

Obesity

Overview:

Related Products:

- | | |
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| <ul style="list-style-type: none"> • Definition of obesity and major causes • Epidemiology of obesity • Obesity and its relationship with other diseases: The risk of type 2 diabetes • Today's therapeutic options • New obesity treatments in development • | <ul style="list-style-type: none"> • Obesity • Obesity & Diabetes • Obesity - Lack of Reimbursement Limits Market Potential • Cannabinoid CB1 receptor antagonists • PARP Inhibitors • Sodium-dependent glucose (co-) transporter (SGLT) Inhibitors |
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Defintion of obesity and major causes

Overweight and obesity often are thought to be the same because both disorders are related to an abnormal or excessive fat accumulation but, according to the WHO (World Health Organization) there are differences between both. Overweight is defined by a body mass index (BMI) that is equal or more than 25 kg/m² but less than 30 kg/m² , and obesity implies a BMI equal or more than 30 kg/m² .

The BMI is an index of weight-for-height commonly used today that indicates , for males and females, if the patient's weight is accord to his/her height, if it is more or less than what it has to be, or if it is the ideal one. The normal range for BMI is between 18.5 kg/m² and 25 kg/m² . Less than 18 kg/m² and more than 25 kg/m² , indicates that there might exist a nutrition disorder. There is evidence that the risk of chronic diseases in the population increases progressively from a BMI of 21 kg/m² . To calculate the index, there is a very simple formula:

$$\text{BMI (kg/m}^2\text{)} = \text{Weight (kg) / Height }^2\text{ (m)}$$

Online BMI calculators such as that from the NHLBI (<http://www.nhlbisupport.com/bmi/>) facilitate calculation of the BMI. This index, however, should be considered as a rough guide because it may not correspond to the same degree of fat distribution in different individuals, although is a simple way to know if we are obese or with overweight.

The body weight is controlled by two mechanisms, one is the food intake, and the other is a neurohumoral mechanism which implicates the adipocyte communication with hypothalamic nucleus of the central nervous system (CNS), which is an appetite control center of the brain, by a polypeptide hormone release at the adipose tissue, named leptin. This hormone acts like an anorexigen factor increasing the release of norepinephrine (NorA) at the sympathetic nervous system terminals of the adipose tissue acting over adipocyte's β 3 -adrenoreceptor increasing fat burn.

The fundamental and most commonly causes of overweight and obesity is the poor population dietary habits, in particular related to a high intake of food with high levels of sugar and fat during the meals (with less levels of vitamins, minerals and other micronutrients), plus the increasing sedentary habits observed in modern communities. This implicates that the calories ingested are more than what the body and the daily activity levels require leading to an energy imbalance. The energy that is not used is stored inside the adipocytes as body fat and, by an accumulative process, finally results in obesity.

The predisposition to become obese is due to a familiar history of obesity, sedentary habits, unhealthy eating habits, and genes that apparently contribute a 25-40% to obesity. Recent studies demonstrated that there are a number of genes defects linked to obesity that include mutations in the leptin gene, the melanocortin-4-receptor, cholesterol side chain cleavage enzyme and the transcription factor PPAR gamma.

La Merie Businee Intelligence has evaluated in a series of research studies the competitive situation of emerging biogeneric products of several product classes. Among them are

- [Obesity](#)
- [Obesity & Diabetes](#)
- [Obesity - Lack of Reimbursement Limits Market Potential](#)
- [Cannabinoid CB1 receptor antagonists](#)
- [PARP Inhibitors](#)
- [Sodium-dependent glucose \(co-\) transporter \(SGLT\) Inhibitors](#)

Epidemiology of obesity

The global shift in diet towards increased intake of energy-dense-foods and the decreasing physical activity due to the increasingly sedentary nature of many types of work, changing ways of transportation and increasingly urbanization, are some of the biggest causes of the increasing obese population in high-income countries. Furthermore, these days is also dramatically changing the situation in low and middle-income countries, particularly in urban settings, lead to the tendency to consume more food rich in fat and sugar and to the insufficient access to sport and fitness facilities.

The global number of people who is suffering from overweight in adult population is approximately 1.6 billion people (age more than 15 years) and at least 400 million of that are obese. Respect to globally childhood obesity, there are at least 20 -million children under 5 that either have overweight or, that can turn into obesity if their parents don't take the necessary measures.

