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Pharmacological treatment of obesity

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OBJECTIVES

To describe the impact of obesity on the health of the individual and to evaluate the different alternatives of treatment.

MATERIAL AND METHODS

A bibliographic research was performed in Pubmed and Medline Plus between 1998 and 2008 with the following terms: obesity, obesity and treatment, orlistat, sibutramine, phytotherapy, nutraceutics.

RESULTS

The consequences of obesity on health, criteria for intervention and objectives of treatment are described. The article also makes an evaluation of the non-pharmacological options of therapy, the role of the different pharmaceutical agents available, phytotherapy, mesotherapy, and surgical treatment.

CONCLUSIONS

Patients who are overweight, associated with a waist hip circumference at risk, and/or other forms of co-morbidity should receive assessment with regards to diet, exercise and lifestyle with the aim to reduce 5-10% of their weight. Pharmacotherapy should be offered to obese patients or those with a BMI>27 kg/m^2 associated with 2 or more forms of co-morbidity when a conservative approach has failed. Medication should be discontinued when, after 3 months, a weight reduction of 5% has not been reached.

No properly designed clinical trials exist that support the use of phytotherapy. These products are not free from adverse effects.

In the case of morbid obesity (BMI>40 kg/m^2) or BMI > 35 kg/m^2 associated with co-morbidity and failure of conservative management, bariatric surgery remains an option. This procedure should be performed in reference centres after an adequate selection is made and posterior nutritional follow up is possible.

Introduction

The WHO *(World Health Organisation)* and the IOTF *(International Obesity Task Force)* have qualified obesity as the " epidemic of the 21st century" and did not include it in the International Classification of Diseases (ICD-10) until 1997. Though recognised from ancient times, obesity has been considered a disease since the 18th century, and continues to increase now even more sharply among children. Its latent development over time and its interdependence with the behaviour of the person makes it difficult to manage. The best mode therefore to affront obesity is through prevention. While it is important to offer treatment on an individual basis, it is equally important to promote social and educational changes that encompass all the environmental factors that favour the growth of obesity.

In May 2004, the 57th World Health Assembly of the WHO approved the world strategy for food and diet, physical activity, and health[1]. Different nations have designed strategies and policies to affront the problem which today affects 300 million people around the world. The prevalence of obesity in the Spanish population in general, is 13.9% among children and juveniles (2-24 years)[2] and 15.5% among the adult population (25-69 years)[3].

In Spain, since 2005, a strategy was designed, NAOS (Strategy for nutrition, physical activity and prevention of obesity)[4], that currently is still being implanted. The results of this initiative can only necessarily be observed after at least 10 years. Meanwhile, the individuals affected with obesity can benefit from various treatment options available which can be employed conjunctly and simultaneously, though the results are not always as successful as hoped for.

Overweight and obesity. Consequences for health

Obesity is defined as excess body fat that pathologically affects the health of the individual. In the normal constitution of an individual, body fat represents 20-30% in women and 12-20% in men (table 1). This constitution varies with age and can be modified depending on different physiological and pathological conditions.

Table 1. Percentage of body fat.

	MEN	WOMEN
Normal weight	12-20%	20-30%
Límit	21-25%	31-33%
Obese	> 25%	> 33%

Measurement of body fat can be carried out by different methods involving studies of body composition: formulas based on anthropometric measurements, imaging (computed tomography, magnetic resonance, DEXA), impedanciometry, isotope dilution, etc. The majority of these methods are employed in investigation. In clinical practice, the degree of obesity is estimated by using the body mass index (BMI). The simplicity in calculation and good correlation with the quantity of fat mass in the general population has made the BMI universally accepted. The BMI was first proposed by Quetelet in 1869 and introduced again by Ancel Keys in 1972. The body mass index of a person is measured as the coefficient between the person´s weight expressed in kilograms and the square of the persons height in metres.

$$\text{BMI} = \frac{\text{weight (Kg)}}{\text{height (metres)}^2}$$

Nevertheless we should not forget that this index may not prove useful in some situations. It does not measure the increase in muscular mass in sportsmen, and though it informs us on the total body fat, it does not do so with regard to the distribution of fat, and its value changes with age[5]. It is a valid index between 20 and 65 years, though it is also employed in persons >65 years as no other more reliable parameter is available for this age group (table 2a)[6]. In children the Cole tables are used (table 2b)[7].

Following this criteria, obesity can be classified in different degrees or quantitatively (tables 3 and 4)[6]. If instead of considering quantitative criteria, we choose a qualitative index (taking into account the body region where fat accumulates) then obesity can be classified as follows:

Table 2a. Desired BMI values according to age Group.

AGE (YEARS)	QUETELET INDEX (Kg/m²)
19-24	19-24
25-34	20-25
35-44	21-26
45-54	22-27
55-64	23-28
65 or older	24-29

Table 2b. BMI limit values to define overweight and obesity according to age and sex (from 2 to 18 years of age).

	OVERWEIGHT BMI 25 kg/m²		OBESITY BMI 30 kg/m²	
AGE	MEN	WOMEN	MEN	WOMEN
2	18.41	18.02	20.09	19.81
2.5	18.13	17.76	19.80	19.55
3	17.89	17.56	19.57	19.36
3.5	17.69	17.40	19.39	19.23
4	17.55	17.28	19.29	19.15
4.5	17.47	17.19	19.26	19.12
5	17.42	17.15	19.30	19.17
5.5	17.45	17.20	19.47	19.34
6	17.55	17.34	19.78	19.65
6.5	17.71	17.53	20.23	20.08
7	17.92	17.75	20.63	20.51
7.5	18.16	18.03	21.09	21.01
8	18.44	18.35	21.60	21.57
8.5	18.76	18.69	22.17	22.18
9	19.10	19.07	22.77	22.81
9.5	19.46	19.45	23.39	23.46
10	19.84	19.86	24.00	24.11
10.5	20.20	20.29	24.57	24.77
11	20.55	20.74	25.10	25.42
11.5	20.89	21.20	25.58	26.05
12	21.22	21.68	26.02	26.67
12.5	21.56	22.14	26.43	27.24
13	21.91	22.58	26.84	27.76
13.5	22.27	22.98	27.25	28.20
14	22.62	23.34	27.63	28.57
14.5	22.96	23.66	27.98	28.87
15	23.29	23.94	28.30	29.11
15.5	23.60	24.17	28.60	29.29
16	23.90	24.37	28.88	29.43
16.5	24.19	24.54	29.14	29.56
17	24.46	24.70	29.41	29.69
17.5	24.73	24.85	29.70	29.84
18	25	25	30	30

Table 3. Classification of obesity according to the Spanish Society for the Study of Obesity (SEEDO, 2007).

CATEGORY	LIMITS OF BMI VALUES (kg/m²)
Insufficient weight	< 18.5
Normal weight	18.5-24.9
Overweight grade I	25-26.9
Overweight grade II	27-29.9
Type I obesity	30-34.9
Type II obesity	35-39.9
Type III obesity (morbid)	40-49.9
Type IV obesity (extreme)	≥ 50

Table 4. Criteria for defining obesity in grades according to the BMI (WHO).

