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Over-the-counter slimming aids

For many people, exercise and a reduced-energy diet, coupled with the need for constant avoidance of tempting, tasty energy-rich foods just seems too difficult. Over-the-counter (OTC) dietary slimming aids, available without a prescription, that promise easy weight loss are clearly an attractive proposition.

Historical background

Supposed weight-reduction agents have been available directly to the public for many years and had their hey-day in the Victorian era, when robust evidence for a product was neither offered nor sought, regulation was non-existent, and postal and newspaper advertising was suddenly overwhelmingly powerful. With no genuine weight-loss products available, the market was suddenly wide open for companies or individuals to hawk and peddle their wares to a gullible population. Cancer cures were popular, remedies for tiredness, nervous disorders and men and women's 'weaknesses' sold well, and obesity cures were among the bestsellers, and most profitable.

One of the first remedies of the 'New Era', in 1893, was the 'unexcelled blood-purifier', Allan's AntiFat, a harmless, vegetable-based remedy sold at many stockists. As is standard for preparations lacking evidence of efficacy, preparations relied on unvalidated testimonials. Allan's AntiFat caused 'a lady' to reduce by 25 pounds (11 kg), and she exclaimed 'I hope to never regain what I have lost'. The American Medical Association analysed the product, and discovered the presence of toxic compounds, including mercury, strychnine, arsenic and even tobacco. But the risk of toxicity from such preparations was not a priority for the consumer, and even tapeworms have allegedly been bought and sold for their weight-reducing effect. Although the precise compounds, and the advertising media have changed, the cynical sentiments behind the flogging of useless anti-obesity products to a gullible public are still thriving.

Lack of evidence

With compliance to conventional weight management programmes notoriously poor, there is a case for safe, effective and acceptable therapeutic options and with a greater emphasis currently on self-care, this becomes a higher priority in societies where obesity is a major public health problem. Certainly OTC slimming-aid products are already widely available and have been for many years. Pharmacy shelves stock sensible, scientifically validated weight-loss remedies, such as meal replacement therapies, and low-energy diets, which are effective, and deemed appropriate by NICE and other bodies, but also contain other, more questionable compounds, which are aggressively marketed to the public but whose actual efficacy in contrast to the claims on the pack, remains an issue. Many of these products are not pharmaceutical agents, therefore pharmacists, doctors, other healthcare professionals and even obesity specialists know little about them, yet their usage is widespread. In a recent survey of 460 pharmacy customers, 20% claimed to have tried an OTC weight-loss product. Some 60% thought that an assessment of weight and height should be taken before supply of these products is made.¹

Manufacturers of OTC slimming aids claim that their products induce significant weight loss without unwanted side-effects, yet many of their ingredients have never undergone rigorous scientific testing and claims about effectiveness are often at best misleading. Unless a product is a licensed medicine as in the case of Alli (OTC orlistat 60-mg capsules) then it is unlikely that the consumer will achieve any weight loss enhanced by the product, and will be subjected to potential adverse events.

Recently in the UK, the Advertising Standards Agency (ASA) instructed the manufacturers of 'Pink Patch' to take down their website targeted specifically at young women. The claims they made for the Pink Patch on the website were, according to a ruling by the ASA, unsubstantiated and the amount of product that needed to be purchased were viewed to be excessive.

The Pink Patch is a good example of the type of product designed solely to be sold as an OTC aid to weight loss but for which there is no evidence, either for the effectiveness of the actual ingredients, or that the technology – a pharmaceutical patch – works in delivering the ingredients into the body. Instructions for use are that one patch is applied to the skin daily. The makers claim the formulation contains *Fucus vesiculosus* (bladder wrack), 5-hydroxytryptophan, guarana, zinc pyruvate, yerba mate, flaxseed oil, lecithin and L-carnitine.

The company behind the agent claim that the manufacturing process for the Pink Patch complies with FDA Good Manufacturing Practice (GMP) yet with no FDA approval for the product, either as a food or as a medicine,

the validity of this claim cannot be easily investigated. Verification of compliance with GMP will only be provided on product licensing and batch approval. There is no means of knowing what amount (concentration) of each ‘active’ ingredient is contained in each patch. This product is not licensed and therefore not subject to inspection by government agencies.

