

Developing Treatments



Obesity



'Fat Fighters'

Developing Treatments for Obesity

The World Health Organization has declared obesity a “global epidemic”. Worldwide there are now at least 300 million clinically obese individuals. In the UK, public health experts estimate that 1 in 3 adults and 43% of manual workers will be obese by 2012.

Obesity contributes to other serious health problems, putting adults at much greater risk of cardiovascular disease, diabetes, respiratory disease, osteoarthritis, certain cancers, and consequently lower life expectancy.

The scientific definition of obesity is someone with a Body Mass Index (BMI) of 30 kg/m² or greater. Obesity is caused by an imbalance between energy intake and energy expenditure. Most people become obese because they eat too much food, drink too much alcohol, and don't take enough exercise.

While dietary modification and physical exercise are the main methods for reducing obesity, drug treatments can play an important part in helping someone lose weight. Doctors now only consider drug treatment if after 3 months the patient has lost less than a 10% of their weight and their BMI is still above 30.

The 'ideal' figure

Historical attitudes to obesity

Nowadays we are bombarded with information on a wide range of different diets and slimming pills to help people lose weight and achieve the 'ideal' figure. However, prior to the 20th century, many social groups didn't have enough food and so a fuller figure was viewed as a sign of wealth and higher social status.

During the 1800s attitudes to obesity changed in the Western world. After centuries of obesity being associated with wealth and social status, people began to see slimness as more desirable. People also became increasingly aware of the health implications of obesity during this period. As a result from the late 1800s manufacturers began produce an increasing range of weight-loss products, to meet growing public demand.

Not all of these early medicines were effective. Many were restricted by scientists' relatively limited understanding of how to help the body lose weight. Others were little more than blatant attempts by manufacturers to cash in on individuals' desire to lose weight quickly.



'Universal Pills No.3', Published by W. Spooner, 377 Strand, London, around 1830 - 1840

This caricature shows a man who is now so obese he is bursting out of his clothes. He carries a picture showing his skeletal appearance before he began taking Morison's Universal Pills No.3.

Many manufacturers during this period advertised how their medicine could give the patient a fuller figure; a body shape seen as ideal at the time.

1. 'Purging the body'

Early obesity treatments (used around 2nd century A.D. – 1960)

The earliest known treatments to promote weight-loss involved giving strong laxative drugs or using emetic drugs to induce vomiting and clear out the patient's digestive system. One of the earliest written accounts about losing weight was by Soranus of Ephesus, who was a Greek physician in the second century AD. His advice included elixirs of laxatives, as well as heat, massage, and exercise. By the early 1800s stomach pumps were another drastic way to help a patient lose weight.

Medicines with a laxative ingredient remained the main treatment for obesity well into the 20th century.

While laxative treatments would have helped people lose weight by restricting the amount of food being absorbed by the digestive tract, their use would have also impaired the absorption of nutrients that were good for one's health.



'Reduction'. Drawn and Etched by H. Heath. Published by William Cole, Newgate Street, London, July 1827

The above caricature is a humorous look at one of the many weight-loss 'cures' in use during the early 1800s.

The operator of a stomach pump energetically pumps out a fat man seated in a chair. Whilst on the left, several healthy but fat patients await their turn. To the right, an unhappy man, who has already undertaken the treatment, inspects his thin, but also saggy figure, in a mirror.



**Bon Kora Treatment, 1941-1947
Manufactured by Lupenn
Pharmaceutical Remedies Limited**

"Builds health while reducing fat quickly"

Bon Kora Treatment is promoted on the packaging as being 'For the elimination of excess fat and for correcting digestive and other disorders such as...constipation'.

