesterol level (+ 7.2 to + 8.9 % as compared to placebo) together with a significant reduction in triglycerides concentrations (- 12.4 to -13.2 % as compared to placebo). Interestingly, the increase in HDL cholesterol concentration was significantly correlated to the increase in plasma adiponectin levels in RIO-Lipids (97). While total and LDL cholesterol levels were not significantly affected, non-HDL cholesterol significant decreased in the rimonabant 20 mg group as compared to the placebo group. In addition, small dense LDL particles were reduced in favour of large LDL particles that are known to be less atherogenic (97). A small reduction in systolic and diastolic blood pressure was observed in all RIO trials, significant in RIO-Lipids performed in subjects with dyslipidemia (97).

Rimonabant also improves insulin sensitivity, as assessed by the HOMA model applied on fasting plasma glucose and insulin concentrations (95, 96) and glucose tolerance, as assessed during an oral glucose tolerance test (97). Fasting and post-glucose load insulin plasma levels were significantly diminished after treatment with rimonabant 20 mg. In a pooled analysis of the three RIO trials performed in non-diabetic patients, more obese subjects improved glucose tolerance and less individuals progressed towards type 2 diabetes in the rimonabant 20 mg group as compared to the placebo group (99).

These data were confirmed in patients with type 2 diabetes, a peculiar group with poor cardiovascular prognosis (98). Again, as compared to placebo, the greater reduction in body weight (- 3.9 kg) and waist circumference (- 3.3 cm) with rimonabant 20 mg was associated with significant increase in HDL cholesterol (+ 8.3 %) and decrease in triglyceride levels (- 16.4 %). In addition, in patients with type 2 diabetic patients, rimonabant 20 mg was associated with a clinically and statistically significant 0.7 % reduction in HbA1c levels, both in patients

receiving metformin and in those treated by sulfonylureas. A modest (- 2.4 mm Hg) but significant reduction in systolic blood pressure was also observed with rimonabant 20 mg in the RIO-Diabetes trial (98), as in RIO-Lipids (97).

Finally, significant reduction in hs-CRP levels was noticed in patients treated with rimonabant 20 mg as compared to placebo in the two trials where this independent cardiovascular risk factor was measured, i.e. RIO-Lipids (97) and RIO-Diabetes (98).

**4) Possible weight-independent effects**

All studies of the RIO-programme demonstrated that part of the favourable changes in the cardiometabolic risk profile could be attributable to weight loss, but part of these occurred beyond weight loss per se. A pooled analysis of all trials of the RIO-programme demonstrated that rimonabant therapy improved multiple cardiometabolic factors to a greater degree than could be attributed to body weight loss alone: overall 45 % of HDL cholesterol increase, 46 % of triglycerides reduction, and 49 % of the diminution of fasting insulin plasma levels could not be explained by weight loss (100). Similarly, in RIO-Diabetes, 55 % of the HbA1c lowering effect occurred beyond weight loss (94). Specific observations of the RIO-Lipids showed that part of the lipid effects of rimonabant, especially the HDL rise, could be attributed to a significant increase in plasma adiponectin concentrations, which was also only partially (less than half) explained by weight reduction (97). These observations are in agreement with the concept of active CB1 receptors in various peripheral organs, such as adipocytes, liver, gut and skeletal muscle, whose blockade could exert favourable metabolic effects independently from weight loss (33, 92, 93).

**5) Long-term clinical trial**

Crescendo ("Comprehensive Rimonabant Evaluation Study of Cardiovascular ENDpoints and Outcomes") is biggest RCT performed in overweight/obese patients. This prospective randomized, multinational, multicenter, double-blind, placebo-controlled, two-arm parallel group trial will assess whether rimonabant (20 mg/day) can impact on reducing the risk of major cardiovascular events in abdominally obese patients with clustering risk factors. The primary objective is to show whether rimonabant reduces the risk of a heart attack, stroke, or death from a myocardial infarct or stroke (combined endpoint) in such patients. The trial will enrol 17,000 patients followed for about 5 years at 125 research centres in the United States, Canada, Europe and Australia. As final result from CRESCENDO are not expected before 2011-2012, surrogate atherosclerosis endpoints will be obtained earlier from two other ongoing clinical trials. The AUDITOR ("Atherosclerosis Underlying Development Assessed By Intima-Media Thickness In Patients On Rimonabant") trial has enrolled 600 participants, with researchers focusing on whether rimonabant (20 mg/day) retards the progression of carotid atherosclerosis over a 24-month period. The STRADIVARIUS ("Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant-The Intravascular Ultrasound Study") trial is enrolling 800 participants, with researchers also focusing on whether rimonabant 20 mg/day retards the progression of coronary atherosclerosis over an 18-month period.