Furthermore, there is no way of discovering, in the absence of proper licensing information, if the ‘active’ ingredients in each patch are able or capable of crossing the skin barrier and therefore entering the blood system. Only by transferring across the skin could the product be effective. Few natural products readily cross the skin, which acts as a natural barrier to keep products out of the body. Patch formulations require chemical modification of drugs to ensure their efficient transcutaneous passage is achieved. Pharmaceutical assessment does not appear to have been undertaken for this product, and would need to be done for each of the ‘active’ ingredients and is a costly and time-consuming process.

The various ingredients claimed to exist in the Pink Patch have had an association with the OTC slimming industry for many years, despite misgivings about their efficacy (see below). It seems that current policy is to clump as many of these ingredients together to convince consumers that where one ingredient is good, more is better. The Pink Patch had a precursor that was based on bladder wrack (*F. vesiculosus*), a naturally occurring seaweed and recognised source of iodine. Fucus was taken by fat Victorians to assist weight loss, at the same time as Irish farmers were using it to fatten pigs. In a patch widely marketed in the 1980s, ‘Le Patch’, the manufacturer claimed that this source of iodine was sufficient to improve thyroid function. Low thyroid function is associated with weight gain but iodine supplementation would only be effective where a genuine deficiency in iodine existed, a rare if not non-existent condition in developed countries. Thyroid dysfunction can be a serious medical condition and must be referred for medical assessment.

Marketing genius

What manufacturers of most OTC slimming-aid products lack in basic pharmaceutical science and pharmacology, they make up for in marketing excellence. They are masters of the four Ps of marketing: product, price, place and promotion, from which they create the product’s marketing mix. Marketing is so successful that some of these products achieve multi-million pound annual sales.

The product – the OTC slimming aid – is generally formulated to look like a medicine: a capsule, a tablet or a patch, giving the impression to the consumer of a medically effective product. Products are expensive, therefore desirable. Marketing theory suggests that if someone purchases a product

that is expensive he or she is more likely, not wishing to lose face, to convince himself of the product's curative properties, even when there is none. Placement of the product is mostly in pharmacies and in herbal shops. The placement in pharmacies is an important part of the marketing mix, as the product's reputation benefits from its association with the pharmacist's. For this reason, pharmacists in particular must carefully consider the implications of stocking and selling such products. A discussion of the ethical consideration appeared in the *Pharmaceutical Journal* in 2008² in which the author suggested that: 'There is clearly a need for a look at how the OTC slimming aid market is being regulated since current regulation is failing to protect the public and perhaps is acting against public health. That said there is also a need for community pharmacies to be more circumspect with a product that make significant claims about losing weight'.

Will community pharmacy continue to supply products of questionable quality and efficacy? Probably, but if they do they run the risk of damaging their considerable reputation. We must keep standards high and only sell things we can stand by. To do anything else is as ridiculous as a religious bookshop selling soft porn.

Promotion, the last of the four Ps, is where manufacturers are at their most inventive. In most countries, strict regulations control product claims, particularly those relating to health. Manufacturers have been highly inventive and creative in overcoming these restrictions, and as a result, in getting their message across. Whereas medical claims for foods and medicines are not allowed, some manufacturers have found ways around this restriction. Traditionally, this was done using personal testimonies used to convince others, for example: 'I could never lose weight until I tried Brand X, now I am a size 10 for the first time in my life.' Yet some manufacturers have been even more inventive and have found a way of manipulating the product regulatory system.

Formoline LU11, a German slimming product registered as a medical device within the EU and launched in the UK in 2008, claims to reduce energy intake from dietary fats, assist long-term weight control and lower low-density lipoprotein cholesterol. If the product were a food or a medicine, it would be illegal to make such claims. However, these claims are made on the basis of the product being registered as a medical device.

The Advertising Standards Authority (ASA) upheld a series of complaints about claims made for a similar product called LIPObind. When queried by the ASA, the Medicines and Healthcare Products Regulatory Authority (MHRA) accepted the fat-binding and weight management claims for LIPObind on the grounds that its performance was assessed by a 'Notified Body'. A Notified Body is any group that are capable of assessing the claims and submitting evidence to the regulatory authority. On following up the evidence, ASA found that the claims could not be backed up by rigorous

scientific trials in people. These products contain chitosan or chitosan-like polymers.

