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Clinica Pediatrica
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Pharmacological treatment in adolescent obesity: how, when and why

OBESITA': anche un problema morale?

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850 milioni di persone nel mondo muoiono di fame

di cui 300 milioni di bambini

1 miliardo di persone in sovrappeso

di cui 320 milioni di bambini obesi

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Pharmacological treatment in adolescent obesity: how, when and **why**

National Estimated Cost of Obesity

Medical expenses accounted for percent of total medical expenditures

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A 2009 study by the Centers for Disease Control and Prevention found that the direct and indirect cost of obesity "is as high as $147 billion annually." The study was based on figures collected in 2006.

Another 2009 study in the journal Health Affairs concluded that the costs of hospitalizations related to childhood obesity rose from $125.9 million in 2001 to $237.6 million in 2005

National Estimated Cost of Obesity

Medical expenses accounted for percent of total medical expenditures

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In UE 2-8 %

Germany 8%
Spain 6%
Italy 4%

Pharmacological treatment in adolescent obesity: how, when and **why**

The report from the International Obesity Taskforce (IOTF) on worldwide prevalence rate shows that the pediatric obesity epidemic has spread globally.

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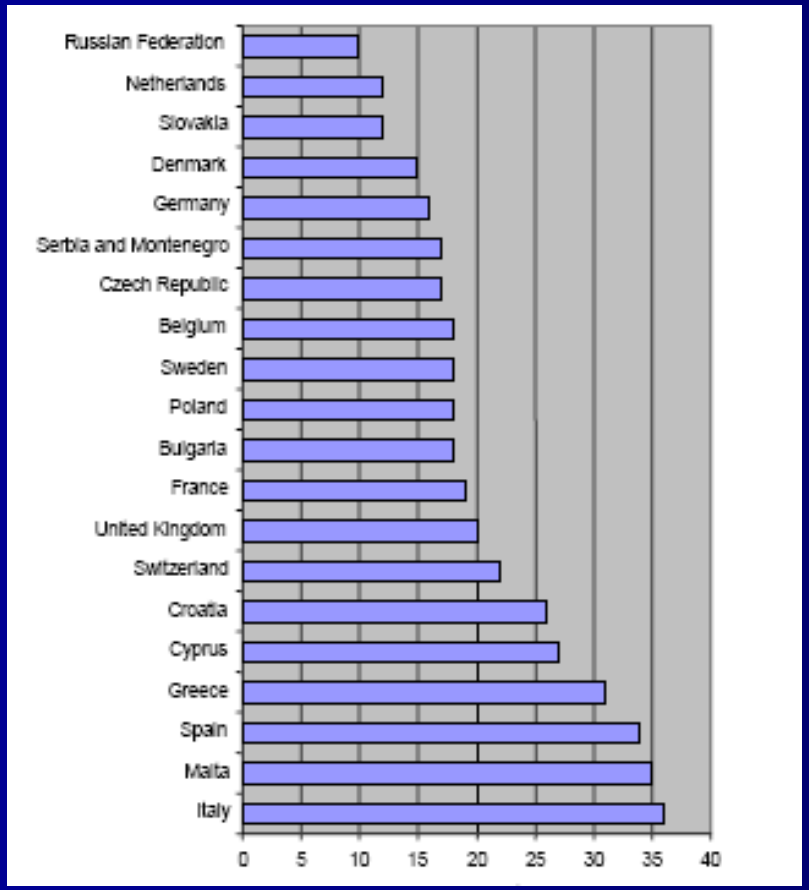
Prevalence of obesity in children 7-11 yr in the WHO European Region



Pharmacological treatment in adolescent obesity: how, when and **why**

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The conventional strategies are a reduction in energy intake, by dietary means and using conventional food items;

An increase in energy expenditure, by increasing physical activity and decreasing sedentary behaviours;

Published results of weight-management programs using conventional therapies show modest success in children and adolescents in the medium to long term;

Also the management with psychological involvement let the problem substantially Unsolved

Annals of Human Biology, July–August 2008; 35(4): 439–448

ORIGINAL ARTICLE

Thirty-year persistence of obesity after presentation to a pediatric obesity clinic

LORENZO IUGHETTI[1], MICHELE DE SIMONE[2], ALBERTO VERROTTI[3], MARIA LAURA IEZZI[2], BARBARA PREDIERI[1], PATRIZIA BRUZZI[1], SERGIO BERNASCONI[4], FIORELLA BALLI[1], & GIORGIO BEDOGNI[5]

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(*Received 11 January 2008; revised 29 April 2008; accepted 24 May 2008*)

Abstract

Background: Few large, long-term studies are available on the relationship between child adult obesity.

Aim: The present study examined the 30-year association between childhood and adult o large sample of girls with essential and uncomplicated obesity.

Subjects and methods: 318 girls who had visited our Pediatric Obesity Clinic between January December 1974 were re-contacted between January 2002 and December 2005. All had an assessment of weight, height and pubertal status at the baseline visit. Anthropo performed again on those who agreed to take part in the follow-up visit. The women practitioners were also asked to compile a health questionnaire. Hypertension, hypercholes hypertriglyceridemia and diabetes were defined according to current guidelines. Rates are ex number of cases per 1000 person-years (PY). Multivariable Poisson regression was used predictors of persistent obesity.

Results: 224 (70%) of the 318 girls took part to the 30-year follow-up study. They had the sam anthropometry of those not available at follow-up. Sixteen per cent of them were still ob 30-year follow-up, giving a persistence rate of obesity of 5.2 × 1000 PY. Tanner stages ≥1 [ra (RR) from 4.73 to 7.74 for different stages, $p \leq 0.021$] and *Z*-score of BMI (RR = 2.72 for $p = 0.019$) were independent predictors of obesity persistence. Having a university deg elementary degree was instead protective (RR = 0.32, $p = 0.009$). The most prevalent co was hypertriglyceridemia (8.8 × 1000 PY), followed by hypercholesterolemia (rate = 8.4 × 1000 PY), hypertension (rate = 5.2 × 1000 PY) and diabetes mellitus (rate = 1.0 × 1000 PY).

