A Historical Overview Upon the Use of Amphetamine Derivatives in the Treatment of Obesity

Ştefana Stăcescu 1, Gabriel Hancu*1, Denisa Podar1, Ștefania Todea1, Amelia Tero-Vescan2

1Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Medicine and Pharmacy from Tîrgu Mureș, Tîrgu Mureș, Romania.
2Department of Biochemistry and Chemistry of Environmental Factors, Faculty of Pharmacy, University of Medicine and Pharmacy from Tîrgu Mureș, Tîrgu Mureș, Romania.

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ABSTRACT
Relatively few medications are available for the management of obesity and all are indicated as adjuncts to increased physical activity, caloric restriction and lifestyle modification. Among different weight-loss drugs, the most intriguing and controversial class is the one of anorexic amphetamines, due to their high efficiency but also relevant side-effects. Several previously approved anorexic amphetamines like fenfluramine, phenylpropanolamine, phenmetrazine and sibutramine have been withdrawn from the market due to unanticipated adverse effects. Nowadays only four amphetamine derivatives are approved for short-term treatment of obesity: amfepramone, benzphetamine, phendimetrazine and phentermine. The article provides an overview of both the history, and the current status, of the use of amphetamine derivatives in the obesity pharmacotherapy.

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Introduction
Obesity is a chronic disease characterized by increased body weight due to excess fat tissue as a result of excess intake and inadequate calorie loss. Its etiopathology is a multifactorial one, involving organic, hereditary, physiological, metabolic, behavioural, psychological and environmental factors (1).

In most cases, obesity results from the energy imbalance produced either by increasing intake, eating high calories foods rich in fat; or by reducing energy consumption due to low basal metabolism or sedentarism (2).

Obesity is linked with a series of comorbidities, the most common being: type 2 diabetes and cardiovascular diseases like hypertension, coronary artery disease and stroke (2).

Obesity treatment methods include diet therapy, physical exercise, behavioural therapy, lifestyle modification, drug therapy and surgical treatment (3).

It is recommended that drug treatment of obesity should be performed under medical supervision and to be part of a more complex program that associates dietary regimen, physical activity and psychological counselling (4).

Currently, several types of drugs can be used to manage obesity: centrally acting medications which impair dietary intake, medications that act peripherally to impair dietary absorption and medications which increase energy expenditure (4).

Drug therapy in obesity is considered a controversial issue because in many cases drugs have a modest contribution (especially on long-term treatment) to weight reduction and sometimes exhibit considerable adverse effects. The use of medications for weight loss is limited and should be monitored for both safety and efficacy purposes (5).

In regulating lipidic metabolism, the hypothalamus is considered the centre of signal processing received by related pathways; cognitive functions and signals from the gastrointestinal tract are involved in short-term regulation, while endocrine stimuli from adipose tissues and liver are involved in both short-term and long-term regulation (5,6).

Anorexies are medicines that reduce the feeling of hunger...
or prolong the feeling of satiety and are used in the treatment of obesity for the progressive diminishing of weight excess (7). Currently there are only a few drugs approved by the Food and Drug Administration (FDA) for obesity treatment and among these only orlistat, lorcaserin and the fixed dose combination phentermine/topiramate are approved for long-term use; the rest being approved only for short-terms use (a few weeks) (Table 1) (5,6).

Table 1. Drugs with FDA-approved indication for the treatment of obesity.

| Drug                  | Target         | Mechanism of action                                      |
|-----------------------|----------------|----------------------------------------------------------|
| Amfepramone           | CNS            | Sympathomimetic - causes appetite suppression             |
| Benzphetamine         | CNS            | Sympathomimetic - causes appetite suppression             |
| Phentermine           | CNS            | Sympathomimetic - causes appetite suppression             |
| Phendimetrazine       | CNS            | Sympathomimetic - causes appetite suppression             |
| Orlistat              | Gastrointestinal tract | Reversible lipase inhibitor – reduces caloric intake |
| Lorcaserin            | CNS            | Selective serotonergic 5-HT₂C receptor agonist – causes appetite suppression - causes appetite suppression |
| Liraglutide           | CNS            | glucagonlike peptide-1 (GLP-1) agonist – reduce hunger, increase satiety |
| Bupropion/Naltrexone  | CNS            | Norepinephrine-dopamine reuptake inhibitor antidepressant/opioid antagonist - causes appetite suppression |
| Phentermine/Topiramate| CNS            | Sympathomimetic/GABA-receptor activation, AMPA/kainite receptor inhibitor, carbonic anhydrase inhibitor, voltage gated ion channel modulation - the exact mechanism of action for the combination is unknown – causes appetite suppression |