OTC diet-aid products

There exist on the market a huge and complex variety of OTC weight control products. The ingredients of these products are thought to act by either one or all of the following mechanisms:

- increase satiety
- decrease in absorption
- increase fat oxidation, increase metabolic rate, or reduce lipogenesis.

Examples of some of these ingredients include L-carnitine and acetyl-L-carnitine, chitosan, chromium, fibre, hydroxycitric acid (HCA), seaweed, green tea, conjugated linoleic acid and lecithin.

With the exception of Alli, which is available OTC in the US and Europe, and for which there is good evidence of safety and efficacy, there is little evidence that other OTC slimming aids work. What follows is an assessment of the current published evidence for the efficacy and safety of the ingredients of popular OTC slimming products. This assessment is based on four detailed review articles.³⁻⁶

Ephedra sinica

Historically, sympathomimetic amines have been used as over-the-counter diet aids, including phenylpropanolamine, *ma huang* (ephedra) and ephedrine. A systematic review of five double-blinded trials concluded that the combination of ephedrine and caffeine is effective in reducing body weight. The most rigorous review⁷, which assessed human studies for longer than 8 weeks, concluded that *E. sinica* and ephedrine promote a modest short-term weight loss of approximately 0.9 kg per month greater than placebo.

It is effective but this efficacy has been associated with a threefold increase in side-effects including psychiatric events, gastrointestinal events and heart palpitations. Indeed, these products became notorious for causing dose-related increases in blood pressure, which may not be problematic in healthy patients but can be hazardous in others. When the use of phenylpropanolamine was correlated with hypertension and stroke, the FDA banned it from the US market in 2000. Likewise, *ma huang* and ephedrine-containing supplements have been removed from the US market.

There currently exist few OTC products with the potential to improve thermogenic properties yet where this is suggested in product promotional

material, overweight patients often are willing to give these new products a try, even in the absence of properly conducted clinical trials.

Chitosan

Products that contain chitosan include:

- Fat Magnets
- LipoBind capsules (chitosan-like polymer)
- Liposorb capsules
- Strobby tablets
- Fat Binder
- Bonsal

Chitosan, is a cationic polysaccharide, and is a derivative of a chitin found in shells of invertebrates, such as crabs and shrimp. It has a highly adsorptive surface and for this reason is widely promoted as a ‘fat blocker.’ Animal studies have shown that chitosan can reduce body weight and a small number of studies in humans have shown a similar effect but many suffer from poor methodology and therefore provide a poor evidence base for chitosan-based products.

A meta-analysis has identified five studies evaluating the effectiveness of chitosan in obesity management.⁸ Mean weight loss with chitosan was 3.3 kg, greater than placebo but major methodological flaws in the studies were identified which greatly limits the conclusion. A well-performed double-blind trial found no significant differences in BMI in 30 overweight individuals receiving chitosan and placebo, yet this has not been repeated in other studies and there is evidence to suggest that the proposed mechanism by which chitosan effects weight loss – fat retention in the gut and expulsion in faeces – does not work. In one study, 7 healthy males consumed >120 g fat per day for 12 days and took chitosan prior to meals and snacks on days 6–9 (15 capsules or 5.25 g chitosan per day). Faecal samples were collected on days 2–12 and were analysed for fat content. Fat content of the faeces did not change from the chitosan-free period, and the authors concluded that the chitosan did not block fat absorption.⁹

In another study, 250 patients were randomised in a 24-week, double-blind, placebo-controlled trial to receive 3 g chitosan per day or placebo. Chitosan treatment did not result in a clinically significant loss of body weight or a significant difference in adverse events.⁹

Other scientific studies confirm these findings⁵ and therefore the evidence available in the literature indicates that there is considerable doubt that chitosan is effective for reducing body weight in humans. Adverse events most frequently included gastrointestinal symptoms such as constipation and flatulence.