## CONCLUSION

The management of obesity requires a multidisciplinary approach including dietary and lifestyle interventions, combined with pharmacological agents if necessary. As obesity is a chronic disease, the results of its treatment should be best appreciated on a long-term basis. Realistic goals should be proposed to the obese patients. To this respect, a 10 % body weight reduction, which is associated with a significant improvement of the metabolic profile, may already be considered as a success of the medical intervention provided that weight regain is avoided. Three compounds have demonstrated beneficial effects on weight reduction and weight maintenance together with specific metabolic additional effects. Studies evaluating the long-term efficacy of marketed anti-obesity agents are limited to orlistat and sibutramine. Both drugs appear modestly effective in promoting weight loss; however, interpretation is limited by high attrition rate. Longer and more methodologically rigorous studies of anti-obesity drugs that are powered to examine endpoints such as mortality and cardiovascular morbidity are required to fully evaluate any potential benefit of such agents. Such long-term trials are ongoing for sibutramine (SCOUT) and for the new compound rimonabant (CRESCENDO).

The recent increase in pharmaceutical companies' efforts toward the treatment of obesity reflects recognition of the related health risks, the growth of knowledge about mechanisms that control energy balance, and the potential market for new compounds. The multiplicity of targets that are available for pharmaceutical intervention illustrates not only the many potential approaches to the pharmacological treatment of obesity, but also the complexity of the processes that regulate energy storage in the body. The better understanding of the neuro-regulation of appetite, and its application as part of evidence-based clinical interventions, could lead to a more coherent approach to obesity treatment. Nevertheless, investigation of potential neuroendocrine targets for appetite suppression suggests redundancy in the systems, which make development of effective agents against single receptors impractical.

Drugs are not currently the answer for the majority of obese individuals. The progressive rise in the prevalence of obesity will inevitably mean that only a small proportion of afflicted patients will actually be treated by long-term drug therapy. What is required is a better way of identifying patients who may particularly benefit from such pharmacological approaches. Discovery of new pharmacological alternatives, leading to a greater efficacy in the promotion of weight reduction without affecting safety, remains a main objective for the treatment of obesity. Wider use of pharmacotherapy and enhanced efficacy for the next generation of anti-obesity drugs certainly promise to reduce obesity related illness if not halt the rise in obesity per se.

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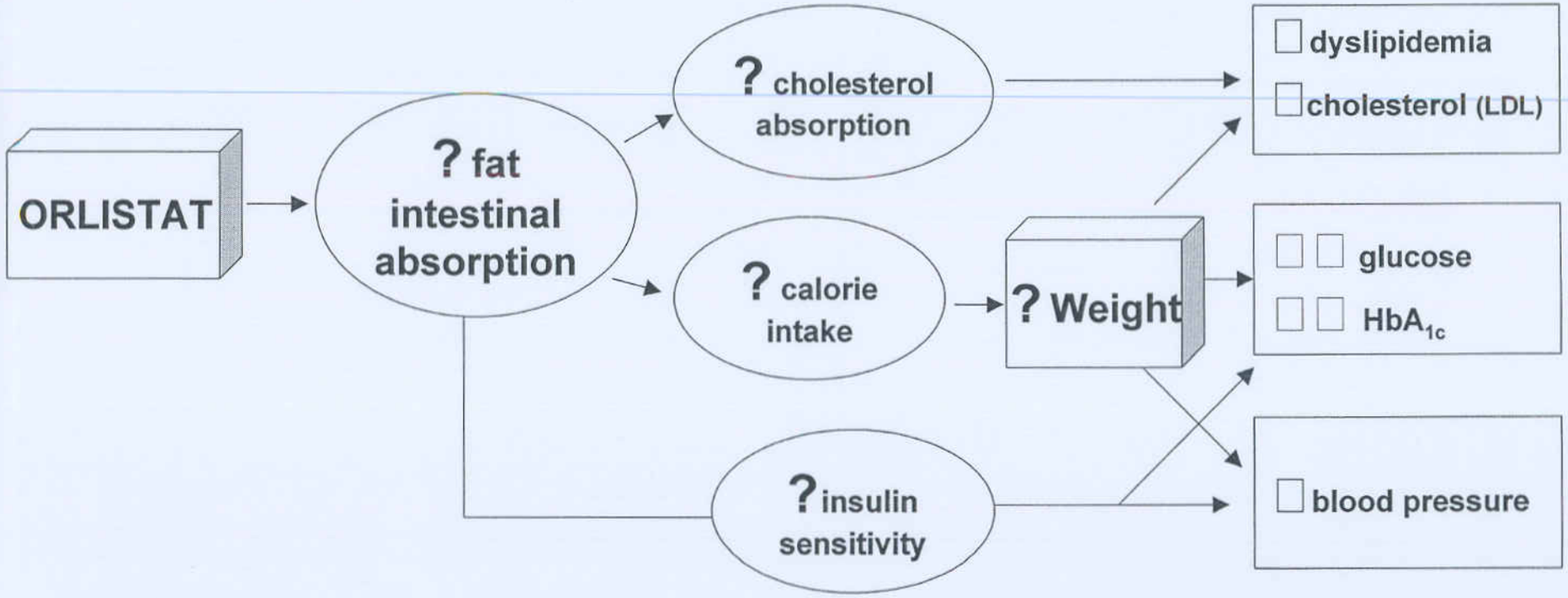
Figure 1 : Scheme of mechanism of action and clinical effects of orlistat.

