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.

References.

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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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10. Carrel AL, *et al.* Growth hormone improves mobility and body composition in infants and toddlers with Prader-Willi syndrome. *J Pediatr* 2004; **145:** 744–9.
11. Mogul HR, *et al.* Growth hormone treatment of adults with Prader-Willi syndrome and growth hormone deficiency improves lean body mass, fractional body fat, and serum triiodothyronine without glucose impairment: results from the United States multicenter trial. *J Clin Endocrinol Metab* 2008; **93:** 1238–45.
12. Stafler P, Wallis C. Prader-Willi syndrome: who can have growth hormone? *Arch Dis Child* 2008; **93:** 341–5.

Adrafinil *(rINN)* ⊗

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

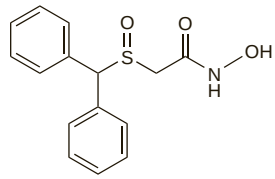
Адрафинил

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

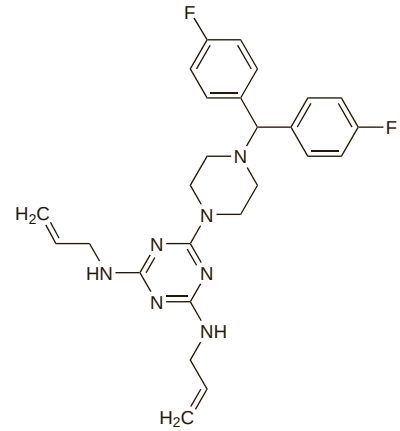
Альмитрина Димезилат

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

Mental impairment. References.

1. Poitrenaud J, *et al.* Almitrine-raubasine and cognitive impairment in the elderly: results of a 6-month controlled multicenter study. *Clin Neuropharmacol* 1990; **13** (suppl 3): S100–S108.
2. Poitrenaud J, *et al.* Time course of age-associated memory impairment in 8037 patients treated with Duxil for 6 months. *Rev Geriatr* 1994; **19:** 531–8.
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4. Allain H, Bentue-Ferrer D. Clinical efficacy of almitrine-raubasine: an overview. *Eur Neurol* 1998; **39** (suppl 1): 39–44.

Respiratory system disorders. Respiratory stimulants (such as almitrine) have a limited and short-term role in acute respiratory failure in chronic obstructive pulmonary disease (p.1112). Almitrine has been reported[1-4] to improve ventilation and blood oxygenation, and to decrease the number of episodes of dyspnoea and hospital admissions, although others[5] have failed to note benefit. There are also reports[6,7] of beneficial effects when used with inhaled nitric oxide in patients with severe hypoxaemic acute respiratory distress syndrome (p.1498) as well as in patients with hypoxia caused by focal lung lesions.[8] However, any modest benefits may be outweighed by the adverse effects, which have included peripheral paraesthesia and weight loss,[1] and headache, urticaria, breathlessness, diarrhoea, chest pain, nausea, and vomiting.[3] The peripheral neuropathy that sometimes occurs during long-term use of almitrine[9,10] may be due to an underlying feature of the pulmonary disease being treated,[11-13] although some disagree with this.[14]

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2. Daskalopoulou E, *et al.* Comparison of almitrine bismesylate and medroxyprogesterone acetate on oxygenation during wakefulness and sleep in patients with chronic obstructive lung disease. *Thorax* 1990; **45:** 666–9.
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4. Górecka D, *et al.* Effects of almitrine bismesylate on arterial blood gases in patients with chronic obstructive pulmonary disease and moderate hypoxaemia: a multicentre, randomised, double-blind, placebo-controlled study. *Respiration* 2003; **70:** 275–83.
5. Sans-Torres J, *et al.* Long-term effects of almitrine bismesylate in COPD patients with chronic hypoxaemia. *Respir Med* 2003; **97:** 599–605. Correction. *ibid.*; 1243.
6. Jolliet P, *et al.* Additive beneficial effects of the prone position, nitric oxide, and almitrine bismesylate on gas exchange and oxygen transport in acute respiratory distress syndrome. *Crit Care Med* 1997; **25:** 786–94.
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10. Gherardi R, *et al.* Peripheral neuropathy in patients treated with almitrine dimesylate. *Lancet* 1985; **i:** 1247–50.
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12. Alani SM, *et al.* Almitrine and peripheral neuropathy. *Lancet* 1985; **ii:** 1251.
13. Moore N, *et al.* Peripheral neuropathy in chronic obstructive lung disease. *Lancet* 1985; **ii:** 1311.
14. Louarn F, Gherardi R. Almitrine and peripheral neuropathy. *Lancet* 1985; **ii:** 1068.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Vectarion†; ***Braz.:*** Vectarion; ***Denm.:*** Vectarion; ***Fr.:*** Vectarion; ***Irl.:*** Vectarion; ***Pol.:*** Armanor; ***Port.:*** Vectarion; ***Rus.:*** Armanor (Арманор); ***Spain:*** Vectarion.