Hoodia gordanii

Trim Easy is claimed to work as an appetite suppressant. Manufacturers of products containing hoodia claim it to be the first truly effective weight management product. Hoodia is derived from the cactus *Hoodia gordanii*, which grows in the Kalahari Desert. Manufacturers claim that, for thousands of years, the bushmen of South Africa have used hoodia to stave off hunger during hunting trips that might last weeks. Featured in a BBC television programme, *60 Minutes*, in 2004 the BBC endorsed the manufacturers' claims and the fact that the plant extract was without side-effects. An active ingredient, P57, was isolated by the company Phytopharm who claim to have undertaken double-blind, placebo-controlled clinical studies in overweight, but otherwise healthy volunteers using the extract.¹⁰

The participants were split into two groups, one group received the P57 and the other received a placebo. Both groups were told to continue their normal diet and exercise. The results, unpublished in a peer-reviewed scientific journal, suggested that the P57 group had a significant reduction in body fat associated with a reduction in daily energy intake compared with placebo but with no side-effects. Indeed Phytopharm claimed that the P57 group ate about 1000 fewer kilocalories per day, speculating that hoodia, or more specifically P57 extract, imitates the effect of glucose on brain neurones. There is little to support this claim or indeed objective evidence of efficacy but Phytopharm made a serious attempt to isolate and endorse a product that, if it proves to work, would have a huge commercial value and might even make a considerable contribution to public health.

Phytopharm theorised that following a meal, blood sugar levels rise and trigger a satiety centre in the brain that stops eating. P57 is claimed to mimic an endogenous satiety neurohormone. Hoodia products, in common with most OTC weight control products, are licensed as food supplements and therefore product quality does not require the rigour required for a licensed medicine. Phytopharm used this as a key marketing ploy, suggesting inferiority of their competitor's product. Development of P57 stalled, and the product has since been passed between pharmaceutical giants, without seeing the light of day. However, it is still described as a 'pipeline product', and may yet prove to be a genuine weight loss agent in the future.

Chromium picolinate

Products that contain chromium include:

- Fat Blaster
- LipoBind.

Chromium is an essential trace element involved in carbohydrate and fat metabolism. Since chromium can enhance insulin sensitivity, decrease circulating insulin levels and improve glucose tolerance, it has been theorised that it could increase satiety, improve body composition (ratio of lean to fat tissue), increase basal metabolic rate and reduce body weight. There currently is no evidence base to support this, with most studies being poor and few reporting efficacy.

Chromium picolinate is an organic compound, which is the main presentation for chromium in OTC slimming products. A meta-analysis of 10 double-blinded RCTs suggested a relatively small reduction of 1.1–1.2 kg compared with placebo in interventions that lasted 6–14 weeks and that this weight loss was not significantly meaningful.

Oral chromium is relatively non-toxic but there are reports of excessive doses of chromium being associated with renal impairment and rhabdomyolysis (muscle wasting due to muscle cell death).

L-Carnitine and acetyl-L-carnitine

L-Carnitine is a cofactor in cellular fat oxidation, which is diminished in obesity because of a reduction in L-carnitine enzyme-related activity. For this theoretical reason, L-carnitine is promoted as a ‘fat-burner’, despite little if any evidence to support its efficacy in obese or overweight humans. In a study on rodents, it was found that compared with placebo, a diet supplemented with L-carnitine was no better at inducing weight loss compared with an energy-restricted diet. A study looking at basketball players, a group that was lean before the study began, showed a reduction in body fat associated with L-carnitine use but not in overall body mass.¹¹ Overall there is little evidence to support the clinical efficacy of this product, as no properly controlled clinical trials have demonstrated its effectiveness in weight loss.

Acetyl-L-carnitine is metabolically similar to L-carnitine and *in vitro* is capable of restoring mitochondrial energy production, and thus is claimed by some to increase energy expenditure. Although some small studies in rodents have shown weight loss associated with acetyl-L-carnitine supplementation, there has been no scientific evidence for weight loss in humans.⁴

Green tea

Green tea has been promoted as a weight-loss supplement for over 20 years and in recent times there has been renewed interest in its use. Green tea contains catechin polyphenols, which have been shown to inhibit COMT, the enzyme responsible for the degradation of noradrenaline. Since noradrenaline has an important role in the control of thermogenesis, basal metabolic rate and fat metabolism, it has been theorised that consumption

of green tea might contribute to weight loss. Work in rats has demonstrated weight loss but this is restored once supplementation is stopped. Tea catechin has been shown to cause appetite loss, which might be the route by which the weight loss is effected.

