SPER Publications and Solutions Pvt. Ltd.

Review Article

Orlistat - an anti-obesity drug - An overview

Ankita Taltia[1], Anitha Roy[2]

[1]CRI, Bachelor of Dental Surgery, Saveetha Dental College and Hospital, Saveetha University, Tamilnadu, India, [2]Faculty of Pharmacology, Saveetha Dental College and Hospital, Saveetha University, Tamilnadu, India

Correspondence: Anitha Roy, Department of Pharmacology, Saveetha Dental College and Hospitals, Saveetha University, 162, Poonammale High Road, Chennai, Tamil Nadu, India. E-mail: anitharoy2015@gmail.com

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 In past years, varied medicine has been approved for the treatment of obesity; but, most of them are withdrawn from the market owing to their adverse effects. In fact, sibutramine licenses are withdrawn owing to an inflated risk of medical disorders and nonfatal infarct or stroke.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. Orlistat, a gastric and pancreatic lipase inhibitor that reduces dietary fat absorption by approximately 30%, has been approved for use for around 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. Over the past 20 years, obesity has become a worldwide concern of frightening proportion. The World Health Organization (WHO) estimates 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.[1]

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. Overweight and obesity lead to serious health consequences including coronary artery disease, stroke, Type-2 diabetes, heart failure, dyslipidemia, hypertension, reproductive and gastrointestinal cancers, gallstones, fatty liver disease, osteoarthritis, and sleep apnea.[2] Modest weight loss in the obese of between 5% and 10% of bodyweight is associated with improvements in cardiovascular risk profiles and reduced incidence of Type-2 diabetes.[3,4]

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, varied medicine has been approved for the treatment of obesity; but, most of them are withdrawn from the market owing to their adverse effects. Orlistat, a gastric and pancreatic lipase inhibitor that reduces dietary fat absorption by approximately 30%, has been approved for use for around 10 years.[5,6] 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.

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Taltia A, Roy A. Orlistat - an anti-obesity drug - An overview. J Adv Pharm Edu Res 2017;7(3):190-193.

Source of Support: Nil, **Conflict of Interest:** None declared

Body Mass Index (BMI)

BMI is a simple index of weight-for-height that is commonly used to classify overweight and obese patients in adults. It is defined as person's weight in kilograms divided by the square of his height in meters (kg/m^2). The WHO definition is a BMI ≥25 is overweight and a BMI ≥30 is obesity.

Orlistat

Weight loss in adults

Orlistat is associated with a small but significant weight loss of around 3% more than diet alone in overweight and obese people (BMI ≥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 ≥5% and ≥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 ($P < 0.05$).[2]

Orlistat is also said to be a cost-effective drug. One analysis, involving overweight and obese nondiabetics, suggests that orlistat is cost-effective only if those achieving at least 5% weight loss after 3 months continue with therapy.[7]

Maintenance and attrition rates

One of the important aspects of any weight management therapy is the prevention of weight regain after initial weight loss. Although there is no data on long-term weight loss, medium-term studies show that weight loss is generally maintained in patients who continue 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; $P < 0.001$).[8] 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.[2]

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.[9]

Comorbidities

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

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.[13]

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 ($P = 0.003$).[8] 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, $P = 0.041$).[14]

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.[2] These changes seem to represent an effect of orlistat on lipid malabsorption rather than an effect of weight loss alone.[15,16]

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), $P = 0.02$.[17]

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.[13]

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.[18] There is limited evidence to suggest that orlistat may be effective in the treatment of women with obesity and menstrual cycle disorders.[19]

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),[20] 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%.[2]

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.[20-22]

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.[23] 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. Significant numbers of patients using orlistat over a prolonged period will need multivitamin supplements containing fat-soluble vitamins.[21,24] Patients should be advised to take them at least 2 h before or after the administration of orlistat.

There is some concern that orlistat may be associated with increased risk of colon cancer. Recent preliminary research on rats shows an association with orlistat and increases in colonic preneoplastic markers.[25] Further research in humans is required. 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.[26,27]

Conclusion

Orlistat is one of the best drugs for obesity. It has been shown to improve glycemic control in Type-2 diabetes and reduce the risk of developing diabetes in overweight and obese individuals with impaired glucose tolerance. It has also been linked to small improvements in BP and lower cholesterol measurements than expected for the level of weight loss. Initial evidence also indicates that orlistat may be useful in the management of NAFLD, menstrual dysfunction, and overweight and obesity in adolescents.

Orlistat does have a place in current clinical practice. Where modest weight loss will benefit those with obesity comorbidity, the addition of orlistat to a program of lifestyle change, diet and physical activity, should be considered.

Acknowledgment

The authors are grateful to the authors/editors of all those journals and books from where the data for this article have been reviewed and discussed.