Historically anorexic drugs failed to meet expectations, several drugs used in the past for the treatment of obesity being withdrawn from therapy due to various safety reasons (Table 2) (8).

Table 2. Past drug therapies in the management of obesity

| Drug                 | Mechanism of action                  | Withdrawal reason                                      |
|----------------------|--------------------------------------|---------------------------------------------------------|
| Amphetamine, Metamphetamine | Sympathomimetic - appetite suppression | High abuse and dependence potential, cardiovascular effects |
| Aminorex             | Sympathomimetic - appetite suppression | Pulmonary hypertension                                  |
| Fenfluramine, Dextfenfluramine | Sympathomimetic - appetite suppression | Valvular heart disease, pulmonary hypertension          |
| Phenylpropanolamine  | Sympathomimetic - appetite suppression | Increased risk of haemorrhagic stroke                    |
| Sibutramine          | Sympathomimetic - appetite suppression | Cardiovascular effects – increased risk of heart attack and stroke |
| Rimonabant           | Inverse agonist of CB₁ cannabinoid receptor | Psychiatric disorders                                   |

Anorectic amphetamines

Amphetamines were used for the first time in the 1930s for the treatment of obesity; however, because of their unfavourable tolerability profile, and questionable long-term efficacy, several amphetamine derivatives were removed from the legal market during the years (9).

Structurally amphetamine is a phenylethylamine derivative, skeleton which is present in the structure of neurotransmitters norepinephrine, serotonin and dopamine. Because amphetamine was associated with a numerous side effects, several other amphetamine congeners were synthesized in order to reduce its central nervous system (CNS) stimulatory effects while maintaining its anorectic ones (10).

The anorectic effects of these substances can be explained by a combination of noradrenergic, serotonergic and dopaminergic mechanisms which produces a fast and effective removal of the excessive adipose tissue. This leads to an increased metabolic rate and stimulation of anorectic hypothalamic neurocircuits and other brain areas. At hypothalamic level, anorectic amphetamines inhibit the centre of hunger and stimulate the centre of satiety (11).

Anorectic amphetamines are nowadays indicated as adjunctive short-term treatment to patients with obesity due to a nutritional imbalance whose body mass index (BMI) is 30 kg/m² (obese) or more and overweight patients due to a nutritional imbalance, with a BMI of 27 kg/m² (overweight) or more and associated high risk factors for obesity, such as type 2 diabetes or dyslipidaemia (12).

Due to their sympathomimetic mechanism of action, amphetamine derivatives can determine substantial medical and psychiatric side effects and have a high abuse and dependence potential (13).

Among the four amphetamine derivatives currently approved in the treatment of obesity, the Drug Enforcement Agency (DEA) classifies phendimetrazine and benzphetamineas class III controlled substances (drugs with a moderate to low
potential for physical and psychological dependence), while phentermine and amfepramone are classified as class IV controlled substances (drugs with a low potential for abuse and low risk of dependence); consequently individuals taking these medicines should be monitored and treatment should be stopped if any sign of addiction is observed (8).

The review presents an historical evaluation of the use of amphetamine derivatives in the treatment of obesity emphasizing on the safety and efficacy of this type of drugs. The chemical structures of the past and present amphetamine drugs used in the treatment of obesity are presented in Figure 1.

