

# Orlistat - an anti-obesity drug - An overview

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## ABSTRACT

Obesity is the fifth leading risk for international deaths. At least 2.8 million adults die per annum as a result of overweight. The current recommendations for the treatment of obesity are embraced inflated physical activity and reduced calories intake. When the activity approach is not appropriate, a medical specialty treatment is usually recommended. Most anti-obesity drugs act on central nervous system to suppress appetite and reduce food intake. In past years, although varied medicines have been admitted for obesity treatment; due to the adverse effects, they have been withdrawn from further use. In fact, sibutramine licenses are withdrawn owing to an inflated risk of medical disorders and nonfatal infarct or stroke. Orlistat is presently the sole accessible selection for the treatment of obesity owing to its safety and positive effects. A gastric and pancreatic lipase inhibitor, orlistat, through reducing dietary fat absorption by approximately 30%, has been used for about 10 years. It also has a positive effect on the comorbidities of obesity and has a significant effect in reducing the risk factors of cardiovascular disease and diabetes mellitus. This article focuses on the efficacy, safety, and significance of orlistat.

**Keywords:** Anti-obesity drugs, obesity, orlistat

## Introduction

Obesity is a condition with abnormal or excessive fat accumulation which can impair health. Obesity has been considered a worldwide concern over the past 20 years. It is been estimated by the World Health Organization (WHO) that there are over 400 million obese and over 1.6 billion overweight adults, a figure which is projected to almost double by 2015. This is not a disease restricted to adults as at least 20 million children under the age of 5 years were overweight in 2005.<sup>[1]</sup>

It is a chronic disorder of multifactorial etiology that is thought to be one among the well-established risk factors of raised morbidity and mortality. It is that the fifth leading risk for international deaths.

Stroke, coronary artery disease, sleep apnea, osteoarthritis, heart failure, dyslipidemia, hypertension, reproductive and

gastrointestinal cancers, Type-2 diabetes, gallstones, and fatty liver disease are among the health related consequences resultant from obesity.<sup>[2]</sup> Improvements in cardiovascular risk profiles and reduced incidence of Type-2 diabetes will result in case of approximately 5-10% bodyweight loss.<sup>[3,4]</sup>

Although a broad spectrum of dietary treatment choices to lower excess weight is offered, there is an agreement among consultants that each one these strategies end in solely a restricted and short weight loss. Even multidisciplinary approaches together with dietary measures, increase in physical activity, and psychotherapy do not give a satisfactory success rate, significantly if long-run results are needed. Therefore, the use of weight lowering drugs has been proposed as a more effective treatment choice for obesity. Anti-obesity drugs are pharmacological agents that reduce or control weight.

In past years, although varied medicines have been admitted for obesity treatment; due to the adverse effects, they have been withdrawn from further use. A gastric and pancreatic lipase inhibitor, orlistat, through reducing dietary fat absorption by approximately 30%, has been used for about 10 years. There is now a growing body of evidence to suggest that orlistat has additional benefits for its safety and positive effects on diabetic management. The aim of this review is to discuss the efficacy, safety, and significance of orlistat.<sup>[5,6]</sup>

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## Body Mass Index (BMI)

A simple index of weight-for-height is called BMI being used for classification of overweight and obese patients in adults. BMI is calculated as person's weight in kilograms divided by the square of his height in meters ( $\text{kg}/\text{m}^2$ ). The WHO definition is a BMI  $\geq 25$  is overweight and a BMI  $\geq 30$  is obesity.

## Orlistat

### Weight loss in adults

Approximate 3% weight loss more than diet alone which can be considered as small, but significant value, is related to orlistat (BMI  $\geq 27$ ). A recent Cochrane meta-analysis including 11 randomized controlled trials (RCTs) using 120 mg orlistat 3 times a day found 2.7 kg or 2.9% greater weight loss in the orlistat group when compared to placebo. Pooled results showed a larger number of participants in the orlistat group achieved clinically significant weight loss, with 21% and 12% achieving  $\geq 5\%$  and  $\geq 10\%$  weight loss, respectively. There were also greater reductions in waist circumference with orlistat therapy compared to placebo with reductions from 0.7 to 3.4 cm ( $P < 0.05$ ).<sup>[2]</sup>

Cost-effectiveness is another beneficial feature of orlistat. Based on an analysis, on overweight and obese nondiabetics, it was suggested that orlistat is cost-effective only if those achieving at least 5% weight loss after 3 months continue with therapy.<sup>[7]</sup>

### Maintenance and attrition rates

Prevention of weight regain after initial weight loss is one of the most important aspects with regard to weight management. No data is available concerning long-term weight loss, but medium-term studies show that weight loss is generally maintained in patients continuing orlistat therapy. XENDOS study which is a 4-year double-blind, randomized, and placebo-controlled trial with orlistat including 3304 overweight patients showed mean weight loss after 4 years was significantly greater with orlistat (5.8 kg vs. 3.0 kg with placebo;  $P < 0.001$ ).<sup>[8]</sup> Furthermore, the 2003 Cochrane meta-analysis showed that orlistat-treated patients regained a smaller percentage of weight compared to placebo-treated patients ( $P < 0.05$  for all studies) over 2 years.<sup>[2]</sup>

Pharmacoepidemiological studies seem to indicate that attrition rates in clinical practice are even higher (64–77%) and the major causes of cessation of treatment are high cost and side effects.<sup>[9]</sup>

## Comorbidities

Weight loss of 5–10% can significantly reduce the risk factors for diabetes<sup>[10]</sup> and cardiovascular disease in high-risk patients.<sup>[11]</sup> Orlistat has been shown to be safe and more effective than diet alone in modifying the risk of coronary artery disease.<sup>[12]</sup>