References

1. WHO. Obesity and Overweight Fact Sheet. WHO; 2006. Available from: http://www.who.int/dietphysicalactivity/publications/facts/obesity/en. [Last accessed on 2017 Oct 01].
2. Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for obesity and overweight. Cochrane Database Syst Rev 2003;4:CD004094.
3. Goldstein DJ. Beneficial health effects of modest weight loss. Int J Obes Relat Metab Disord 1992;16:397-415.
4. Padwal RS, Majumdar SR. Drug treatments for obesity: Orlistat, sibutramine, and rimonabant. Lancet 2007;369:71-7.
5. Zhi J, Melia AT, Guerciolini R, Kinberg J, Hauptman JB, Patel IH, *et al.* Retrospective population-based analysis of the dose-response (fecal fat excretion) relationship of orlistat in normal and obese volunteers. Clin Pharmacol Ther 1994;56:82-5.
6. Hauptman J. Orlistat: Selective inhibition of caloric absorption can affect long-term body weight. Endocrine 2000;13:201-6.
7. Lacey LA, Wolf A, O'shea D, Erny S, Ruof J. Cost-effectiveness of orlistat for the treatment of overweight and obese patients in Ireland. Int J Obes (Lond) 2005;29:975-82.
8. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of Type 2 diabetes in obese patients. Diabetes Care 2004;27:155-61.
9. Vray M, Joubert JM, Eschwege E, Liard F, Fagnani F, Montestruc F, *et al.* Results from the observational study EPIGRAM: Management of excess weight in general practice and follow-up of patients treated with orlistat. Therapie 2005;60:17-24.
10. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, *et al.* Reduction in the incidence of Type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
11. Douketis JD, Macie C, Thabane L, Williamson DF. Systematic review of long-term weight loss studies in obese adults: Clinical significance and applicability to clinical practice. Int J Obes (Lond) 2005;29:1153-67.
12. Lindgärde F. The effect of orlistat on body weight and coronary heart disease risk profile in obese patients: The Swedish Multimorbidity Study. J Intern Med 2000;248:245-54.
13. Norris SL, Zhang X, Avenell A, Gregg E, Brown TJ, Schmid CH, *et al.* Long-term non-pharmacologic weight loss interventions for adults with Type 2 diabetes. Cochrane Database Syst Rev 2005;2:CD004095.
14. Richelsen B, Tonstad S, Rossner S, Toubro S, Niskanen L, Madsbad S, *et al.* Effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet in abdominally obese patients: A 3-year randomized, placebo-controlled study. Diabetes Care 2007;30:27-32.
15. Dixon JB, O'Brien P. A disparity between conventional lipid and insulin resistance markers at body mass index levels greater than 34 kg/m(2). Int J Obes Relat Metab Disord 2001;25:793-7.
16. Mittendorfer B, Ostlund RE Jr, Patterson BW, Klein S. Orlistat inhibits dietary cholesterol absorption. Obes Res 2001;9:599-604.
17. Hutton B, Fergusson D. Changes in body weight and serum lipid profile in obese patients treated with orlistat in addition to a hypocaloric diet: A systematic review of randomized clinical trials. Am J Clin Nutr 2004;80:1461-8.
18. Zelber-Sagi S, Kessler A, Brazowsky E, Webb M, Lurie Y, Santo M, *et al.* A double-blind randomized placebo-controlled trial of orlistat for the treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2006;4:639-44.
19. Totoian ES, Frolova NG, Manasian AS, Akopian MA, Magevosian AA, Arutiunian ZH. Use of orlistat (xenical) in the treatment of women with obesity and disorders of menstrual cycle. Georgian Med News 2006;139:20-2.
20. McNeely W, Benfield P. Orlistat. Drugs 1998;56:241-9.
21. Sjostrom L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, *et al.*

Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients European Multicentre Orlistat Study Group. Lancet 1998;352:167-72.

22. McDuffie JR, Calis KA, Booth SL, Uwaifo GI, Yanovski JA. Effects of orlistat on fat-soluble vitamins in obese adolescents. Pharmacotherapy 2002;22:814-22.
23. Gotfredsen A, Hendel HW, Andersen T. Influence of orlistat on bone turnover and body composition. Int J Obes Relat Metab Disord 2001;25:1154-60.
24. Finer N, James WP, Kopelman PG, Lean ME, Williams G. One-year treatment of obesity: A randomized, double-blind, placebo-controlled, multicentre study of orlistat, a gastrointestinal lipase inhibitor. Int J Obes Relat Metab Disord 2000;24:306-13.
25. Garcia SB, Barros LT, Turatti A, Martinello F, Modiano P, Ribeiro-Silva A, *et al*. The anti-obesity agent Orlistat is associated to increase in colonic preneoplastic markers in rats treated with a chemical carcinogen. Cancer Lett 2006;240:221-4.
26. Ferraz RR, Tiselius HG, Heilberg IP. Fat malabsorption induced by gastrointestinal lipase inhibitor leads to an increase in urinary oxalate excretion. Kidney Int 2004;66:676-82.
27. Singh A, Sarkar SR, Gaber LW, Perazella MA. Acute oxalate nephropathy associated with orlistat, a gastrointestinal lipase inhibitor. Am J Kidney Dis 2007;49:153-7.