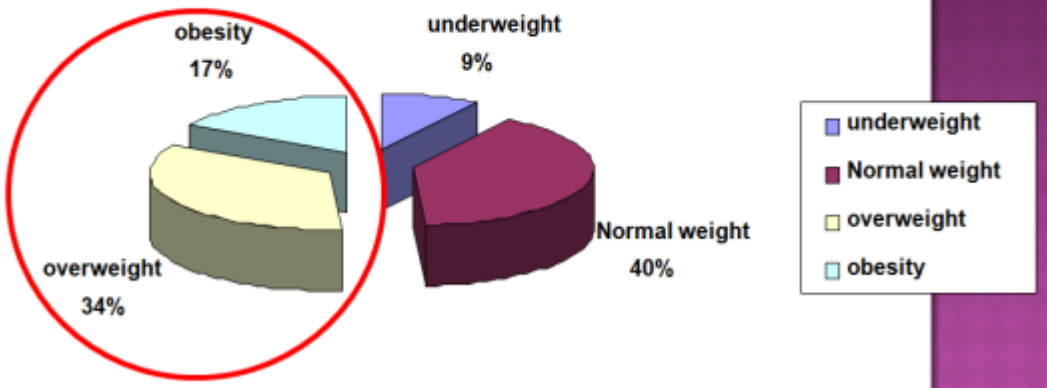
Conclusion: The study reinforces the notion that obesity should be prevented at an early age and shows that adolescents with severe obesity and low educational degree are at greater risk of becoming obese adults.

Keywords: *Childhood, obesity, incidence, body mass index, risk factors*

A 30-year history of overweight and obese female children in Italy: life-time overweight and adult morbidity

Iughetti L , De Simone M, Verrotti A, Iezzi ML

Annals Human Biology.35 (4), 439-448 **2008**



Pharmacological treatment in adolescent obesity: how, when and **why**

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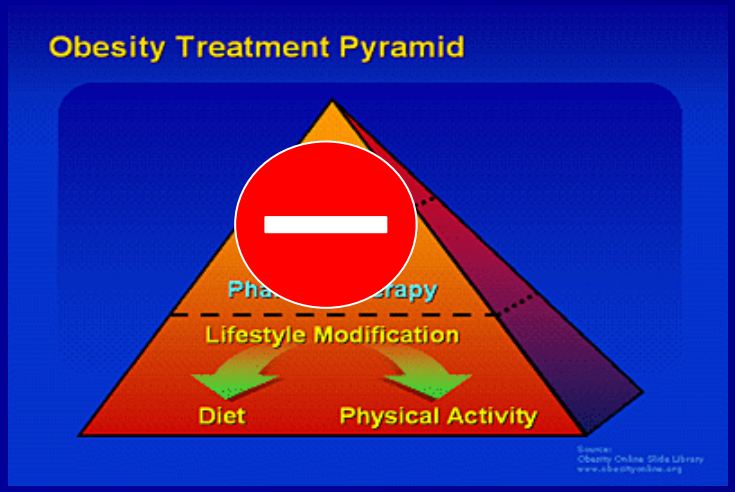
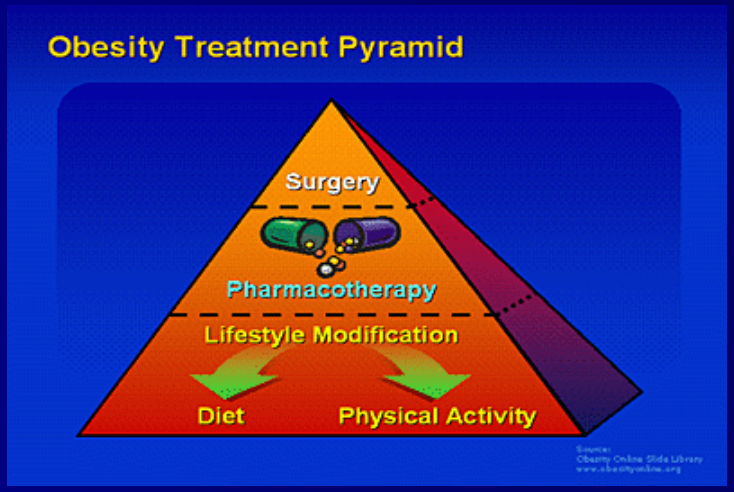
These considerations recently promoted an interest in pharmacological interventions





The utility of pharmacotherapy in adolescents has been reviewed

Pharmacotherapy of childhood obesity: an evidence-based,conceptual approach
Freemark M - *Diabetes Care 2007*

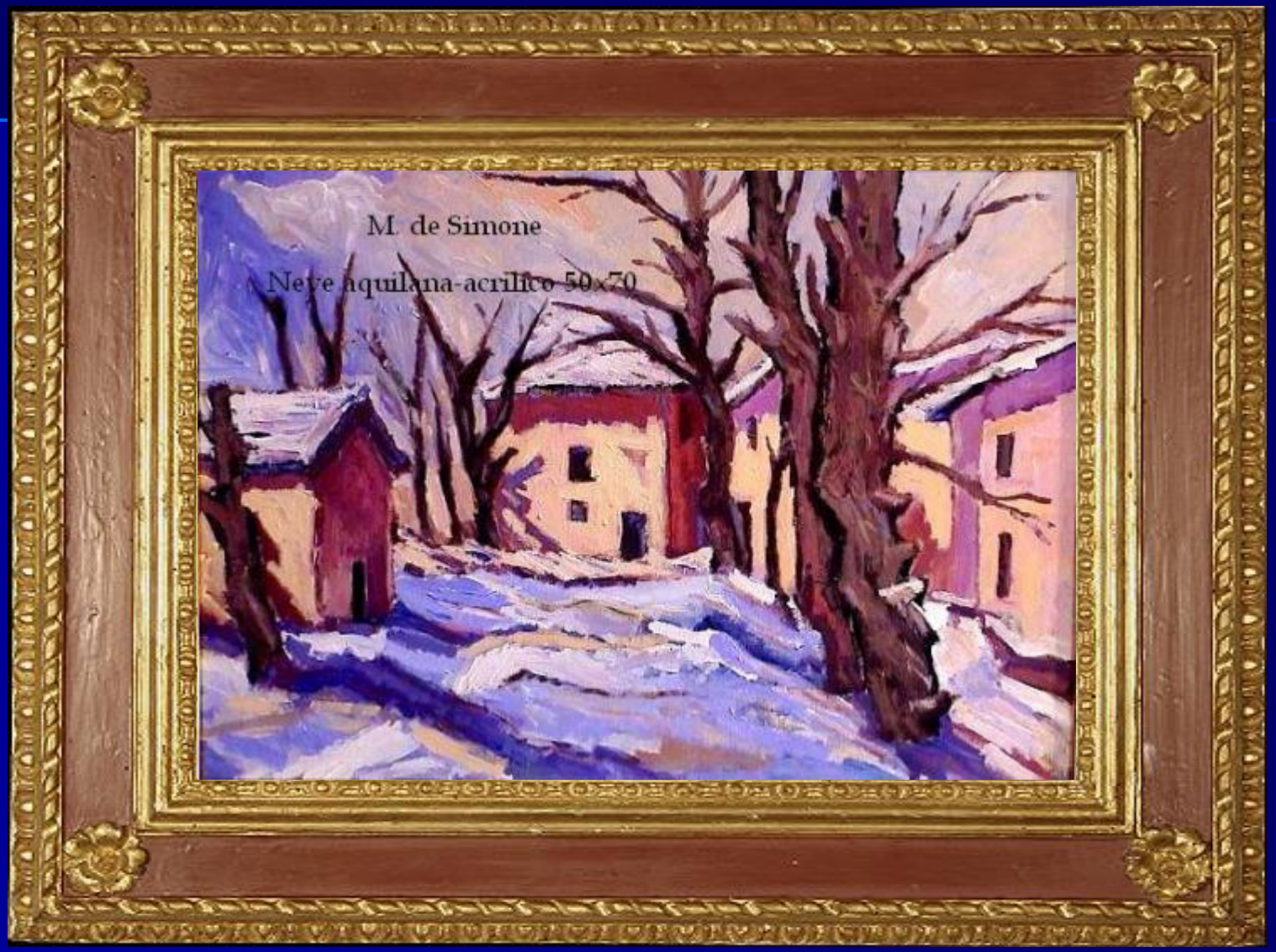
Pharmacotherapeutic options for overweight adolescents
Dunican KC et al - *Ann Pharmacother 2007*