CATEGORY	BMI (kg/m²)
Normal weight	18.5-24.9
Overweight (grade I obesity)	25-29.9
Grade II obesity	30-34.9
Grado III obesity	35-39.9
Grade IV obesity	≥ 40

· central, denominated android, faciotroncular, abdominal or “apple shaped”.

· peripheral, also denominated gynoid, gluteofemoral or “pear shaped.”

In this case, measurement can be carried out with different methods, where imaging with computed tomography and magnetic resonance prove the most indicated. In clinical practice the measurement of the waist hip index is employed or even the waist perimeter given their good correlation with the quantity of fat in the upper part of the body and/or its accumulation in the abdominal area. With this index difficulties may arise in carrying out proper measurements of the waist in cases of severe obesity and in cases of previous surgical intervention of the abdomen. Moreover, racial differences should be taken into consideration[8]. The references for measurement used in different studies are as follows:

· the slenderest point of the waist *(Anthropometric Standardization Reference Manual)*

· the mid-point between the last rib and the iliac crest (WHO)

· immediately above the iliac crest (*NIH and NHANES III,* SEEDO)

Overweight and obese people should start with diet and lifestyle changes.

The values of waist measurements considered at risk differ according to various consensus (tables 5a[6,9,10,11] and 5b[12]). The distribution of abdominal fat and adipose tissue also has an influence on the development of complications. This occurs especially with visceral adipose tissue and intra and inter muscular fat, which tend to be associated with metabolic complications, vascular disease, lung disease and some tumours. The total body indexes and total body fat are more frequently associated with bone joint, digestive and circulatory complications and the development of some tumours.

Both classifications are basic and complementary. The pathological consequences of obesity gradually increase depending on the grade of obesity and can multiply exponentially if the fat deposits are located centrally.

The consequences of excess fat in the organism are many and widely varied. The development of some or other complications will depend on various factors: genetic, weight, sex, age, diet, physical activity, degree of stress, physiological and pathological conditions. Genetic studies have revealed that a significant proportion of variations in body composition can be explained by inherited differences. The genetic component is defined in terms of a series of contributing and interacting genes.

It has been shown that increase in weight is associated with an ***increase in overall mortality***. Mortality in patients with morbid obesity is twelve times higher than the general population, –if we focus on the population between 25-34 years– and decreases with age. In patients between 65 and 74 years, overall mortality is twice as high as in the general population. Obesity is responsible for the reduction in life expectancy by about 7 years in both sexes, whether smokers or not. Just as happens with tobacco, the deleterious effects of obesity appear years after the risk factor has been acquired, in this case, weight gain[13].

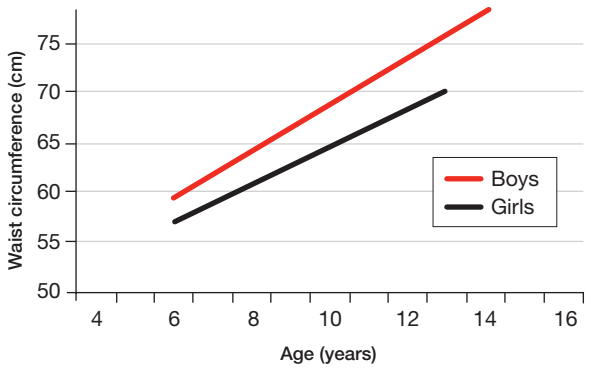
The distribution of body fat is also another important factor affecting the increase in mortality. When the coefficient circumference of the waist/circumference of the hip (WHR) is raised, indicating central obesity, then mortality and the risk of cardiac ischemia increases. Lastly, the quantity of weight gain accumulated from 18 years onwards is also associated with an increase in mortality. An increase in more than 10 kg is associated with an increase in death from coronary disease. Recently a trial was published suggesting that, both general and abdominal adiposity are associated with increased mortality. This study supported the use of the waist circumference index or the waist-hip circumference index/coefficient along with the BMI as additional indicators to evaluate the risk of death[14]. A sedentary lifestyle contributes to obesity and by itself represents a risk factor for mortality by any cause, perhaps due to the increase in adiposity. There are many diseases linked to weight gain. These will be outlined below.

Table 5a. Values of waist measurements at risk according to different consensus.

		RISK STARTS	HIGH RISK
	ETHNIC GROUPS	MEN/WOMEN (cm)	MEN/WOMEN (cm)
IDF consensus, 2005	Europeans*	94 / 80	100 / 93
	South – Asian**	90 / 80	
	Chinese	90 / 80	
	Japanese	85 / 90	
ATP III consensus, 2001		94 / 82	102 / 88
EGIR consensus, 1999			94 / 80
SEEDO consensus, 2007		95 / 80	102 / 88

*In the USA the values of ATP III will continue to be used in clincal contexts.
**Studies with regard to recommendations for races from Central and South America, Sub Saharian Africa and arab populations are underway. The employment of epidemiological Studies and ethnic groups are recommended even though they may be displaced from the place of origin.

Table 5b. Values of waist measurements at risk in children.



Metabolic complications

The risk of **type 2 diabetes mellitus** increases with the grade of obesity, with its duration and the central distribution of body fat. The effect of obesity located around the trunk increases synergetically with the BMI. The risk is 2.9 times higher when the BMI is >27.8 in men and 27.3 in women among the population between 20 an 75 years. Looking at the age group between 20-45 years, the risk increases by 3.8.

Sixteen percent of the obese are **hypertensive** and epidemiological data show that there is a direct relationship between android obesity, hyperinsulinism and high blood pressure. According to the Framingham study, obesity accounted for 78% and 65% of high blood pressure in men and women respectively.

Central obesity contributes to the development of **dyslipemia** with a decrease in HDL cholesterol levels and an increase in triglycerides and LDL-2 cholesterol particles (small and oxidised) which constitutes a more atherogenic profile.

The accumulation of central fat contributes to insulin resistance and hyperinsulinism, thus increasing vascular risk. Visceral tissue adiposity, which is metabolically more active, secretes multiple substances that generate a pro-coagulant and pro-inflammatory state. This contributes to the development and growth of the atherosclerotic plate and produces an increase in sympathetic activity with vascular, renal and cardiac repercussions.

Hyperuricemia and gout appear more frequently in centrally distributed obesity.

Cardiovascular complications

Obesity increases the risk of developing peripheral vascular disease, ischemia and cardiac hypertrophy. Heart failure, which develops more frequently in the obese individual, is related to the duration of obesity[15]. Approximately 10-14% of the cases can be attributed exclusively to obesity. Phlebitis, lymphedema and the varicose syndrome is more frequent especially in ginoid type obesity.