The projection of the WHO by the year 2015 is that approximately 2.3 billion adults will be overweight and more than 700 million will be obese.

Read more at:

- <http://www.who.int/topics/obesity/en/> and
- <http://www.obesity.org/subs/childhood>

Obesity and its relationship with other diseases: The risk of type 2 diabetes

Together with the BMI, there exists another parameter to consider in the patient evaluation for obesity and it lead to the risk of suffer obesity-related diseases. The waist to hip circumference ratio provides useful information of fat distribution. An abdominal fat distribution is associated with greater risks, such as cardiovascular diseases, than those associated with a peripheral fat distribution. Women that have a waist circumference over 88 cm and men with more than 102 cm , are more likely to become ill as a result of obesity.

Overweight and obesity are lead to serious health consequences, in particular related to chronic diseases such as:

- Type 2 diabetes.
- Cardiovascular diseases, like heart disease and stroke.
- Hypertension.
- Respiratory problems.
- Gallbladder diseases.
- Musculoskeletal disorder, such as osteoarthritis.
- Sleep apnea.
- Certain cancers such as: endometrial, colon, gall bladder, prostate, kidney, and postmenopausal breast.

Childhood obesity is associated with a higher chance of premature death and disability in adulthood.

One of the most important health consequences is the development of type 2 diabetes: 80% of the patients who suffer from diabetes are obese. The incidence of this disease rises with increasing severity of obesity and also with weight gain per se, independent of the BMI. And it is closely associated with excess adipose tissue localized in the abdominal, particularly visceral, region. The abdominal fat catabolism produces free fatty acids that reach the liver, but they cannot be metabolized because of the existence of an insulin resistance mechanism.

Weight loss has been reported to improve glucose tolerance, increase insulin sensitivity, improve lipid profiles, and reduce the requirement of hypoglycemic therapy, which together result in an amelioration of the diabetic state.

Today's therapeutic options

First line in treatment of obesity is to limit energy intake from total fats and shift fat consumption away from saturated fats to unsaturated fats, increase consumption of fruits and vegetables, limit the intake of sugars, and increase the physical activity, for the short-term management of regular, moderate-intensity activity on most days.

When all of these recommendations are not enough to reduce weight, there are some surgery procedures and pharmacological treatments for the management of obesity.

Regarding surgery, there are different procedures, like gastric banding and gastrointestinal bypass, which are the most efficacious and long-lasting treatments for obesity, but they have a high associated surgical risk, high cost and limited availability meaning that its use is restricted just to severe cases.

A number of pharmacologic agents had been used in obese patients in combination with dietary interventions to produce weight loss, but these generally shot-term approaches have proven to be largely unsuccessful. Most of the drugs used act on the CNS to suppress appetite, and that may lead to some serious complications, in fact their use has been withdrawn or strictly regulated.

Considering the currently approved pharmacological therapies for obesity, there are only few drugs actually in use. At the moment, the only drugs approved to treat obesity are: Abbott Laboratories' centrally-acting Reductil/Meridia (sibutramine); Roche's Xenical (orlistat), a lipase inhibitor and, recently approved, Sanofi Aventis' Acomplia (rimonabant), an oral appetite suppressant that is taken once a day and works by blocking cannabinoid binding to the CB-1 receptors found on the surface of cells.

Refer to drugs acting centrally to affect appetite and energy regulation, the amphetamine-like drugs act as sympathomimetics on the hypothalamus, and mimic the stimulation of the central nervous system. Some agents of this group were approved by US FDA, for example, diethylpropion (Tenuate), phendimetrazine (Bontril) and phentermine (Fastin), for the short-term management of exogenous obesity. However, the use of these drugs is restricted because of their particular side-effect profiles, including primary pulmonary hypertension, cardiac valvulopathy, tremor, insomnia, tachycardia, hypertension, and the potential risk for abuse and dependence.

Sibutramine (Meridia-Abbot) is a weak noradrenergic and serotonergic (5-HT) re-uptake inhibitor approved by the US FDA. It acts within the CNS to reduce energy intake and increase energy expenditure. It has a limited use because of the side effects associated including increased heart rate and blood pressure (tachycardia and hypertension, respectively), mostly observed after initiation of treatment. Although these effects are generally transitory, treatment requires to be monitored.