A small study in humans ($n = 10$) has shown that green tea increased 24-hour energy expenditure.¹² Interestingly, in this study that compared green tea, caffeine and placebo, caffeine was shown to have no effect on energy expenditure. However, a larger study over a longer period of time looked at the weight gain in a group who had lost 7.5% of body weight through dieting. Green tea was no better than placebo in halting the regain of weight and there was no noted increase in metabolism in the green-tea group. Green tea is relatively safe given the number of people who routinely use it as a daily beverage, and no side-effects were reported in these studies.

Conjugated linoleic acid

Studies in rodents have demonstrated a reduction in body fat and body weight after treatment with conjugated linoleic acid (CLA) supplements. For this reason CLA supplements have been promoted OTC as a weight-loss aid. However, there is little evidence that CLA supplements reduce body weight or body fat in humans. More worryingly, studies in rodents have shown that CLA supplementation is associated with liver hypertrophy and insulin resistance and this must be of concern to anyone wishing to use them. However no human trials to date have demonstrated such adverse events, even in higher than normal doses.⁴

CLA is thought to achieve its weight loss effect in rodents by a number of routes: increased energy expenditure, reduced fat cell size, increasing apoptosis of fat cells and the inhibition of lipogenesis in the liver or increasing fat oxidation. For this reason and since CLA is a complex mixture of linoleic acids bonded at different locations, it might be that not all CLA supplement are equivalent. One clinical trial, which suggested that there was little evidence of efficacy, concentrated only on studies that incorporated *trans*-10 and *cis*-12 isomers. About 90% of CLA from food intake is in the form of *cis*-9 and *trans*-11 isomers. A lack of standardisation of CLA isomers in studies may explain the often contradictory evidence from scientific studies.

Hydroxycitric acid

Products that contain hydroxycitric acid include:

- Fat Blaster
- Healthtrim tablets.

Hydroxycitric acid is obtained from extracts of *Garcinia cambogia* and has been shown to inhibit the citrate cleavage enzyme, suppress *de-novo* fatty acid synthesis and food intake. In this way it is theorised it decreases body weight gain.

Although a number of studies in humans support the efficacy of HCA in weight loss, all studies suffer from significant methodological deficiencies that bring the relevance of the findings into question. For example, in some studies HCA was administered in combination with chromium or chitosan or used with a low-fat diet, making an assessment of the effect of HCA difficult. In one study two groups were assessed, one on a low-energy diet and the other on the same low-energy diet with HCA supplementation. Both groups were followed over 12 weeks and, although both groups lost significant amounts of weight, there was no difference between them.¹³

In one double-blind, randomised, controlled trial, which tested the benefits of 3 g *G. cambogia* extract in patients with an average BMI of 32 kg/m², results suggested the absence of a significantly greater weight loss in the treatment group than in the placebo group⁶ yet other studies show conflicting results. Overall the evidence is not compelling and adverse events have been reported and include headache, upper respiratory tract symptoms and gastrointestinal symptoms, particularly stomach pain.

Non-starch polysaccharides (fibre)

Products that contain fibre include:

- Fibre Slim
- Vitafibre
- Celluvac.

Based on the F-Plan Diet theme, some commercial companies identified an opportunity to market fibre-based products that increase satiety and so reduce energy intake. Where this has been shown to happen, for example, in the context of the F-Plan Diet, the amount of fibre needed to support and maintain weight loss is larger than the amount normally provided from fibre supplements. There exists no evidence that these supplements can induce significant weight loss in the long term.⁴

Certainly a high consumption of fibre supplements is associated with bloating, diarrhoea and nausea. Large quantities of bran may reduce absorption of vitamins and minerals – not a problem with water-soluble fibres (pectin and psyllium).

Herbal diuretics

Products that contain herbal diuretics include:

- Adios (boldo and dandelion root)
- Waterban.