Rise in antiobesity drug prescribing for children and adolescents in the UK: a population study
Russel M Viner et al - *BJCP 2009*

Pharmacotherapy and Weight-Loss Supplements for Treatment of Paediatric Obesity
A Rogovik et al – *Drug 2010*

Lifestyle modification and metformin as long-term treatment options for obese adolescents: study protocol
A Justine Wilson et al– *BMC Public Health 2011*

Pharmacological treatment in adolescent obesity: how, when and why



Pharmacological treatment in adolescent obesity: how, when and why

A recent guideline suggests considering pharmacotherapy in:

1. obese adolescent *(BMI above 40 kg/m^2)* only after failure of a formal program of intensive lifestyle modification;

2. obese or overweight adolescent only if severe comorbidities persist despite intensive lifestyle modification, particularly in subject with a strong family history for type 2 diabetes or premature cardiovascular disease.

3. Pharmacotherapy should be provided only by clinicians who are experienced in the use of antiobesity agents and aware of the potential for adverse reactions

G. P. August et al "Prevention and treatment of pediatric obesity: an endocrine society clinical practice guideline based on expert opinion," *JCEM, vol. 93, 12*, 2008.

SPECIAL FEATURE

Clinical Practice Guideline

Prevention and Treatment of Pediatric Obesity: An Endocrine Society Clinical Practice Guideline Based on Expert Opinion

Gilbert P. August, Sonia Caprio, Ilene Fennoy, Michael Freemark, Francine R. Kaufman, Robert H. Lustig, Janet H. Silverstein, Phyllis W. Speiser, Dennis M. Styne, and Victor M. Montori

Professor Emeritus of Pediatrics, George Washington University School of Medicine (G.P.A.), Washington, D.C. 20037; Yale University School of Medicine (S.C.), New Haven, Connecticut 06510; Columbia University (I.F.), New York, New York 10027; Duke University Medical Center (M.F.), Durham, North Carolina 27710; Children's Hospital of Los Angeles (F.R.K.), Los Angeles, California 90027; University of California San Francisco (R.H.L.), San Francisco, California 94143; University of Florida (J.H.S.), Gainesville, Florida 32611; Schneider Children's Hospital (P.W.S.), New Hyde Park, New York 11040; University of California–Davis Medical Center (D.M.S.), Sacramento, California 95817; and Mayo Clinic (V.M.M.), Rochester, Minnesota 55905

Objective: Our objective was to formulate practice guidelines for the treatment and prevention of pediatric obesity.

Conclusions: We recommend defining overweight as body mass index (BMI) in at least the 85th percentile but < the 95th percentile and obesity as BMI in at least the 95th percentile against routine endocrine studies unless the height velocity is attenuated or inappropriate for the family background or stage of puberty; referring patients to a geneticist if there is evidence of a genetic syndrome; evaluating for obesity-associated comorbidities in children with BMI in at least the 85th percentile; and prescribing and supporting intensive lifestyle (dietary, physical activity, and behavioral) modification as the prerequisite for any treatment.

We suggest that pharmacotherapy (in combination with lifestyle modification) be considered in: 1) obese children only after failure of a formal program of intensive lifestyle modification; and 2) overweight children only if severe comorbidities persist despite intensive lifestyle modification, particularly in children with a strong family history of type 2 diabetes or premature cardiovascular disease. Pharmacotherapy should be provided only by clinicians who are experienced in the use of antiobesity agents and aware of the potential for adverse reactions. We suggest bariatric surgery for adolescents with BMI above 50 kg/m^2, or BMI above 40 kg/m^2 with severe comorbidities in whom lifestyle modifications and/or pharmacotherapy have failed. Candidates for surgery and their families must be psychologically stable and capable of adhering to lifestyle modifications. Access to experienced surgeons and sophisticated multidisciplinary teams who assess the benefits and risks of surgery is obligatory.

We emphasize the prevention of obesity by recommending breast-feeding of infants for at least 6 months and advocating that schools provide for 60 min of moderate to vigorous daily exercise in all grades. We suggest that clinicians educate children and parents through anticipatory guidance about healthy dietary and activity habits, and we advocate for restricting the availability of unhealthy food choices in schools, policies to ban advertising unhealthy food choices to children, and community redesign to maximize opportunities for safe walking and bike riding to school, athletic activities, and neighborhood shopping. (*J Clin Endocrinol Metab* 93: 4576–4599, 2008)

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Abbreviations: ALT, Alanine aminotransferase; BMI, body mass index; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; IR, insulin resistance; LAGB, laparoscopic adjustable gastric banding; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary disease; RYGB, Roux-en-Y gastric bypass; T2DM, type 2 diabetes mellitus.

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Review Article

Pharmacological Treatment of Obesity in Children and Adolescents : Present and Future

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Academic Editor: A. Halpern

The prevalence of overweight and obesity is increasing in children and adolescents worldwide raising the question on the approach to this condition because of the potential morbidity, mortality, and economic tolls. Dietetic and behavioral treatments alone have only limited success; consequently, discussion on strategies for treating childhood and adolescent obesity has been promoted. Considering that our knowledge on the physiological systems regulating food intake and body weight is considerably increased, many studies have underlined the scientific and clinical relevance of potential treatments based on management of peripheral or central neuropeptides signals by drugs. In this paper we analyze the data on the currently approved obesity pharmacological treatment suggesting the new potential drugs.

