# Orlistat: an update after the first decade of clinical experience

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Approximately a decade has pasted since the introduction of orlistat for the treatment of obesity. A considerable amount of clinical trial evidence has been accumulated to demonstrate that orlistat is safe and effective both for induction of weight loss and also in weight maintenance. No serious side effects have emerged, either in clinical studies or during postmarketing surveillance. Despite the documented efficacy, adoption of orlistat for the treatment of overweight and obese individuals has been slow. Many factors appear to be responsible, including its relatively modest effect compared with the magnitude of the obesity problem and the failure of many government and private insurance agencies to cover the costs of orlistat and indeed other antiobesity treatments. Obesity is clearly a multifactorial problem that is likely to benefit from a combination of different treatment approaches. Orlistat should be viewed as a safe and useful adjuvant therapy in the treatment of this disease.

## Mechanism of action

Orlistat, or tetrahydrolipstatin, is an orally active lipase inhibitor which reduces dietary fat absorption and is marketed under the brand name Xenical®. It represents the first agent in this class of drugs to reach the market and has been widely available for use in the treatment of overweight and obese states in most countries for 5 years or more. It has clinical indications for, and it is efficacious in both general obesity and obesity associated with Type 2 diabetes and other comorbid states. Orlistat's efficacy has been clearly established in a number of clinical trials including those of the randomized double-blind, placebo-controlled variety. In both developed and developing countries, obesity is approaching epidemic proportions. Many, if not the majority of obese individuals, have the metabolic syndrome and the associated increased risks of vascular disease. It is these individuals which are likely to present a considerable burden on the healthcare system where pharmacotherapy for obesity seems most likely to be justified. Despite compelling efficacy data, the use of orlistat in the treatment of obesity has only been adopted slowly by the medical community and government and private healthcare providers.

Although orlistat is active – at least *in vitro* – against a variety of lipases, in clinical use its activity is restricted to pancreatic and intestinal lipase present in the lumen of the small intestine since there is very little systemic absorption of orlistat. It covalently binds the active serine residue in pancreatic lipase – Ser-152 – and as a consequent inactivates the enzyme [1]. When taken with meals it partially inhibits pancreatic lipase degradation of complex fats and thereby reduces fat absorption. For reasons that are not immediately apparent, inhibition of fat absorption is relatively modest being restricted on average to about 20% of ingested fat at maximal doses. Both its weight loss, weight maintenance and its side effects are explicable by its inhibition of lipase in the small intestine.

## Efficacy

The concept that intestinal lipase inhibition could be utilized for the treatment of obesity was demonstrated in a small single-blind study published in 1993 [2]. The first multicenter clinical trial establishing the efficacy of orlistat was published in 1995 by Drent and colleagues [3]. Orlistat has been proven to be effective in inducing weight loss in a variety of different adult populations independent of age, degree of obesity, gender and ethnicity. For example, Poston and colleagues studied obese Mexican–American women who lost on average 8.8% body weight over 12 months and experienced significant reductions in waist circumference, low density lipoprotein (LDL) and total cholesterol [4]. In most studies, orlistat treatment has been combined with a modestly calorie-reduced diet. However, the effect of orlistat is usually approximately 5% greater than in the placebo control group indicating the additional effect of orlistat over and above the calorie reduced diet. A meta-analysis of 23 randomized controlled trials evaluating the effectiveness of orlistat for

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weight loss or maintenance of weight loss in overweight or obese patients was performed by O'Meara and colleagues [5]. The largest beneficial effects were seen in patients with uncomplicated obesity who reported statistically significant differences in favor of orlistat for weight loss and possibly more importantly, beneficial changes in cardiovascular risk factors. Similar results were seen in trials in obese patients with defined cardiovascular risk factors at baseline, whereas the smallest effects were observed in patients with Type 2 diabetes [5]. These data underlie an observation which is commonly observed in clinical practice, namely that patients with Type 2 diabetes appear to be more refractory to weight loss treatments generally than those that are nondiabetic. There are limited data on the use of orlistat in obese adolescents and children. However, it appears to be efficacious in these individuals [6]. In a small pilot study comparing the efficacy of orlistat as an adjunctive treatment for obesity between African–American and Caucasian adolescents, both groups benefited. However, African–American adolescents exhibited significantly less improvement in weight, body mass index, waist circumference and insulin sensitivity. Improvements in cholesterol were not significantly different between African–Americans and Caucasians [6].