### Type-2 diabetes mellitus

A 2005 Cochrane meta-analysis involving 22 RCTs examining the benefits of pharmacotherapy for weight loss in Type-2 diabetes shows

evidence that orlistat can achieve statistically significant short-term weight loss when used as a primary weight reduction therapy among adults with Type-2 diabetes. Pooled data on orlistat overall follow-up periods demonstrated a loss of 2.0 kg (95% confidence interval: 1.3–2.8). Pooled reduction for hemoglobin A1c was 0.5% with follow-up between 24 and 57 weeks.<sup>[13]</sup>

Over 4 years of treatment with orlistat in the XENDOS study, the risk of developing diabetes was found to be 37.3% lower compared to placebo ( $P = 0.003$ ).<sup>[8]</sup> In the 21% of subjects that had impaired glucose tolerance at baseline, the incidence of diabetes over the 4 years was decreased by 45.0% with orlistat therapy. This finding has been supported by a more recent RCT which showed that the incidence of new Type-2 diabetes was significantly decreased in patients using orlistat for weight maintenance after initial weight loss (8/153 new cases Type-2 diabetes vs. 17/156 cases,  $P = 0.041$ ).<sup>[14]</sup>

## Hypertension and dyslipidemia

Several meta-analyses have shown modest improvements in blood pressure (BP) and serum cholesterol in patients taking orlistat.

The 2003 Cochrane meta-analysis showed a significant net decrease in systolic BP in the orlistat group of 1.8 mmHg and diastolic BP 1.6 mmHg. There were also greater reductions in total cholesterol levels 0.33 mmol/L and low-density lipoprotein (LDL) 0.27 mmol/L. No clinically significant effects on triglycerides or high-density lipoprotein (HDL) cholesterol were observed.<sup>[2]</sup> These changes seem to represent an effect of orlistat on lipid malabsorption rather than an effect of weight loss alone.<sup>[15,16]</sup>

A recent review of 28 RCTs comparing orlistat to placebo for 6 months supported this data showing a significant decrease in total cholesterol 0.3 mmol/L (0.57–0.28) and LDL 0.34 mmol/L (0.36–0.32) both  $P < 0.001$ . Smaller decreases were seen in serum triglycerides 0.08 mmol/L (0.1–0.06,  $P < 0.001$ ) and HDL 0.06 (0.011–0.01),  $P = 0.02$ .<sup>[17]</sup>

The 2005 Cochrane meta-analysis involving Type-2 diabetics also showed that orlistat was associated with statistically significant improvements in total cholesterol, LDL, and triglycerides that were sustained at 52-week follow up.<sup>[13]</sup>

### Other effects of orlistat

Other obesity-related comorbidities which have been studied include nonalcoholic fatty liver disease and disorders of menstrual cycle. A recent RCT involving 44 patients with nonalcoholic fatty liver disease (NAFLD) showed that orlistat improves serum ALT levels and steatosis on ultrasound in NAFLD patients. The authors argue that this effect is beyond that expected from the weight reduction alone.<sup>[18]</sup> There is limited evidence to suggest that orlistat may be effective in the treatment of women with obesity and menstrual cycle disorders.<sup>[19]</sup>

### Adverse effects

As a result of its mode of action, the predominant adverse effects of orlistat occur directly or indirectly through the gastrointestinal tract.

The bioavailability of orlistat is <1% (due to low systemic absorption and high first-pass metabolism),<sup>[20]</sup> and thus, direct systemic side effects are less common than with other anti-obesity medications.

The most commonly reported adverse effects of orlistat include steatorrhea, bloating, oily spotting, fecal urgency, and fecal incontinence. The percentage of patients experiencing at least one of these side effects appears to be around 16%–40%.<sup>[21]</sup>

Perhaps the most psychologically disturbing side effect, fecal incontinence is found in around 7% of patients. There is some concern that orlistat may lower the absorption of the fat-soluble Vitamins A, D, E, and K.<sup>[20,22]</sup>

A RCT investigating the impact of orlistat on Vitamin D absorption, bone turnover, and bone density found that orlistat induces a relative increase in bone turnover and a net resorption of bone, possibly due to malabsorption of Vitamin D and calcium.<sup>[23]</sup> However, the authors argue that these changes can be explained by weight loss itself. The XENDOS study showed reductions in all fat-soluble vitamins except Vitamin D. Multivitamin supplements containing fat-soluble vitamins are needed for the patients using orlistat over a prolonged period.<sup>[21,24]</sup> Taking them at least 2 hours before or after the administration of orlistat, should be advised to the patients.

Recently, there has been a concern which indicates that orlistat may be associated with increased risk of colon cancer which is based on a preliminary research on rats.<sup>[25]</sup> The increased presentation for free fatty acids to the lower gastrointestinal tract, produced by combining a lipase inhibitor with a fatty diet, is thought to increase oxalate absorption and thus heighten risk of kidney stones and renal impairment.<sup>[26,27]</sup> As a conclusion, further research in humans is required.

## Conclusion

Orlistat is one of the best drugs for obesity. Improving glycemic control in Type-2 diabetes and reducing the risk of developing diabetes in obese individuals with impaired glucose tolerance are among the other beneficial roles of orlistat. Moreover, it is associated with improvements in BP and lower cholesterol measurements than expected for the level of weight loss. More to the point, orlistat may be useful in the management of NAFLD, menstrual dysfunction, and overweight and obesity in adolescents with regard to initial evidences.

Orlistat plays a significant role in the current clinical practice. In cases that modest weight loss will benefit those with obesity comorbidity, there should be a consideration towards the addition of orlistat to a program of lifestyle change, diet and physical activity.

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