Review of the Clinical Effect of Orlistat

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Abstract. Obesity has been a main risk for the development of diabetes mellitus, cardiovascular diseases and many other chronic problems worldwide. Lifestyle modification is the best way to lose weight but very hard to implement, thus pharmacotherapy is regarded as a good add-on to dietary and lifestyle therapies. This review provides an overview of the olistat, a drug for obesity approved by FDA, about its mechanism of action, efficacy for obesity and some other diseases including cardiovascular disease, type 2 diabetes and some cancers, as well as its safety and adverse effects.

1. Introduction
Since 1980, worldwide obesity has more than doubled. In 2014, at least 1.9 billion adults were overweight, of which about 600 million were obese [1]. A study in 2012 estimated that, obesity and severe obesity prevalence will increase 33% and 130%, respectively, over the next 2 decades (to 2014) [2]. Obesity usually causes a high risk of developing type 2 diabetes mellitus and cardiovascular disease. Relative to normal weight, a person with BMI >= 35 was associated with significantly higher all-cause mortality [3].
Changing the lifestyle is still the main way to lose weight. Moderate weight loss (about 5 to 10 percent) by lifestyle changes can reduce the risk of obesity-related diseases [4]. However, this method is always difficult to implement and the weight rebound is common. Bariatric surgery can provide robust and persistent weight loss effect, but this method is only recommended for patients with severe obesity (body mass index (BMI) ≥ 40) [5]. Besides, the high cost of surgery, postoperative follow-up and complications make it unlikely to be a universally acceptable treatment for the majority of patients with obesity. Thus, in the treatment of obesity, drugs that prevent weight regain seem to be necessary. In view of this, many anti-obesity drugs, like sibutramine and rimonabant, have been development and used, however, because of serious side effects, the safety of anti-obesity drugs has always been a controversial issue [6].
Orlistat is the only OTC weight-loss drug approved by the FDA and EMA [7, 8] and is currently marketed. It has been proved as an effective, selective inhibitor of gastric and pancreatic lipases enzymes whose main function is digesting fat from diet. At present, orlistat is also an auxiliary means of clinical treatment of obesity-related type 2 diabetes and cardiovascular disease [9-13]. There are some studies suggesting that orlistat may have other potential clinical applications, such as the treatment of chylous ascites. However, although orlistat's effect is highly selective, it still has some side effects reported. The aim of this paper is to present an overview of the clinical effect of orlistat.

2. Mechanisms of Action
Orlistat, also named as tetrahydrolipstatin (Fig. 1A), is marketed as the prescription drug under the trade names of Xenical or Alli. It is a saturated derivative of lipstatin, a natural product isolated from Streptomyces toxytricini (Fig. 1B) [14]. Like the lipstatin, an irreversible inhibitor of pancreatic lipase, orlistat also has inhibitory effect on pancreatic and gastric lipases [15, 16]. These two enzymes play key
roles in the absorption of fat by hydrolyzing the triacylglycerols (TGs) into free fatty acids and monoacylglycerols, which are then absorbed by the body [11, 17]. However orlistat has little or no activity against amylase, trypsin, chymotrypsin and phospholipases. It works in the gastrointestinal tract only [18]. In the digestive tract, orlistat can bind covalently to the active serine site in the lipase enzyme to prevent the enzyme from hydrolyzing TGs into free fatty acids, which are absorbable for the cells and the undigested TGs are then excreted in feces [11, 17]. Thus the inhibition of lipases by orlistat will consequently inhibit the absorption of dietary fats, leading to a reduced caloric intake.

![Chemical structures of orlistat (A) and lipstatin (B)](image)

**Figure 1.** Chemical structures of orlistat (A) and lipstatin (B)

Recently, Alqahtani et al. found that orlistat was able to limit cholesterol absorption by inhibition of the cholesterol transport protein Niemann-Pick C1-like 1 (NPC1L1) as another mechanism of action [18]. Moreover, orlistat was also found to inhibit the fatty acid synthase (FAS) that is specifically upregulated in many tumor cells [19, 20]. According to the crystal structure of the complex (Fig. 2), orlistat can be a substrate of thioesterase domain comprised of two subdomains [21]. Moreover, this FAS inhibition by orlistat can induce endoplasmic reticulum stress and inhibit tumor growth [20, 22, 23].