Gastrointestinal complications

These patients frequently develop hernia of the hiatus, and gastro-oesophagic reflux, cholelitiasis, and esteathosis and non alcoholic esteato-hepatitis (NASH).

Bone-joint disease

This originates and/or worsens with an increase in weight. Complications of the bone joint represent one of the most important components of the economic burden of obesity. Hyperuricemia and avascular necrosis of the femoral head are also more frequent in obese individuals.

Respiratory complications

The sleep apnoea-hypo-apnoea syndrome (SAHS) and the obesity-hypoventilation syndrome (SOH) develop more frequently as the BMI increases. Patients with SAHS are obese in 70% of the cases. Obesity is the greatest predictor of severity in SAHS. In patients with a BMI >40 kg/m^2, SAHS appears in all cases. For each 6 kg/m^2 increment in BMI, the risk of SAHS increases by four.

Neurological complications

Just as with cardiac ischemia, obesity, mainly central type, is an independent risk factor for the development of cerebrovascular disease. Syndromes involving peripheral nerve entrapment, and

A weight loss of 5-10% produces a significant reduction in cardiovascular risk.

benign intracranial hypertension or pseudotumour cerebri are also frequent among the obese.

Cancer risk

Obesity is associated with an increase in certain types of cancers. These include renal, bile duct, pancreatic, colon, prosthate, endometrial and breast cancers in women after menopause. In cases of morbid obesity there is an increase in mortality by those cancers, that is by 1.52 and 1.62 times in men and women respectively.

Obstetric and gynaecological complications

The most frequent complications are polyquistic ovary syndrome, infertility, obstetric complications and perinatal risk for both mother and child.

Psychiatric disease

Psychiatric disorders are seen more frequently in obese individuals mainly syndromes related to depression.

Skin complications

Various skin disorders are associated with obesity including estriae, achantosis nigricans, molluscum pendulum, intertrigium, furunculosis, and plantar hyperqueratoses.

Another consequence of obesity is a modification in the pharmacological kinetics of drugs in relation to changes in volume distribution and renal excretion. ***Surgical risk*** also increases with regard to complications affecting the lungs, thrombosis, and more frequently wound infections, and delayed scarring of wounds.

As a result of all the above, obesity brings about incapacity, early retirement and a tremendous economic burden on the patient and health systems. In Spain, these costs have been estimated to be about 2,500 million euros per annum (revised up to 2002) and represents nearly 7% of health expenditure[16]. Different international studies published show that the costs derived from obesity account for 2-8% of the global health expenditure of the countries analysed. The variation in costs was related to the definition employed for obesity (BMI>27 kg/m^2 or BMI>30 kg/m^2) and the type of analysis employed.

Criteria for intervention in obesity and objectives for treatment

A series of management interventions based on the BMI, fat distribution, age and associated comorbidity have been accepted under consensus. Before describing these criteria for intervention, we should recall that the fundamental principle behind management is adhesion to treatment, because this implies a modification in habits. Therefore, it is primordial that, whatever BMI the patient has, he or she should be willing to be treated. Nor should we forget that we are going to find that not many patients will solicit treatment unless indicated.

The population with a BMI between **18.5-24.5 kg/m^2 or normal weight** do not have any indication for treatment. Nevertheless, patients of these characteristics with a personal history of family obesity, waist-hip risk, and/or metabolic complications, should be closely monitored to avoid weight gain.

The population with a BMI between **25-26.9 kg/m^2 or grade I overweight** are candidates for medical assessment for obesity to evaluate fat distribution, evolution over time and associated cardiovascular risk factors. If fat distribution is not central and there is no comorbidity, then medical intervention is not indicated. On the contrary, a management plan should be initiated to modify diet habits, physical activity and periodical clinical follow up.

In the population with a BMI between **27-29.9 kg/m^2 or grade II overweight** with peripheral fat distribution and no associated risk factors, then intervention is optional. If risk factors do exist then intervention is obligatory with the goal of reducing at least 5% of the initial weight. Treatment is always initiated by diet modifications, and increase in exercise. If after three months of treatment this goal is not achieved then pharmacotherapy may be justified.

Treatment should be obligatory in the population with a BMI between **30-34.9 kg/m^2 (grade I obesity)**. Besides diet and exercise, associated comorbidities should be treated. The employment of anti-obesity pharmacotherapy may be beneficial, once exhausting all other means of treatment in changing habits. The goals of management are to lose 5-10% of body weight.

In the population with a BMI of **35-39.9 (grade II obesity)** it is very likely that comorbidity exists. The strategy to follow is similar to the previous case, but with a goal in reduction of weight of 10%. If this is not achieved within a prudential period of

6 to 12 months, then the patient should be referred to a hospital unit with specialised care in the management of obesity.

Patients with a BMI between **40-49.9 (morbid or grade III obesity)** o **BMI>50 kg/m^2 (extreme or grade IV obesity)** imply severity. They should be referred for speciality care and besides the treatments outlined up to now, bariatric surgical options should also be considered.

The primary goal of management should be the reduction of body fat mass in all body regions (and perhaps particularly visceral fat) with the maximum conservation of the lean body mass. This goal is linked to an improvement in comorbidity and global cardiovascular risk and better conservation of weight lost. All treatments that produce a rapid loss in weight provoke a greater loss in lean body mass and are considered unacceptable if the percentage of weight loss exceeds 25% of the lean body mass[17]. For this reason, the goals of treatment are always directed towards the attainment of an acceptable weight, not the ideal weight. The secondary goals are the control and improvement of diseases, cardiovascular risk factors and the prevention of the deterioration in the quality of life.

Management is considered satisfactory when there is a loss of about 5-10% of the initial weight in 6 months and weight maintenance persists over time. With this loss there is a notable improvement in existing metabolic complications and prevention of the development of others (table 6)[18].

Table 6. Clinical repercussion of moderate weight loss (10 kg).

Mortality	Total mortality ↓ 20-25%
	↓ 30-40% mortality in relation to diabetes
	↓ 40-50% of cancers related to obesity
Blood presure	↓ ~10 mm Hg systolic blood pressure
	↓ ~20 mm Hg in dyastolic blood pressure
Diabetes	↓ >50% in risk for diabetes
	↓ 30-50% basal glycemia
	↓ 15% in HbA1c
Lípidos	↓ 10% total cholesterol
	↓ 15% LDL-c, ↑ 8% c-HDL, triglycerides ↓ 30%

In order to achieve these goals, the therapeutic tools available are multiple and should be associated in the majority of cases. Changes in lifestyle is the principal tool for management and should be carried out in all individuals to be treated. Modifications in diet are necessary and are directed towards a reduction in caloric intake while maintaining a balanced supply of all nutrients. An increase in physical activity achieves maintenance of lean body mass and lost weight. Moreover, in some cases pharmacotherapy is indicated, where while not definitive in resolving the disease, leads to better control of the disease in situations of increased risk. Lastly, in selected cases of morbid obesity, the surgical option may be indicated.

In the case of obesity, or a BMI > 27 kg/m^2 with comorbidities, pharmachological management should be considered.

