

# Clinical Pharmacotherapy for Obesity: Current Drugs and Those in Advanced Development

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**Abstract:** The current obesity pandemic imposes a major global disease burden. Levels of non-communicable diseases such as type 2 diabetes, cardiovascular disease and some cancers will continue to rise unless an effective approach to treat obesity is found. Sustained weight loss of between 5-10% in the obese, by various means, confers marked health benefits. The currently available pharmacotherapies, orlistat and sibutramine, can induce weight loss of between 5-10% over 2 years or more. In trials, orlistat and sibutramine induced weight loss tends to be only between 2-4 kg greater than that produced by placebo control. However, this additional placebo subtracted weight loss produces marked additional improvements in diabetes and cardiovascular risk factors. Moreover, in the 4 year long XENDOS trial, the modest placebo subtracted weight loss produced by orlistat (2.8 kg) reduced the incidence of diabetes by over a third in those with normal glucose tolerance, and by nearly half in those with impaired glucose tolerance. Despite this, prescription sales of sibutramine in the US have apparently remained static and those of orlistat have fallen, with the drug now entering the global over-the-counter medication market. Recent data on potential anti-obesity drugs currently under going phase III trials, such as Rimonabant and Topiramate, demonstrate these drugs produce greater and more prolonged weight loss. 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.

## OBESITY AND ITS CONSEQUENCES

Obesity has come to be recognised as a critical global health issue. Rates of obesity in North America and in most European countries have more than doubled in the last 20 years. In many of these countries, over half the adult population are now either overweight or obese. Obesity is a risk factor for non-communicable diseases such as non-insulin dependent diabetes (NIDDM), cardiovascular disease (CVD) and various types of cancer (WHO). Like the prevalence of obesity, the prevalence of obesity-related diseases such as diabetes also continues to rise. For instance, Mokdad *et al.* (2003) [1] have graphically documented the concurrent rise in obesity and type-2 diabetes across the states of the US between 1991 and 2001. In the US, obesity may soon 'over take' tobacco use as the prime external modifiable cause of death [2]. The impact of this obesity-associated morbidity and mortality has already had an enormous impact on global health care and welfare systems and this economic burden is only set to increase. Health care providers thus require economically viable interventions to reduce the projected costs of future disease. Moreover, obesity *per se* and obesity-related diseases together have a huge impact on an individual's daily functioning, and consequently on their quality of life. This results in a huge demand from those already obese for an effective and affordable approach to deal with their adiposity.

## BENEFITS OF WEIGHT LOSS

Numerous trials and weight loss interventions have demonstrated that modest weight loss and continued weight control confer sustainable improvements in health. Data from studies of nutritional interventions, exercise promotion and behavioural modification programmes or combinations of these all demonstrate that modest weight loss reduces risk factors for diabetes, cancer and cardiovascular disease such as high fasting and post-prandial blood glucose, HbA<sub>1c</sub> (glycosylated haemoglobin), insulin, total plasma cholesterol, low density lipoproteins (LDL), triglycerides, uric acid and blood pressure. Moreover, some data from longitudinal studies also indicate a reduced liability to subsequently develop the disease state after a successful and sustained period of modest weight loss. Whilst it is impossible to cover such a vast literature within the scope of the review there are specific clinical benefits associated with weight loss at 1 year. Weight loss below 5% still produces an improved cardiovascular risk profile. Weight loss over 5% produces a reduction in risk of the development of diabetes and a marked improvement in quality of life. Weight loss over 10% is associated with decreased mortality [3-6].

As detailed later, in specific subsections, many of these beneficial effects of 5-10% weight loss are also produced by both orlistat and sibutramine. Whilst current pharmacological interventions may not produce the dramatic weight loss desired by the patient, their benefits in terms of the individual's future health, and consequently their quality of life, would appear clear. However, due to the fact that clinical trials rarely last over 2 years, and these trials recruit individuals, even those with a specified co-morbidity, who are relatively healthy, there is little direct evidence that

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obesity drugs reduces obesity-associated morbidity and mortality [7]. So in drug trials, the changes in specific disease risk factors, easily observed even within trials of modest length, act as a proxy for future health.

### TACKLING OBESITY: ROLE OF PHARMACOTHERAPY

Any national or global strategy to tackle the prevalence of non-communicable disease must address the current obesity pandemic. Serious reductions in the prevalence of NIDDM, CVD or cancer cannot occur whilst levels of obesity continue to rise. To prevent obesity the individual needs to ensure that their total energy intake does not exceed their total energy output (i.e. maintain a neutral energy balance). For the obese individual to lose weight they must ensure their energy expenditure outstrips their intake (i.e. maintain a negative energy balance). Obesity has been traditionally challenged with prescribed and self-initiated diets, exercise and behavioural modification. Whilst it can be argued that these techniques are rarely comprehensively and unremittingly employed to produce weight loss, they have still failed to halt the obesity pandemic. Given the enormity of the obesity problem, adjunctive pharmacotherapy provides an attractive solution. Ideally, anti-obesity drugs, in combination with dieting and exercise, would promote negative energy balance thereby making weight loss for the individual easier. This effect would sustain compliance with the whole treatment program, and facilitate the appropriate lifestyle changes to prevent weight gain.

Any anti-obesity drug should be safe, effective and selectively target systems modulating energy balance. The mechanism by which a drug either increases energy expenditure and / or reduces energy intake should be proven and well established. From the patient's perspective medication should be easy to take (preferably oral administration) and tolerable, producing the minimum of discomfort and disruption. Finally, a drug should be affordable and provide improvements in health that outweigh the cost of intervention.