![Crystal structure of human fatty acid synthase](image)

**Figure 2.** Crystal structure of human fatty acid synthase (rainbow color, N-terminus = blue, C-terminus = red) inhibited by orlistat (space-filling model; carbon = grey, oxygen = red, nitrogen = blue) (21).

### 3. Weight-reducing Effect of Orlistat

It has been reported that using orlistat will produce significant weight loss and has been confirmed by long-term studies. The effect of orlistat was measured using the value of 24 h faecal fat excretion as a representative pharmacodynamic parameter. When having well balanced, mildly low-calorie diet, the application of treatment dose (120 mg, main meals) of orlistat can inhibit a part of fat absorption similar to the 30% of the intake of fat, which equivalent to about 200 extra calories [15, 18]. Several studies have shown that using orlistat for a year with energy restriction diets lead to a greater weight loss than placebo with energy restriction [24-27]. A double blind research with 657 orlistat-treated subjects (120 mg) and 223 placebo-treated subjects which both received a controlled-energy diet for a year showed that orlistat-treated subject gain more weight lost (about 8.76 kg/year) than placebo-treated subjects
(about 5.81 kg/year)[27]. Another similar one-year study proved that the orlistat (120 mg) treated group (1,561 person, 268 male and 1,293 female with an average weight about 97.0 kg) lost more weight than the placebo group (1,119 person, 174 male and 954 female with an average weight about 97.2 kg) for about 9.2% (8.92 kg) and 5.8% (5.63 kg) [24]. A meta-analysis was conducted on more than 10,000 patients in clinical trials and the result showed a mean placebo subtracted weight loss of 2.9 kg over 12 months of treatment [28]. Other similar analysis showed that orlistat treatment at the full dose of 120 mg three-times-daily for 12–18 months yields a placebo-subtracted weight loss of 2.6–2.9% [28-31]. Orlistat treatment at low dose of 60 mg three-times-daily has been available without prescription in some markets since 2007. A 4-month study conducted with the low-dose orlistat yielded a weight loss of 1.2 kg relative to placebo [32].

In longer-term studies, orlistat’s effect on preventing weight regain is also documented [27, 33, 34]. Without a controlled-energy diet, patient who received orlistat treatment (120mg) regain less weight during the second year than placebo (about 3.2 kg vs 5.63 kg) [27]. In addition, conclusion from a 4-year trial included about over 3,000 obese subjects demonstrated that mean weight loss after 4 years by lifestyle changes with orlistat treatment (5.8 kg) was significantly greater than with placebo (3.0 kg) [33]. Also, orlistat was found to be cost-effective in obese patients, if after 3 months of treatment, only treatment responders continue treatment [35].

Moreover, orlistat has been approved by the FDA for the treatment of obesity of children and teens from 12 to 16 years old [36] but orlistat’s effectiveness in pediatric obesity is controversial [37-40]. There has been one research considering orlistat as an invalid anti-obesity drug for children [40] while the others thinking it effective to treat the pediatric obesity with orlistat[37-39].

4. Other Efficacies of Orlistat

Diabetes mellitus. Obesity is an important risk factor for type 2 diabetes and weight loss in patients with type 2 diabetes is associated with improved glycemic control and reduced cardiovascular disease risk factors. A research on 391 obese men and women with type 2 diabetes (aged > 18 years, had a BMI of 28–40 kg/m²) revealed that after 1 year of treatment, the orlistat group (120 mg) lost 6.2 ± 0.45% (mean ± SEM) of initial body weight vs. 4.3 ± 0.49% in the placebo group (P < 0.001). Orlistat treatment plus diet compared with placebo plus diet was associated with significant improvement in glycemic control, as reflected in decreases in HbA1c (P < 0.001) and fasting plasma glucose (P < 0.001) and in dosage reductions of oral sulfonylurea medication (P < 0.01), suggesting that orlistat is an effective treatment in obese patients with type 2 diabetes with respect to clinically meaningful weight loss and maintenance of weight loss, improved glycemic control, and improved lipid profile[41]. A long time study found that, compared with lifestyle changes alone, orlistat plus lifestyle changes resulted in a greater reduction in the incidence of type 2 diabetes over 4 years and produced greater weight loss in a clinically representative obese population [33].