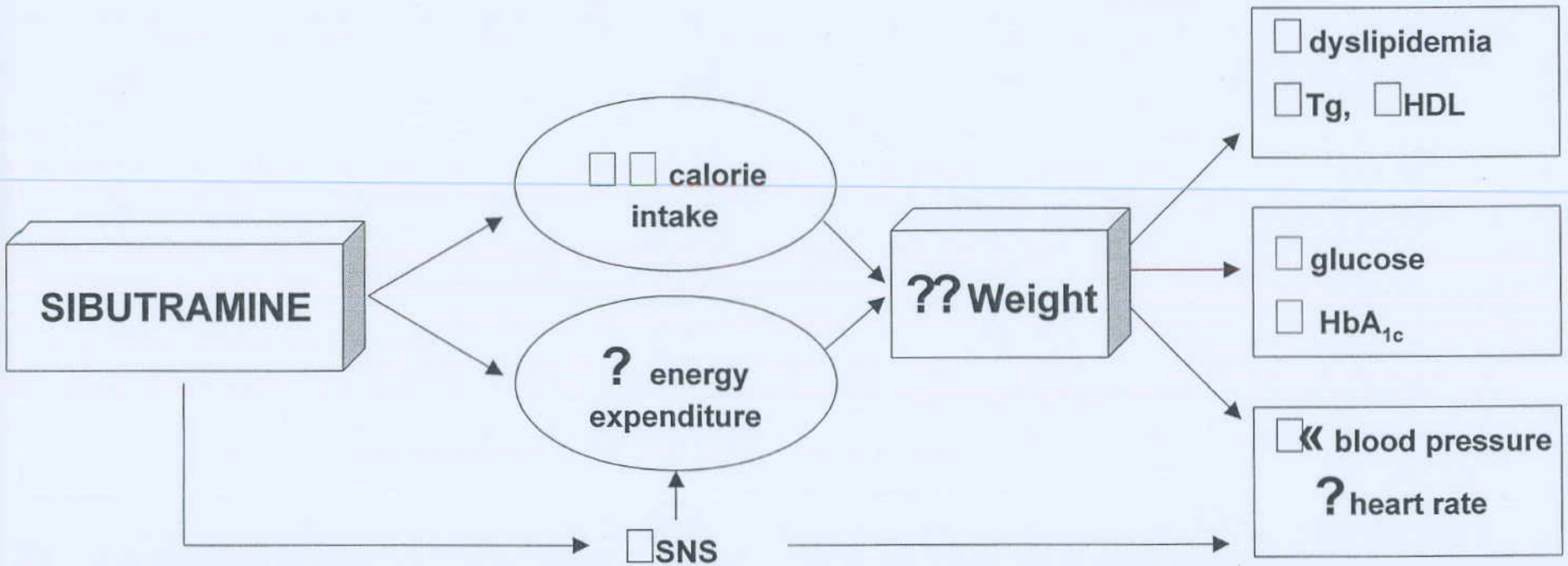
Figure 2 : Scheme of mechanism of action and clinical effects of sibutramine.