Diuretics, both herbal and pharmaceutical, have been widely used for weight loss. Sportsmen, such as Olympic wrestlers sometimes took them before a match, in order to make the correct weight for the bout. Although weight is temporarily reduced, due to the reduction in fluid load, there are no health benefits conferred by these products, except when correctly prescribed for separate conditions. Dandelion has long been known to have diuretic effect, and laxative properties; Culpeper referred to dandelion as ‘piss-a-beds’: ‘It openeth the passages of the urine both in young and old; powerfully cleanseth imposthumes and inward ulcers in the urinary passages . . . And whoever is drawing towards a consumption, or an evil disposition of the whole body . . . shall find a wonderful help. It helpeth also to procure rest and sleep to bodies distempered by the heat of ague-fits, or otherwise.’

There seems to be no evidence of modern usage of these products, and the situation is unlikely to change, given the spurious and transient nature of any weight loss induced.

Lecithin

Products that contain lecithin include:

- Nature’s Aid Trim-it.

Lecithin is a phospholipid found in egg yolks, liver, peanuts and soya beans. Lecithin is thought to prevent the deposition of fat in fat cells. A well-conducted Swedish study examining the effect of lecithin supplementation and its effect on weight did not find any significant benefits in weight loss.

Guarana and yerba mate

Yerba mate (*Ilex paraguariensis*) is an evergreen tree that is native to South America. It is often combined in OTC weight-loss preparation with guarana (*Paullinia cupana*).

Both these plants are sources of stimulant chemical agents, caffeine and xanthine, respectively. There is some evidence that extracts from these plants that are very high in caffeine have been able to prolong gastric emptying time. However, there is little evidence that, as stimulants, they are effective in raising the body’s basal metabolic rate to such a degree as to cause weight loss. There is, however, evidence that pseudoephedrine (a related chemical stimulant) is effective in doing this and there have been some cases where ‘natural’ slimming aids containing these plant extracts were adulterated with

pseudoephedrine and this has been associated with adverse events on the heart.³

5-Hydroxytryptophan

Hydroxytryptophan (5-HTP) is a naturally occurring amino acid that is thought to have a mild psychoactive effect. It can cross the blood-brain barrier and in the brain is metabolised to 5-HT (serotonin), a brain neurotransmitter associated with depression when deficient. 5-HTP is normally sold as a food supplement in doses of 50–100 mg per tablet for oral use. There is some evidence of its efficacy in treating depression but not for its role in weight control. Serotonin, noradrenaline and dopamine are all neurotransmitters associated with both mood and appetite regulation. The modern generation of prescribable antidepressants – selective serotonin reuptake inhibitors (SSRIs) – act by increasing serotonin, and sometimes noradrenaline levels in the brain. The SSRI fluoxetine (Prozac) was noted to induce mild weight loss during the first 6 months of treatment, and sibutramine, a similar compound, was found to have no effect on mood, but to induce significant weight loss, and is now successfully marketed as a weight-loss drug. These prescription products are clearly not available over the counter.

Plantago psyllium

Psyllium is a water-soluble fibre derived from the husks of ripe seeds of *Plantago ovata*. One double-blind randomised, controlled trial, which included patients with type 2 diabetes and a mean BMI of 29 kg/m², found no significant changes in body weight in either the treatment or the placebo group. There were no reports of side-effects.

Hydroxymethylbutyrate

Hydroxymethylbutyrate is a metabolite of leucine that has been shown to have anti-catabolic action through inhibiting protein breakdown. Products containing HMB are primarily targeted at body builders who wish to change body composition and improve muscle mass. There is some evidence to support this outcome but the few trials that are published have methodological problems and therefore more studies are required.

Pyruvate

Pyruvate is created in the body through glycolysis. Supplementation with pyruvate seems to enhance exercise performance and improve measures of

body composition. There exist two randomised, controlled trials involving patients with a BMI of 25 kg/m² or more but neither showed any greater effect on weight compared with placebo so the conclusion is that pyruvate is an aid to body composition changes but that weight loss is weak.

Orlistat

Orlistat (Alli) is the only FDA-approved over-the-counter medication currently approved for weight loss. It was launched in the US in 2007 and in many European countries following EMEA approval in April 2009. The drug selectively inhibits gastrointestinal and pancreatic lipase activity, resulting in a 25–33% reduction of dietary fat absorption.