Cardiovascular risk. In addition to weight loss, orlistat has proven to be beneficial for reducing obesity-related risk factors of cardiovascular disease, mainly in reduction on lipid profile and blood pressure. Orlistat therapy also resulted in significantly greater improvements than placebo in several lipid parameters, namely, greater reductions in total cholesterol, (P < 0.001), LDL cholesterol (P < 0.001), triglycerides (P < 0.05), apolipoprotein B (P < 0.001), and the LDL-to-HDL cholesterol ratio (P < 0.001) [41]. The triglycerides and LDL cholesterol were 10 to 12 percent lower than expected of the weight reduction in orlistat-treated patients. This fact is explained by a 25 percent reduction in the amount of intestinal cholesterol absorption that the drug causes [42]. The other literature suggests that the levels of cholesterol and LDL-C with orlistat were not very different from the placebo group at the beginning and will be increased during in the 2-year-treatment. But the increasing in the orlistat group (120mg) is significantly smaller than the placebo group [27]. The decrease in lipid fluxes was associated with lower abdominal fat content, compared with a 44 percent reduction in weight loss due to diet alone [43].

Binge eating disorder. Golay et al. found that the 24 weeks of treatment with 120 mg of orlistat in combination with a mildly reduced-calorie diet resulted in a significantly greater weight loss than for patients receiving placebo (-7.4% vs. -2.3%). The overall Eating Disorder Inventory 2 score at week 24 was significantly lower in patients treated with orlistat than in those in the placebo group. [44].
Cancer. Orlistat was found to be a promising anticancer drug because it can block the FAS activity, which then lead to the endoplasmic reticulum stress in tumor cells and it can inhibit endothelial cell proliferation and angiogenesis, and consequently delay tumor progression on a variety of cancer cells, including prostate, breast, ovary, and melanoma cancer cells [22]. In 2004, Kridel et al. found that orlistat was a novel inhibitor of the thioesterase domain of FAS, an enzyme strongly linked to tumor progression and it could halt tumor cell proliferation, induce tumor cell apoptosis, and inhibit the growth of prostate tumor cells in nude mice [20]. In the next year, antitumoral effects of orlistat against the human breast cancer cell line SK-BR3 were proven [45]. Moreover, specific inhibition of FAS activity by the antiobesity drug orlistat was found to be able to significantly reduce proliferation and promote apoptosis in the mouse metastatic melanoma cell line B16-F10 [46]. All these studies indicated that orlistat might be a potential anti-tumor drug; however, the related clinical research is needed.

Knee osteoarthritis. A study on 50 women (aged 45-65 years with knee osteoarthritis stage II-III Kellgren-Lawrence and obesity (BMI > 30 kg/m²)) revealed that weight reduction was more signified in the group of patients on orlistat therapy (120 mg) by 9.05% (average 9.5 kg), compared with patients who were only on a low-caloric diet which the weight has decreased by 2.54% (average 2.66 kg). Besides, WOMAC pain for patients who are on orlistat therapy decreased by 48.7% and was significantly lower (P = 0.012) than in the control group, where the rate declined by only 32.2%. These data indicated that weight loss, especially while taking orlistat that reduce weight by obese patients with knee osteoarthritis leads to a reduction in the clinical developments of knee osteoarthritis [47].