1. Introduction

The report from the International Obesity Taskforce (IOTF) on worldwide prevalence rate shows that the pediatric obesity epidemic has spread globally. The worldwide prevalence of overweight in children and adolescents is approximately 10% with many western countries approaching 30%. In fact, some countries in economic transition have also prevalence rate increase higher than those in the United States (US) [1–3].

Because of the number of the subjects, obesity is now recognized as a healthcare issue on an epidemic scale in both adult and pediatric populations, but it yet remains an unsolved medical problem [4].

The successful management of obesity is theoretically possible through lifestyle changes including diet modifications [5] and increased physical activity. The literature analysis demonstrated, however, that significant results were obtained only in a limited number of subjects and for a relatively short time period: also the management with psychological involvement let the problem substantially unsolved. These considerations recently promoted an interest in pharmacological interventions and bariatric surgery [4].

The renewed interest for a pharmacological approach depends on the knowledge of physiological systems involved in the control of food intake and body weight that has considerably increased over the past decade. A powerful and complex physiological system, based on both afferent and efferent signals, regulating food intake and energy homeostasis, has been elucidated. This system consists of multiple pathways with redundancy signals that are transmitted by both blood and peripheral nerves, which are integrated in brain centres with subsequent regulation of central neuropeptides which in turn modulate feeding and energy expenditure. Appetite includes different aspects of eating patterns, such as frequency and size of eating, choice of high-fat or low-fat foods, energy density of consumed foods, variety of accepted foods, palatability of diet, and variability in day-to-day intake. Feeding behavior is controlled by a series of short-term hormonal, psychological, and neural signals. All signals act at several central nervous system (CNS) sites, but the pathways converge on the hypothalamus, a central region of feeding regulation, containing numerous peptides and neurotransmitters that influence food intake [6]. CNS also regulates energy homeostasis on the basis of peripheral signals from the gastrointestinal tract (GIT) and adipose tissue.

Pharmacological treatment in adolescent obesity: how, when and why

History of anti-obesity drugs

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La storia farmacologica del trattamento dell'obesità è costellata da una serie di fallimenti spesso drammatici

Alla fine dell'800 prodotti galenici, prodotti da banco a base di iodio o di derivati tiroidei furono utilizzati

Negli anni '30 l'impiego del Dinitrofenolo produsse gravi neuropatie e comparsa di cataratta

Dal 1937 in poi l'Amfetamina fu ampiamente utilizzata con effetti di grave dipendenza

Nel 1997 ritiro dal commercio della Flenfuramina/Fentermina per gravi valvulopatie cardiache ed ipertensione polmonare

Ne conseguì, quindi, sempre maggiore sconcerto nei riguardi della terapia farmacologica

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- Drugs Affecting Central Mechanisms
- Drugs Affecting Peripheral Mechanisms

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Table 1: Neurotransmitters influencing appetite.

Neurotransmitters that increase food intake	Neurotransmitters that decrease food intake
Agouti-related peptide	Alpha melanocyte-stimulating hormone
Neuropeptide Y	Bombesin-/gastrin-releasing peptide
Melanin-concentrating hormone	Calcitonin gene-related peptide
Orexin	Cholecystokinin
Galanin	Corticotrophin-releasing factor
Ghrelin	Dopamine
Nitric oxide	GABA
Noradrenaline	Glucagon
Opioids (particularly μ and κ agonists)	Glucagon-like peptide 1 (7–36) amide
	Neurotensin
	Serotonin

Table 2: Selected GI, pancreatic, and adipose tissue peptides that regulate food intake.

Peptide	Main site of synthesis	Receptors mediating feeding effects	Effect on food intake
CCK	Proximal intestinal I cells	CCK1R	inhibition
GLP-1	Distal intestinal L cells	GLP-1R	inhibition
Oxyntomodulin	Distal intestinal L cells	GLP-1R and others	inhibition
PYY	Distal intestinal L cells	Y2R	inhibition
Enterostatin	Exocrine pancreas	F1-ATPase beta subunit	inhibition
APO AIV	Intestinal epithelial cells	Unknown	inhibition
PP	Pancreatic F cells	Y4R, Y5R	inhibition
Amylin	Pancreatic beta cells	CTRS, RAMPS	inhibition
GRP and NMB	Gastric myenteric neurons	GRPR	inhibition
Gastric leptin	Gastric chief and P cells	Leptin receptor	inhibition
Ghrelin	Gastric x/a-like cells	Ghrelin receptor	stimulation
Insulin	Pancreatic beta cells	Insulin receptor	inhibition
Leptin	Adipocytes	Leptin receptor	inhibition
Adiponectin	Adipocytes	Adiponectin receptor	inhibition

CTRs: calcitonin receptors; RAMPs: receptor activity-modifying proteins; GRP: gastrin-releasing peptide; NMB: neuromedin B; GRPR: GRP receptor.

Pharmacological treatment in adolescent obesity: how, when and why

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Up to now, only three drugs have been reported to reduce weight and/or BMI in adolescents :

Drugs	Pharmacological Actions	Mechanisms of action	Adverse events
SIBUTRAMINE	Inhibitor of the reuptake of serotonin	Anorectic Antidepressant	Cardiovascular events
ORLISTAT	Pancreatic lipase inhibitor	reduce fat absorption	GI events
METFORMIN	Contrasts insulin resistance	increases insulin sensitivity	GI events

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Table III. Clinical trials of sibutramine in children

Study	No. of pts	Duration (mo)	Dosage	Type of trial	BMI change
Berkowitz et al., 2003[29]	82	12	5–15 mg/d	Randomized, double-blind, placebo-controlled (first 6 mo), then open-label treatment	–1.7 kg/m² (vs placebo at 6 mo)
Berkowitz et al., 2006[30]	498	12	10–15 mg/d	Randomized, double-blind, placebo-controlled	–3.0 kg/m² (vs placebo)
Godoy-Matos et al., 2005[31]	60	6	10 mg/d	Randomized, double-blind, placebo-controlled	–2.7 kg/m² (vs placebo)
Violante-Ortiz et al., 2005[32]	67	6	10 mg/d	Single group	–3.6 kg/m² (vs baseline)
Garcia-Morales et al., 2006[33]	46	6	10 mg/d	Randomized, double-blind, placebo-controlled	–1.2 kg/m² (vs placebo)
Reisler et al., 2006[34]	20	12	10 mg/d	Single group, most dropped out after 6 mo	–4.1 kg/m² (vs baseline at 6 mo)

BMI = body mass index.