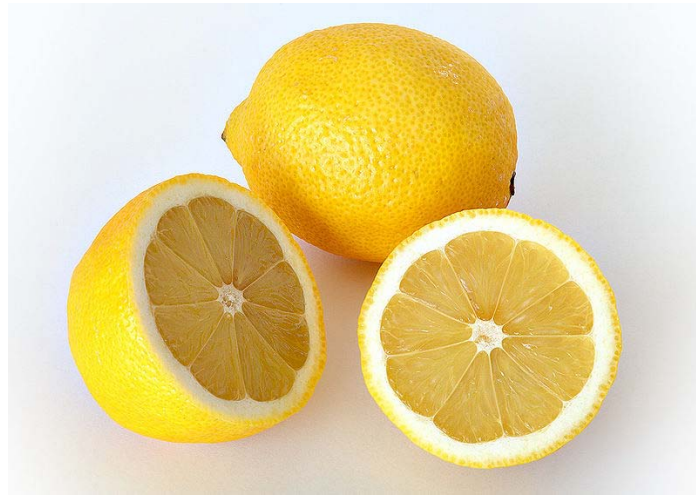
Bon Kora Treatment ingredients included magnesium sulphate, popularly known as Epsom Salts, a purgative used for emptying the bowel. Another ingredient alder buckthorn bark was used as a laxative for constipation.

**Marienbad Anti-Obesity Tablets, 1941-1959
Manufactured by Sanarol Brand Products**

Marienbad Anti-Obesity Tablets contained cascara sagrada, aloes, podophyllum, and rhubarb root, all of which are laxatives. Marienbad salt contains sodium sulphate, also a powerful laxative, which was used to treat obesity by stopping the body absorbing food.

2. 'Sucking lemons'

Lemon juice preparations (used around 1850 – 1940)



"The belief that sucking lemons will make one thin is widespread" - **Secret Remedies, published by the British Medical Association, 1909.**



Antipon medicine, 1904-1940 Manufactured by The "Antipon" Company

When launched in 1903 Antipon was 'The great permanent cure for corpulence'. It was later promoted from 1915 as 'The liquid compound for the reduction of obesity'. The manufacturer's claimed it reduced weight by 3lbs every day it was used!

The main ingredient is citric acid, no doubt included because some people believed that drinking lemon juice reduced weight.

3. 'No diet necessary!' Cosmetic weight-loss preparations

Manufacturers exploiting an individual's desire to lose weight easily is not a recent phenomenon. Many early preparations were promoted as dramatically reducing weight without the user having to restrict what they ate.

Two of the most outlandish claims came from the makers of La-Mar Reducing Soap and Clarks' Salts for Fat People. Both of which it was claimed could dissolve or wash away excess fat!



Clarks' Salts for Fat People, 1921-1938 Manufactured by Clarks, Paris, France

Clarks' Salts for Fat People were bath salts. The makers claimed on the wrapper that *"The Clarks' salt baths act very rapidly on the fatty parts of the body and dissolve all unnecessary flesh. Without changing your diet or taking drugs they tonify the whole system and bring about a slender shape and a graceful bearing"*. The ingredients are not known.

La-Mar Reducing Soap, 1926-1937
Manufactured by La-Mar Laboratories Limited

The manufacturer claimed that La-Mar Reducing Soap would “*Wash away fat and years of age*”. To illustrate the miraculous properties of the soap the packaging featured an illustration of a woman during the 3 stages of using the soap. The soap’s ingredients are not known.

4. ‘Stimulating weight-loss?’

Bladderwrack seaweed preparations (used around 1840-1945)

Fucus vesiculosus or Bladderwrack seaweed had been a popular weight-loss treatment since Victorian times. *Fucus* contains iodine, a chemical element discovered by scientists in 1812. Iodine was believed to stimulate the thyroid gland, causing weight-loss.



Fucus is still used today in some current Over-The-Counter weight-loss preparations, including ‘Adios’. However, despite being used as a weight-loss treatment for around 190 years there is still not enough scientific evidence to prove that *fucus* causes weight-loss. Indeed, *fucus* was once used by Irish farmers to fatten their pigs!

Allan's Anti-Fat medicine; 1893-1915
Manufactured by Botanic Medicine Company

"The great remedy for corpulence" (being overweight)

Allan's Anti-Fat contained fucus. The packaging claims *"The Anti-Fat aids digestion and cures dyspepsia. It acts solely upon the food in the stomach, regulating and putting the liver and discharging organs in good working order"*.