### CURRENT PHARMACOTHERAPY

#### Orlistat (Xenical)

Targeting appetite mechanisms to reduce intake is the most popular pharmacological approach to reducing energy intake, but blocking the digestion and/or absorption of nutrients is an alternative means of reducing energy intake. This is indeed one of the mechanisms by which obesity surgery produces weight loss (along with physically limiting the amount which can be consumed). However, the pharmacological approach to inhibiting the breakdown and absorption of nutrients within the gut has the potential to be more subtle and far less invasive.

The Roche compound, Orlistat (N-fromyl-L-leucine (s)-1-[[[(2S,3S)-3-hexyl-4-oxooxetan-2-yl]methyl]dodecyl ester), represents the first successful example of such a pharmacological approach although others are now under development. Current advice suggests that orlistat 120mg (marketed globally as Xenical) should be taken three times a day with meals. Reported side effects of orlistat include flatus with discharge, oily spotting and oily stool. More severe problems

such as faecal urgency, incontinence and abdominal pain can also occur. These symptoms are associated with the mechanism of action of orlistat and result from a large amount of undigested fat passing through the gastrointestinal tract. Such side effects normally subside as patients modify their diet, reducing their dietary fat intake. Because orlistat blocks the digestion of fat in the gut the availability of fat soluble vitamins (vitamins A, D, E and K) is an issue. Studies have shown that levels of the absorbed vitamins decrease during orlistat treatment but remain within normal range in most users [8-10]. No evidence of specific vitamins or mineral deficiencies has been observed during clinical trials (e.g. Pace *et al.*, 2001 [11]). However, it is recommended that those taking orlistat should also take vitamin supplements. In addition new data suggests that kidney stones may be a problem. Rodent data suggest that higher levels of unabsorbed fat and bile acids, resulting from orlistat treatment, may react with calcium in the intestine. This results in a fall in free calcium to which oxalate normally binds. Higher oxalate levels are then found in urine, elevating kidney stone production [12].

### ORLISTAT MECHANISM OF ACTION: LIPASE INHIBITION

Orlistat is a hydrogenated derivative of a lipostatin isolated from soil bacteria (*Streptomyces toxytricini*) and an inhibitor of gastrointestinal lipases. As such orlistat blocks the breakdown of ingested dietary fat. In effect the drug irreversibly blocks the active site of the enzyme preventing the hydrolysis of triglycerides into absorbable fatty acids and monoglycerides [13-15]. The undigested, and thus unabsorbable, fat is consequently excreted. Indeed a single dose of orlistat, given to participants consuming a diet containing 30% dietary fats, subsequently passed stools which contained approximately a third of this fat, undigested [16, 17]. Orlistat dose dependently increases daily fat excretion from trace in placebo to approx 30g at the highest orlistat dose employed [9]. This dose dependent increase in fat excretion is associated with a 6 month weight loss in the obese. It has been claimed that those receiving orlistat for weight loss show a decrease in blood lipids and cholesterol above and beyond that expected to be produced by the weight reducing effects of orlistat alone [18-20]. Whether this confers any additional therapeutic benefit is unclear.

The inhibition of lipases also has an impact on the release of endogenous satiety peptide cholecystokinin (CCK). CCK is a critical gut derived episodic signal inhibiting food intake. Levels of plasma CCK are stimulated by the hydrolysis of dietary fat to fatty acids by lipases within the gut [21]. It has been suggested that orlistat induced lipase inhibition may undermine normal CCK mediated suppression of appetite. Schwiser *et al.* (1997) [14] demonstrated that orlistat reduced the endogenous CCK response to a high fat meal in humans. Similarly, Hildebrand *et al.*, (1998) [21] found that orlistat dose-dependently inhibited lipase activity and postprandial fatty acid levels within the duodenum in humans. This was associated with a marked suppression of plasma CCK. Could orlistat induced suppression of CCK release have an impact on appetite? Matzinger *et al.*, (2000) [22] found that the fat infusions into gut inhibited subsequent food intake in humans, but this effect was abolished by orlistat-induced

inhibition of fat hydrolysis. Similarly, O'Donovan *et al.* (2003) [23] found that orlistat reduced the endogenous response CCK to a preload, an effect associated with a significant increase in subsequent energy intake. These studies would seem to suggest that orlistat may promote hyperphagia through the suppression of endogenous CCK release, possibly undermining its weight loss efficacy. However it should be noted other studies have shown that orlistat does not alter endogenous CCK levels, meal induced CCK release nor meal induced satiety [24-26]. To conclude, orlistat induced fat avoidance and reduced CCK response could both potentially increase daily energy intake and negatively impact upon the efficacy of orlistat.

### ORLISTAT MECHANISM OF ACTION: MODIFICATION OF DIETARY INTAKE

Whilst very little orlistat is absorbed into the body [27], and the drug has no systemic action, the drug may additionally modulate feeding behaviour. The consumption of a high fat diet in conjunction with orlistat results in aversive gastrointestinal side effects. Avoidance of these effects may modulate food choice, reducing the amounts of dietary fat those on orlistat are willing to consume. Given that the consumption of dietary fat has been specifically linked with obesity in humans, a reduction in fat consumption would aid weight control. In rats orlistat treatment does dose-dependently decrease fat intake leading to compensatory increases in the intake of protein and carbohydrate [28]. Paradoxically, this orlistat-induced effect on food choice causes an actual increase in total caloric intake in the rodents. However, in the same study orlistat still significantly inhibited body weight gain. Similarly, in humans orlistat treatment (72 weeks) has been shown to lead to a significant increase in the consumption of carbohydrate [29]. Those who had lost the least weight over the 72 weeks (less than 5% from baseline) had apparently increased their self reported carbohydrate consumption the most. It would seem that the orlistat induced dietary modification can in certain circumstances promote hyperphagia, again possibly undermining its weight loss efficacy.