**Past anorexic amphetamine drugs**

![Chemical structure of anorexic amphetamines.](image)

**Current anorexic amphetamine drugs**

![Chemical structure of anorexic amphetamines.](image)

*Figure 1. Chemical structure of anorexic amphetamines.*
1. Past anorexic amphetamine drugs

1.1. Amphetamine

Amphetamine (methyl-phenylethylamine) was synthesized in 1887, but has not been used in therapy until 1933, when its CNS stimulant effects were described and exploited. It was observed that patients with depression under treatment with amphetamine lost weight and consequently amphetamine was identified as a revolutionary treatment for obesity. It acts as an indirect sympathomimetic, by stimulating the release of norepinephrine in the CNS adrenergic synapses, inhibiting dopamine uptake in central dopaminergic synapses and stimulating dopaminergic receptors (10). Amphetamine possess central stimulant, anorexigenic and sympathomimetic actions being the prototype of this class. It has a high abuse potential with several reported harmful side effects. The addictive and abuse potential of amphetamine prevented its pharmacological use in the treatment of obesity and led to the development of chemically related amphetamine analogues, designed to retain the anorexigenic effect, but with improved safety profiles (14).

Currently amphetamine is classified by the DEA as class II controlled substances (drug with high potential for abuse, its use potentially leading to severe psychological or physical dependence). Amphetamine is used in the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy, but unauthorized possession and distribution is strictly controlled due to risks associated with its recreational use (14).

1.2. Aminorex

Aminorex (5-phenyl-4,5-dihydro-1,3-oxazol-2-amine) is an amphetamine-like anorexic drug which increases the release of norepinephrine (15). It was approved in 1965 in some European countries for the treatment of obesity but not in the USA. It was withdrawn in 1972 due to association of its use with pulmonary hypertension (16).

It has a relatively high abuse potential, being classified by DEA as a class I controlled substances (drug with no currently accepted medical use and high potential for abuse) (8).

1.3. Fenfluramine - Dexfenfluramine

Fenfluramine (N-ethyl-1-[3-(trifluoromethyl) phenyl] propan-2-amine) is a phenylamine derivative containing a trifluoromethyl substituent (17). It has a distinct mechanism of action as it acts primarily as a serotonin releasing agent, modulating serotonin transporter function. Its main active metabolite, norfenfluramine acts as a norepinephrine releasing agent (17). It was approved in 1973 and later was used in combination with phentermine (Phen-Fen), a norepinephrine releasing agent, resulting in a well-balanced norepinephrine-serotonin release (18).

It was also used as the S-isomer of fenfluramine, dexfenfluramine, which was approved in 1996 to improve tolerability (19). Both drugs were withdrawn from therapy in 1997, due to concerns about the cardiovascular side-effects, being associated with serious cardiovascular side effects (valvular heart lesions, pulmonary hypertension, and cardiac fibrosis). Further investigation showed that fenfluramine is metabolized in norfenfuramine, which is an agonist of the 5-HTB serotonin receptor (abundantly present in the endocardium); activation of this receptor resulting in heart valvular lesions (20).

1.4. Phenmetrazine - Phendimetrazine

Phenmetrazine (3-methyl-2-phenylmorpholine) is a substituted amphetamine derivative with a morpholine ring; its structure incorporates both the backbone of amphetamine molecules and a morpholine ring substituted with both a phenyl and a methyl group (21).

It acts as a sympathomimetic drug stimulating the release of norepinephrine and dopamine, its effect on serotonine being negligible (21). I was first introduced in therapy in 1954 as an anorexigenic drug without the side effects of amphetamine; however, it was withdrawn in the late 1960s and early 1970s due to high abuse potential and incidence of recreational use (22).

It was replaced with phendimetrazine ((2S,3S)-3,4-dimethyl-2-phenylmorpholine) which is a produg of phenmetrazine, based on the addition of a methyl group onto the amphetamine skeleton (23).

Phendimetrazine is still used until today being considered an extended release and less abusable version of phenmetrazine. It is available in the form of 35 mg extended release tablets (5).

1.5. Phenylpropanolamine

Phenylpropanolamine ((1R,2S)-2-amino-1-phenylpropan-1-ol) is a sympathomimetic agent structurally related with pseudoephedrine (24).

It was synthesized in 1910 and initially used to treat nasal congestion. Its effectiveness in decreasing food intake was recognised in 1939 but only in 1976 FDA approved its use in the short-term treatment of obesity (24).

Use of phenylpropanolamine was associated with haemorrhagic stroke in women being treated for obesity and consequently withdrawn from the market in 2000 (25).