Table I. Clinical trials of orlistat in children

Study	No. of pts	Duration (mo)	Dosage	Type of trial	BMI change
McDuffie et al., 2004[18]	20	6	120 mg tid	Single group	–2.0 kg/m² (vs baseline)
Norgren et al., 2003[19]	11	3	120 mg tid–qid	Single group	–1.9 kg/m² (vs baseline)
Ozkan et al., 2004[20]	42	5–15	120 mg tid	Randomized, open-label, controlled	–4.2 kg/m² (vs control)
Chanoine et al., 2005[21]	539	12	120 mg tid	Randomized, double-blind, placebo-controlled	–0.9 kg/m² (vs placebo)
Maahs et al., 2006[22]	40	6	120 mg tid	Randomized, double-blind, placebo-controlled	–0.5 kg/m² (vs placebo, non-significant)

BMI = body mass index; **qid** = four times daily; **tid** = three times daily.

Table II. Clinical trials of metformin in children

Study	No. of pts	Duration (mo)	Dosage	Type of trial	BMI change
Kay et al., 2001[23]	24	2	850 mg bid	Randomized, double-blind, placebo-controlled	Weight change –2.7 kg (vs placebo)
Srinivasan et al., 2006[24]	28	6	1 g bid	Randomized, double-blind, placebo-controlled	–1.3 kg/m² (vs placebo)
Fu et al., 2007[25]	30	3	500 mg bid	Non-randomized, open-label	–3.2 kg/m² (vs baseline)
Klein et al., 2006[26]	39	4	850 mg bid	Randomized, double-blind, placebo-controlled	–1.1 kg/m² (vs placebo)
Atabek and Pirgon, 2008[27]	120	6	500 mg bid	Randomized, double-blind, placebo-controlled	–1.8 kg/m² (vs placebo)
Love-Osborne et al., 2008[28]	85	6	500 mg qid–850 mg bid	Randomized, double-blind, placebo-controlled	–0.8 kg/m² (vs placebo)

bid = twice daily; **BMI** = body mass index; **qid** = four times daily.

Sibutramine

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Neurotransmitter reuptake inhibitor which
enhances satiety by inhibiting the reuptake of serotonin,
norepinephrine and dopamine

not FDA-approved for <16 yr of age

Diabetes Care
Vol 28,4 2005

Effect of sibutramine on weight management and metabolic control in Type 2 Diabetes: A meta-analysis of clinical studies

R. Vettor et al

M. de Simone

A total of 1,093 obese patients with type 2 diabetes (552 treated with sibutramine and 541 treated with Placebo were analyzed

Individualised management programme achieved weight loss in 77% of obese patients and sustained weight loss in most

Patients had substantial decreases over the first 6 months with respect to *triglycerides, VLDL cholesterol, insulin, C peptide, and uric acid*; these changes were sustained in the sibutramine group but not the placebo group. *HDL cholesterol concentrations rose substantially* in the second year patients continuing therapy for 2 years.

Pharmacotherapy and Weight-Loss Supplements for Treatment of Paediatric Obesity
Drugs: 2010, 70 (3)

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Table III. Clinical trials of sibutramine in children

Study	No. of pts	Duration (mo)	Dosage	Type of trial	BMI change
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BMI = body mass index.

Sibutramine

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Adverse events

Tachycardia, hypertension, palpitations,
insomnia, anxiety, nervousness,
depression

SIBUTRAMINA

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AIFA Agenzia Italiana del Farmaco

Nota Informativa Importante sui medicinali a base di Sibutramina del 19/01/2010

Sicurezza

19/01/2010

Si comunica la sospensione dell'autorizzazione all'immissione in commercio nell'Unione Europea (EU) dei medicinali contenenti sibutramina. I medicinali a base di sibutramina sono indicati come terapia integrativa nell'ambito di un programma di gestione del peso corporeo per il trattamento dell'obesità.

Sulla base dei risultati dello studio "Sibutramine Cardiovascular OUTcomes" (SCOUT), il Comitato per i Medicinali per uso Umano (CHMP) dell'Agenzia Europea dei Medicinali ha concluso che il profilo rischio/beneficio di sibutramina non può più considerarsi favorevole.

ORLISTAT

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It is approved since 1998 for weight management in overweight and obese adults in more than 120 countries, and to date more than 22 million patients have received this Drug

FDA in December 2003 approved Orlistat use in adolescents aged 12 to 18 years old with a BMI (kg/m2) *> 2 units* above the reference value at the 95th percentile for age and gender

ORLISTAT

M. de Simone

Inhibitor of pancreatic lipase reducing dietary fat absorption. The compound is a partially hydrated derivative of an endogenous lipstatin produced by *Streptomyces toxytricini*

Orlistat binds irreversibly to the active sites of lipase through covalent binding. Approximately one-third of triglyceride intakes does not undergo digestion and is not absorbed by small intestine, crossing the GI tract and being eliminated.

ORLISTAT

M. de Simone

In adults, orlistat has a good safety profile, is generally well tolerated, has minimal systemic absorption, and determines clinically meaningful and sustained decreases in weight and BMI when combined with a mildly hypocaloric diet and exercise.

Adverse events

Borborygmi, flatus, abdominal cramps,
fecal incontinence, oily spotting,
vitamin malabsorption

Pharmacotherapy and Weight-Loss Supplements for Treatment of Paediatric Obesity
Drugs: 2010, 70 (3)

M. de Simone

Table I. Clinical trials of orlistat in children

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BMI = body mass index; **qid** = four times daily; **tid** = three times daily.

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Effect of Orlistat on Weight and Body Composition in Obese Adolescents

A Randomized Controlled Trial

Jean-Pierre Chanoine, MD, PhD
Sarah Hampl, MD, FAAP
Craig Jensen, MD
Mark Boldrin, MS
Jonathan Hauptman, MD

Context The prevalence of overweight and obesity in children and adolescents is increasing rapidly. In this population, behavioral therapy alone has had limited success in providing meaningful, sustained weight reduction, and pharmacological treatment has not been extensively studied.

Objective To determine the efficacy and safety of orlistat in weight management of adolescents.

Design, Setting, and Patients Multicenter, 54-week (August 2000-October 2002), randomized, double-blind study of 539 obese adolescents (aged 12-16 years; body mass index [BMI] ≥2 units above the 95th percentile) at 32 centers in the United States and Canada.

Interventions A 120-mg dose of orlistat (n=357) or placebo (n=182) 3 times daily for 1 year, plus a mildly hypocaloric diet (30% fat calories), exercise, and behavioral therapy.

Main Outcome Measures Change in BMI; secondary measures included changes in waist and hip circumference, weight loss, lipid measurements, and glucose and insulin responses to oral glucose challenge.

