Review Article

# A review on benefits and toxicity of orlistat therapy

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**ABSTRACT**

Orlistat is an antiobesity drug, used for long-term treatment of weight loss in obese adults with a reduced calorie, low-fat diet, and exercise program. Recently, many studies are suggesting that more than the weight reduction, orlistat therapy confers with many other therapeutic benefits in diabetes, hypertension, dyslipidemia, Polycystic Ovary syndrome, nonalcoholic fatty liver, and breast cancer. Simultaneously, there are studies that are reporting the toxicity such as nephrotoxicity, hepatotoxicity, and gastrointestinal side effects. It is important to consider the toxicity profile of the drug while prescribing orlistat, particularly in geriatrics, renal and liver disease patients. Furthermore, studies should be conducted to find the long-term side effects and other benefits of orlistat therapy.

**KEY WORDS:** Antiobesity, Benefits, Orlistat, Toxicity

## INTRODUCTION

According to the WHO, the global estimation of overweight people was around 1.9 billion, among that 650 million were obese.[1] Obesity predisposes to various chronic disease conditions such as hypertension, dyslipidemia, type 2 diabetes mellitus, osteoarthritis, stroke, gall stones, and other cardiovascular diseases.[2] Reducing weight helps in reducing the risk of morbidity and mortality due to these disease conditions.[3]

Orlistat is an anti-obesity drug that induces weight loss by lowering dietary fat absorption and it also helps to control the blood glucose in diabetes, to improve the lipid profile, and other metabolic markers. The American Food and Drug Administration approved orlistat by 2006 for long-term treatment of weight loss in overweight adults with a reduced calorie, low-fat diet, and exercise program. The maximum dose of orlistat is 180 mg in three divided doses per day.[4] It is an oral reverse gastric and pancreatic lipase inhibitor acts by binding covalently to the serine residue of the active site of gastric and pancreatic lipase. Orlistat partially inhibits hydrolysis of triglycerides, thus reducing the subsequent absorption of monoglycerides and free fatty acids.[5] The drug found to be having antidiabetic and anti-atherogenic properties and also helps to prevent metabolic syndrome in overweight people. The use of orlistat has been associated with several mild-to-moderate gastrointestinal adverse effects, nephrotoxicity, and hepatotoxicity.[6] Recent studies are suggesting that more than the weight reduction, orlistat therapy confers with many other therapeutic benefits. Simultaneously, there are studies that are reporting the toxicity and newer side effects of the orlistat. This study reviewed both the beneficial outcomes and the adverse effects of orlistat.

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## DISCUSSION

### Benefits of Orlistat

Orlistat used for long-term treatment of weight loss in obese adults with a reduced calorie, low-fat diet, and exercise program. A systematic review reported that along with the dietary modification, the drug had improved the weight loss more significantly.[6] A meta-analysis study also reported that patients treated with orlistat lost more weight compared with the placebo.[7]

A randomized controlled trial (RCT) conducted on polycystic ovarian syndrome (PCOS) patients to study the efficacy of orlistat compared with metformin and exercise, and the results showed that orlistat is as effective as metformin in reducing weight and achieves similar ovulation rates in obese PCOS patients. However, orlistat has minimal side effects and it is better tolerated compared with metformin.[8]

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Another study conducted by Jacob *et al.* on 2009 that orlistat users with diabetic mellitus achieving weight loss and has a beneficial effect in combination with insulin or oral antidiabetic drugs, its clinical efficacy shows that orlistat produces a greater decrease in HbA1c compared with placebo. This effect includes improvement of insulin sensitivity, reduction of postprandial plasma non-esterified fatty acids, decreased visceral adipose tissue, and stimulation of glucagon-like peptide-1 secretion in the lower small intestine.[9]

A meta-analysis study was conducted by Sharma and Golay to evaluate the effect of orlistat-induced weight loss on blood pressure and heart rate in obese patients with hypertension. The groups received orlistat 120 mg or placebo 3 times daily, in conjunction with a mildly reduced calorie diet given for 1 year. Primarily, changes in body weight were noted. Blood pressure, heart rate, and systolic workload were assessed as secondary efficacy parameters, and the result stated that orlistat helps in the greater reduction of systolic and diastolic blood pressure. Therefore, the study suggested that the drug can be used in the management of hypertension in overweight and obese patients.[10]

A study conducted by Mittendorfer *et al.*, on 2001, demonstrated that orlistat inhibits dietary cholesterol absorption by the inhibition of cholesterol transport protein Niemann-Pick C1-like 1, cholesterol that is absorbed by the small intestine is incorporated within chylomicrons and delivered into the systemic circulation. Adipose tissue and muscle endothelial lipoprotein lipase hydrolyze and deplete the triglyceride component of chylomicrons, leaving behind cholesterol-rich chylomicron remnants. These remnants are taken up by the liver through LDL receptor-mediated endocytosis. Hepatic cholesteryl ester content regulates LDL receptor activity, so that when hepatocyte cholesterol content is low, LDL receptor expression and its activity would be up regulated, thereby orlistat decrease the cholesterol absorption and contribute to reduction in serum cholesterol concentration. It also helps in the reductions in total cholesterol, triglycerides, LDL, and small dense LDL particles than lipid-lowering agent independent of weight loss.[11]

