Aliment Pharmacol Ther 1999; 13: 997–1002.

Review article: malnutrition and maltreatment—a comment on orlistat for the treatment of obesity

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Accepted for publication 4 May 1999

SUMMARY

The prevalence of obesity has doubled in the last 10 years and is now reaching epidemic proportions. There is a significant comorbidity and financial cost associated with this disorder. Orlistat is an intestinal lipase inhibitor that is approved for the treatment of obesity.

Recent randomized, double-blind, placebo-controlled trials have demonstrated the benefit of orlistat used in conjunction with a hypocaloric (low-fat) diet in facilitating weight reduction and the long-term maintenance of this weight loss. Patients treated with orlistat lost a greater amount of initial body weight compared to those who received placebo. After 24 months of treatment, weight loss of more than 5% was maintained in a greater number of those treated with orlistat. This was associated with significant reductions in cardiovascular risk factors (cholesterol, LDL cholesterol, LDL:HDL cholesterol ratio). The main adverse events are related to fat malabsorption, with potential losses of fat-soluble vitamins and other compounds.

Orlistat as a treatment for obesity, when prescribed within present guidelines, can aid modest weight loss in about one-third of patients. More importantly, it can assist in the maintenance of weight loss with major medical benefits for these patients.

INTRODUCTION

Malnutrition is prevalent in all parts of the globe, but for different reasons, and in recent years it has been recognized that it can include both undernutrition and overnutrition. Both terms can be applied to specific nutrients or to total nutrition, where overnutrition is synonymous with obesity. In developing countries undernutrition is still more prevalent, although with Westernization the frequency of obesity is increasing. It is not uncommon for both conditions to coexist, undernutrition amongst the deprived and overnutrition rapidly becoming prevalent in the more wealthy. The developed world still has a problem with undernutrition, but overnutrition and obesity have long since become a more pressing health and economic issue.[1]

The scale of the health problem was recognized by the World Health Organization in the recently published consultation on obesity.[2] Obesity is a chronic disease attributable to a sedentary lifestyle and high-fat energy-dense diet, thus it is theoretically preventable. It affects children as well as adults in both developed and developing countries. The recent Scottish Health Survey[3] revealed that 1.8% of the general population were frankly undernourished (BMI < 18.5). However, a much greater proportion of both men (39.7%) and women (29.9%) were overweight (BMI 25–30) and 15.9% of men and 17.3% of women with a BMI > 30 could be diagnosed as obese.

The prevalence of obesity is increasing in most countries, and has doubled in the UK in the last decade.[4] A sinister trend throughout the world is for obesity to change from a disease of affluence to one of

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deprivation. Thus in Scotland, obesity is twice as prevalent in social classes IV/V than in social class I.[3] Obesity produces multiple symptoms and disabilities directly, and is associated with significant secondary comorbidity. Heart disease, hypertension, stroke, diabetes, osteoarthritis and several major cancers (breast, colon, prostate, endometrium) are more frequent in obese subjects[5] and represent significant financial burdens upon health resources. More difficult to cost are the symptoms, disabilities and depression associated with obesity impacting on quality of life and work capacity.[6] The implications of this suggest that while efforts to prevent obesity should be redoubled, we can no longer be complacent about the treatment of this disorder. The WHO report states that obesity should be regarded as today's principal neglected public health problem.

There are clear differences between individuals with respect to their tendency to gain weight under the same conditions. However, there remains a simple truth that people who consume less calories than they burn up will inevitably lose weight. Prolonged strenuous exercise is usually impractical for the obese, but dietary restriction is a beguilingly simple prescription. When patients fail to lose weight after dietary advice it is only because they have failed to adhere to that advice. Such patients are usually labelled 'non-compliant' and are often disbarred from further help. This victim-blaming approach is sadly common, often leading patients to seek help from private clinics with different motives. To date, the medical treatment of obesity has centred on centrally acting appetite suppressants. Drugs such as phentermine have been available for many years and, although having the potential to contribute modest amounts of weight loss, they have never had proper assessment in terms of safety or efficacy. Fenfluramine and its purified enantiomer, dexfenfluramine, were better studied, but were withdrawn because of a possible association with valvular heart defects when taken together with phentermine.[7] In practice a high proportion of patients had unacceptable minor side-effects and the very rare serious complication of pulmonary hypertension was much publicized. The demand for an effective and safe drug treatment for obesity has continued, and one can cynically attribute this search to more aesthetic motives of the general populace rather than to a genuine recognition of the morbidity and health costs associated with obesity. However, evidence shows that people seeking help with their obesity want to feel better, not just to look better: a critical distinction. The epidemic growth of obesity and increasing demands for effective treatments prompted the Royal College of Physicians to publish guidelines on the use of anti-obesity drugs.[8] While recognizing that the mainstay of treatment should remain dietary, with behavioural and exercise modification, anti-obesity drugs may benefit selected patients who have failed to lose weight by standard methods. Public expectations were recently raised with the arrival of orlistat, which is now licensed for use in the treatment of obesity in the UK and European Union.