Results There was a decrease in BMI in both treatment groups up to week 12, thereafter stabilizing with orlistat but increasing beyond baseline with placebo. At the end of the study, BMI had decreased by 0.55 with orlistat but increased by 0.31 with placebo (P=.001). Compared with 15.7% of the placebo group, 26.5% of participants taking orlistat had a 5% or higher decrease in BMI (P=.005); 4.5% and 13.3%, respectively, had a 10% or higher decrease in BMI (P=.002). At study end, weight had increased 0.53 kg with orlistat and 3.14 kg with placebo (P<.001). Dual-energy x-ray absorptiometry showed that this difference was explained by changes in fat mass. Waist circumference decreased in the orlistat group but increased in the placebo group (–1.33 cm vs +0.12 cm; P<.05). Generally mild to moderate gastrointestinal tract adverse events occurred in 9% to 50% of the orlistat group and in 1% to 13% of the placebo group.

Conclusions In combination with diet, exercise, and behavioral modification, orlistat statistically significantly improved weight management in obese adolescents compared with placebo. The use of orlistat for 1 year in this adolescent population did not raise major safety issues although gastrointestinal adverse events were more common in the orlistat group.

JAMA. 2005;293:2873-2883 www.jama.com

THE PREVALENCE OF OVERweight in adolescents is increasing worldwide. In the United States, the proportion of adolescents with a body mass index (BMI) at or above the 95th percentile for age, a widely accepted definition of obesity in adolescents,[1,2] has increased 15.5% to 23.4% in certain ethnic minorities.[3] A similar picture is seen in European countries: the prevalence of overweight in adolescents has increased 8% to 21% in northern European countries and 17% to 23% in southern European countries.[4]

Excess weight in adolescents is associated with an increased risk of disorders such as hyperlipidemia and type 2 diabetes[5] and can result in decreased emotional and physical quality of life.[6,7] In addition, childhood obesity results in increased risk of morbidity and mortality in adulthood.[8,9] Long-term follow-up studies of children and adolescents indicate that overweight children have a 15-fold greater risk of becoming overweight adults compared with those children and adolescents who were not overweight.[8] Effective weight management in children and adolescents may therefore have important immediate and future societal health benefits.

Treatment of obesity in the pediatric age group, and in particular during adolescence,[10] is notoriously difficult. While behavioral therapy has had some success in treating obesity in young children (aged 6-12 years), most stud-

For editorial comment see p 2932.

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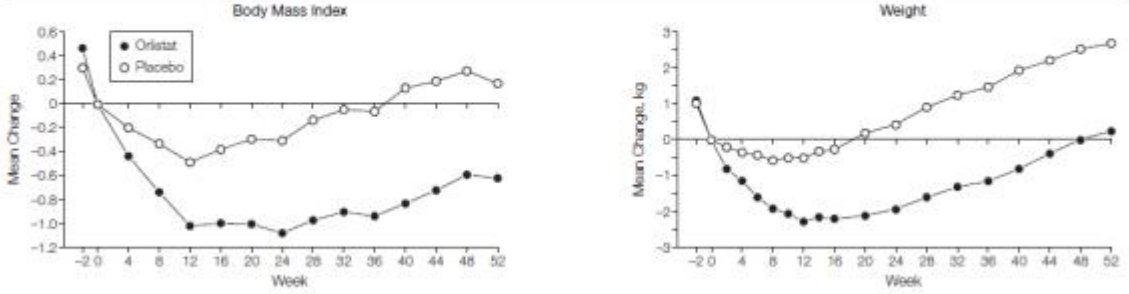
Figure 2. Change in Mean Body Mass Index and Weight



P = .001 for body mass index (orlistat vs placebo). *P*<.001 for weight change (orlistat vs placebo). Body Mass Index is calculated as weight in kilograms divided by the square of height in meters. Coefficient of variation is about 14% for each data point for body mass index and about 16% for weight.

Table 4. Secondary Efficacy End Points

	Placebo		Orlistat		
	LSM Change vs Baseline	No. of Participants (n = 181)	LSM Change vs Baseline	No. of Participants (n = 352)	*P* Value
Circumference, cm					
Waist	−0.89	178	−2.67	347	.01
Hip	−0.10	178	−1.52	347	.01
Blood pressure, mm Hg					
Diastolic	+1.30	180	−0.51	347	.04
Systolic	+1.31	180	+1.09	347	.84
Cholesterol, mg/dL					
Total	+3.39	163	+2.26	323	.59
HDL	−0.31	163	+0.07	323	.62
LDL	+0.88	162	−0.99	322	.29
Ratio of LDL to HDL	+0.04	162	−0.07	322	.08
Triglycerides, mg/dL	+11.68	163	+17.90	323	.30
Insulin, μIU/mL					
At 0 min	−5.4	132	−2.8	271	.41
At 120 min	−20.6	133	−25.7	276	.44
Glucose, mg/dL					
Fasting at 0 min	−5.24	136	−2.40	282	.06
At 120 min	−10.11	136	−11.20	283	.68

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; LSM, least squares mean.

Effect of Orlistat on Weight and Body Composition in Obese Adolescents

A Randomized Controlled Trial

M. de Simone

Table 5. Participants With Gastrointestinal Tract Adverse Events

Gastrointestinal Tract Adverse Event	No. (%) of Participants Taking Placebo (n = 181)			No. (%) of Participants Taking Orlistat (n = 352)		
	Total With Adverse Event	1 Adverse Event	>1 Adverse Event	Total With Adverse Event	1 Adverse Event	>1 Adverse Event
Fatty/oily stool	15 (8.3)	10 (5.5)	5 (2.8)	177 (50.3)	122 (34.7)	55 (15.6)
Oily spotting	7 (3.9)	5 (2.8)	2 (1.1)	102 (29.0)	72 (20.5)	30 (8.5)
Oily evacuation	3 (1.7)	1 (0.6)	2 (1.1)	82 (23.3)	51 (14.5)	31 (8.8)
Abdominal pain	20 (11.0)	14 (7.7)	6 (3.3)	77 (21.9)	54 (15.3)	23 (6.5)
Fecal urgency	20 (11.0)	11 (6.1)	9 (5.0)	73 (20.7)	48 (13.6)	25 (7.1)
Flatus with discharge	5 (2.8)	4 (2.2)	1 (0.6)	70 (19.9)	48 (13.6)	22 (6.3)
Soft stool	19 (10.5)	17 (9.4)	2 (1.1)	53 (15.1)	47 (13.4)	6 (1.7)
Nausea	23 (12.7)	20 (11.0)	3 (1.7)	52 (14.8)	48 (13.6)	4 (1.1)
Increased defecation	16 (8.8)	16 (8.8)	0	48 (13.6)	42 (11.9)	6 (1.7)
Flatulence	8 (4.4)	4 (2.2)	4 (2.2)	32 (9.1)	29 (8.2)	3 (0.8)
Fecal incontinence	1 (0.6)	1 (0.6)	0	31 (8.8)	24 (6.8)	7 (2.0)

METFORMIN

is currently being used in more than 90 countries worldwide.