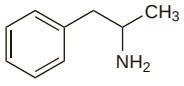
Multi-ingredient: ***Fr.:*** Duxil†; ***Hong Kong:*** Duxaril; ***Philipp.:*** Duxaril; ***Port.:*** Duxil; Transoxyl†; ***Singapore:*** Duxaril; ***Spain:*** Duxor†; ***Thai.:*** Duxaril.

Amfetamine *(BAN, rINN)* ⊗

Amfetamiini; Amfetamin; Amfétamine; Amfetaminum; Amphetamine; Amphetaminum; Anfetamina; Racemic Desoxynorephedrine. (*R,S*)-α-Methylphenethylamine.

Амфетамин

$C_9H_{13}N$ = 135.2.
CAS — 300-62-9 (amfetamine); 139-10-6 (amfetamine phosphate).
ATC — N06BA01.
ATC Vet — QN06BA01.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of amfetamine:
A; Affe; Aimies; Amf; Amfa; Amfis; Amp; Amph; Amphes; Amphet; Anfes; Anfetas; A-Plus; Back dex; Bam; Bambinos; Bass; B-bombs; Beans; Bennie; Bennies; Benny and the Jets; Bens; Benz; Benzedrine; Benzidrine; Berick; Billy; Billy Whizz; Biphetamine; Bippies; Black beauties; Black birds; Black bombers; Black cadillacs; Black hollies; Black mollies; Black and white; Blacks; Blue belly; Blue boy; Blue mollies; Bolt; Bombido; Bombita; Bombitas; Boostant; Bottles; Brain pills; Brain ticklers; Brownies; Browns; Bumblebees; Candy; Cartwheels; Chalk; Chicken powder; Chocolate; Christina; Christmas tree; Clear rocks; Coast to coast; Coasts to coasts; Colorado Rockies; Co-pilot; Crank; Crisscross; Croke; Cross tops; Cross-tops; Crossroads; Crystal; Crystal methadrine; Debs; Dex; Dexadrine; Dexedrine; Dexies; Diamonds; Diet Coke; Diet pills; Dolls; Dominoes; Double cross; Drivers; Eve; Eye opener; Eye openers; Fast; Fast balls; Fastin; Fives; Fly Boys; Football; Footballs; Forwards; French blue; French blues; Gaggler; Gas; GB's; Glass; Go; Go-ee; Goey; Greenies; Halloo-Wach; Hanyak; Head drugs; Head fruit; Hearts; Hi speeds; High speed; Höökipulveri; Horse heads; Hydro; Iboga; Ice; Inbetweens; Jam; Jam cecil; Jelly baby; Jelly bean; Jelly beans; Johnny go fast; Jolly bean; Jolly beans; Jugs; Khat; L.A.; La Glass; LA ice; LA turnarounds; Leapers; Lid poppers; Lid proppers; Lightning; Lip poppers; Little bomb; Little Guys; Louee; Louie; Macka; 357 Magnum; 357 Magnums; MAO; Marathons; Marching Powder; Meth; Methedrine; Methlies Quik; Mini beans; Mini berries; Minibennie; Mollies; Monoamine oxidase; Morning shoot; Morning shot; Nineteen; Nitro; Nugget; Oranges; Peaches; Pep; Pep pills; Pervitiini; Pink hearts; Pixies; Pollutants; Powder; Proszek; Pulver; Purple hearts; Rhythm; Rippers; Road dope; Rosa; Roses; Shight; Shighty; Slammin'; Slamming; Slipvins; Snap; Snow; Snow pallets; Sparkle plenty; Sparklers; Speckled birds; Speckled eggs; Speed; Speed ball; Speed balls; Speed cristal; Speedball; Spivias; Splash; Splivins; Sprinkles; Star; Strawberry shortcake; Sulph; Sulphate; Sulphates; Sweeties; Sweets; Tens; The C; Thrusters; Toffee whizz; Topette; TR-6s; Truck drivers; Turkey; Turnabout; Turnarounds; Tweak; Tweek; Up; Uppers; Uppies; U.S.P.; Wake amine; Wake ups; Water; West Coast turnarounds; Wheels; Whiffle dust; Whiffledust; White; White Cross; White Crunch; Whites; Whiz; Whizz; Wire; X; X-mas tree; Zoomers.