Orlistat, tetra-hydrolipstatin (Xenical, Roche), is a chemically synthesized hydrogenated derivate of lipstatin (a natural product of *Streptomyces toxytricini*). It's an inhibitor of gastric and pancreatic lipases, which are the primary enzymes responsible for the hydrolysis and subsequent absorption of dietary fat in the lumen of gastrointestinal tract, blocking irreversibly its active sites and decreasing systemic fat absorption. The unabsorbed fat is excreted into the feces.

Concerning the efficacy, it results just in an additional loss of 3-4% of the body weight over diet alone in a 2 year period. Although its action is restricted peripherally it has socially unacceptable side effects like oily spotting, abdominal pain, fecal urgency and incontinence, which finally limits its use, and it has the potential to reduce absorption of the fat-soluble vitamins A, D and E.

Acomplia (Rimonabant) marketed by Sanofi-Aventis, works by blocking receptors of a substance called cannabinoid 1, CB1, which stimulates hunger and other cravings in the brain and is also present in fat tissue , reducing the patient's urge to overeat and adjust the body's metabolism of fats and sugars. This process results in improvements in body weight and levels of blood sugars, bad fats and good cholesterol, reducing risks of heart disease and diabetes.

Marketing of Acomplia was first approved by the European Medicines Agency in June 2006. Since then, Sanofi has introduced the drug in six European Union countries: Britain , Denmark , Finland , Ireland , Germany and Austria . The drug has also been introduced in Norway and Argentina . Sanofi most likely would win permission to market Acomplia in the United States by mid-2007, and recently received an approvable letter from the FDA.

Abbot is well placed to maximize the market potential of Reductil/Meridia. The company recorded sales of \$272 million for the drug in 2002 Sales in 2004 was \$352 million, and its expectations for 2008 are forecast to grow up to \$425 million.

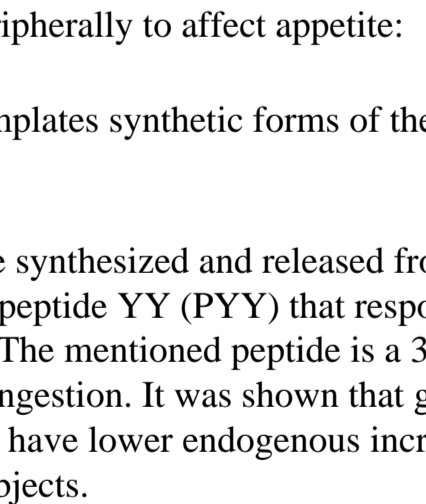
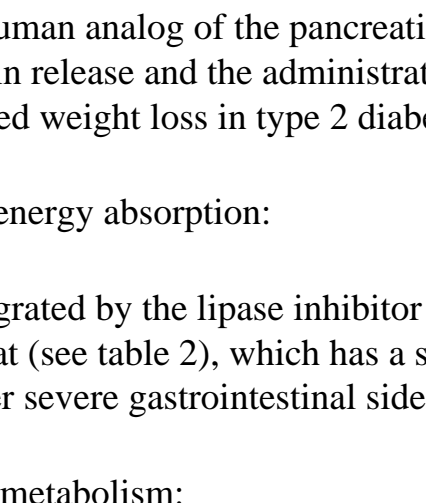
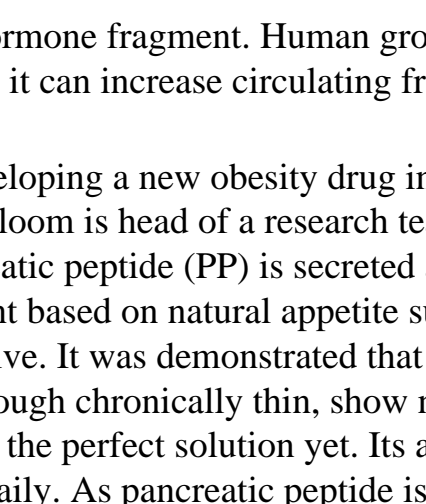
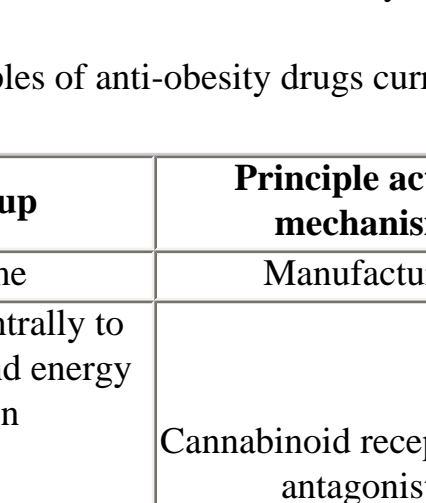
Despite what are perceived as relatively modest effects on weight loss, Xenical and Meridia account for a market valued at a little over \$1 billion, while Sanofi-Aventis has high hopes for Acomplia, which debuted last year, predicting that sales will be in the 'billions of dollars' range at peak. According to some estimates, Acomplia could generate sales of \$3 billion a year. But revenue from the drug started low in the third quarter of 2006, at €11 million, or \$14 million.