Lacey's Reducing Chewing Gum, 1915-1922
Manufactured by Lacey's (London) Limited

"A pleasant and convenient way of reducing weight. No dieting - Absolutely harmless".

Incorporating fucus seaweed in chewing gum was one of the more novel ways that manufacturers marketed this weight-loss ingredient.

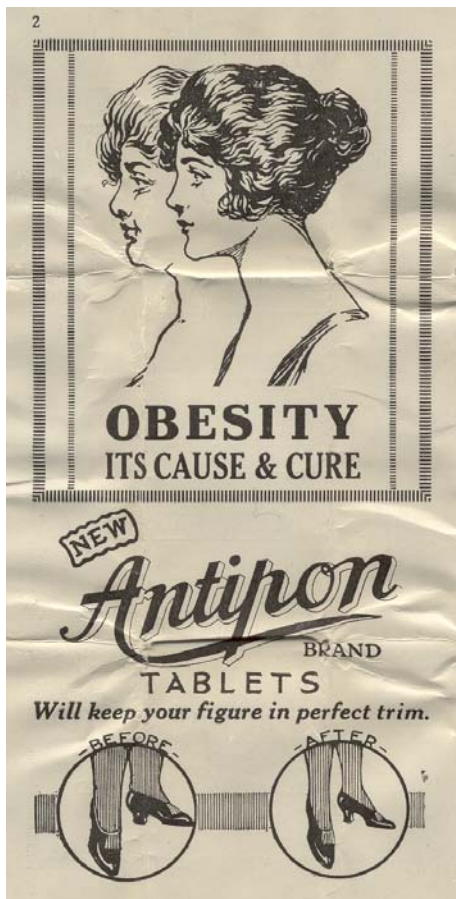
The manufacturers of Lacey's Reducing Chewing Gum claimed; *"the chewing of Lacey's excites the salivary glands, so that the food you have eaten digests with new efficiency - and it is no longer allowed to go on making more unwanted weight"*. The ingredients included fucus seaweed; *"chosen for its influence on*

... those glands whose inefficient functioning is so often the cause of superfluous flesh".

The makers also claimed the gum was a beauty treatment too because *"chewing exercises the facial muscles and fills out hollows and arrests sagging contours"*

Antipon Brand Obesity Tablets, 1930-1942 Manufactured by The Antipon Laboratories

"Graceful and Slim, Always in Trim, Thanks to Antipon Brand Tablets"



As well as fucus, Antipon Brand Obesity Tablets contained frangula, rhamnus, aloes, and rhubarb all of which are laxatives used in the treatment of constipation.

Clynol Brand Berries capsules, 1936-1942 Manufactured by Parker Belmont and Company

Clynol Brand Berries contained fucus, along with phenolphthalein. Phenolphthalein was a laxative used to treat constipation. It has now been withdrawn in many countries because of concern over its potential to cause cancer following reports of tumours in rodents.

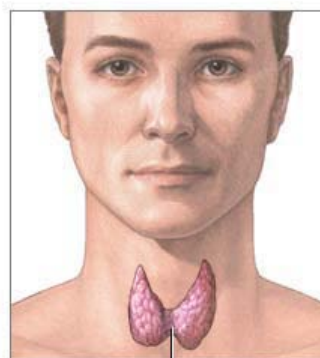
Adios tablets, 2009 Manufactured by Diomed Herbals

Adios are slimming tablets, containing fucus, currently available over the counter in pharmacies. According to the manufacturers they are currently *"the UK's No. 1 selling*

slimming tablet"; and promoted as *"effective, natural, herbal medicines which help speed up weight-loss by acting on the body's metabolism"*.

5. 'Burning fat' Thyroid hormone preparations (used 1904-1958)

The thyroid gland controls how quickly the body burns energy (the metabolic rate). Some obese patients suffer from an under-active thyroid which means their body takes longer to burn energy. This makes it easier for them to gain weight and harder to lose it.



Thyroid

© ADAM, Inc.

Thyroid hormone medicines were introduced in order to encourage a more active thyroid in obese patients, increasing a person's metabolism of fat. Thyroid medicines were mainly prepared using thyroid tissues obtained from an ox, sheep or pig.