### ORLISTAT EFFICACY

The effects of orlistat on body weight have been detailed in too many studies to be reviewed comprehensively here. Instead the author would like to refer the reader to a number of recent and highly detailed reviews of orlistat clinical trials [30-33]. Initial 12-week orlistat efficacy and tolerability studies demonstrated that orlistat given in conjunction with a hypocaloric diet could induce marked weight loss. Drent *et al.*, (1993) [111] gave orlistat 50 mg three times a day or placebo to healthy obese volunteers, in a double blind, parallel group design. Those receiving orlistat lost  $4.3 \pm 3.3$  kg compared to placebo  $2.1 \pm 2.8$  kg (placebo subtracted weight loss of 2.2 kg). In a study employing a large dose of 120 mg orlistat 3 times daily, those in the orlistat group lost  $4.2 \pm 3.5$  kg compare to  $3.0 \pm 1.9$  kg in the placebo group (Drent *et al.*, 1995) [35]. In a longer study, Van Gaal *et al.* (1998) [9] studied the effects of 30 mg, 60 mg, 120 mg and 240 mg orlistat three times daily on the body weight 676 obese volunteers over a six month period in a randomised, double blind trial. The 60 mg, 120 mg and 240 mg doses of

orlistat all produced significantly greater weight loss than placebo. At week 24 the weight loss was: placebo = 6.5%; 30 mg = 8.5%; 60 mg = 8.8%, 120 mg = 9.8%; and 240 mg = 9.5%.

Sjöström *et al.*, (1998) [36] conducted a major two-year long randomised control trial to assess the efficacy of orlistat 120 mg in 743 obese patients. In the first year participants were prescribed a hypocaloric diet and were given either placebo or 120 mg orlistat. All groups lost weight from their initial baseline. At the end of the first year those on placebo had lost 6.1 kg (6.1%) whilst those on orlistat had lost 10.3 kg (10.2%). At the end of the first year patients were then randomly reallocated again to either placebo or orlistat, and prescribed a weight maintenance diet. At the end of the study those given orlistat for 2 years, and those switched from placebo to orlistat in the second year had the greatest loss in body weight (approx. 8%) compared to those on placebo for 2 years (approx. 4%) or those switched from orlistat to placebo at the end of the first year (approx. 6%).

Firstly, Sjöström *et al.*, (1998) [36] demonstrated that a year of orlistat treatment was an effective way of inducing weight loss. This has been seen in other studies in which a year of orlistat treatment has induced weight loss of between 5.4%-9.7% [37a, 38-40, 112]. Sjöström *et al.*, (1998) [36] also showed that prescribing orlistat after a year of weight loss by diet seemed to be the most effective way of perpetuating further weight loss. In comparison, Hill *et al.*, (1999) [37b] showed that a year of orlistat treatment was effective at preventing weight regain, but not inducing further weight loss, after six months of pre drug dieting. With regard to weight regain, Sjöström *et al.*, (1998) [36] also showed, in those continually receiving orlistat, regain observed in the second year of treatment was significantly less than that in placebo control, a finding replicated in a number of other studies [38, 40, 41]. Thus, orlistat is significantly more effective at inducing weight loss and preventing weight regain than diet alone.

### ORLISTAT AND OBESITY RELATED HEALTH RISKS

Despite the fact that orlistat only produces a small placebo subtracted weight loss ranging between 1% and 4% over a year, this does have a positive impact on health in the obese. Orlistat induced weight loss has been shown to produce the beneficial effects on key risk factors for non-communicable diseases in numerous one and two year studies. Again, the studies are too numerous to report in detail here. However, orlistat treatment (120 mg) has specifically been shown to reduce blood pressure, even in those obese with inadequately controlled hypertension [42]. The drug also reduces other indicators of cardiovascular problems and diabetes such as total serum cholesterol, LDL-cholesterol, triglycerides, fasting glucose, HbA<sub>1c</sub> etc. [37, 40, 43-51].

Perhaps the longest orlistat study, XENDOS (XENical in the prevention of Diabetes in Obese Subjects), gives the clearest indication of the health benefits of continued use of orlistat [52]. This study examined the effect of orlistat plus lifestyle changes for the prevention of diabetes over a 4-year period. The study was conducted in 22 centres in Sweden,

recruiting 3304 obese patients. As with previous studies marked weight loss was observed in first year. This was significant greater in the orlistat group (10.6 kg versus 6.2 kg in placebo). Weight regain was seen in both the placebo and orlistat groups in the subsequent three years. After four years the mean weight loss in the orlistat group was 5.8 kg compared to 3.0 kg in the placebo, with 26% of the orlistat treated patients maintaining 10% or more weight loss over the full trial period. Whilst both weight loss from baseline and placebo subtracted weight loss over four years was modest, orlistat treatment markedly decreased the development of diabetes during the four-year study period. Specifically, there was a 37% decrease in the incidence of diabetes in those who started the study with normal glucose tolerance. In those who started the study with impaired glucose tolerance, orlistat reduced the cumulative incidence of diabetes over the 4 years by 45%.