Unlike in the United States , most European governments pay for expensive prescription medicines for their citizens. But European governments are increasingly wary of the high prices charged by pharmaceutical companies for new drugs, and they are forcing prices down and narrowing the range of subsidized medicines available. In Denmark , Acomplia is available only to patients with a certain body-mass index and life-threatening conditions related to obesity such as Type 2 diabetes, according to Sanofi. But in Ireland , there will be relatively few restrictions when the drug becomes available under a national insurance plan.

Recently, in February 2007, FDA approved a new version of orlistat to be sold over-the-counter in the US . A low-dose version of Xenical (Orlistat, Roche) marketed by GlaxoSmithKline will be sold under the brand name Alli (pronounced AL-eye). It consists in a 60-mg capsule to be taken up to three times a day, with each fat-containing meal. Xenical (Roche), approved in 1999 and indicated at 120 mg up to three times a day, will continue to be marketed as a prescription drug. The FDA said the Alli label indications will be for use in adults ages 18 or older along with a reduced-calorie, low-fat diet, and an exercise program.

Data presented at the 2006 Annual Scientific Meeting of NAASO, The Obesity Society, found that low-dose Orlistat (60 mg) in conjunction with a reduced-calorie diet, provided significantly greater reductions in LDL cholesterol and weight loss when compared to treatment with placebo and a reduced-calorie diet. Xenical will remain available by prescription for obesity management and for those who should be treated under the care of a physician.

TABLE 1: A resume overview of this tree group of obesity drugs on the US market:

Drug name and manufacturer	Molecule structure	Principle action mechanism	Launched	2005 US sales (source: IMS Health)
Orlistat (Xenical) Roche- GlaxoSmithKline		Blocks fat absorption in the gut	1998	\$87 million (peak sales of \$936 million in 2001)
Sibutramine (Meridia) Abbot		Monoamines re-uptake inhibitors producing feeling of fullness	1999	\$56 million
Phentermine (Adipex-P) Gate Pharmaceuticals / Medeva Pharmaceuticals		Increases levels of catecholamines, producing feeling of fullness	1970	\$43 million
Rimonabant (Acomplia) Sanofi- Aventis		Reduce the patient's urge to overeat, and adjust the body's metabolism of fats and sugars	2006	Approvable letter from the FDA. Approve in US. Could generate sales for \$3 billion a year

New obesity treatments in development

There are a number of agents that are being developed by the pharmaceutical industry today which could be grouped according their general mechanism of action.as shown in TABLE 2.

- Drugs acting centrally to affect appetite and energy regulation:

This group includes 5-HT 2C agonists, and other therapies such as amphetamine derivate (phentermine) combined with an anticonvulsant (topiramate); dopamine and norepinephrine re-uptake inhibitor (bupropion) combined with an opioid receptor antagonist (naltrexone).

Anorectic medications targeting 5-HT system are typically derived from β -phenylethylamine, and mediate their effect by influencing noradrenergic, dopaminergic and serotonergic neurotransmission. Increasing the availability of 5-HT by affecting its release and re-uptake in the synaptic cleft, or the direct activation of the 5-HT receptors, reduces food consumption, whereas decreasing 5-HT receptor activation produces the opposite effect.