Another systematic review and meta-analysis study that evaluated the efficacy and safety of orlistat in the treatment of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) concluded that orlistat may reduce the damage to hepatocytes by decreasing the fat accumulation in liver and thereby decrease the level of ALT, AST and GGT compared to baseline in patients with NAFLD, however there were no significant difference in NASH patients; however, it does not show any significant differences in patients with NASH. These findings demonstrate that orlistat could serve as a therapeutic drug to improve biochemical indicators of liver damage, but not as a first choice drug for the management of NAFLD or NASH; thus, suggesting a novel palliative drug only for the treatment of NAFLD.[12]

A review investigated the effect of orlistat on the growth of cancer cells and reported that it has a toxic effect on tumor cells and inhibits the growth of cancer cells by enhancing the apoptosis without affecting normal cells. It has an antiproliferative effect on breast cancer cells through suppression of Her2/neu expression and block the activity of fatty acid synthase, the drug-induced ploy ADP-ribose polymerase and affect apoptosis by caspase on a breast tumor cell.[13]

**Toxicity of Orlistat**

A randomized clinical trial studied the efficacy and tolerability of orlistat in 228 obese patients, where 7% of patients developed gallbladder abnormalities (mostly asymptomatic stones detected by ultrasound). Renal abnormalities (mainly stones and cysts) developed in 3% of orlistat-treated patients and also gastrointestinal adverse events such as abdominal pain, liquid stools, increased defecation, and esophagitis in few.[14,15] Another critical evaluation of toxicity and safety concern in orlistat therapy for obesity shown the evidence of mild hepatic dysfunction exhibiting a non-statistically significant increase in the liver enzyme, alanine aminotransferase, and bilirubin following orlistat therapy.[16]

A self-controlled case series conducted in 2013 by Douglas *et al.,* on the association between orlistat and acute liver injury, reported massive hepatocellular necrosis which leads to hepatic failure and death. Among 94,695 patients who received orlistat, 988 cases of acute liver injury were identified, with 335 confirmed as definite cases, and 653 as probable cases. The increased incidence of liver injury was reported and the mechanism of toxicity was not identified.[17] In a benefit-risk assessment of orlistat in the treatment of obesity, Sumithran *et al.* mentioned that in the year 1997–2011 about 21 cases were reported severe liver toxicity in which orlistat 120 mg was considered as a possible cause, and there were nine reports between 2007 and 2011 of liver failure in people who were using 60 mg of orlistat.[17]

A randomized clinical trial conducted for 24 weeks in 109 patients, in which 52 patients are given with placebo and 57 patients are given with orlistat. The results revealed that the subjects treated with orlistat, affected with severe exacerbation of gallstones which are treated with cholecystectomy and moderate cystic duct leak.[18] A critical review on the adverse effects of

orlistat by Theodosis *et al.* reported that cholelithiasis in patients taking orlistat. However, there have been at least 99 reports of pancreatitis associated with the use of this drug. Cholelithiasis and increased alcohol consumption by obese subjects seem to be the most obvious links between orlistat and pancreatitis. However, orlistat was reported to be associated with acute pancreatitis with normal amylase in one male patient who had no evidence of biliary disease and was abstinent from alcohol.[6]

Nwobodo in his critical evaluation found that the incidence of renal stone formation is increased with orlistat use, and the underlying mechanism of acute kidney injury associated with orlistat is related to enteric hyperoxaluria, in which fats are unabsorbed in the small intestine, leading to formation of calcium soaps with consequent reduction in free enteric calcium.[16] Furthermore, a randomized, placebo-controlled multicenter trial, reported that moderate kidney stone exacerbation treated with lithotripsy which was induced by intake of orlistat (60 mg).[7]

Another RCT, studied the adverse effects of orlistat on 95 patients and evaluated urinary oxalate crystals in patients receiving orlistat therapy and suggested an increased intestinal absorption of dietary oxalate, results in increased excretion of urinary oxalates which may increase the risk of stone formation. Weir *et al.* studied acute kidney injury on orlistat and reported a similar result.[19,20] Another review by Ahmed has focused on the current studies impact of orlistat on renal function and outcomes suggested that orlistat administration may precipitate oxalate nephropathy and renal stone disease.[21,22] Beyea *et al.* in the review of therapeutic advances in drug safety also suggested that orlistat has a possibility of developing an increased risk of acute kidney injury.[23]

A randomized placebo-controlled trial of orlistat for weight loss done by Sjöström *et al.* suggested that long-term treatment with orlistat is associated with addiction and tolerance and other side effects of orlistat observed are fatty or oily stools, increased defecation, oily spotting, abdominal pain, fecal inconvenience, fecal urgency, flatulence, and headache.[24] Marwan *et al.*, in 2012, studied a series of cases and reported that orlistat with a dose of 120 mg causes an oral aphthous ulcer.[25]

## CONCLUSION

Obesity is associated with increased risk of much disorder, where orlistat is an anti-obesity drug used in obese patients for weight loss. The drug was found to have beneficial effects in hypertension, diabetes, dyslipidemia, PCOS, NAFLD, and in breast cancer other than weight loss. Simultaneously, the drug was found to have toxicities such as nephrotoxicity hepatotoxicity and gastrointestinal side effects. Hence, it is important to consider the toxicity profile of the drug while prescribing orlistat, particularly in geriatrics, renal and liver disease patients. Therefore, further more studies should be conducted to find the long-term side effects and to confirm the other benefits of orlistat therapy.

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