Non pharmacological treatment of obesity

This includes the basic management approach to all obese patients including dietary advice, physical activity and behavioural changes.

Diet plan

Before prescribing any diet plan, we should know what the daily intake of the patient is, the patients daily schedule, work and physical activity and we should inquire about the consumption of alcohol, etc. This will help adapt the new dietary directives as close as possible to the patients preferences. The diet plan should be made on an individual basis, balanced, sufficient, acceptable and explained to the patient. With diet treatment it is fundamental to reduce the energy intake to between 500 and 1,000 kcal/day of the normal daily intake. This should be done whenever the dietary intake is not below 1,500 kcal/day in order to guarantee the necessary daily intake of macronutrients, vitamins and oligoelements.

Over the years, a great number of exotic, pintoresque, and pseudoscientific diets known as “miracle” diets have proliferated. The objective of these diets is to attain maximum weight reductions in very short periods of time. On the whole, these diets can be grouped as unbalanced, hypocaloric, exclusive and dissociative.

It has been demonstrated that extreme type diets (whatever the distribution of macronutrients) pro-

Pharmacotherapy should be discontinued if after 3 months a 5% weight reduction is not reached.

duce great losses in adherents in the long term, besides alterations in body composition, renal function, loss in micronutrients, and induction of disorders in diet habits, etc, especially if followed for a long period[19]. Given all this, the balance of nutrients advised is similar to that of a balanced diet (table 7). Some diets such as the VLCD or very low caloric diets that usually offer 400-800 Kcal are available commercially. They are employed under strict medical control for a period of 16 weeks and in morbid obesity with the aim of improving associated comorbidity.

Table 7. Proposal of percentage distribution of energy and nutrients in the planning for a hypocaloric diet.

NUTRIENTS	ENERGY
Carbohydrates	45 – 55 %
Proteins	15 – 25 %
Total fats	25 – 35 %
Saturated	< 7 %
Monounsaturated	15 – 20 %
Polyunsaturated	< 7 %
Trans fatty acids	< 2 %
Fibre (g)	20 – 40 g

A plan for physical activity

This should always be included in conjunction with a diet plan and adjusted according to the preferences of the patient. The International Association for the Study of Obesity (IASO) offers two separate recommendations[20]. The first makes a reference to the need to carry out 45-60 minutes of physical activity daily (315-420 minutes per week) as a preventive action for overweight subjects to avoid becoming obese. The second recommendation is directed towards the phases of maintenance of weight, where 60-90 minutes of daily moderate exercise is suggested (420-630 minutes), that is, that in which the heart rate reaches between 60-75% of the maximum frequency (maximum heart rate = 220-age in years) to avoid regaining the weight lost. These recommendations have been endorsed by other health institutions and scientific societies[21].

Behaviour changes

Behaviour interventions directed towards helping obese individuals to follow a healthy diet and increase their physical activity progressively have proven effective as a treatment option in reducing and maintaining weight[22,23]. This intense conductual therapy, organised especially in groups, is more efective than the conventional treatment with diet, medication and routine visits[24]. The use of self-vigilance, stimulus control, cognitive reconstructing, stress control, social support, management of contingencies, resolution of problems, physical activity and prevention of relapse can help individuals to reduce at least 10% of body weight. Maintenance of this lost weight is produced in a sub-group of these patients, whenever the active intervention is continued. Obesity, as in any other chronic disease, requires long life supervision by a health worker and active self treatment by the patient.

Pharmacological treatment of obesity

History of the pharmacological treatment of obesity

The different commercial agents available for treating obesity and the principal adverse effects associated with their use are described in table 8.

Indications for pharmacological treatment

It is important to emphasize that the agents should never be employed isolatedly and with no previous changes in diet, exercise and lifestyle for a period between three to six months.

Pharmacological treatment should be used in patients with a BMI > 30 kg/m^2 or >27 kg/m^2 associated with major comorbidity and when the goals of treatment have not been acheived after lifestyle changes. The association of more than one drug for treatment does not improve the results obtained despite the fact that the mechanisms of action of each agent is different from each other.

In Spain, only two weight loss agents are approved: sibutramine (Reductil®, Meridia®) and Orlistat (Xenical®). Until recently another agent known as rimonabant (Acomplia®) was available, but the European Medicines Agency ordered its withdrawal

Table 8. Drugs marketed for the treatment of obesity and main side effects.

DATE	DRUG	EFFECT
1893	Thyroid hormone	Arrhythmias and sudden death
1934	Dinitrophenol	Cataract, neuropathy, death due to liver toxicity
1937	Amphetamines	Addiction, hipertension, cardiac toxicity and sudden death
1967	Rainbow pills*	Death
1971	Phentermine	Pulmonary hipertension
1997	Phenfluoramine/phentermine	Valvular insufficiency

* Rainbow pills: an associaton of amphetamines, thyroid hormone, diuretics and digitalis.

in October 2008 due to safety problems related to psychiatric disorders (table 9).

Goals for treatment and criteria for success

Success of treatment is measured by the percentage of weight loss and the improvement in associated morbidity. Thus a "good" response is considered when there is a 5% weight loss within 3 to 6 months; a "very good" response when there is a 10-15% loss of weight and an "excellent" response when there is a weight loss of more than 15% of the basal weight after six months of treatment.

The National Institute for Health and Clinical Excellence (NICE)[25] recommends a revision of patients treatment every 3 months, and if there is no weight loss of 5% of basal weight, then the treatment should be discontinued. Pharmacotherapy does not cure obesity. When the maximum therapeutic effect has been reached then further weight loss should be halted. When the treatment is suspended, some of the weight lost may be recuperated.

Approved agents for the treatment of obesity

Orlistat (Xenical™)

· **Mechanism.** This drug is a gastric and pancreatic lipase inhibitor. As a result of its action ingested fats are not hydrolysed to glycerol and fatty acids and fecal excretion is increased. It is estimated that the digestion and absorption of 30% of the fat ingested is blocked. This inhibition is dose dependent. This agent can only be obtained with a medical prescription, though it is not financed by the social security.

· **Dose.** Orlistat is available in 120 mg capsules and the advised dosis is three times a day before the main meals. It has been authorised for four years now. The optimum duration of treatment is not clear and should be carried out on an individual basis. Its use is approved for individuals from 12 years of age.

· **Pharmacokinetics.** Less than 1% of the agent is absorbed and passes on to the general circulation and is degraded into two main metabolites. It does not alter the pharmacokinetics of other drugs except for cyclosporine, amiodarone and can potentiate the effects of warfarin. It can also reduce the absorption of liposoluble vitamins.