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The potential clinical application of metformin in the pediatric population was first described in a small published study in 8–14-year-old obese Children

(A. Lutjens et al " *Helvetica Paediatrica Acta*" 1976)

Not FDA approved for the treatment of obesity
Approved for Diabetes >10 yr

METFORMIN

is currently being used in more than 90 countries worldwide.

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- Inhibition of hepatic gluconeogenesis
- increased insulin-mediated glucose disposal
- Inhibition of fatty acid oxidation
- Reduction of intestinal glucose absorption

The exact mechanism of intracellular action of metformin remains uncertain

METFORMIN

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Metformin therapy for insulin resistance and obesity is safe and well tolerated and has a beneficial effect on weight, BMI, waist circumference, abdominal fat, fasting insulin, and fasting glucose

According to recent studies, the major effect of metformin may be a powerful inhibition of appetite

Because the major component of metabolic syndrome is weight excess, by contrasting it, this drug can also be able to prevent most of its consequences on health.

Pharmacotherapy and Weight-Loss Supplements for Treatment of Paediatric Obesity
Drugs: 2010, 70 (3)

M. de Simone

Table II. Clinical trials of metformin in children

Study	No. of pts	Duration (mo)	Dosage	Type of trial	BMI change
Kay et al., 2001[23]	24	2	850 mg bid	Randomized, double-blind, placebo-controlled	Weight change –2.7 kg (vs placebo)
Srinivasan et al., 2006[24]	28	6	1 g bid	Randomized, double-blind, placebo-controlled	–1.3 kg/m^2 (vs placebo)
Fu et al., 2007[25]	30	3	500 mg bid	Non-randomized, open-label	–3.2 kg/m^2 (vs baseline)
Klein et al., 2006[26]	39	4	850 mg bid	Randomized, double-blind, placebo-controlled	–1.1 kg/m^2 (vs placebo)
Atabek and Pirgon, 2008[27]	120	6	500 mg bid	Randomized, double-blind, placebo-controlled	–1.8 kg/m^2 (vs placebo)
Love-Osborne et al., 2008[28]	85	6	500 mg qid–850 mg bid	Randomized, double-blind, placebo-controlled	–0.8 kg/m^2 (vs placebo)

bid = twice daily; **BMI** = body mass index; **qid** = four times daily.

Effects of Metformin on Body Weight and Body Composition in Obese Insulin-resistant Children: A Randomized Clinical Trial

Jack A. Yanovski; Jonathan Krakoff; Christine G. Salaita; Jennifer R. McDuffie; Merel Kozlosky; Nancy G. Sebring; James C. Reynolds; Sheila M. Brady; Karim A. Calis

Authors and Disclosures

Posted: 02/09/2011; Diabetes. 2011;60(2):477-485.