## Orlistat as a weight maintenance agent

Although most of the orlistat studies reported to date have been relatively short term 3 to 12 months, it is apparent that weight loss does not appear to continue and body weight tends to stabilize 3 to 6 months after initiation of orlistat therapy. As stated above, weight loss is modest, usually of the order of 4 to 8 kg, and many subjects are left with a stable body weight considerably above their ideal body weight and disappointingly often remain in the obese or overweight category. However, there are data that suggest that orlistat, in addition to its use for induction of weight loss, is also useful in weight maintenance [7]. The latter concept has been formally tested in crossover studies where relaxation of dietary calorie restriction was allowed and the difference in weight gain between the placebo and orlistat group persisted [8]. Thus, although the majority of obese individuals appear to plateau at a weight considerably above their ideal body weight, there is evidence in this situation that orlistat has ongoing efficacy in weight maintenance over the 2-year study.

## Does orlistat have beneficial effects over & above weight loss?

Weight reduction, by any means including the use of antiobesity drugs, is likely to improve all aspects of the metabolic syndrome and therefore confer benefit on the vascular system. This is certainly true in the case of orlistat-induced weight loss [8,9]. An interesting study by Tiikkainen and colleagues attempted to determine whether orlistat treatment had additional benefits over and above simple weight reduction [10]. In their study they compared two groups of women that lost approximately 8% body weight over a 3 to 6 month period either using orlistat or placebo combined with a hypocaloric diet. Surprisingly, while a significantly more marked reduction in intra-abdominal fat was observed in the orlistat group, the improvement in insulin sensitivity was similar after weight loss in both groups suggesting that weight loss rather than inhibition of fat absorption enhances insulin sensitivity. However, a decrease in fat absorption by orlistat appears to have more marked effects on intra-abdominal fat, which suggests that exogenous fat or its composition may influence fat distribution. In contrast in a study of similar design undertaken by Kelley and colleagues, orlistat resulted in greater improvement in free fatty acid levels and insulin sensitivity than placebo-treated subjects for equivalent weight loss despite identical decreases in visceral adipose tissue, fat mass, thigh adiposity and hepatic steatosis [11]. Orlistat treatment is also associated with beneficial effects on plasma levels of adiponectin, an adipokine thought to be important in modulating insulin sensitivity and protection against atherosclerosis [12,13]. However, further studies are still required to determine whether orlistat has additional beneficial effects on insulin sensitivity over and above weight loss.

Not unexpectedly, given the mechanism of action of orlistat, the beneficial effects on lipid profiles appear to be significantly greater in orlistat-treated subjects compared with placebo-treated subjects, even when matched for comparable degrees of weight loss [8]. However, in one study where orlistat was used in conjunction with dietary restriction, no improvement in endothelial function was observed [14]. In a short-term study of 43 subjects with uncomplicated obesity, Brook and colleagues observed significant improvements in LDL-cholesterol, fasting insulin and a decrease in leptin concentrations; but no decrease in flow- or nitroglycerin-mediated dilation of the brachial artery

despite moderate weight reduction of approximately 6% body weight [14]. This latter study is somewhat worrying since one of the principle long-term aims of treating obese subjects would be to reduce the vascular risk. Reduction in vascular risk is likely to require long-term, if not lifelong treatment. Clearly, while there are promising data with orlistat treatment using surrogate markers, there is a need for long-term orlistat studies with hard end points, such as cardiovascular events and death.

The effect of orlistat on gastric emptying – the glycemic and incretin hormone responses to a meal containing fat and glucose components in patients with Type 2 diabetes – has been investigated [15]. Gastric emptying was faster after orlistat compared with control and postprandial blood glucose and plasma insulin were higher than controls. Plasma glucagon-like peptide-1 and glucose-dependent insulintropic polypeptide were less after orlistat [15]. The authors suggested that inhibition of fat digestion by orlistat may exacerbate postprandial glycemia as a result of more rapid gastric emptying and a diminished incretin response. However, this effect appears to be clinically unimportant and contrasts with other data in Type 2 diabetic patients. In a randomized placebo-controlled double-blind clinical trial in Type 2 diabetic patients, orlistat-treated patients had significantly lower HbA1c and greater reductions in oral hypoglycemic medications than the placebo-treated group [16]. Although the reduction in HbA1c seen in orlistat trials an approximately 1 to 2% absolute reduction – is comparable with those reported in some efficacy studies with antidiabetic drugs, there is no evidence that orlistat has effects on glycemic control over and above weight loss. In reports from both Hollander and colleagues and Kelley and colleagues, the reduction in HbA1c was not different in placebo- and orlistat-treated groups [11,16]. However, this was not the case in the ORLIstat and CArdiovascular risk profile in patients with metabolic syndrome and type 2 DIAbetes (ORLICARDIA) study where a significantly greater reduction in HbA1c was apparent in the orlistat-treated group [9].