Amfetamine Sulfate *(rINNM)* ⊗

Amfetamiinisulfaatti; Amfétamine, sulfate d'; Amfetamine Sulphate *(BANM)*; Amfetamini sulfas; Amfetamino sulfatas; Amfetaminsulfat; Amfetamin-sulfát; Amfetamin-szulfát; Amphetamine Sulfate; Amphetamine Sulphate; Amphetamini Sulfas; Phenaminum; Phenylaminopropanum Racemicum Sulfuricum; Sulfato de anfetamina. (*R,S*)-α-Methylphenethylamine sulphate.

Амфетамина Сульфат

$(C_9H_{13}N)_2,H_2SO_4$ = 368.5.
CAS — 60-13-9.
ATC — N06BA01.
ATC Vet — QN06BA01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Amfetamine Sulphate). A white or almost white powder. Freely soluble in water; slightly soluble in alcohol. Protect from light.
USP 31 (Amphetamine Sulfate). A white odourless crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in ether. Its solutions are acid to litmus, having a pH of 5 to 6.

Incompatibility. Amfetamine sulfate is incompatible with alkalis and calcium salts.

Profile
Amfetamine is an indirect-acting sympathomimetic with actions and uses similar to those of its isomer dexamfetamine (p.2153). Amfetamine, amfetamine sulfate, and amfetamine aspartate are given orally in doses similar to those of dexamfetamine sulfate. The laevo-isomer, levamfetamine was formerly used in a similar manner. Amfetamine, being volatile, was formerly given by inhalation.

Breast feeding. Amfetamine is concentrated in breast milk and the American Academy of Pediatrics has stated[1] that it has caused irritability and poor sleep pattern in breast-feeding infants when used as a drug of abuse by mothers.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/04/04)

Preparations

USP 31: Amphetamine Sulfate Tablets.

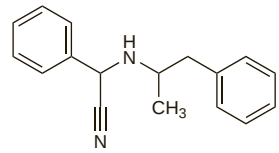
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Belg.:*** Epipropane; ***Canad.:*** Adderall; ***USA:*** Adderall.

Amfetaminil *(rINN)* ⊗

Amfétaminil; Amfetaminilum; Amphetaminil; Anfetaminilo. α-(α-Methylphenethylamino)-α-phenylacetonitrile.

Амфетаминил

$C_{17}H_{18}N_2$ = 250.3.
CAS — 17590-01-1.



Profile
Amfetaminil is a central stimulant that has been given orally in the treatment of narcolepsy.

Preparations

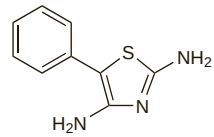
Proprietary Preparations (details are given in Part 3)
Ger.: AN 1†.

Amiphenazole Hydrochloride *(BANM, rINNM)* ⊗

Amiphénazol, Chlorhydrate d'; Amiphenazole Chloride; Amiphenazoli Hydrochloridum; Hidrocloruro de amifenazol. 5-Phenylthiazole-2,4-diamine hydrochloride.

Амифеназола Гидрохлорид

$C_9H_9N_3S,HCl$ = 227.7.
CAS — 490-55-1 (amiphenazole); 942-31-4 (amiphenazole hydrochloride).



(amiphenazole)

Profile
Amiphenazole hydrochloride has properties similar to those of doxapram hydrochloride (p.2155) and has been used intramuscularly or intravenously as a respiratory stimulant.

Lichenoid reactions have been reported in addition to those reactions expected from its central activity.

Ammonium Camphocarbonate

Canfocarbonato de amonio.

$C_{11}H_{19}NO_3$ = 213.3.
CAS — 5972-75-8.

Profile
Ammonium camphocarbonate has been used in preparations for the treatment of respiratory-tract disorders.

Preparations

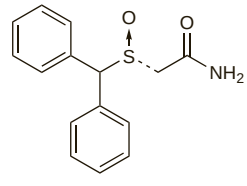
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Spain:*** Pulmofasa.

Armodafinil *(USAN, rINN)* ⊗

Armodafinilo; Armodafinilum; CEP-10953; CRL-40982. 2-[(*R*)-(Diphenylmethyl)sulfinyl]acetamide.

Армодафинил

$C_{15}H_{15}NO_2S$ = 273.4.
CAS — 112111-43-0.



Profile
Armodafinil is the *R*-enantiomer of modafinil (p.2160) and is used similarly in the treatment of excessive daytime sleepiness associated with the narcoleptic syndrome (p.2148), obstructive sleep apnoea, and shift-work sleep disorder. In the treatment of the narcoleptic syndrome or obstructive sleep apnoea, armodafinil is given orally in a single dose of 150 or 250 mg in the morning. For the management of shift-work sleep disorder, the