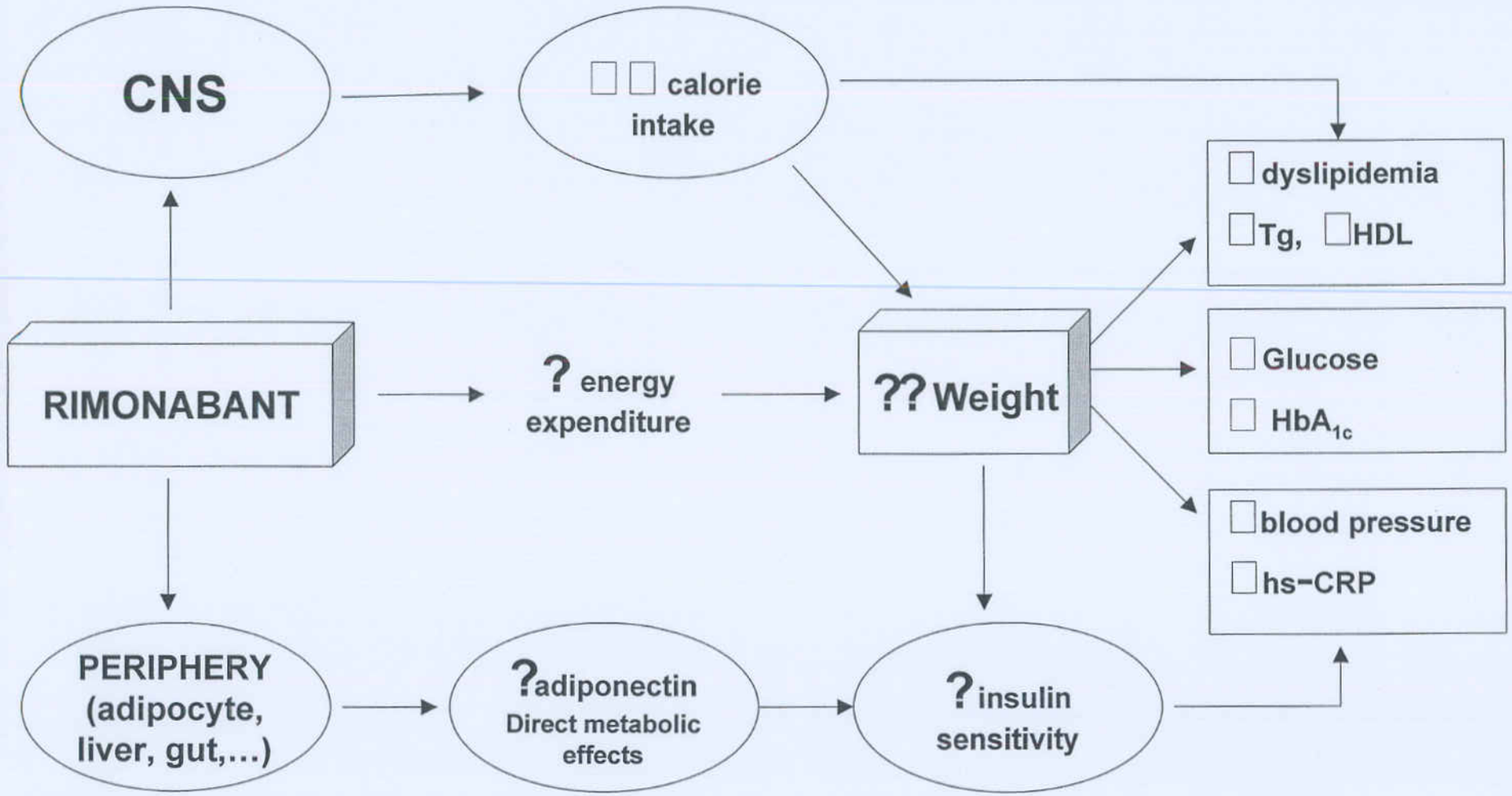
Figure 3 : Scheme of mechanism of action and clinical effects of rimonabant.

Table 1 : Comparison of orlistat, sibutramine and rimonabant. GI = gastrointestinal. NE = norepinephrine. 5HT = 5-hydroxytryptamine or serotonin. SNS : Sympathetic Nervous System.

| Effects | Orlistat | Sibutramine | Rimonabant |
|---|---|---|---|
| Mode of action | GI lipase inhibitor | NE/5HT reuptake inhibitor | CB1 receptor blocker |
| Usual dosage | 3 x 120 mg per day | 10-20 mg per day | 20 mg per day |
| Mechanisms | ↓ fat absorption | ↓ food intake | ↓ food intake |
| | (+ ↓ fat consumption) | Mild ↑ thermogenesis | Peripheral effects |
| Specific action | ↓ LDL cholesterol | ↑ HDL cholesterol | ↑ adiponectin |
| Side effects | Gastrointestinal (flatus, oily stools, faecal urgency, …) | ↑ heart rate (SNS) (↑) blood pressure | Nausea Anxiety, depressed mood |


ORLISTAT
? fat intestinal absorption
? cholesterol absorption
? calorie intake
? insulin sensitivity
? Weight
dyslipidemia
cholesterol (LDL)
glucose
HbA1c
blood pressure


SIBUTRAMINE
calorie intake
? energy expenditure
?? Weight
dyslipidemia
Tg, HDL
glucose
HbA1c
blood pressure
? heart rate
SNS


CNS
calorie intake
dyslipidemia
Tg, HDL
RIMONABANT
? energy expenditure
?? Weight
Glucose
HbA1c
blood pressure
hs-CRP
PERIPHERY (adipocyte, liver, gut,…)
?adiponectin
Direct metabolic effects
? insulin sensitivity