· **Efficacy.** Ten clinical trials using exclusively orlistat against placebo have been carried out. These trials show that the combined treatment with orlistat and diet is effective in reducing body weight and in reducing the recuperated weight after disconitnuing treatment[26]. In the XENDOS trial, a mean reduction of 2.7 kg was shown against placebo. In a four year follow up study, when the proportion of patients that achieved a loss of more than 10% of their initial weight, the orlistat group obtained better results than the placebo group (26% vs 16% respectively). There was a loss of more than 5% in the initial 53% of the patients under orlistat compared to 37% of patients under placebo. On the

Table 9. Drugs approved for the treatment of obesity.

MAIN SUBSTANCE	PRESENTATION	PRICE (€)	DOSE (DDD)	DAILY COST (€)
Orlistat	Xenical 120 mg 84 caps	99.49	120 mg/8h	3.55
Sibutramine	Reductil 10 mg 28 caps	48.39	10-15 mg/day	1.73-1.78
	Reductil 15 mg 28 caps	49.95		

other hand, adverse effects were frequent, and a reflection of this was only 43% of the patients concluded the trial.

Its employment in diabetes patients achieves a greater reduction in body weight than when diet therapy is used exclusively. With this there is an improved control of diabetes. Orlistat reduces the rate of conversion from carbohydrate intolerance to diabetes by 37%[27].

Other studies have also been carried out in adolescents showing orlistat´s effectiveness and safety in weight loss in this group[28]. In fact, it was the first drug approved for the treatment of infant and juvenile obesity (over 12 years).

Treatment with orlistat reduces LDL-c levels more effectively than the reduction due to weight loss by itself. Moreover, its effectiveness has been shown in reducing postprandial lipemia. Systolic and diastolic blood pressure is also reduced by 1.5 mmHg.

· **Side effects.** The most frequent and important effects are of digestive origin, including flatulence, abdominal colic, fecal incintinence, and oily spotting of the underwear. These effects appear in 15-30% of the cases[29]. Levels of liposoluble vitamins may be reduced, where Vitamin D is the most affected.

Pregnancy and breast feeding. Its use should be avoided during thes periods.

With respect to orlistat´s use with other weight loss agents, studies carried out evaluating combined treatments did not show any further improvement in weight loss than that obtained exclusively with the use of sibutramine[30].

Sibutramine (Reductil™, Meridia™)

This agent was approved for treatment of obesity in 1997 in the USA, and in 1999 in Europe. In Italy, its use was discontinued for some months in 2002 after suspicions arose regarding the safey of the agent, in relation to the deaths of two patients. Their relation to the drug was not confirmed posteriorly. Medical prescription is necessary though it is not financed by the social security.

· **Mechanism of action.** This agent blocks the uptake of serotonine, noradrenaline and to a less degree, dopamine at nerve terminals. It does not adhere to any known neuronal receptor within the CNS. The reinforcement of the effects of serotonin (HT2A/2C receptors) and noradrenaline uptake (beta 1) centrally is responsible for the sensation of safety. Meanwhile the effect on peripheral noradrenergic receptors (beta 3) provoke an increase in caloric expenditure by augmenting the metabolic rate. This mechanism produces satiety, consequently reducing food intake while controversy exists about its possible thermogenic effect.

· **Dosis.** There are 10 and 15 mg capsules available in the market. The initial recommended dose is 10 mg /day and the dose is adjusted according to response. Doses of more than 15 mg per day are not recommended nor approved. The use of sibutramine is approved for up to 2 years. The optimum duration of treatment is not clear and should be decided individually. It can be employed from 12 years of age.

· **Pharmacokinetics.** The agent is absorbed rapidly after administration and maximum plasmatic levels are reached within 1-2 hours. Its plasmatic life is short and it is metabolized in two active compunds. It is metabolised in the liver through the P450 citochrome (CYP3A4 isoenzyme).

· **Efficacy.** Fourteen trials with sibutramine have been published evaluating its response using different doses, weight maintenance, effects in diabetes patients, patients with hypertension and adolescents.

Even though a dose-response relation was observed, only a 5-15 mg daily dose is approved. The effect of treatment with sibutramine appears similar when used continuously than when empoyed during 12 week intervals. Patients treated with sibutramine achieved greater weight loss and a higher rate of maintained weight when compared to patients under dietary treatment exclusively[31]. The mean weight loss in the studies was 4.6% of the initial weight with a 48% rate of patients abandoning treatment. This weight loss is related to a reduction in the LDL-c levels and triglycerides.

The initial effect of the drug in weight loss predicts its long term response. In diabetes patients weight loss and improved metabolic control is achieved although there is no improvement in blood pressure[32,33].

It has also proved to be effective in adolescents but in some cases a lower dose or withdrawal is recommended due to hypertension or increased heart rate[34].

With respect to its role in hypertensive patients, treatment with sibutramine produces an increment in blood pressure[31,35].

· **Side effects.** Systolic and diastolic blood pressures are increased by 1-3 mmHg and the pulse rate by 4-5 beats per minute. Moreover, dry mouth, nausea, headache, insomnia, constipation and nervouseness have been described. In general these effects cease with time and do not requiere suspension of treatment. There is no evidence of cardiac valve disorders or pulmonary hypertension.

· **Contraindications.** Sibutramine should de avoided in the following situations:
- Patients with cardiac ischemia, arrhythmias, or heart failure. The SCOUT trial is currently underway to show a reduction in stroke and myocardial infarction in high risk obese patients. The first analysis of this trial has been published showing that sibutramine seems effective, well tolerated and safe among this population, when previously its use was contraindicated[36].
- Patients under treatment with serotonin uptake blockers or monoamine oxidase inhibitors.
- Patient treated with erythromycin or ketoconazole.
- Pregnancy and breastfeeding.

Phentermine and **diethylpropion** are two other sympatheticomimetic agents approved exclusively in the USA for treating obesity. Their use is approved for short periods (<12 months) due to the potential risk for addiction. Phenylpropanolamine was withdrawn from the market due to the risk of hemorrhagic infarction in women.

There is no evidence to support the effectiveness of products derived from phytotherapy. They can have serious side effects.

Rimonabant (Acomplia™)

This drug was approved in Europe for the treatment of obesity, though recently its commercialization has been suspended. It has not been employed in the USA.

It is a drug that exclusively blocks the cannabinoid I receptor (CB1) that intervenes in the regulation of appetite and body weight. The expression of the CB1 receptors is widely distributed and includes the cerebrum and many peripheral tissues such as adipose tissue, muscle, liver and the digestive system. The endocannabinoid system (ECS) acts centrally at the hypothalamus where it exerts an influence on the orexigenic signal. It has also been shown that it interacts with other hypothalmic neuropeptides which are known to participate in the regulation of the intake of food and energy homeostasis.

The ESC also acts peripherally stimulating the acivity of lipoprotein lipase in adipose tissue which thus reduces the formation of fat by the adipose tissue and liver and inceases the capture of glucose in skeletal muscle.

The motive for its withdrawal from the market has been the high amount of psychiatric related side effects among patients under treatment with this drug (twice as that in the cases of placebo and another 12 cases of suicide) which appear higher than in the initial studies performed before the drug was commercialised[37].