### ORLISTAT LIKE DRUGS

Clinical data on orlistat demonstrates that lipase inhibition is an effective means of weight control and tackling obesity related health risks. However, the associated gastrointestinal side effects, which like the drugs efficacy increase dose dependently [9], may effect the compliance with treatment. ATL-962 (Alizyme Pharmaceuticals, UK) is another lipase inhibitor currently undergoing clinical trials. In a 12 week randomised, double blind, multi-centre study three doses of ALT-962 were given to the obese (n=372) [53]. At week 12 the weight loss was: placebo = 2.08 kg; 60 mg = 3.32 kg, 120 mg = 3.45 kg; and 240 mg = 4.05 kg. All doses significantly reduced body weight compared to placebo, producing comparable weight loss to orlistat. This was achieved with markedly fewer GI side effects than those reported for orlistat (comparative data extrapolated from published orlistat trials). It would seem ATL-962 is as effective as orlistat but may be better tolerated. However, it is difficult to understand how ATL-962 achieves weight loss through lipase inhibition without causing the GI related side effects.

### SIBUTRAMINE (MERIDIA, REDUCTIL)

Targeting the human appetite system has traditionally been both the most utilised and the most researched pharmacological approach to dealing with obesity. By changing our subjective appetite response to food, appetite suppressant drugs should modify eating behaviour and so reduce caloric intake. Sibutramine hydrochloride monohydrate 9N-[1-[1(4-chlorophenyl)cyclobutyl]-3-methylbutyl]-N,N-dimethylamine hydrochloride monohydrate), a beta-phanethylamine, is currently the only central acting anti-obesity compound approved for use in most countries. This Abbott Pharmaceuticals drug, prescribed under the name Meridia in North America, and Reductil elsewhere.

Sibutramine is a nor-adrenergic and serotonergic reuptake inhibitor that enhances both satiety and thermogenesis. Upon administration sibutramine is rapidly broken down into its first (BTS 54354) and then second (BTS 54505) metabolites. It is to these metabolites sibutramine predominately owes its action. The metabolites are both far more potent reuptake inhibitors *in vivo*. The drug, and its active metabolites, are believed to have comparatively little

direct activity at monoaminergic receptors and do not promote NA or 5-HT release. Sibutramine's metabolites are also inhibitors dopamine reuptake at the higher doses range but at doses much greater than are required to produce either hypophagia or thermogenesis [54]. The use of nor-adrenergic drugs (such as phenylpropanolamine, diethylpropion, mazindol and phentermine) and of serotonergic drugs (such as fenfluramine and d-fenfluramine) either alone or in combination (phentermine and fenfluramine) was the mainstay of obesity treatment during the 1980's and 1990's. However, sibutramine was initially developed during that period as an anti-depressant, and it was only during its initial clinical trials it was noted that those given the compound lost a significant amount of body weight.

Current advice suggests that sibutramine 10 mg should be taken once daily. The dose can be increased to 15 mg for those failing to lose sufficient weight and can tolerate it. For those who cannot tolerate the 10 mg dose, the dose can be reduced 5 mg a day. Cardiovascular side effects include an increase in systolic and diastolic blood pressure, and increase in heart rate (see later), tachycardia and palpitations and vasodilatation. Gastrointestinal side effects include constipation and nausea. Other side effects include dry mouth, insomnia, light-headedness, paraesthesia and aesthesia. Most side effects occur within the first four weeks of treatment and decrease in severity and frequency with time. Sibutramine shouldn't be given with or within two weeks of treatment with other centrally acting drugs. The drug also should not be given to those with a serious history of cardiovascular problems. Sibutramine has low abuse potential; with the drug having no rewarding properties at 20 mg, and aversive effects at much higher doses [55, 56].

### SIBUTRAMINE'S MECHANISM OF ACTION: APPETITE

The pharmacological mechanism by which sibutramine induced satiety appears to indicate both NA and 5-HT reuptake are critical. Behavioural data in rodents suggests that the changes induced by sibutramine on appetite are more akin to those produced by serotonergic rather than non-serotonergic drugs [57]. Specifically, the behavioural profile in rodents produced by sibutramine is similar to that produced by serotonin releasing and reuptake inhibiting drug d-fenfluramine, the serotonin reuptake inhibitors fluoxetine and sertraline, and the highly selective 5-HT<sub>1B</sub> and 5-HT<sub>2C</sub> receptors agonists and not that produced by nor-adrenergic drugs such as d-amphetamine. However, pharmacological studies reveal that 1 adrenoceptors are critically involved in sibutramine's effect on food intake, with some role also for 2 adrenoceptors and serotonergic 5-HT<sub>2A/2C</sub> receptors [58].

Like the 5-HT drugs it has superseded, sibutramine reduces food intake by reducing hunger and enhancing within meal satiety. In fact the effects of sibutramine on food intake and eating behaviour in humans are identical to those produced by both d-fenfluramine and the more selective 5-HT receptor subtype agonist mCPP [59]. Laboratory based studies have shown sibutramine reduces both food intake and hunger in the lean. For instance Hansen *et al.* (1998) [60] demonstrated that a single dose of sibutramine (30 mg) enhanced the satiety response to a fixed breakfast in lean

males. A single dose of sibutramine (15 mg) given to lean males also produced a significant decrease in total calories consumed across the day and in self-reported hunger [61].

The effects of sibutramine on food intake and appetite in the obese were first detailed by Rolls *et al.* (1998) [62] in a double blind placebo controlled cross over study. A group of non-dieting obese women ( $n = 12$ , BMI = 36.4 kg/m<sup>2</sup>) were given placebo control and two doses of sibutramine (10, 30 mg) once a day. Each treatment lasted 14 days and was followed by a 14-day wash out period. During each treatment phase of the study the effect of treatment on food intake and appetite were measured on two experimental days (days 7 and 14). Sibutramine 30 mg reduced total food intake on day 7 (23% from placebo) and Sibutramine 10 mg and 30 mg reduced total food intake on day 14 (a 19% and 26% reduction respectively) [62]. Sibutramine-induced hypophagia was accompanied by reduction of pre-meal hunger and prospective consumption. These changes in food intake and in appetite were accompanied by significant drug induced weight loss (10 mg = 0.8 kg, 30 mg = 1.2 kg at day 14) compared to placebo. In an eight-week study of the effects of sibutramine (15 mg) on body weight, energy expenditure and appetite in obese men sibutramine treatment again reduced hunger, anticipated food consumption and enhanced satiety [63]. Changes in food intake and in appetite were accompanied by weight loss (15 mg = 2.4 kg loss, placebo = 0.3 kg gain), suggesting that the hypophagic action of sibutramine was critical in its anti-obesity action.