Orlistat has been available by prescription in a dose of 120 mg (Xenical), where the evidence for its use is robust, and was switched to OTC firstly in the US where the FDA approved a 60-mg dose 3 times daily with meals or shortly after. A reduced-calorie diet, smaller meal portions, and a maximum of 15 g of fat per meal are recommended by the manufacturer. Side-effects are minimal, with most common adverse events being gastrointestinal, most often caused by more fat consumption than is recommended.

The pivotal studies from the original orlistat 120 mg licence were supportive for orlistat 60 mg, the OTC strength. These studies were double-blind, double-dummy, randomised, parallel-group, placebo-controlled, multicentre studies and included a 60-mg arm as well as the 120-mg arm. The main objective of these studies was to determine the weight-loss effect of 60 mg orlistat, 120 mg orlistat, or placebo administered three times daily in combination with a mildly hypocaloric diet, during the first year of treatment.¹⁴

One study, a multicentre, double-blind, randomised, placebo-controlled, parallel-group study conducted in overweight patients with a BMI of 25 kg/m² or more and under 28 kg/m² assessed the efficacy of orlistat 60 mg three times daily plus diet compared with placebo plus diet on change in the body weight over 16 weeks in subjects with BMI of 25 kg/m² or more to under 28 kg/m².¹⁵

Orlistat 60 mg was shown to increase weight loss in overweight and obese subjects compared with placebo. The weight loss increases with increased baseline BMI measurements such that the obese subject benefited more than the overweight or normal weight subject.

Results demonstrate efficacy of the 60 mg strength in subjects with a BMI of 28 kg/m² or more with 45% achieving a weight loss of over 5% of baseline body weight and 21% achieving a weight loss of over 10% of baseline body weight (compared with 29.3% and 11.5% respectively in the placebo group). This degree of weight loss is clinically significant with regard to the risk factors for diabetes and cardiovascular disease.

There was less evidence of efficacy in subjects with a BMI of 25–28 kg/m² and the OTC licence indication will be for individuals with a BMI of 28 kg/m² or more. In these subjects the actual weight loss was small (3–4.5 kg over 3–4 months) and only 1.15 kg more than the placebo group on average but appears to continue while the medication is taken and not to plateau after a short time.

In further studies, results for the 60 mg dose remained significant in all the sensitivity analyses at 6 months but the baseline carried forward analysis was not significant for the 60 mg dose at 12 months.

Whereas the effect size is modest and smaller than seen with the prescription-only approved dose of 120 mg, its clinical relevance could be associated with a significant public health gain.

Withdrawal

Two studies conducted with orlistat 120 mg demonstrated some weight gain following discontinuation of therapy. However these patients were allowed to take a eucaloric diet rather than being encouraged to continue a low-energy diet. Importantly the results did not demonstrate a ‘rebound’ weight gain where the weight rose to above the baseline weight. The success of any attempt to lose weight is dependent upon the consumer’s willingness to change lifestyle habits in the long term and orlistat is no different from other weight-loss aids in this respect. In fact because of its mode of action, orlistat encourages a change to less fatty foods that may help consumers to maintain a healthier lifestyle after stopping treatment.¹⁶

In the placebo-controlled studies, fewer subjects dropped out of the orlistat groups compared with the placebo groups and in a ‘real-life’ study, most subjects successfully maintained their diet while 32% increased the amount of exercise they took while taking orlistat.

The proposed indication for orlistat 60 mg does not include the use in children and adolescents under 18 years of age.

A pooled analysis of the data from the two pivotal studies of the original marketing authorization application demonstrated a similar efficacy of the 60 mg orlistat to that seen with 120 mg orlistat in patients with a BMI of 28 kg/m² or more (figure 14.1).

Based on the pooled analysis, the adjusted mean change from baseline after 6 months of treatment was –2.09 kg, –4.40 kg and –5.18 kg for placebo, 60 mg and 120 mg, respectively in the intent-to-treat population (ITT) population ($p < 0.001$ for the comparisons with placebo). There was some further weight loss in all three groups over the next 6 months of treatment. Adjusted mean change from baseline after 12 months of treatment was –2.32 kg, –4.78 kg and –5.56 kg for placebo, 60 mg and 120 mg, respectively, in the ITT population ($p < 0.001$ for the comparisons with placebo). Based on the comparison of the adjusted mean change from