MECHANISM OF ACTION OF ORLISTAT

Orlistat is the first commercially available specific intestinal lipase inhibitor. The function of endogenous lipase is to facilitate absorption of dietary fat. Virtually all dietary fat is in the form of triglycerides; these are broken down to monoglycerides and free fatty acids by lipases. Binding with bile salts forms micelles which help to make the dietary fat sufficiently soluble to enable absorption across the intestinal mucosa and reassembly as lipoproteins. If endogenous lipase is deficient, as in patients with pancreatic disease, steatorrhoea and weight loss develop due to fat malabsorption. The aim of orlistat is to induce pharmacologically a state similar to partial pancreatectomy. Orlistat appears to consistently reduce the absorption of dietary fat up to a maximal level of 30% and causes it to be excreted in the faeces. For obvious practical reasons, it is advisable to follow a low-fat diet. Orlistat is recommended at a dose of 120 mg t.d.s., and it appears that even with higher doses of the drug, fat malabsorption is not increased greatly above this level. The result is limited weight loss, augmenting the efforts of the patient to modify their diet. However, a compensatory increase in appetite is still possible, but this varies between individuals. The inhibition of endogenous lipase reduces postprandial CCK release and pancreatobiliary secretion, and increases gastric emptying.[9] CCK and its agonists suppress appetite through vagal stimulation. Therefore the effects of orlistat on CCK release may adversely affect appetite and limit its efficacy. Orlistat is not absorbed and therefore does not have any central actions that have been associated with some of the problems with other anti-obesity treatments. This obviously limits potential harmful effects and abuse of the drug.

CLINICAL TRIALS OF ORLISTAT

While orlistat will never achieve the dramatic weight reductions associated with the surgical treatments for obesity, it should play a role in facilitating the achievement and maintenance of more modest but medically valuable weight loss and maintenance in the long term. Short-term (12–16 weeks) placebo-controlled studies have shown that orlistat, used in combination with dietary restriction, leads to additional weight loss.[10] Recent randomized placebo-controlled studies have demonstrated the benefit of orlistat in the longer-term treatment of obesity.[12–14] A multicentre study based in the UK recruited 228 patients (BMI 30–43 kg/m^2) with a mean weight of 97 kg, to examine the benefits of orlistat over a 12 month treatment period (Finer *et al.*, unpublished data). All patients were prescribed a hypocaloric diet (600 kcal/day deficit) with a fat content of less than 30% for a run-in period of 4 weeks, and then continued for 12 months in combination with either orlistat 120 mg t.d.s. or placebo. Out of the initial recruitment, 139 patients completed the 1 year treatment period. After 1 year the orlistat-treated group had lost an average of 8.5% of initial body weight, compared to 5.4% in the placebo-treated group. Over one-third of the treatment group lost more than 5% of initial body weight compared to 21% of the placebo group. The treatment group also had statistically significant reductions in serum cholesterol, LDL cholesterol, and LDL:HDL cholesterol ratio.

A similar, although larger (743 patients) multicentre 2 year European study examined not only the role of orlistat in weight reduction but also its effects on the maintenance of weight loss.[11] The protocol for the first 12 month treatment period was similar to that used in the previous 1 year UK study. However, for the second 12 months, patients were randomly reassigned to orlistat or placebo, and instead of a hypocaloric diet, patients were advised about a weight maintenance or eucaloric diet. After 12 months the orlistat-treated group achieved an average weight loss of 10.2%, compared to 6.1% in the placebo-treated group. Patients who continued on orlistat for a further 12 months regained half as much weight as those who were changed to a placebo treatment ($P < 0.001$). Patients who were switched from placebo to orlistat lost an additional 0.9 kg in year 2. This is in comparison to those who remained on placebo for the second year and regained an average of 2.5 kg in weight ($P < 0.001$). After 2 years' continuous treatment with orlistat, 57.1% maintained a weight loss of more than 5% compared to 37.4% of the placebo group. For those in the orlistat-treated group, the benefits of weight loss were demonstrated by a reduction in cardiovascular risk factors such as cholesterol, LDL cholesterol and LDL:HDL cholesterol ratio, and by serum concentrations of glucose and insulin.