Barkeling *et al.*, (2003) [64] carried out a short term randomised double blind placebo controlled trial to examine the effects of sibutramine on appetite in the obese, and to see whether these predicted weight loss on a subsequent long-term trial. After 14 days treatment with 15mg sibutramine or placebo the participants were invited into the laboratory to consume an ad libitum lunch. Sibutramine produced a 16% kcal reduction in energy intake at the test lunch during this double blind study. After completing both placebo and drug treatments, and after a wash out period, all the patients were allocated to a long-term open label sibutramine trial. After 10 months on the open label study (no placebo) the participants had lost on average 10.9 kg in body weight from baseline. Moreover, the initial effect of sibutramine on appetite (from the initial study) predicted the effect of sibutramine on body weight during the subsequent open label trial.

#### **SIBUTRAMINE MECHANISM OF ACTION: ENERGY EXPENDITURE**

Sibutramine also supposedly controls weight by increasing energy expenditure. The stimulatory effect on sibutramine on thermogenesis in rodents is well established [54]. Central NA and 5-HT reuptake inhibition which leads to sympathetic activation of brown adipose tissue [54, 65]. Preclinical evidence demonstrated that sibutramine could induce weight loss in the absence of any effect on food intake [66]. Similarly, Hanotin *et al.*, (1998) [67] found sibutramine produced significant weight loss over 12 weeks in obese humans without any self reported changes in appetite (with the exception of a reduced craving for savoury food). These data suggest that sibutramine induced increased

energy expenditure may be sufficient to produce weight loss in the absence of any modification of appetite.

However, many studies in humans have failed to show such marked sibutramine induced increases in energy expenditure. Notably, [68] Seagle *et al.* (1998) gave sibutramine (two doses 10mg and 30 mg a day) or placebo to 44 over weight volunteers (BMI 27-40 kg/m<sup>2</sup>). The treatment period lasted 8 weeks and participants were also put on a low calorie diet. Seagle and colleagues measured Resting Metabolic Rate (RMR) after the first day of dosing and then at 8 weeks. Although, both doses of sibutramine induced significant weight loss over the eight-week period the drug did not increase RMR, compared with placebo control.

Subsequently, Hansen *et al.* (1999) [63] assessed the impact of sibutramine (15 mg) on energy expenditure via indirect calorimetry in obese volunteers ( $n=32$ , BMI = 33.9±0.5 kg/m<sup>2</sup>) prior to and at the end of 8 weeks of treatment. The participants remained in the respiratory chamber on each occasion for 32 hours in total. During the 8 weeks the volunteers receiving sibutramine lost 2.4 kg in body weight compared to a gain of 0.3 kg on the placebo control group. Hansen and colleagues again found no increase in energy expenditure in the volunteers treated with sibutramine (compared to placebo) confirming the findings of Seagle *et al.* (1998) [68]. However, when changes in 24-hour energy expenditure were adjusted for weight loss, it was found sibutramine did modify energy expenditure. Specifically, the weight loss induced decrease in energy expenditure observed in the placebo condition was partially blocked by sibutramine. Walsh and colleagues found similar results (1999) [69].

In humans, sibutramine induced increases in energy expenditure are less pronounced and may be less important for the therapeutic efficacy of sibutramine. However, the fact sibutramine raises SNS activity, which at least blocks weight loss induced reductions in metabolic rate, no doubt adds to the drugs clinical efficacy. Sympathetic stimulatory activity also raises issues of safety specifically in the use of the drug in patients with severe cardiovascular problems such as congestive heart failure, coronary artery disease, hypertension, stroke and arrhythmia.

#### **SIBUTRAMINE EFFICACY**

As stated previously it was during phase 1 and 2 clinical trials as an antidepressant medication that the weight loss inducing effects of sibutramine were noted in the non-obese participants. Consequently an initial study was devised to establish the safety and efficacy of sibutramine for weight control. Sixty-one obese patients (baseline weight or BMI not given) were enrolled into an eight-week parallel group double-blind placebo controlled study (Weintraub *et al.*, 1991) [70]. The doses of sibutramine employed were 5 mg and 20 mg taken once a day after breakfast. In addition all participants were prescribed caloric restriction, exercise and behavioural modification. Both doses of sibutramine induced significantly greater weight loss than observed in the placebo control over the eight weeks of treatment. The weight loss from baseline in those completing the study ( $n=55$ ) was 1.4 kg (1.3%), 2.9 kg (3.0%) and 5.0 kg (5.1%) for placebo, 5

mg and 20 mg sibutramine respectively. Similar, effects were seen in two 12-week studies [68a, 71].

