Obesity

Obesity results from an imbalance between energy intake and energy expenditure and increases the risk of cardiovascular disease, diabetes mellitus, gallstones, respiratory disease, osteoarthritis, and some forms of cancer. The prevalence of obesity is increasing especially in developed countries. Obesity may be defined in terms of the body-mass index (BMI), which is the weight (kg) divided by the square of the height (m^2):

- BMI 25.0 to 29.9: overweight
- BMI 30.0 to 34.9: obese, moderate risk of co-morbidity
- BMI 35.0 to 39.9: obese, severe risk of co-morbidity
- BMI 40.0 or more: obese, very severe risk of co-morbidity

Weight loss appears to improve control of diabetes mellitus and hypertension, and to reduce cardiovascular risk factors but long-term benefits are difficult to assess as weight is often regained.

Initial management involves dietary modification and includes calorie restriction and changes in the dietary proportions of fat, protein, and carbohydrates. Physical activity should also be increased and excess alcohol avoided. These measures should be followed for at least 3 months. If there has then been less than 10% reduction in weight and the BMI is still above 30, drug treatment may be considered. For patients with associated risk factors such as diabetes mellitus, ischaemic heart disease, hyperlipidaemias, hypertension, or sleep apnoea, drugs may be considered when the BMI is 27 or 28. Combination drug therapy is not recommended. Drugs should be given initially for 12 weeks. If weight loss is less than 5% then they should be considered a failure and stopped. If weight loss is more than 5% they may be continued and the patient monitored at monthly intervals. Treatment should be stopped once the BMI falls below 30 (or 27/28 as appropriate, see above), or if weight is regained, or there is any suspicion of toxicity.

Many drugs are capable of reducing appetite and have been used as such in the treatment of obesity. Both centrally acting (appetite suppressant, anorectic) drugs and those with a local action on the gastrointestinal tract have been used. However, toxicity has been a major problem with centrally acting drugs and very few are still in current use.

Appetite suppressants can be divided into two main groups: central stimulants that act on central catecholamine pathways and drugs acting on central serotonin pathways. Stimulants such as the amfetamines and phenmetrazine are no longer recommended because of their addictive potential. Other stimulants that have been used include diethylpropion, phentermine, mazindol, and phenylpropanolamine but they are also no longer recommended. The serotonergic drugs dexfenfluramine and fenfluramine were formerly used in long-term therapy (up to 1 year) but have both been associated with valvular heart defects and have generally been withdrawn worldwide. There have also been reports of valvular heart defects in patients receiving combinations of anorectics. UK and US guidelines therefore emphasise the centrally acting serotonin and noradrenaline reuptake inhibitor sibutramine, and the gastric lipase inhibitor orlistat, as appropriate choices for the drug treatment of obesity, in combination with diet and exercise. Rimonabant, a cannabinoid type-1 receptor antagonist, is also used as an adjunct in the treatment of obesity (although it was not mentioned in the guidelines). A systematic review of long-term studies (1 year or more) found orlistat, rimonabant, and sibutramine to be modestly effective in reducing weight; however, further studies, particularly on safety, are warranted.

Many other drugs have been tried, including fluoxetine, which has met with some success, and ephedrine with caffeine. The antiepileptics topiramate and zonisamide have also been investigated. Bulk-forming drugs such as methylcellulose and sterculia have been used in an attempt to control appetite by the local effect they might exert when they swell in the gastrointestinal tract, but there is little evidence of efficacy. Nondigestible fat substitutes such as sucrose polyesters have been promoted by the food industry, as part of a strategy to reduce fat and calories in the diet to aid body-weight control.

The control of appetite and the mechanisms of obesity are under investigation. A gene, called the ob-gene, and its protein product, leptin, have been identified and appear to be involved in regulation of food intake.

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Prader-Willi syndrome

Compulsive eating and a voracious appetite are two of the many clinical features of Prader-Willi syndrome, a congenital disorder characterised by infantile hypotonia, hypogonadism, and facial dysmorphism, with subsequent development of abnormalities of behaviour and intellect.[1,2] Supervision and restricted access to food are the mainstay in preventing obesity, but are commonly not sufficient. Fluoxetine may decrease food intake in some patients. It has also been tried for associated self-mutilatory behaviour (skin picking) with variable results.[3,4] Growth hormone may be of benefit in increasing associated short stature and decreasing percentage body fat,[5-11] but close surveillance of glucose homoeostasis is advisable and there have been reports of fatalities in patients with severe obesity or risk factors for respiratory impairment or obstruction.[12] Anorectics have been ineffective.[2]

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Adrafinil *(rINN)* ⊗

Adrafinilo; Adrafinilum; CRL-40028. 2-[(Diphenylmethyl)sulfinyl]acetohydroxamic acid.

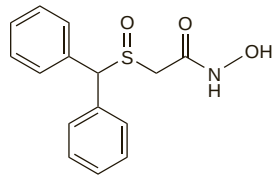
Адрафинил

$C_{15}H_{15}NO_3S$ = 289.3.

CAS — 63547-13-7.

ATC — N06BX17.

ATC Vet — QN06BX17.



Profile

Adrafinil is a central stimulant and alpha$_1$-adrenergic agonist chemically related to modafinil (p.2160). It is given orally for mental function impairment in the elderly in doses of 600 mg to 1.2 g daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Olmifon.

Almitrine Dimesilate *(BANM, rINNM)*

Almitrine Bismesylate; Almitrine, Dimésilate d'; Almitrine Dimesylate; Almitrine Mesylate *(USAN)*; Almitrini Dimesilas; Dimesilato de almitrina; S-2620 (almitrine or almitrine dimesilate). *NN'*-Diallyl-6-[4-(4,4'-difluorobenzhydryl)piperazin-1-yl]-1,3,5-triazine-2,4-diyldiamine bis(methanesulphonate).

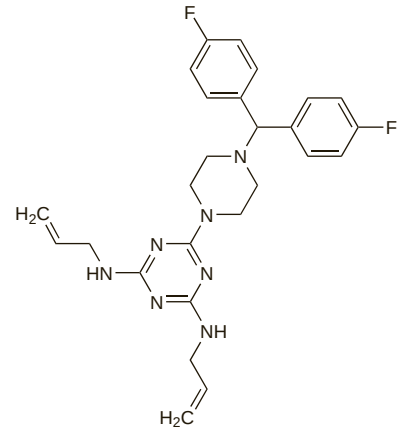
Альмитрина Димезилат

$C_{26}H_{29}F_2N_7,2CH_4SO_3$ = 669.8.

CAS — 27469-53-0 (almitrine); 29608-49-9 (almitrine dimesilate).

ATC — R07AB07.

ATC Vet — QR07AB07.



(almitrine)

Pharmacopoeias. In *Chin.*

Profile

Almitrine dimesilate has been used as a respiratory stimulant in acute respiratory failure associated with conditions such as chronic obstructive pulmonary disease. Usual oral doses range from 50 to 100 mg daily and treatment may be intermittent. Up to 3 mg/kg has been given daily by intravenous infusion in 2 or 3 divided doses, each dose being infused over 2 hours. It is also available in a compound preparation with raubasine for mental function impairment in the elderly.