1.6. Sibutramine

Sibutramine (1-[1-(4-chlorophenyl) cyclobutyl]-N, N3-trimethylbutan-1-amine) is a phenylethylamine derivative with unique structural characteristics and mechanism of action (26).

Its mechanism of action is related by inhibition of central reuptake of serotonin, norepinephrine, and to a lesser extent dopamine. The therapeutic effects of sibutramine are mainly mediated by its active metabolites (mono-demethylsibutramine and di-demethylsibutramine); as the plasma half-life of sibutramine is 1.1 hours, while for its pharmacologically active metabolites 14 and 16 hours,
respectively. Clinical studies showed that the two main metabolites are fold more potent in inhibiting norepinephrine and serotonin reuptake compared with dopamine reuptake. Unlike other anorexic amphetamines sibutramine does not interfere with the release of neurotransmitters (26).

Sibutramine weight loss effects are explainable through the early apparition of satiety feelings, reduced appetite and induction of thermogenesis, by attenuating the adaptive reduction of the metabolic rate during the weight loss process. The weight loss is also accompanied by beneficial changes in lipid plasma levels and glycaemic control at patients with dyslipidaemia or type 2 diabetes. It was approved in 1997 for the long-term treatment of obesity (27). However, sibutramine has been associated with increased risks of myocardial infarction and stroke in patients with previous history of cardiovascular events and therefore the substance has been withdrawn from the market in EU and USA in 2010 respectively 2011; but is still in use in several countries from Asia and South America (28).

Also, sibutramine is the anorexic amphetamine generally used in counterfeiting slimming products, which represents a serious public health problem (29). Its abuse potential is relatively low (26).

Figure 2. Time line of amphetamines used in the therapy of obesity from beginning until today.
2. Current anorexic amphetamine drugs
2.1. Amfepramone (Diethylpropion)

Amfepramone (2-(diethylamino)-1-phenylpropan-1-one) is phynylethylamine amphetamine type drug, an N, N-diethyl analogue of cathinone (30).

Structurally it is related with bupropion (amfebutamone) (2-(tert-butylamino)-1-(3-chlorophenyl) propan-1-one), an antidepressant agent (norepinephrine-dopamine reuptake inhibitor - NDR) used as a smoking cessation aid but also as a weight loss medicine in combination with the opioid antagonist naltrexone (30).

Amfepramone is an indirect sympathomimetic stimulant drug, which stimulates the release norepinephrine and to a lesser extent dopamine, thereby increasing levels of neurotransmitters in the brain. Experimental studies performed in animals have shown that the inhibition of appetite is due to neuronal stimulation of the lateral hypothalamus. Amfepramone may stimulate also other adrenergic peripheral areas, which can lead to side effects (hypertension, tachypnea, and mydriasis); however, the incidence of these unwanted actions is relatively low compared to other sympathomimetics (30).

It is extensively metabolized through N-dealkylation and reduction, its main active metabolites are ethylaminopropiophenone (ethcathinone) and 2-N-diethylamino 1-phenylpropanol (diethylmorphseudoephedrine), both exhibiting central and anorexic stimulating action (30).

It was approved in 1959 and is used as an adjuvant in the short-term therapy for patients with obesity and a BMI of at least 30 kg/m², who did not achieve a corresponding weight reduction with dietary regimen and lifestyle changes. The duration of treatment is generally between 4-6 weeks and should not exceed three months. In case of a treatment which lasts more than 4 weeks, the benefit should be carefully assessed against the possible risks (31).

The evaluation of a placebo-controlled, double-blind clinical study showed that, depending on the duration of treatment, weight loss after administration of amfepramone is 4-6% after 4 weeks, 5-7% after 8 weeks and 7-10% after 12 weeks (32).

As with other amphetamine-type anorexics, epidemiological studies have shown that the use of amfepramone is a risk factor in developing pulmonary arterial hypertension, which can be signalled by the installation of effort dyspnoea. This anorexic drug should be given with caution to epileptic patients, some reports suggesting that amfepramone may induce an increase in the incidence of seizures (32).