However, in some cases doctors prescribed thyroid medicines where obesity wasn't caused by an under-active thyroid gland. While thyroid hormones did produce weight loss, their use resulted in the burning up of lean tissue as well as fat. Another negative outcome on the patient's health was that thyroid preparations produce an increase in heart rate.



'Tabloid' Brand Thyroid Gland tablets, 1911 – 1932
Manufactured by Burroughs Wellcome and Company

Elixir Polyglandin medicine, 1949 – 1953
Manufactured by Allen and Hanburys Limited

Elixir Polyglandin contained fresh thyroid gland and fresh pituitary gland. Scientists included pituitary gland, combined with thyroid, to improve the rate at which a patient's body burnt energy.

6. 'Reducing hunger'

Amphetamine-based preparations (used 1945-1975)

By the late 1930s, scientists had discovered that amphetamines suppressed a patient's appetite. Unlike thyroid, amphetamines do not increase the metabolic rate. Amphetamine-based preparations were administered for short periods to help obese patients accept a restricted diet more easily.

Manufacturers also combined thyroid hormones and dexamphetamine in the treatment of obesity. These medicines combined the appetite suppressant properties of amphetamine, with thyroid's influence on the metabolic rate.

However, amphetamines stimulated the central nervous system and had many adverse side effects including irritability, restlessness, insomnia and anxiety. The use of amphetamines for prolonged periods could also lead to addiction. For this reason, and their potential to be abused, medical practitioners discouraged the use of amphetamines by the late 1970s.



Stimplete Elixir, around 1967

Manufactured by John Wyeth and Brother Limited

Stimplete Elixir was for the treatment of mild depression and as a support for obese patients on a reduced diet. It contained dexamphetamine sulphate and phenobarbitone. Phenobarbitone depresses the central nervous system reducing anxiety and insomnia caused by the stimulating effect of dexamphetamine.

Dexten tablets, around 1967
Manufactured by Nicholas Laboratories Limited

Contained dexamphetamine sulphate. 1 Dexten tablet taken in the morning suppressed the appetite for 10-12 hours. Patients took them in the morning so that they were less likely to cause insomnia at night.

Durophet capsules; 1967-1989
Manufactured by Riker Laboratories

Contained dexamphetamine sulphate & amphetamine.

Glandiposan & Glandiposan Forte tablets, around 1958
Manufactured by Gideon Richter (Great Britain) Limited

Combined thyroid and dexamphetamine sulphate

Thyrodex tablets, around 1967
Manufactured by Paines and Byrne Limited

Combined thyroid and dexamphetamine sulphate

7. 'Reducing hunger'

The anorectic agents; phenmetrazine, phentermine, & mazindol (used 1955-2000)



Pharmaceutical scientists designed anorectic agents to assist obese individuals living on a restricted diet by suppressing their appetite.

Compared with amphetamines, anorectic agents were seen as an improved treatment for obesity because they had less of a stimulant action on the central nervous system. Because drug dependence developed more slowly they also had less abuse potential.

At first scientists believed that anorectic agents had little effect on the cardiovascular system. However, scientists later discovered some anorectic agents could have a harmful effect on obese patients with heart problems. As a result of these findings in 2000 the European Commission requested the withdrawal of all anorectic agents from the European market including mazindol, phenmetrazine, and phentermine.

Anorectic agents were of limited use in the treatment of obesity because patients quickly developed tolerance to them and so they could only be used for short periods.



**Preludin tablets & Preludin Tablongets, 1962-1972
Manufactured by Boehringer Ingelheim Limited**

“One tablonget on rising will give day-long control of appetite”

Preludin tablets & Preludin Tablongets contain phenmetrazine hydrochloride.

Apart from reducing the craving for food, phenmetrazine made dieting more bearable by elevating a person's mood and increasing vitality, thereby reducing potential apathy and depression. Because researchers believed that phenmetrazine in therapeutic doses had little effect on the cardiovascular system, Preludin was also given to obese patients with cardiovascular disease, including hypertension.