In the recently reported 4-year, double-blind, prospective Xenical in the prEventioN of Diabetes in Obese Subjects (XENDOS) sudy, orlistat plus lifestyle changes produced greater weight loss and resulted in a greater reduction in the incidence of Type 2 diabetes than lifestyle changes alone [17]. The risk reduction in the cumulative incidence of diabetes was greater than 40% and was largely explained by decreased progression of subjects with impaired glucose tolerance (IGT) to diabetes. Significantly greater weight loss was observed in IGT subjects treated with orlistat than IGT subjects treated with placebo making the difference in weight loss a likely explanation for the protective effect against diabetes apparent in the orlistat-treated subjects [17]. The failure to demonstrate clinical advantages over and above simple weight loss, if confirmed in other longer term studies, would not necessarily negate the usefulness of orlistat, since it is very difficult to achieve meaningful weight loss in the majority of obese patients in clinical practice. However, any added benefit of orlistat over and above weight loss is likely to be met with enthusiasm. As discussed above, there are some indications from shorter term studies to suggest that that there may be beneficial effects of orlistat over and above weight loss in certain parameters such as lipids, adipokines and fat distribution. It remains to be determined whether these differential effects translate into meaningful long-term benefits.

## Orlistat side effects

Although there was some initial concern regarding the potential carcinogenicity of orlistat with an apparent increase in new breast cancer cases diagnosed in orlistat-treated patients during early registration studies, these concerns have not been substantiated by postmarketing surveillance [101]. In fact, recent *in vitro* studies have suggested orlistat, or drugs of this class, may have potential anticancer activity. In studies using human prostate cancer cells, Kridel and colleagues have shown that orlistat inhibits tumor cell proliferation, induces apoptosis, and inhibits the growth of PC-3 tumors in nude mice by virtue of its ability to inhibit fatty acid synthase [18]. At doses used clinically and with the limited systemic absorption, it is unlikely that inhibition of fatty acid synthase in prostate or other tissues is clinically important. The exception may be the colonic epithelium. As yet there appears to be no data on the incidence of colorectal cancer in orlistat-treated patients. However, these *in vitro* data are reassuring and will certainly stimulate further research into potential anticancer effects of orlistat and other agents in this class.

A potential, but as yet clinically unimportant side effect of orlistat, is the increased risk of gall stones which are already more prevalent in obese and overweight individuals than lean subjects. Orlistat significantly impaired gall bladder

motility an effect which becomes less marked but persists even with long-term treatment [19]. The actual magnitude of the increased risk of clinically significant gall bladder disease in orlistat-treated subjects is not known.

The most troublesome side effects from the patient's point of view relate to the modest degree of fat malabsorption induced by orlistat. Fecal spotting, anal leakage, oily stools and increased flatulence are troublesome side effects of the medication observed in up to 20% of patients [7,8], and appears to occur in subjects with subclinical anorectal dysfunction [20]. These subjects have lower rectal compliance, heightened rectal sensitivity and weaker resting sphincter pressure than patients who do not experience this problem [20]. However, side effects are mostly seen during the first few months of treatment, usually occur as a single episode and do not usually persist [20]. Not only do these symptoms tend to abate with time, long-term treatment with orlistat does not appear to be associated with adverse effects on anorectal function or continence [20]. With reassurance and some dietary avoidance, patients can be encouraged to persist with the medication. In fact, in the reported registration trials withdrawal due to these side effects was surprisingly modest or the order of 8.8% in the orlistat-treated group and 5% in the placebo-treated group [102].

Mild reductions in vitamin E levels have been observed in orlistat-treated subjects [2]. Reduction in serum levels of other fat-soluble vitamins have not been observed but it is commonly recommended that subjects treated with orlistat take a daily multivitamin supplement containing all fat-soluble vitamins.