There is only one metaanalysis that includes studies performed with the three drugs[38]. It was concluded that the three drugs only modestly reduce weight (less than 5 kg) and the rate of weight regain once treatment is suspended is similar. The three agents have different effects on the cardiovascular profile and specific side effects. There is yet no information of the effects of these drugs on cardiovascular mortality and morbidity, though there are trials initiated to investigate these effects (SCOUT with sibutramine, CRESCENDO with rimonabant). The financing of these medical treatments should be evaluated in the context of the statements recollected in the consensus document of the NAOS and SEEDO strategies[39].

Pharmacotherapy should be employed to help patients to maintain their weight or continue losing it, but only after previously undertaking simultaneous treatment with diet, physical activity and lifestyle changes. The choice of one or another drug should be made according to the patients' comorbidities and concomitant treatments[40].

Drugs not approved for the treatment of obesity

There is a series of drugs employed in the treatment of various diseases in which a favourable profile has been observed in weight reduction. They have been studied as possible anti-obesity drugs, but none of them has been approved to treat obesity.

Topiramate (Topamax™)

This is an anticonvulsant commercialised and approved for the treatment of epilepsy and migraine. In a metaanalysis of the trials carried out with this agent a 6.5% weight loss was observed in the patients. The side effects however were important: paraesthesia, drowsiness, difficulty in concentration and metabolic acidosis. For these reasons, this agent is currently not considered a valid option to treat obesity.

Zonisamide (Zonegran™)

This is an anticonvulsant with serotoninergic and dopaminergic action, besides blocking sodium and calcium channels. Its use as an anti-epileptic agent showed weight loss effects, which led to its evaluaton as an anti-obesity drug. It is however currently not recommended for treating obesity.

Fluoxetine (Fluoxetine EFG, Prozac™, Adofen™, Reneuron™, Foxetin™, Fluoxac™, Ansilan™, Neupax™, Zepax™)

This is an antidepressant that inhibits the uptake of serotinin. Its dosis as an anti-obesity agent is 60 mg/day, three times the dosis as an antidepressant. Its anti-obesity action is clear in the first 6 months of treatment, followed by a period of weight regain in 50% of the cases[41]. Thus it is not currently considered part of anti-obesity phamacotherapy per se, though it is certainly taken into account when employed in obese patients with depressive syndromes.

Bupropion (Zyntavac™, Elontril™)

Currently it is employed as an antidepressant and in tobacco dishabituation. It acts through the noradrenergic path. It is derived from diethylpropion, an anorexigenic amphetamine. In studies carried out with bupropion-treated patients, an important reduction in weight was observed, though the number of patients was very small[42].

Metformin (Metformin EFG, Dianben™)

This agent belongs to the biguanide class used to treat type 2 diabetes mellitus patients either solely or in combination with other drugs or insulin. Although it cannot be classified as an anti-obesity drug, it is considered the elective treatment in type 2 diabetes patients with obesity or overweight, because it can reduce up to 5% of the weight of these patients.

Exenatide (Byetta™)

This is an analog of the glucagon-like peptide, GLP-1, that has been approved for the treatment of type 2 diabetes mellitus either solely or in combination with metformine, sulphonylureas, or thiazolidindiones. GLP-1 is secreted by L cells in response to food rich in carbohydrates and fats. Amongst its actions, there is a reduction in appetite, delay in gastric emptying, supression of the glucagon release and an increase in the release of insulin stimulated by glucose.

Trials performed have shown an improvement in glycemic controls, reduction in weight during treatment and an improvement in the lipid profile and blood pressure. This drug can produce nausea, though this effect is not very important. Some cases of necrohemorrhagic pancreatitis associated with treatment with exenatide have been reported. It is administered subcutaneously twice a day.

Experimental drugs that can be used to reduce weight

Liraglutide

This glucagon like peptide (GLP-1) analog is awaiting commercialisation for the treatment of type 2 diabetes mellitus in 2009. It is administered once a day by subcutaneous injection. Trials have shown an important reduction in weight in those patients treated with liraglutide, to the extent that phase III studies are now underway to test the drug efficacy as a anti-obesity agent for long term weight loss. There are also head-to-head studies of this agent with orlistat, though they are not expected to finish until 2011.

Pramlintide

This is an amylin analog. It slows gastric emptying, reduces postprandial elevations of glucose and im-

proves diabetes control. It is administered by subcutaneous injection. In trials carried out on diabetes patients, only modest reductions in weight were observed. It is not available on the market.

Cetilistat

This agent is a pancreatic lipase inhibitor that is not absorbed in the intestine and which has similar sde effects to orlistat. It is currently under phase III studies.

Tesofensine

This is a pre-sinaptic noradrenaline-serotonin-dopamine reuptake inhibitor. Phase II studies with this agent have just been published. Weight loss achieved was twice that from the current drugs available. The main side effects include: dry mouth, nausea, insomnia, constipation and diarrhoea. The increase in blood pressure and heart rate were not significant with respect to placebo[43].

Peptide YY

This is an incretin peptide released naturally by L intestinal cells that reduce food intake by the sensation of satiety via the hypothalmus (arcuate nucleus). It adheres to NP,Y-2 receptors and slows down gastrointestinal movements, reducing food intake by 33% in patients[44]. It is administered by intranasal delivery. It is currently in phase I of clinical development.

Leptin

This peptide is produced by adipose tissue and is responsible for the regulation of the body´s energy intake and expenditure. Studies have shown that there is state of resistance to leptin in obese patients, while the administration of super-physiological doses do not stimulate weight loss. Only a small trial showed that this agent could help avoiding regain of weight lost by its effect on energy expenditure[45]. It is effective in some patients with lipodystrophy.

Oxyntomodulin

This is another naturally ocurring incretin-like agent produced by L cells which is found to suppress appetite. It is still under investigation.

Other agents under study include melanocortin receptor agonists, ciliary neurotrophic factor, neuropeptide Y, and ghrelin hormone.

Master formulas

Master formulas employed in the treatment of obesity combine amphetamines, sedatives, diuretics, thyroid hormones or determined talc from endocrine glands[46]. In many occasions the composition of each capsule is distinct, meaning that the desired effect is not continued. With regard to the employement of these products, it can be said that weight loss is a minor effect, given the high incidence and severity of side effects produced which overwhelm the desired slimming effect. Even though their use is prohibited and penalised legally, the prescription, preparation and dispensation for treating obesity[47] is currently obtained and even more efficiently through the internet.

These products produce severe side effects including behavioural disorders, arrhythmias, coronary ischemia, thyroid gland alterations, addictions, etc.[48]. Moreover there is a danger of inhaling the talc of different animal products which can possibly transmit infectious diseases. For all these reasons, the efforts to control and eliminate these practices must continue, by denonucing the side effects and prosecuting the dispensers of these products. At the same time an effort should be made to maintain satisfactory treatment offers to patients suffering from this chronic disease.