Subsequent clinical studies established that sibutramine produced dose related weight loss over a 6-month period [68b, 72, 73]. A large six month dose ranging study, conducted at seven clinical centres [72, 73], demonstrated that doses of sibutramine 5 mg to 30 mg significantly reduced body weight when compared to both measures at baseline and the placebo control [74]. As well as receiving either one of the doses of sibutramine or placebo, volunteers were also prescribed a reduced calorie diet, exercise and behavioural modification. Of the 1047 obese volunteers (weight =  $95.3 \pm 13.5$  kg, BMI  $34.5 \pm 2.97$  kg/m<sup>2</sup>) recruited to the study 683 completed the full trial. Analysis of weight was conducted only on those who completed the full 24 weeks of the study. At week 24 the weight loss from baseline was: placebo = 1.3 kg (1.2%); 1 mg = 2.4 kg (2.7%); 5 mg = 3.7 kg (3.9%), 10 mg = 5.7 kg (6.1%); 15 mg = 7.0 kg (7.4%), 20 mg = 8.2 kg (8.8%); and 30 mg = 9.0 kg (9.4%). At the dose of 10 mg 59.6% of the patients have lost 5% or more of their initial body weight (compared to 19.5% placebo) and 34.7% had lost 10% or more (0% in placebo). Interestingly the patients' weight loss in the early stages of the trial predicted their ultimate weight loss over the full 24 weeks. Specifically those patients who lost 4 lb or more in the first four weeks of sibutramine were far more likely achieve 5% weight loss above and beyond placebo weight loss. A number of others studies replicated these findings, demonstrating that over 24 weeks, doses of sibutramine, 10 mg, 15 mg and 20 mg produced significant weight loss both from baseline and compared to placebo control [75-80].

The efficacy of sibutramine in reducing body weight has been observed in numerous studies ranging in duration for 2 to 24 weeks. However, fewer studies have examined its effect over a year or more of treatment. Apfelbaum *et al.* (1999) [81] were the first to demonstrate the effect of one-year treatment with sibutramine on body weight. The study was designed to assess if sibutramine (10 mg) could further reduce the body weight of obese patients who had already lost 6 kg on four weeks of a very low calorie diet (VLCD). Those maintained on sibutramine post VLCD lost a further  $5.2 \pm 7.5$  kg during the subsequent year, whilst those given placebo regained  $0.5 \pm 5.7$  kg in weight.

In the STORM (Sibutramine Trial of Obesity Reduction and Maintenance) randomised double blind trial, conduction in eight European centres, 605 obese patients were prescribed sibutramine (10 mg) with a low calorie diet over a 6 month period [82]. At the end of this open label run in phase the diet phase ended and patients entered an 18-month randomised, double blind placebo controlled study. Those patients (n = 467) who had successfully lost at least 5% of their initial body weight were then randomly allocated to either a sibutramine (10 mg) or placebo treatment.

During the subsequent randomised double blind trial, the group maintained on sibutramine (n = 350) appeared to show little weight regains for the next 12 months and only slight regain thereafter. Their body weight at the study end point was  $9.3 \pm 5.5$  kg lower than at pre-run in baseline 24 months earlier. In contrast the placebo group (n = 114) appeared to start to regain weight within two months of entering the trial.

Their body weight was  $5.5 \pm 5.9$  kg lower than at initial baseline 24 months previously [83]. By the end of the study a significantly greater proportion of individuals had maintained either 5% or 10% weight loss in the sibutramine group compared to placebo. The weight loss-inducing efficacy of sibutramine has been observed in a number of other one and two year studies [84-87, 114]. In examining data from studies conducted over a year or more, irrespective of specific protocols or patient populations (diabetic or none diabetic, hypertensives etc.), it is apparent that the dynamic phase of sibutramine induced weight loss occurs within the first 6 months of treatment. Thereafter sibutramine stabilises body weight at a significantly lower level than at the pre-treatment (i.e. baseline). In a meta-analysis of these studies, Arterburn *et al.* (2004) [7] concluded that over a period of one-year sibutramine reduced body weight by 4.45 kg more than placebo. Whether sibutramine treatment beyond two years continues to prevent regain is unclear.

### SIBUTRAMINE AND OBESITY RELATED HEALTH RISKS

The weight loss produced by sibutramine has a number of effects on key risk factors for non-communicable diseases. Perhaps the most critical of issues, considering sympathetic activity of sibutramine, is cardiovascular function. Sibutramine has been shown to increase Heart Rate (3-7 beats per minute) and blood pressure (20% patients BP increase of 2-3 mmHg). These adrenergic side effects are in particular a concern for patients with hypertension. However, McMahon *et al.*, (2000), [84] demonstrated that sibutramine is both safe and effective in patients with controlled hypertension (i.e. taking other medication). A small significant and transient increase in blood pressure and pulse rate was observed in those given sibutramine. In fact sibutramine induced weight loss may reduce blood pressure in overweight and obese hypertensive patients over time [88]. At least initial rises in blood pressure and heart rate tend to occur early in sibutramine treatment and tend to partially subside. In a meta-analysis of twenty-one placebo-controlled trials, Kim *et al.* (2003) [89] concluded that sibutramine did significantly raise blood pressure, but only very slightly. Therefore, current recommended practice, closely monitoring of blood pressure at the start of sibutramine treatment, seems appropriate. It is also recommended that sibutramine is not used in those with severe cardiovascular problems.

Despite the issues around blood pressure and heart rate, sibutramine treatment does produce beneficial reductions in serum triglycerides levels and increases high-density lipoprotein cholesterol (HDL-C) concentrations [7, 78, 81, 82, 84, 86]. High triglycerides and low HDL-C are both key risk factors for the development of cardiovascular problems. Numerous studies have demonstrated that sibutramine induced weight loss is associated with improved glycaemic control and a reduction in other diabetes risk factors (blood pressure, insulin sensitivity, fasting blood glucose levels, triglyceride levels and LDL-C) [72, 77, 79, 90, 91].