Chylous ascites. Chylous ascites is a rare disease with a rate of about 0.005% in the hospital admissions which mostly are associated with cirrhosis [48, 49]. The first-line therapy to control chylous ascites is to minimize the lymph flow of patients by a low-fat diet. This approach is not necessarily successful, especially for those who fail to restrict their dietary [50]. There is one case that chylous ascites resulted from cirrhosis was successfully treated with a comprehensive treatment that combined orlistat with the placement of a transjugular intrahepatic portosystemic shunt (TIPS) in a patient who is dietary noncompliance. It is a 47-year-old man has a new form of celiac ascites and chylothorax with poor diet restriction compliance. The triglycerides of his ascites were 585 mg/dL, while the triglycerides of the pleural fluid were 691 mg/dL. Orlistat later joined his treatment. Half a week later, his ascites chylous component was resolved. Correspondingly, his ascites triglyceride dropped to 66 mg/ dL, while the pleural effusion triglyceride dropped to 247 mg/ dL [50].

5. Adverse Effects of Orlistat

There have been some studies showing that orlistat is not noticeable interference the physiological process of gastrointestinal tract (gastric emptying and acidity, gallbladder motility, bile composition and lithogenicity) or disrupt the mineral and electrolyte balance system. Also, they suggested that orlistat did not affect the absorption and pharmacokinetics of other drugs commonly used by obese patients such as oral contraceptives, glyburide, pravastatin, slow-release nifedipine or drugs which has a narrow therapeutic index [12] and the relevant markers of calcium, parathyroid hormone will not change during orlistat treatment [51]. However, numerous evidences were providing to describe the adverse effects of orlistat.

Gastrointestinal side effects. The adverse effects associated with the orlistat mechanism are mainly the gastrointestinal side effects due to the increased fat in faeces; include fatty stool (14% of patients) and fecal incontinence (4% of patients) [51]. Nevertheless, the gastrointestinal side effects of orlistat may be prevented by concomitant prescription of natural fibers (psyllium mucilloid) [52]. Oily stools and flatulence can also be controlled by reducing the dietary fat content to about 15 grams per meal [53].

Interference with nutrient and drug absorption. Circulating concentrations of the fat soluble vitamins A, D, E, K and β-carotene reductions (mostly fluctuated in the reference ranges) were seen in the orlistat treated people, so a multivitamin tablet containing vitamins A, D, E, K, and β-carotene was recommended to be taken once a day, at bedtime, when using orlistat. Orlistat may interfere with the absorption of some drugs, notably warfarin, thyroxine, oral contraceptives and anticonvulsants [51]. It
is notable that orlistat will reduce the blood cyclosporine concentration [54], therefore orlistat should not be used in patients taking cyclosporine.

**Liver damage.** Sporadic cases about potential liver toxicity with orlistat have been reported in the literature since 2001 [55]. In 2012, a recent comprehensive review of the European Medicines Agency reported that 21 cases of severe liver damage worldwide were associated with orlistat use between 2007 and 2011. However, an April 2013 study published in the British Medical Journal [56] looked at 94,695 patients receiving orlistat in the UK between 1999 and 2011. This study showed no evidence of an increased risk of liver injury during treatment. Obesity itself is also associated with non-alcoholic fatty liver disease, and evidence from case series suggests that orlistat might improve liver function in such patients [57]. Douglas and colleagues found no evidence of a higher rate of severe liver impairment events in those patients using orlistat, and their study assured that, though abnormal liver function is common in patients who are obese, it is unlikely to be caused by orlistat [51, 56, 58].

**Drug abuse.** Orlistat has low abuse potential because it is not a CNS anorectic agent, but the abuse of orlistat was sporadically reported in normal weight women with an eating disorder in USA, Spain and India [59-61]).

6. Conclusion

Although there are some limitations, orlistat is still a good auxiliary means of lifestyle changes, which will cause weight loss and reduce the risk of disease and improve the life quality of obese people. Moreover, orlistat is likely to be a pleiotropic drug to treat other diseases like type 2 diabetes mellitus and cancer. Most of the adverse reactions and potential interactions with orlistat are well characterized. As long as following the prescribed guidelines, its treatment of obesity is still valid, with benefits outweigh the risks.

7. References

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