Most recently, the results of a similar, although larger, 2 year study from the USA were published.[12] The study design was similar to that of Sjostrom *et al.* except that in the second year a group of orlistat-treated patients were re-randomized to receive orlistat 60 mg t.d.s. At the end of year 1, the orlistat-treated group had lost an average of 8.8% of initial body weight compared to 5.8% in the placebo-treated group ($P < 0.001$). In addition, 38.9% of the orlistat group had lost more than 10% of initial body weight compared to 24.8% of the placebo group ($P = 0.004$). Those treated with orlistat for the first year and who continued to receive 120 mg during the second year, regained significantly less of their first year weight loss (3.2 kg) than those who received orlistat 60 mg (4.26 kg) or placebo (5.63 kg), $P < 0.001$. Importantly, 34.1% of those who received orlistat 120 mg for the 2 years maintained a weight loss of more than 10% of initial body weight compared to 17.5% of those who received placebo for the 2 year trial period ($P = 0.02$). Treatment with orlistat 120 mg was associated with benefits in waist circumference, systolic and diastolic blood pressure, total cholesterol, LDL cholesterol and fasting insulin levels. In addition, orlistat has been shown to reduce cardiovascular risk factors in obese subjects,[15] to improve the lipid profile in patients with primary hyperlipidaemia,[16] and in obese subjects with type 2 diabetes, to help bring about and maintain significant weight loss, improve glycaemic control and lipid profile.[17]

The double-blind trials show conclusively that orlistat works and that the weight loss brings similar metabolic benefits to weight loss by diet alone. However, the results of double-blind placebo-controlled trials do not give a good indication of expected results in routine practice because, as with most drugs, orlistat is ineffective in a proportion of patients. For this reason, the EU licence has specified very precise guidelines. The prescribing of orlistat is recommended for the treatment of obesity in those with a BMI 30 kg/m^2, or BMI 28 kg/m^2 with associated risk factors (e.g. hypertension, hyperlipidaemia, type II diabetes). The dose of

orlistat used is 120 mg t.d.s. and it is prescribed in conjunction with a mildly hypocaloric diet with a fat content of less than 30%. Treatment should only be initiated if the patient can demonstrate a weight loss of at least 2.5 kg over a 4 week run-in period through dietary adjustment alone. This is a necessary requirement for maximizing the cost-effectiveness of drug treatments. Patients who fail to lose weight after diet and non-drug treatments are less likely to respond to anti-obesity drugs and more likely to relapse on cessation. If after 12 weeks of treatment with orlistat the patient has not lost 5% of body weight, treatment should be discontinued. When these guidelines are applied, only about one-third of all patients entered into the European trial would continue beyond 12 weeks of treatment. However, for those patients a mean weight loss of 16% of initial weight will be achieved at 12 months. This is a dramatic result likely to have major medical benefits for people unable to control their weight problem by lifestyle measures.

As yet there are no data available on the use of orlistat for longer than 2 years, but there is no suggestion that the drug loses effectiveness, so to withdraw the drug if it is effective would seem foolish. The majority of 'adverse events' associated with treatment are related to the expected effects of fat malabsorption on the gastrointestinal tract. These include increased defecation, loose oily stools, faecal urgency or leakage, increased flatulence and abdominal discomfort. Symptoms tended to occur early in the treatment and were of short duration (Finer *et al.*, unpublished data).[11] Some investigators have suggested that there may be an 'antabuse' effect, reinforcing compliance with a low-fat diet,[10, 13, 14] although others have reported that records of fat intake were similar in the orlistat and placebo groups (Finer *et al.*, unpublished data).[18]

Recognizing the association between high-fat diets and colon cancer, the increased delivery of fat to the colon with orlistat has raised concerns about a possible increased risk of colon cancer. More than 5000 patients have completed clinical trials using orlistat and no cases of colon cancer have been reported.[18] Colonic biopsies from patients receiving orlistat have shown no increase in cell turnover despite higher levels of faecal fat.[19] Obviously longer-term observations are needed, but this evidence is reassuring. The absorption of fat-soluble vitamins (A, D, E and K) and β-carotene may be impaired. Although significant reductions in some of the fat-soluble vitamins have been reported, values tend to remain within normal reference ranges,[20] with a small number of patients who had repeated reductions being prescribed supplements. A check of blood levels after 2 years would be advisable. Theoretically, weight loss and vitamin K malabsorption may affect the efficacy of warfarin, but in opposite directions: INR levels should be monitored more closely.