### ORLISTAT VERSES SIBUTRAMINE

Few direct comparisons of the efficacy of orlistat and sibutramine have been published. One of the few direct

comparisons suggests that sibutramine 10mg a day is more effective than orlistat 120 mg three times daily at reducing body weight over a six month period [92]. In this open label study those in the sibutramine group lost 13.6% of their body weight from baseline, whilst those in the orlistat group lost 9.06%. No placebo group was included in this study. In another open label study, comparing sibutramine and orlistat alone, or in combination, researchers found sibutramine alone, or in combination with orlistat, were the most effective at decreasing Body Mass Index (BMI) in the obese [93]. However, orlistat was more effective at reducing waist circumference, a measure of abdominal fat. This suggests that whilst orlistat may be less effective at reducing body mass *per se*, orlistat-induced changes in fat distribution may specifically reduce cardiovascular risk. Wadden *et al.* (2000) [94] also demonstrated that combination therapy (orlistat plus sibutramine) proved little more effective than monotherapy. However, it should be noted in both of these studies that the sample sizes for each treatment group were very small.

Despite the lack of direct comparisons between orlistat and sibutramine, the increasing numbers of published studies of the long term clinical effects of both orlistat and sibutramine on body weight and other parameters have allowed systematic reviews and in some cases statistical meta-analyses of the comparative safety, efficacy and tolerability of these two drugs. Such reviews and meta-analyses have isolated studies that truly fit the regulatory 'gold standard' for fully randomised, double blind, placebo controlled clinical trials. Moreover, given the nature of obesity interventions, which generally take time to induce any substantial weight loss and suppress possible, regain, authors have excluded trials, which are generally shorter than one year.

An important consideration when reviewing such data is not only the nature of the intervention but also the inclusion of data in the final analyses. The most common and accepted approach to dealing with missing data has been 'Last Observation Carried Forward' (LOCF). In LOCF, as the name suggests, the last measure taken for an individual at any point during a trial is projected forward, through all subsequent data points, to the end of the trial. Weight loss in both placebo and drug groups tend to be reduced in magnitude when using a LOCF rather than completers only analysis. More inclusive forms of analysis include intention to treat (ITT). The inclusion criteria for intention to treat analysis vary between studies. However, analysis can potentially include any one who received placebo or drug at least on one occasion within the trial. ITT tends not only to include 'drop-outs' but also a number of protocol 'violators' i.e. those who missed appointments, or failed to take all of the medication during the trial, or were found to be taking other medications or using other non-approved weight loss products. ITT analysis provides the most 'real world' estimation of the drugs efficacy, i.e. how the drug will actually be used and the weight loss it will produce. Moreover, ITT analysis includes the most data possible for the critical analysis of drug safety.

Haddock and colleagues (2002) [31] examined 108 studies of pharmacotherapy for obesity collected from the 1950s. Their search excluded studies that were not peer

reviewed, had no control or comparison group or random allocation to treatment groups. The final meta-analysis included data on drugs once the mainstay of obesity pharmacotherapy, some long since discontinued, some recently removed from sale and some still in partial use as either prescription drugs or Over-the-Counter (OTC) weight loss products. The most striking conclusion was that no drug (including orlistat and sibutramine) produced weight loss greater than 4% (around 1 BMI point) above and beyond the placebo. Moreover, no drug, or class of drug demonstrated any clear superiority over any others. The largest effect size (0.90) was produced by sibutramine (placebo-subtracted weight loss of 2.37 kg). Their analysis also suggested drug combinations rather than administration of single anti-obesity agents produced far greater effects. Padwal *et al* (2003) [32] carried out a systematic review and meta-analysis of orlistat and sibutramine pharmacotherapy for obesity. Only studies that were double blind, randomised controlled studies of over one year with follow-up were included in the statistical analysis. Of these, apparently only eleven orlistat and three sibutramine published studies met their stated inclusion criteria. According to Padwal and colleagues, those receiving orlistat had a 2.7kg decrease in body weight beyond placebo (placebo-subtracted weight loss) whilst the figure for sibutramine was 4.3kg.

## FUTURE PHARMACOTHERAPY

### Current Criteria for the Evaluation of New Anti-Obesity Drugs

Before a new anti-obesity compound can be approved for use it must be proven to be both safe and effective. The American Food and Drugs Administration (FDA) and the European agency for the Evaluation of Medicinal Products (EMA) set the guidelines by which drugs currently under development are assessed. These are detailed on the agencies web sites and in other reviews [20]. Once an anti-obesity drug has passed through initial trials to test its safety and establish effective and tolerable doses, the drug's clinical efficacy must be tested against a placebo in larger scale, longer term randomised double blind trials.

Both the FDA and EMA understandably demand that any anti-obesity drug should produce significantly greater weight loss compared to placebo control over any trial. The FDA specifically demands that placebo-subtracted weight loss (i.e. drug induced weight loss minus placebo induced weight loss) is greater than 5%. Moreover, significantly more individuals in the drug treated group should have lost 5% or more of their initial body weight compared to placebo. The EMA alternatively demands that the weight loss in the drug group is greater than 10% from baseline. Moreover, significantly more individuals in the drug treated group should have lost 10% or more of their initial body weight compared to placebo. The secondary outcome of anti-obesity drug trials is to ensure that this weight loss is sustained and that it produces a significant reduction in risk factors for a number of obesity related co-morbidities (e.g. fasting blood glucose, HbA<sub>1c</sub>, insulin, total plasma cholesterol, LDL-cholesterol, triglycerides, uric acid and blood pressure). The FDA also demands that drugs reduce total body fat mass and alter body fat distribution (both specific risk factors in their

own right for ill health). Finally, drug induced weight loss should have made a positive impact on life style (e.g. health related quality of life) (see Table 1).