Phytotherapy

Many consider phytotherapy as a complementary aid to losing weight and reality shows that products derived from phytotherapy are consumed with no medical control. According to some studies carried out in Spain, 49% of young people and adults with overweight (BMI>27 kg/m^2) consume prepared products to reduce weight[49]. Usually plants with diuretic effects, laxatives, stimulants and other products that interfere with the body´s lipid metabolism are employed[50]. These products come under different presentations: infusions of dried plants, capsules, syrups and extracts, and mixtures of primary substances in different proportions. Many of these products are available for sale to the public in different combinations. However, the anti-obesity effect is not real and none of these products can be recommended for the treatment of obesity[51]. The only exception could be the case of *Ephedra sinica* or *Ma-huang* whose main active substance is ephedrine. However, many side effects were observed with its use, including behaviour related disorders, cardiac, neurological, di-

gestive and sympatheticomimetic effects, which led to its prohibition. Its effects are potentiated by associated use with guarana and mate. On the 6 February 2004 the drug regulating organism in the USA, the Food and Drug Administration (FDA), issued a final judgement banning the sale of the diet supplements containing ephedrine alkaloids like *Ephedra sinica*.

Among the **laxatives**, we find stimulants and bulk producing agents. Stimulants specially, rhubarb or senna *(Cassia angustifolia),* Alder buckthorn *(Rhamnus frangula)* and the Cascara sagrada *(Rhamnus pursiana)* possess anthaquinon active substances. Their action produces irritation to the small intestine provoking a reflex increase in peristalsis, and an accompanying purgative effect of liquid and electrolytes. Prolonged use can provokes the creation of an atonic intestine and can produce importants disorders in water balance and electrolytes.

Bulk forming laxatives provide a sensation of satiety. They are generally complex polysaccharides that pass through the intestine undigested, hydrated and increase the fecal mass. The most employed are kelp, bladderwrack or seaweed *(Fucus vesiculosus),* the isphagula husk or plantina rosa *(Plantago ovata Forsk),* the konjac plant, glucomanano (the rhyzome of *Amorphophallus Konjac*) and guar gum *(Cynamopsis tetragonolobus)*. Kelp, besides its mucilage content, contains iodine, (up to 1% of its dry weight) and therefore can have effects on the thyroid gland. Another product nopal, *(Opuntia ficus)* is known in Spain as Chumbera. Its salient feature is a high content of soluble and non-soluble fibre that produces a sensation of satiety and a reduction in the intestinal absorption of fats. There is no scientific evidence however that links this product with weight loss.

Within the group of **diuretic plants**, the most employed are orthosiphon or Java tea *(Orthosiphon stamineus),* silver birch *(Betuna pendula),* field horsetail or common horse tail *(Equisetum arvense),* annual nettle *(Urtica ureas* y *Urtica diádica),* and dandelion *(Taraxacum officinale)*.

The group of stimulants refer to those plants which either directly or indirectly have an adrenergic effect. The most frequent of these include: plants rich in caffeine like green tea *(Camellia sinensis)*, the guarana *(Paullinia cupana)*, plants rich in ephedrine like the ephedra *(Ephedra sinica)* also known as the adrenaline vegetable. This group also includes other plants like Yerba mate *(Ilex paraguariense)* which is combined with guarana and damiana *(Turnera diffusa)*. They have a high content of caffeine that prolongs gastric emptying. Yohimbe *(Pausinystalia yohimbe)* an α-2 adrenergic blocker has also been used. Results of studies of yohimbe in obesity have not been conclusive. Synephrine (*Citrus Aurantium* or bitter orange) is a sympatheticomimetic amine with similar structural and pharmacological properties to ephedrine and phenylpropanolamine. Currently there are no human studies with this product.

Among the plants that block the synthesis of fatty acids is the la *Garcinia Cambogia*, rich in hydroxycitric acid that inhibits citrate-lyase. Some recognise an antiobesity effect of plants with coloretic-cholagogue properties such as artichoke, boldo, marian thistle, curcuma, dandelion root, fumitory, olive nettle, black radish, rosemary, tea, lime tea and thyme.

In some occasions some tranquilizing plants are associated: amapola poppy, orange blossom, herb louisa, hop or humulus, camomile tea, melissa, passiflower, lime tea, valerian, and verbena.

Ayurvedic preparations (triphala) are composed of equal parts of Amalaki *(Emblica officinalis),* Bibhitaki *(Terminalia bellirica)* and Haritaki *(Terminalia chebula).* There is a double blind trial where a reduction on body weight was observed of up to 8 kg, though the number of patients was too small to generate any solid conclusions.

Along with these compounds, other products that are not derived from plants are available for sale as coadjuvants to antiobesity treatment. One of them is ***chromium picolinate*** complex which is an organic compound of trivalent chromium and picolinate acid (a natiral derivative of tryptophan). In the meta analysis published its effect on weight loss was not clinically significant. Another product is ***Chitosan***, a cationic polysaccharide obtained from the exoskeleton of crustaceans which is attributed to possess the property of a reduction in fat absorption. Studies published have brought about doubt with regard to its effectiveness.

Piruvate has been employed as a supplement to improve performance in exercise and improve body composition. Its effect is weak. In the same way, ß-hidroxy-methylbutyrate, a metabolite of leucine has an anticatabolic effect on protein metabolism.

Conjugated linoleic acid or CLA (TonalinTM)is found in vegetable acids, milk and meat of rumiants. Experiments carried out in rodents, show a

favourable modification in body composition, unlike those studies carried out in humans.

L- Carnitine is an aminoacid found in human muscle tissue and in meat, fish and milk. It is responsible for the transport of fatty acids into the mytocondria. However, there is no scientific evidence of its efficacy as an anti obesity agent.

As we have noted, none of these compounds have been shown effective or safe[52] in the treatment of obesity, and they are not free from producing side effects. The studies carried out are limited due to design errors, short periods (less than one year), small samples, and obtention of results that do not outweigh the concurrent side effects. Moreover, in many occasions they are consumed with no medical control and can worsen existing diseases. Therefore, they should be taken into account when carrying out the medical history of obese patients (table 10). With increasing frequency, countries are taking more legal steps to control the consumption of these products given the risk to public health[53].

Table 10. Documented side effects of phytotherapy used in the treatment of obesity.

COMPOUND	SIDE EFFECTS
Chitosan	Digestive: constipation, pain, flatulence
Yohimbine	Insomnia, nervousness, headache
Chromium picolinate complex	Rhabdomyolisis and renal failure. Dubious injurious effect in chromosomes (animals)
Hydroxicitic acid	Abdominal pain.
G. cambogia	Digestive and respiratory.
Ayurvedic preparations	Nauseas and diarrhoea

Mesotherapy

This evidently belongs to the field of aesthetics, though today treatments such as “lipo-dissolutions” with injections of Lipostabil (a compound of phosphatidylcholine and deoxycholate) are used to treat obesity. Not ony does it not treat obesity, this agent has not been tested in well designed clinical trials nor has it been approved by drug agencies. Nevertheless it is highly consumed. Adverse reactions have been notified such as haematomas, pain at the injection sites, allergic and hypersensitivity reactions.