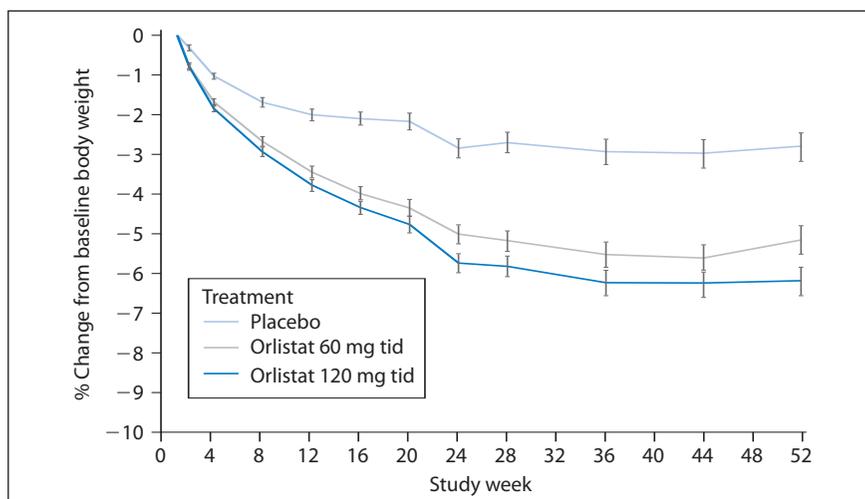


Figure 14.1 Relative change from baseline weight.

baseline for the 60-mg dose, 92% of the efficacy at 12 months was achieved at the 6-month timepoint.

A study of ‘actual use’ of orlistat 60 mg demonstrated an 80% customer satisfaction rate, alongside a median weight loss of around 5% after 60 days or more of use. Other, randomised, placebo-controlled studies showed a weight reduction of 50% more than diet and physical activity alone. Evidence shows that the use of orlistat 60 mg improves patterns of food purchases, suggesting a long-term commitment to healthy eating.

In a follow-up study, an overwhelming majority of subjects (>90%), indicated that they were very successful or somewhat successful in maintaining their diet. These results remained consistent at every interview for the duration of the study.

At study completion, approximately 32% of subjects indicated that they exercised more than they did prior to study enrolment.

Safety

Orlistat 120 mg has been on the market since 1998 and therefore there has been extensive patient exposure and there are no safety concerns. A number of studies have been completed with orlistat 60-mg capsules in the US and these provide further safety data for the product.

When any drug is switched to OTC there are always concerns that individuals who chose to use the product might take a higher dose than recommended. In studies there was no evidence of overdosing on 60 mg orlistat.

Drug interactions with orlistat are rare yet there exists a theoretical interaction between warfarin and orlistat based on orlistat’s potential to reduce absorption of the fat-soluble vitamin K in the gut. One case of warfarin

levels rising in a patient concomitantly taking orlistat has been reported in the US yet orlistat has been used widely across the world for a number of years and has been used in patients who are concomitantly using warfarin, yet post-marketing surveillance does not indicate a potential problem. Similarly, agents for other weight-related conditions, especially type 2 diabetes, may need adjusting as weight is lost, and it is important to liaise with general practice.

Pharmacist's role

In Europe orlistat will be restricted to pharmacy supply and therefore the pharmacist and pharmacy support staff will play a key role in the successful use of the product in managing obesity. Some pharmacists have derisively referred to orlistat as 'gastric Antabuse' or 'fried food punishment'. While this graphically describes the effect of orlistat, pharmacists can provide a more balanced explanation of orlistat for prospective users. Orlistat was never meant to be a weight-loss miracle – it is an aid to weight loss in patients who are already committed to becoming thinner. Such a patient will demonstrate that commitment, by voluntarily following a low-fat diet and exercising more, even prior to beginning therapy with orlistat.

Patients taking orlistat must commit to daily intake of a multivitamin containing beta-carotene and vitamins A, D, E, and K. As orlistat affects their absorption, failure to ingest them could lead to vitamin deficiencies, each with its well-known group of adverse effects.

Conclusion

There exists a huge market for a range of OTC slimming aids sold in the US and in Europe, mainly through pharmacies and health stores. With the exception of OTC orlistat, there exists very little evidence of efficacy for most of these products, and where efficacy does exist, there is the potential for adverse effects.

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