### DRUGS CURRENTLY IN PHASE III

#### Rimonabant

A number of compounds have been, are currently or are just about to start phase III clinical trials. Currently, perhaps the most prominent is Rimonabant (also known as SR141716 and recently named Acomplia) an endocannabinoid CB1 receptor inverse agonist. Rimonabant (from Sanofi-Synthelabo) has been developed to treat obesity and to aid smoking cessation, both major risk factors for cardiovascular problems. The efficacy of rimonabant in reducing food intake and reducing body weight/inhibiting body weight gain in rodents has been well established [95-98]. Rimonabant has also been shown to reduce food intake, hunger and body weight in overweight and obese men over 7 days of treatment [99]. In a 12-week study in 287 obese patients rimonabant produced significant dose dependent reductions in both body weight, and waist circumference [100] confirming its efficacy in the obese. It should be noted that because rimonabant aids smoking cessation and also reduces abdominal fat both key cardiovascular risk factors this drug might be particularly useful in the prevention and treatment of cardiovascular disease.

Rimonabant is currently undergoing four phase III clinical trials. In one of these, RIO (Rimonabant In Obesity studies) – Lipids, a 20 mg dose of the drug has been shown to reduce body weight by 8.2 kg over one year (placebo subtracted loss of 5.8 kg) [101]. Notably the initial period of weight loss on rimonabant continued for 9 months before it reached a plateau (longer than for both orlistat and sibutramine). Interestingly, there is already a rimonabant like compound, SLV-190 (from Solvay Pharmaceuticals and Bristol Myers Squibb), starting phase I clinical development.

#### TOPIRAMATE

Some of the newer anticonvulsants such as Zonisamide, Flenbate and Topiramate have been shown to induce weight loss within the clinic [102-105] Ameringen *et al.*, 2002.

These drugs each have unique pharmacology and act on a wide number of neurotransmitter mechanisms. Many of these pharmacological actions could singly or in combination account for their effects on body weight. For instance topiramate enhances GABA activity, blocks voltage dependent Na<sup>+</sup> channels, and antagonises AMPA glutamate receptors. There is no available data in humans on whether topiramate induced weight loss is primarily due to reduced energy intake, or how energy intake is possibly reduced (i.e. selective action on appetite). Data from rodent studies suggest that topiramate both reduces food intake and inhibits fat deposition, the latter effect probably accounting for the weight loss [106, 107].

Bray *et al.*, (2003) [108] demonstrated that topiramate dose-dependently induced weight loss in the obese in a six month randomized, placebo-controlled trial. Mean weight loss from baseline at week 24 was: 64 mg/d = 5.0%, 96 mg/d = 4.8%, 192 mg/d = 6.3% and 384 mg/d 6.3% (compared to placebo = 2.6%), giving a placebo subtracted weight loss for the two highest topiramate doses of 3.7%. A two-year international multi-site trial topiramate was discontinued because of concerns over tolerability (terminated at week 60). However, those receiving 256 mg a day lost 9.7% of their body weight over the 60 weeks (compared to 1.7% in placebo). As with rimonabant, topiramate continued to produce weight loss after 6 months of treatment [109]. In fact this was observed until week 48 of the trial. The side effects associated with the tolerability issue were CNS in origin and included psychomotor difficulties. Johnson and Johnson are currently reformulating the drug to enhance tolerability.

#### SUMMARY

Current pharmacotherapy, with either orlistat or sibutramine, produces significant weight loss from baseline of around 5-10% over a year. Weight loss tends to plateau at 6 months and some weight regain is seen thereafter. However, even the modest placebo subtracted weight loss produced by these currently used medications (approx. orlistat 2.4 kg; sibutramine 4.0 kg) does lead to marked improvements in health, specifically a reduction in risk factors for both cardiovascular disease and diabetes. In the

**Table 1. Criteria for Evaluation of Drugs Used in Weight Control (EU & US) Primary and Secondary End Points**

American Food and Drugs Administration (FDA)	European agency for the Evaluation of Medicinal Products (EMA)
• Drug induces significantly greater WL than placebo	• Drug induces significantly greater WL than placebo
• WL 5% more than placebo	• WL10% from baseline
• More individuals achieve 5% WL on drug than placebo	• More individuals achieve 10% WL on drug than placebo
• Reduces body fat mass & alters body fat distribution	• Significant and meaningful reductions in disease risk factors
• Significant and meaningful reductions in disease risk factors	• Improved quality of life
• Studies in diabetics recommended	
• Positive impact on life (improved quality life)	

WL = Weight loss

case of orlistat there is a marked reduction in the incidence of diabetes in response to treatment, which is particularly impressive in patients with glucose intolerance.

Despite the clear health benefits of both orlistat and sibutramine treatment the general use of medication to treat obesity in the US has fallen since 1997 (mainly due to the withdrawal of fenfluramine and d-fenfluramine at that particular time) [110]. In the US orlistat prescription sales have recently fallen and this drug is soon to become an over the counter (OTC) weight loss product with Roche having successfully negotiated the sale of OTC rights to GlaxoSmithKline in the US. The drug is already available OTC in Australia and various pharmaceutical companies are bidding for European OTC rights. Prescription sales of sibutramine in the US have also remained static in the last few years despite the continuing rise in obesity and obesity related illness. Newer drugs currently in phase III trials such as rimonabant and topiramate promise both greater and more prolonged weight loss, presumably accompanied by greater improvements in health. Enhanced efficacy may make these drugs more appealing to both health care providers and the obese.

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