It is available in 25 mg immediate release and 75 mg sustained release capsules. The last administration should be at least 4 hours before bedtime, given that it can cause a state of restlessness and insomnia. In case of a more that 4 weeks treatment; the benefit should be carefully assessed against the possible risks. Its abuse potential is believed to be relatively low, however long-term treatment may increase the risk of pharmacological tolerance and dependence, in cases of predisposed patients (5).

2.2. Benzphetamine

Benzphetamine ((2S)-N-benzyl-N-methyl-1-phenylpropan-2-amine) is a substituted sympathomimetic amine that reduces appetite; the large N-benzyl substituent decreasing CNS excitatory properties while anorexigenic properties are retained. It is used in the form of the pure enantiomer, S-dextrobenzphetamine (33).

Benzphetamine is a stimulant of norepinephrine and to a lesser extent dopamine release from storage sites in the lateral hypothalamic feeding centre, producing a decrease in appetite (33).

It is metabolized in dextroamphetamine and dextrometamphetamine, undergoing in vivo conversion to substances with high addiction and abuse potential (34).

It is used for the short-term treatment of obesity for patients who have been unable to lose weight through exercise and diet alone (5).

It is available in the form of 25mg tablets. Benzphetamine has a relatively good safety profile with side effects similar, but less frequent, to those associated with other anorexic amphetamines (5).

2.3. Phentermine

Phentermine (2-methyl-1-phenylpropan-2-amine) is a substituted amphetamine sympathomimetic stimulant with a methyl substituent on the phenylethylamine side chain, substitution which reduce CNS stimulation (35).

It increases the release and reuptake of norepinephrine and to a lesser extent dopamine, its anorexiant effect occurs as a result of satiety-centre stimulation in hypothalamic and limbic areas of the brain (35).

It was first introduced in therapy in 1959 and remains one of the most frequently prescribed anti-obesity drug (35). It was used also as a drug combination with the serotonin releasing agent fenfluramine, however it was withdrawn from the market in 1997 due to fenfluramine cardiovascular side-effects(31). Another fixed dose combination with the anticonvulsant drug topiramate was introduced in therapy in 2012 (36).

Phentermine is prescribed for short-term treatment of obesity (up to 12 weeks treatment) but the combination phentermine/topiramate is indicated as an adjunct to a reduced-calorie diet and increased physical activity for long-term weight management (37).

The most common reported side effects after phentermine administration are dry mouth and insomnia; but phentermine administration was also associated with cardiovascular complications including primary pulmonary hypertension (36).

A clinical trial comparing phentermine treatment in alternating months with continuous treatment showed the same weight loss in a period of 6 months; consequently alternate-month therapy with phentermine may be the way to use phentermine for the long-term treatment of obesity (38).

It is marketed alone in 15,30, and 37.5 mg capsules or in combination with topiramate in 3.75/23, 7.5/46, 11.25/69 and 15/92 mg capsules. Its abuse potential is low (5).
Conclusion

Many amphetamines derivatives were withdrawn from the market due to side effects and high potential for addiction and amphetamines cannot be administered safely over a long-term treatment (13).

Phentermine, amfepramone, benzphetamine and phendimetrazine are used in the short-term treatment of obesity as an adjunct to a reduced-calorie diet and increased physical activity. The combination phentermine-topiramate is used in the long-term treatment of obesity. Fenfluramine was found to increase the risk for pulmonary hypertension and valvular heart disease and sibutramine was withdrawn because of cardio-vascular adverse events (myocardial infarction, stroke) (39,40).

By raising CNS activity or/and diminishing energy expenditure, decreasing appetite and food intake, amphetamine derivatives can be considered as an efficient alternative in weight reduction. However, products that caused release of monoamines were linked with cardiovascular adverse effects, while monoamine re-uptake inhibitors were associated with drug abuse and high dependence potential (41).

Weight-loss medicines are among the most prominently adulterated medicines, and the adulterants are usually anorexic amphetamines; this market being fed by the growing discrepancy between overweight modern societies, the contemporary idealized figure and the restrictive prescribing of weight-loss medicines.

Obesity is considered a chronic disease; hence it requires long-term therapy, however currently, there is a lack of high-quality evidence from long-term studies of both the efficacy and safety of anorexic amphetamine use as serious safety concerns have resulted in the withdrawal of some drugs that had originally received market approval.

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