Surgical treatment of obesity

The employment of bariatric surgery initiated by Kremer in 1954 has increased spectacularly over the last few years. The progressive development of surgical techniques has reduced short term complications. At the same time, improved follow up care of these patients in the long term has reduced the incidence of nutritional complications. Nevertheless, key factors for success in surgical management are careful selection and continued follow up of candidates.

Currently, previously known techniques are still employed in surgical treatment. These include restrictive methods, malabsorption and combined techniques, of which gastric by-pass, carried out preferably under laparoscopy, remains the elective method of choice.

The indications for surgical treatment are: morbid obesity or BMI>40 kg/m^2 and those patinets with BMI>35 kg/m^2 who present 2 or more associated and concurrent diseases and other additional requisites outlined in table 11.

Table 11. Criteria for the selection of patients with morbid obesity for bariatric surgery.

Age: 18-55 years.
BMI: ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with major comorbidities associated susceptible to improve after weight loss.
Morbid obesity established for at least 5 years.
Continued failures of correctly supervised conservative treatments
Absence of endocrinological disorders that cause morbid obesity.
Psychological stability: · Absence of alcohol and drug abuse. · Absence of major pshychiatric disorders (schizophrenia, psychosis), mental retardation, alimentary disorders (bullimia)
Capacity to comprehend the mechanisms of weight loss through surgery and the understanding that the desired results are not always obtained.
Understand that the goal of surgery is not to reach the ideal weight.
A commitment to adhere to the norms of follow up after surgery.
Informed consent after having recieved all the necessary information (oral and written).
Women in child bearing age should avoid pregnancy at least one year after surgery.

Mortality associated with bariatric surgery oscillates between 1-2% and surgical morbidity reaches to about 10%, including medical and surgical complications. Among surgical complications, the most frequent include deshiscence of sutures, marginal ulcers, gastro-gastric communications, stenosis of the gastrojejunal anastomoses and eventration (up to 50%) in cases of open surgery. As for medical complications, we find vomiting, diarrhoea, dumping syndrome, malabsorption of vitamins, oligoelements and in occasions, protein

malnutrition. In order to avoid the complications, it is necessary to carry out nutritional followups throughout the patients life span and ensure daily supplementation of liposoluble vitamins, calcium, folic acid and in occasions iron and zinc. In addition, to obtain maximum benefit and minimise complications, the patient should adhere to a diet plan. Nevertheless, severe medical problems that are incorrigible with a conservative approach may occur and "undoing" of the surgical technique may be requiered.

Surgery should be offered in a centre doted with a multidisplinary team of experts to carefully sellect and follow patients and with adequate technical equipment and experienced personnel[54]. In other words, the intervention should be performed in reference centres.

Bariatric surgery achieves greater weight loss than with conventional treatment. The maximum body weight loss is obtained 1 to 2 years after surgery. Posteriorly, after a period of weight regain, weight it is maintained on the long term[56,57]. Moreover, an improvement of the main comorbities associated with obesity is observed in relation to the surgical technique employed. It has also been demonstrated that there is a reduction in mortality after surgical management of obesity. It is important to take in to account that after one or two years of weight reduction, the patient should be referred for plastic surgery. It is also worth mentioning that there exists a percentage of failure with respect to weight loss (approximately 12-15%) and in occasions, surgical reinterventions become necessary.

There are two other possible treatments: one the one hand, the gastric pacemaker, which consists of an electric stimulator placed in the minor gastric curvature which currently is under clinical investigation. On the other hand, the intragastric balloon is another option limited to use for upto 6 months, which is indicated when conservative management fails and when the surgical option is too risky. However, no sufficient data is available on the clinical course of patients with this treatment option in the long-term nor on its possible side effects.

Information on primary care in Navarre

According to the results obtained from the computer based clinical records in Navarre, the registered data with regard to BMI is very low (<35%) in patients under 65 years. From this age onwards, approximately 60% of the patients have their BMI recorded in the clinical record (table 12). In the case of the waist circumference, recording is even less. In patients under 65 years, approximately 25% have this information registered (table 13).

Given this information, it would be convenient to make an effort to improve the recollection of data in order to carry out any effective intervention in prevention and treatment of overweight and obesity among our population.

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Table 12. Proportion of patients whose BMI is registered in clinical records according to age groups.

AGE GROUPS	MEAN	STAND. DEV.	PERCENTILE 25	PERCENTILE 50	PERCENTILE 75
14-24 years	25.9	14.7	14.1	23.1	33.3
25-44 years	15.3	13.4	6.5	11.7	19.7
45-64 years	33.3	17.6	21.0	31.0	44.5
≥ 65 years	57.4	22.1	43.7	61.6	74.2

Table 13. Proportion of patients wih waist circumference measurements registered in clinical records according to age groups.

AGE GROUPS	MEAN	STAND. DEV.	PERCENTILE 25	PERCENTILE 50	PERCENTILE 75
14-24 years	4.3	8.4	0.9	1.9	3.7
25-44 years	5.2	10.5	0.8	2.1	4.5
45-64 years	13.1	11.9	5.0	10.0	17.0
≥ 65 years	24.8	20.3	7.7	19.2	39.3

Conclusions

All patients with overweight, associated with a waist circumference risk and/or comorbidity, and those with obesity, should relieve specific couselling as far as changes in diet, exercise and lifestyle habits directed to losing weight and/or weight maintenance.

The objective of losing weight should be 5-10% of the habitual weight, taking in to account that with this measure there is an improvement in cardiovascular parameters.

In obese patients and those with BMI>27 kg/m^2 associated with two or more comorbidities, pharmacological management should be offered, if the goals of weight loss with conservative measures are not met after 3-6 months.

It is recommended that pharmacological treatment should be suspended if after three months a reduction in body weight of up to 5% has not been reached.

There are no well designed clinical trials that support the use of products derived from phytotherapy to treat obesity. Given the current elevated consumption of these products, an inquiry into the use of these substances should always be made and recorded during the clinical interview with patients. This is important because of the possible side effects and modifications in the pharmacokinetics and dynamics of other drugs. As the SEEDO promulgates, the public administration should vigilate treatments offered for obesity with no scientific support. This should be contrasted in such a way that patients are not defrauded by miraculous promises.

For patients with morbid obesity (BMI>40 kg/m^2) or with a BMI >35 kg/m^2 associated with comorbidities, in which all therapeutic means have been exhausted, bariatric surgery remains a valid option. This should always be carried out in reference centres after assuring adequate sellection of patients and proper nutritional follow up.

The information regarding the recollection of the BMI and the waist hip circumference in the clinical records in primary care in Navarre is rather scarce. It would be convenient to improve the registration of this data in order to carry out interventions directed to the prevention and treatment of overweight and obese patients among our population.

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