A 'LIFESTYLE DRUG' OR A REDISCOVERED DISEASE?

The final years of the 20th century have seen the launch of two new pharmaceutical products, orlistat (Xenical) and sildenafil (Viagra), which have generated colossal controversy as 'lifestyle drugs', with debate between the general public, medical profession and health authorities about the benefits, both perceived and actual, and the financial costs of these novel treatments. Following much heated discussion, health authorities within the UK are now gradually authorizing the availability of these agents on NHS prescription. The relationships between evidence, guidelines and practice seem to be different for obesity than for other major diseases.

Curiously, although the prevalence of undernutrition in Western society has declined considerably, there appears to be far more enthusiasm for nutritional support and intervention than for the treatment of obesity. There is evidence to support the use of nutritional intervention in only a limited number of clinical situations, yet in the USA, 1% of the total health budget is spent on nutritional support.[21] Obesity and diseases associated with this condition account for 3–7% of total health costs,[22] a similar amount to diabetes, epilepsy or major cancers, yet the only treatment readily available in the community or hospital setting is dietary instruction, which has limited benefit and clearly fails many patients. Recognizing the rising costs of obesity, SIGN have published guidelines which suggest that the aim should not be the attainment of an ideal weight, but rather the promotion of the concept of weight management.[23] This should include the achievement of a modest amount of weight loss followed by a programme to encourage maintenance of any weight loss achieved. It is recommended that a target of 5–10% of body weight is sufficient to improve health for most people. Obese patients who can achieve and maintain a weight reduction of 5–10% have reductions in cardiovascular risk factors and an improvement in a range of

comorbidities.[24, 25] Dietary restriction and lifestyle changes will be the initial treatment of choice. For a few, surgical intervention may be required. But for those who fail dietary restrictions or have obesity-associated risk factors, orlistat appears to be a suitable agent for therapeutic trial. It is at present the only licensed pharmaceutical agent available to combat obesity, although in the near future other promising agents are likely to become available (sibutramine, leptin).

DRUGS OF THE FUTURE

Obese patients have much greater difficulty in avoiding weight gain (or regain) than in achieving weight loss. Most have successfully lost weight in the past. Future drugs will probably have a greater role in preventing weight gain than in promoting loss, and regulatory authorities will need to recognize this distinction.

Sibutramine is a combined serotonin and noradrenaline re-uptake inhibitor that reduces food intake by enhancing satiety. It also has mild thermogenic actions that limit the normal reduction in metabolic rate that is associated with weight loss. Double-blind clinical trials have shown that mean weight loss with sibutramine is 3–5 kg greater than with placebo and that it is effective in up to 90% of patients, who can be identified as those who lose 2 kg in the first month of treatment.[26] Sibutramine is currently licensed for use in the USA and is likely to be available in the UK and Europe in the near future.

Clinical trials using leptin for the treatment of obesity are currently under way. Leptin, a peptide hormone produced by adipose tissue, appears to act upon the hypothalamus to help regulate appetite.[27] In experimental animals, the circulating hormone appears to have a strong relationship with the level of body fat and its absence is associated with obesity. The more adipose tissue present, the more leptin is produced. However, although obese subjects produce more leptin, they seem to be relatively less sensitive to it. Some may benefit from additional therapy with leptin, but careful identification of responsive patients will be needed. A variety of other pharmacological avenues are currently being explored including manipulation of neuropeptide Y, cholecystokinin and other peptides.

If the recommendations and guidelines for the prescribing of orlistat are followed, it represents a suitable treatment for obesity to reduce long-term health costs, recognizing that still only a proportion of patients will be successful and other treatments are needed. The EU guidelines probably represent the most extreme limitations on the use of orlistat, but should ensure excellent results. However, they will probably require some revision if we are to help the 10–20% of patients unable to lose weight by simple dietary advice but who could maintain 10–20% weight loss on orlistat. At present such patients fall outside prescribing guidelines, and they may continue to gravitate towards private clinics. As recommended by the Royal College of Physicians, any programme for weight management should include clearly defined procedures for monitoring progress.[8] This includes weighing the efficacy of anti-obesity drugs in clinical practice against safety and costs, and identifying potential abuse. It should also be important to monitor the actions taken by patients dissatisfied by NHS services to control their weight problems. Future evaluation of orlistat in clinical practice will determine the fate of this novel anti-obesity drug.

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