Phentermine is an amphetamine derivate compound which acts like other amphetamines increasing energy waste by its sympathomimetic activity, and topiramate is an anticonvulsant drug which has multifactorial effects on the CNS, involving blockade of voltage-dependent sodium channels, action on the gamma amino butyric acid (GABA) and glutamate systems. It was found that the sum of this to drugs increases body weight loss more than when they are administered alone.

Bupropion and naltrexone have been reported to synergistically stimulate the pro-opiomelanocortin (POMC) system that is associated to reducing food intake by blocking a β -endorphin-mediated inhibition of POMC neurons.

- Drugs acting peripherally to affect appetite:

This group contemplates synthetic forms of the appetite suppressing hormone PYY (3-36) , drugs which delays gastric emptying.

Many peptides are synthesized and released from the gastrointestinal tract, several of which are known to modulate eating behavior, such as peptide YY (PYY) that responds to nutrients within the gut by interacting with specific receptors to regulate appetite. The mentioned peptide is a 36-aminoacid peptide synthesized from endocrine L cells of the distal gut in response to food ingestion. It was shown that graded infusions of PYY (3-36) reduced appetite and food consumption. Obese individuals have lower endogenous increases in PYY (3-36) levels in response to calorie intake in comparison with normal-weight subjects.

Pramlintide is a human analog of the pancreatic β -cell hormone amylin, a potentially satiety factor. Food intake stimulates endogenous amylin release and the administration of exogenous amylin reduces food intake too. Clinical data showed that pramlintide induced weight loss in type 2 diabetic patients over a 26-week period of administration.

- Drugs blocking energy absorption:

This group is integrated by the lipase inhibitor drugs. Nowadays there is only one drug in clinical development of this group (the cetilistat (see table 2)), which has a similar action mechanism to orlistat, but it has proved a favorable side-effect profile (90% fewer severe gastrointestinal side effects) compared with that reported for orlistat.

- Drugs acting on metabolism:

Human growth hormone fragment. Human growth hormone (hGH) has lipolytic/antilipogenic properties. As an inhibitor of lipoprotein lipase, it can increase circulating free fatty acids and ultimately reduce fat-cells mass.

Scientists are developing a new obesity drug inspired by a natural hormone in the gut that tells the body when it is full. Professor Steve Bloom is head of a research team at Imperial College London's Hatterly Hill Hospital which discovered pancreatic peptide (PP) is secreted after every meal and signals to the brain to stop eating. According to Prof Bloom, a treatment based on natural appetite suppressant, mimicking the body's response to being full, has the potential to be safe and effective. It was demonstrated that people with benign PP-secreting tumors have elevated levels of the hormone and although chronically thin, show no other side effects. When the tumors are removed, the patients gain weight. However, PP isn't the perfect solution yet. Its appetite suppressing effects only last up to 24 hours so it currently needs to be administered daily. As pancreatic peptide is naturally occurring, a drug based on it could be used in people of all ages and also in cases of mild to moderate obesity.

TABLE 2: Examples of anti-obesity drugs currently in different phases of development:

Drug group	Principle action mechanism	Compounds		Development status
Drug name	Manufacturer			
Drugs acting centrally to affect appetite and energy regulation	Cannabinoid receptor CB1 antagonists	CP-954, 598	Pfizer	Phase II
5-HT 2C agonists	APD-356	Arena Pharmaceuticals Inc.	Phase IIb	
Amphetamine derivate (phentermine) and anticonvulsant (topiramate)	Qnexa (phentermine + topiramate)	Vivus	Phase II	
Dopamine and norepinephrine re-uptake inhibitor (bupropion) and opioid receptor antagonist (naltrexone)	Contrave (bupropion + naltrexone)	Orexigen	Phase II	
Synthetic form of the appetite suppressing hormone PYY (3-36)	PYY (3-36)	Nastech Pharmaceutical Co Inc.	Phase II	
Drugs acting peripherally to affect appetite	Y 2 and Y 4 agonist	TM30338	7TMPharma	Phase I/II
Delays gastric emptying	Pramlintide	Amylin Pharmaceuticals	Phase II	
Lipase inhibitor	ATL-962 (Cetilistat)	Alizyme	Phase III to begin this year	
Drugs blocking energy absorption	Human growth hormone fragment that promotes fat-burn	AOD-9604	Metabolic Pharmaceuticals Ltd.	Phase IIc