When launched in 1956 Preludin tablets were initially available from pharmacies, without a doctor's prescription. However by 1961 health professionals advised that patients only be prescribed phenmetrazine hydrochloride for a maximum of 4 weeks, as prolonged treatment with large doses could lead to severe nervous depression and addiction with psychotic reactions.

Ionamine 15 capsules, around 1977
Manufactured by Pennwalt Pharmaceuticals U.K.

Ionamine 15 capsules contain phentermine.

Pulmonary hypertension was later reported in some patients receiving phentermine. In addition, valvular heart disease was reported in up to 30% of patients receiving phentermine when combined with fenfluramine, another anorectic drug.

Although valvular heart disease was not associated with phentermine treatment alone, its license was withdrawn in the European Union in 2001.

Teronac tablets, 1977-1982
Manufactured by Wander Pharmaceuticals

Teronac tablets contain mazindol.

Compared with either phentermine or amphetamines, mazindol caused less central nervous system stimulation and fewer adverse cardiovascular effects. As a result obese patients with mild to moderate hypertension could be treated with mazindol.

8. 'Controlling the appetite'
Methylcellulose(available 1993 - present day)

Methylcellulose is a bulk forming agent, used as an aid to control appetite. When taken with water before meals it fills up the stomach reducing the amount of food the individual needs to eat.

Although methylcellulose is still licensed in the UK as a treatment for obesity many scientists now believe there is no evidence that it works, or for its safety since large quantities can block the intestines.

**Celevac tablets 500mg, 2001
Manufactured by Monmouth
Pharmaceuticals Limited**

Celevac tablets contain methylcellulose.



**9. 'Feeling full'
Sibutramine (available 2000 - present day)**

Sibutramine works by manipulating brain signals that enhance the feeling of fullness. As a result the patient does not eat too much food, because smaller quantities of food satisfy them.

Sibutramine also prevents the reduction of the basal metabolic rate (BMR) usually experienced by people on restricted diets. By maintaining the BMR sibutramine allows patients to continue to burn calories and /or body fat and lose weight.

Sibutramine is not suitable for all obese patients particularly people with cardiovascular disorders.



**Reductil 10 mg; 2001
Manufactured by Knoll
AG, Germany**

Reductil 10 mg tablets
contain sibutramine
hydrochloride.

10. 'Reducing the absorption of fat' Orlistat & Formoline (available 1999- present day)

Both Orlistat and Formoline are advertised as products that help people to lose weight by reducing the amount of dietary fat absorbed by the body.

Orlistat works by inhibiting the breakdown of dietary fat. Rather than being absorbed, and potentially stored by the body, Orlistat causes up to 30% of dietary fat to pass unabsorbed through the gastro-intestinal tract. The unabsorbed dietary fat is excreted through bowel movements.

Patients taking Orlistat have to keep to a reduced fat diet and avoid high fat foods in order to limit the possibility of side-effects. These can include upset bowel movements and flatulence with oily discharge.

An Over The Counter alternative is Formoline L112 Weight Management Tablets, which contain a naturally sourced fibre derived from shellfish.

The manufacturers claim the fibre in the tablets binds to fat from food in the digestive tract so that it's not absorbed by the body. The fibre is not digestible and is excreted, along with the fat, in bowel movements.

However, as Formoline is a 'medical device' and not a licensed weight-loss drug it has undergone significantly fewer clinical tests than Orlistat, and many health professionals are unsure that it can reduce the amount of fat the body absorbs.



**Xenical 120mg, 2008
Manufactured by
Roche Registration
Limited**

Xenical 120mg tablets
contain orlistat.

**Formoline L112 Weight
Management Tablets,
2009
Manufactured by SSL
International**

Formoline L112 tablets
contain polyglucosamine,
a fibre derived from
shellfish.

Weight loss pill for just £1 a day

(Headline from **METRO** 22.01.2009)

Orlistat is currently a Prescription Only Medicine. However, in January 2009 the European Commission recommended that Orlistat 60mg tablets become available in pharmacies without a doctor's prescription.