## Expert opinion

In this author's experience, amongst patients who discontinue orlistat, a common reason offered is perceived lack of apparent efficacy. Part of this relates to the patient's unrealistic expectations of what is achievable in terms of weight reduction over the short term. Even in the clinical trial setting, orlistat treatment combined with hypocaloric diets are associated with modest weight loss usually requiring a 6 month period to achieve maximal effect. There are few data that relate to the nonresponder rates to orlistat but clearly there are some obese patients who have largely eliminated excess fat from their diets and these patients are unlikely to achieve meaningful weight loss with orlistat. The recent enthusiasm by the lay public for low carbohydrate, high fat, Atkin's-type diets is likely to make orlistat side effects more problematic.

There is also evidence that weight loss induced by orlistat is self-limiting and this may account for a poor response or lack of response in some obese patients. It is well known that the mean weight loss induced by orlistat is less than expected for the degree of fat malabsorption [21]. Although orlistat administration does not appear to alter short term physiological responses, such as cholecystokinin levels or behavioral measures of satiety in response to high fat meals in healthy subjects [22], it has been clearly demonstrated, at least in normal weight healthy subjects, that orlistat treatment attenuates the acute inhibitory effect of fat on subsequent energy intake [21]. In the study reported by O'Donovan and colleagues, the increase in energy intake following orlistat treatment approximates the energy lost due to fat malabsorption. In the absence of a clinical trial setting, where calorie intake is carefully documented and controlled, this gradual increase in energy intake could limit the ongoing weight loss effect of orlistat.

There has been some reluctance on the part of the medical profession, government and private insurers to accept overweight and obesity as medical conditions warranting treatment. As a consequence, the cost of orlistat is not covered by many government and private insurance organizations. For example, orlistat is not remunerated in the majority of Canadian Provinces. As a consequence, many subjects who would benefit from this treatment simply cannot afford it and more importantly, the failure of government and private organizations to remunerate patients for orlistat treatment undermines the therapeutic value of this medication in the treatment of obesity in the eyes of the public.

## Outlook

Clearly, the efficacy of orlistat in weight loss and maintenance has been well documented over the last half decade. It is also apparent that treatment with orlistat has beneficial effects on surrogate markers of vascular disease risk and there is evidence to suggest that it can prevent or delay the onset of Type 2 diabetes in subjects at increased risk for developing the condition. There is even some suggestion that there may be positive health benefits of orlistat treatment over and above weight loss. However, what is still required are longer term studies which clearly establish positive effects on hard outcomes such as cardiovascular events, stroke and death. These types of studies

**Highlights**

- Orlistat has proven efficacy in inducing weight loss and in weight maintenance in a variety of different adult populations independent of age, degree of obesity, comorbid states, gender and ethnicity.
- It is free of long term serious side effects, in particular, there is no increased risk of malignancy.
- The weight loss effects are modest and weight stabilization occurs after 3 to 6 months. The mechanisms underlying this are unclear and still under investigation.
- Orlistat effects are modest and should be considered only as part of the ongoing management of obese and overweight patients.

would be required to encourage long-term use which is an essential component of weight maintenance. Many patients discontinue the medication after their weight stabilizes only to see their weight rebound to their original or greater weight. Added positive health benefits would encourage both patients and physicians to continue with the medication as a weight maintenance therapy.

How long patients should take orlistat is unclear. However, if obesity is a vascular risk factor, such as high cholesterol or high blood pressure, then treatment of obesity should be lifelong. Thus, there would appear to be no need to discontinue agents such as orlistat if there is evidence of ongoing efficacy in weight maintenance.

Clearly, pancreatic lipase inhibitors are only one component of the potential armamentarium in the fight against obesity. Hypocalorie diets, prescribed exercise and lifestyle modification should remain the cornerstone of treatment. These have all been shown to have positive effects in clinical trials. However, practical methods of implementing these treatment modalities at a reasonable cost in the general population still need to be developed. Although pharmacotherapy with orlistat and other agents seem expensive, the cost of these drugs pales in comparison with the costs associated with diet and exercise treatment arms in clinical trials. Furthermore, the fact that patient acceptance of dietary restriction, exercise programs and lifestyle change is very low will ensure that safe antiobesity agents such as orlistat will remain as useful adjuvant therapy in the treatment of obesity. In summary, orlistat is a safe, efficacious agent for the treatment of overweight and obese states. Clearly it is likely to be most useful as part of an overall weight management program involving a variety of modalities. Greatest cost benefit is likely to be realized in obese patients with comorbidities such as vascular disease, dyslipidemia and impaired glucose homeostasis.

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