The move was welcomed by the National Obesity Forum who said it would protect consumers who were 'spending millions of pounds each year on fad diets, unproven "miracle pills" and potentially unsafe weight-loss supplements'.



LETHAL OBSESSION

Weight loss is a vital part of cardiovascular risk management and weight loss with Xenical can have a significant impact upon key risk factors.^{1,3} When you help change their weight, you help change their future.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Roche Products Limited. Please contact Roche Drug Safety Centre on: 01707 367554

Roche **PRESCRIBING INFORMATION. XENICAL (orlistat).** Indications: XENICAL is indicated in conjunction with a mildly hypocaloric diet for the treatment of obese patients with a BMI ≥ 30 kg/m², or BMI ≥ 28 kg/m² with associated risk factors. Treatment should be discontinued after 12 weeks if patients have been unable to lose $\geq 5\%$ of their body weight. **Dosage and administration:** One capsule immediately before, during or up to one hour after meals (only 33% of calorie intake from fat). **Contra-indications:** Chronic malabsorption syndrome, cholestasis, breast-feeding, known hypersensitivity to any component of the product. **Precautions:** Monitor anti-diabetic drug treatment. Co-administration of orlistat with ciclosporin is not recommended. Treatment may potentially impair the absorption of fat-soluble vitamins (A, D, E, and K); patients should be advised to have a diet rich in fruit and vegetables. The 39792055N August 2008.

possibility of experiencing gastrointestinal events may increase when orlistat is taken with a diet high in fat. Caution should be exercised when prescribing to pregnant women. Studies have shown no interaction between orlistat and oral contraceptives, however an additional contraceptive method is recommended to prevent possible failure of oral contraception that could occur in case of severe diarrhoea. Rare cases of rectal bleeding, generally of mild intensity have been reported and prescribers should investigate further if symptoms are severe or persistent. **Drug Interactions:** A decrease in ciclosporin levels has been observed in an interaction study. Co-administration with acarbose should be avoided. INR values should be monitored if patient is on warfarin or other anticoagulants. Reinforcement of clinical and ECG monitoring is warranted if patient is on amiodarone. **Side-effects:** Please consult the Summary of Product Characteristics for full details of adverse events. **Common:** Influenza, anxiety, headache, respiratory infection, urinary tract infection, menstrual irregularity, fatigue and gastrointestinal such as oily spotting, abdominal pain, increased defecation and flatulence. Treatment adverse events in type 2 diabetes included hypoglycaemia and abdominal distension. The incidence of adverse events decreased with prolonged use of orlistat. **Serious:** Very rare cases of increases in liver transaminases and alkaline phosphatase and also cases of hepatitis. Very rare cases of urticular eruptions, diverticulitis and cholelithiasis. Rare hypersensitivity reactions of

angioedema, bronchospasm and anaphylaxis. **Legal Category:** POM. **Presentation and Basic NHS Cost:** Xenical 120mg (84 capsules) £33.58. **Marketing Authorisation Number:** EU/1/98/071/003 (84 capsule blister pack). **Marketing Authorisation Holder:** Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, UK. Further information is available on request. Xenical is a registered trade mark. **Date of preparation:** June 2007. **References:** 1. Hollander PA et al. Diabetes Care 1998; 21: 1288-1294. 2. Harefield M and Sachse G. Diabetes Obes Metab 2002; 4: 415-423. 3. Sharma AM and Golley A. J Hypertens 2002; 20: 1873-1878. 4. Broom I et al. Br J Cardiol 2002; 9: 460-468. 5. Torgerson JS et al. Diabetes Care 2004; 27: 155-161.

XENICAL
orlistat 120mg

Block fat and help change their future

Advertisement for Xenical orlistat 120mg, 2008

To highlight the dangers of being overweight the advert shows an image of a skull in the food at the bottom of a take-away container.

Further Information

- The Royal Pharmaceutical Society has produced a quick reference guide on Obesity and Weight Management for pharmacists:

www.rpharms.com/public-health-issues/obesity-and-weight-management.asp

- The National Obesity Forum (An independent charity, working to improve the prevention and management of obesity):

www.nationalobesityforum.org.uk