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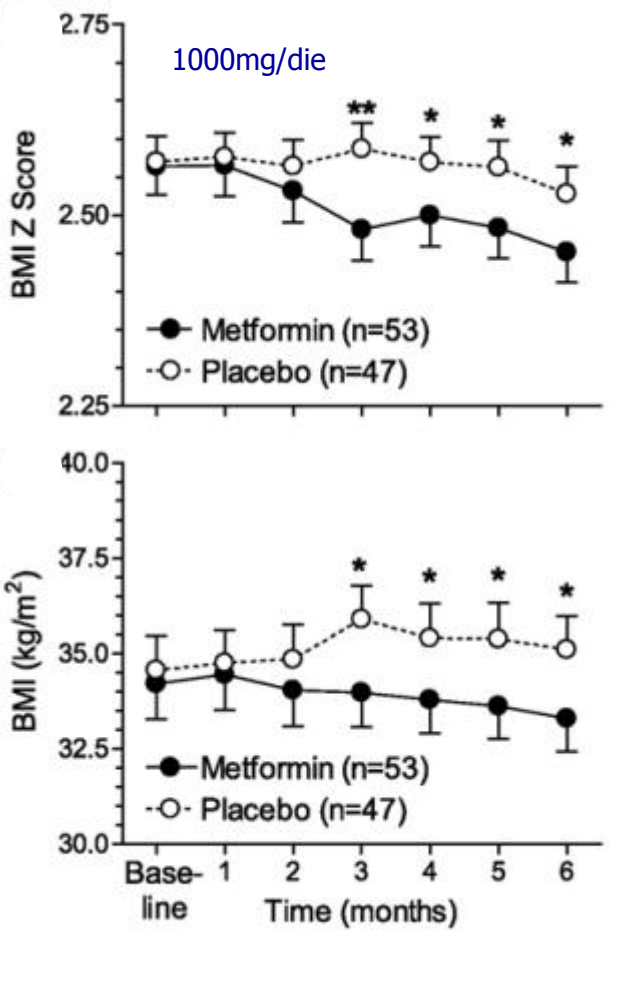
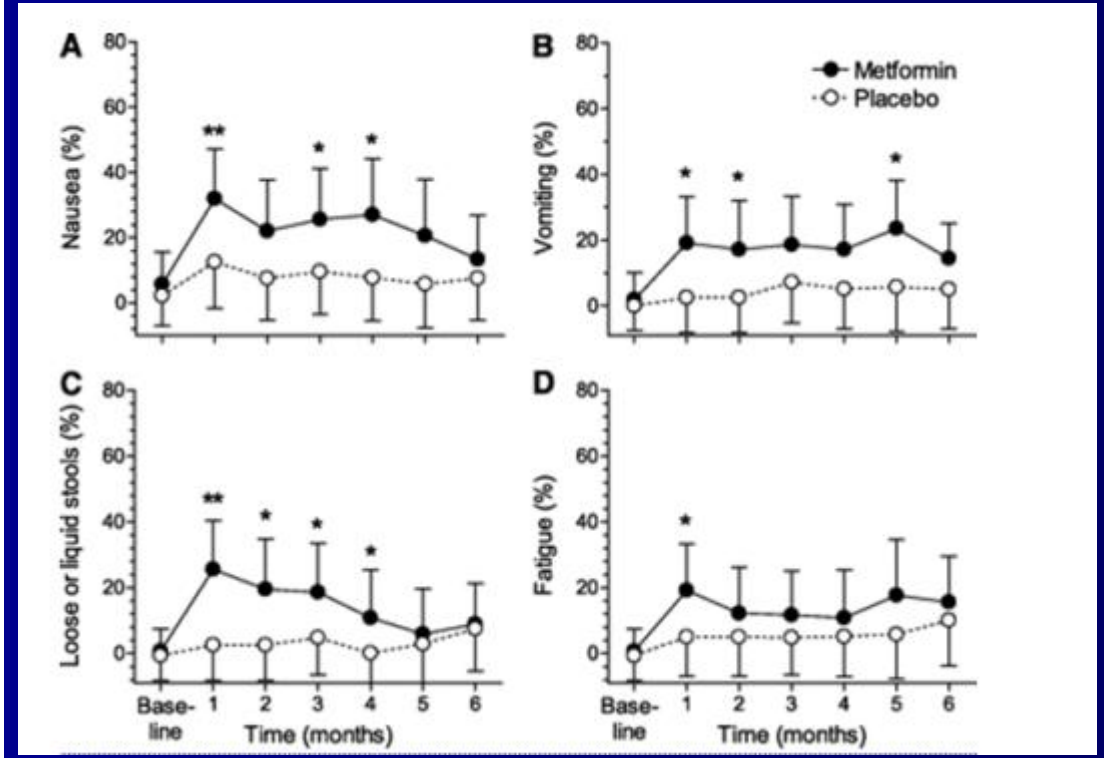
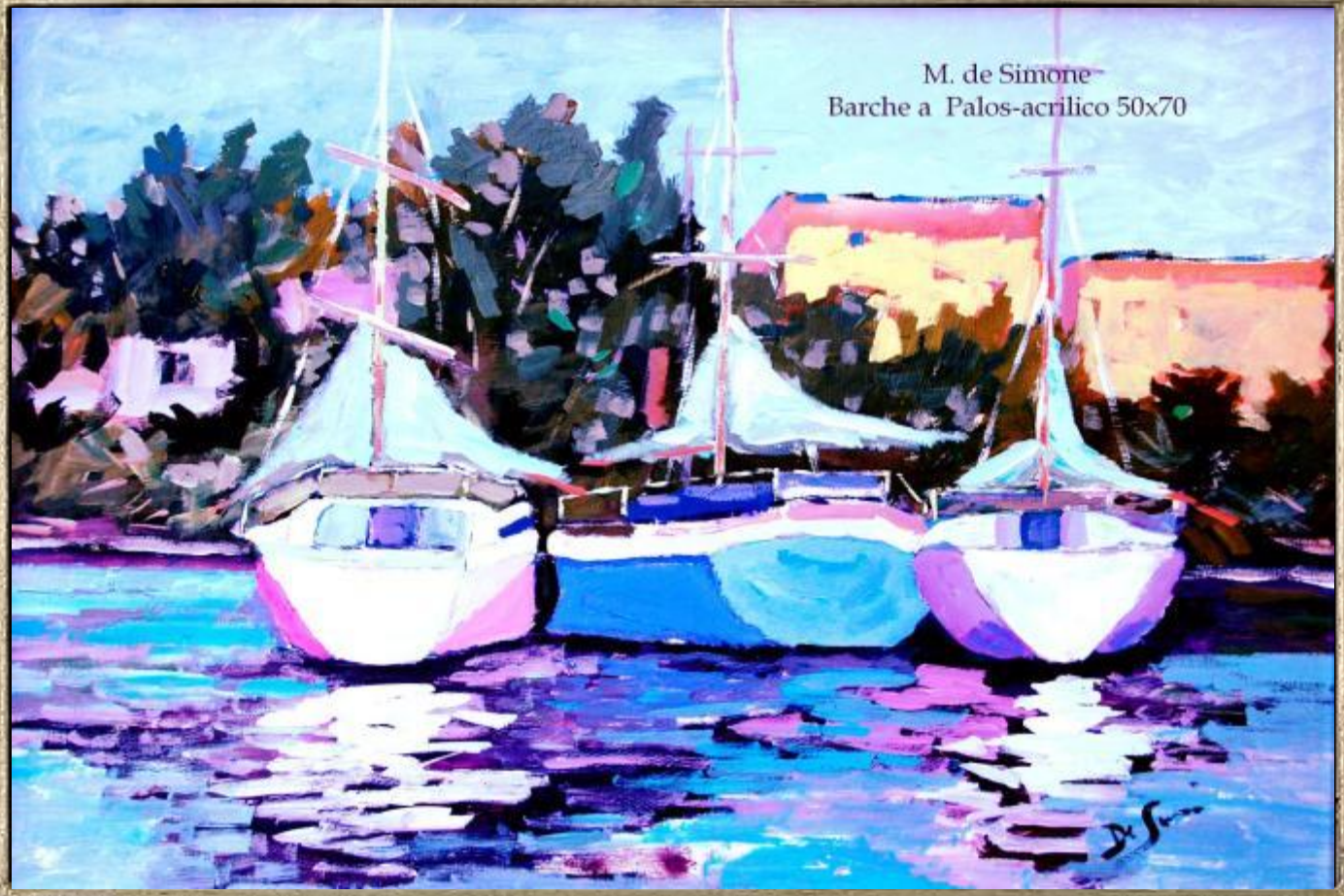




Current Available Drugs



Peripheral Mechanisms

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	Pharmacological Actions	Mechanisms of action	Adverse events
Pramlintide	soluble synthetic analogue of amylin	anorectic effects	headache ,dizziness injection site events and nausea
Cetilistat (ATL-962)	novel gastrointestinal lipase inhibitor	reduce fat and cholesterol absorption	flatus with discharge and oily spotting
Exendin-4, Liraglutide	agonist of the glucagone like peptide 1 (GLP-1)	stimulation of insulin secretion	nausea

Pramlintide

Pramlintide (Pro25, Pro28, Pro29-amylin), is approved in US as an adjunct to insulin for subcutaneous use in patients with type 1 or type 2 diabetes who are not able to achieve glucose control through optimal insulin therapy.

reduction in body weight and BMI
Hemoglobin glycosylated levels

*R*eviews Drug Discovery, *Nature* 2006.

Pramlintide

Recently, an association with metreleptin *(leptin agonist)* showed interesting results (Pramlintide/Metreleptin (360 g/5 mg b.i.d.)

The greater reduction in body weight was significant as early as week 4, and weight loss continued throughout the study, without evidence of a plateau.

E. Ravussin, et al - *Obesity* 2009

Cetilistat (ATL-962)

Reduce fat and cholesterol absorption

Adverse events were generally mild
to moderate in intensity(flatus with discharge and oily spotting).

M. Hallschmid et al JCEM 2009

Exendin-4

Exendin-4 (exenatide) is a natural agonist of the glucagone like peptide 1(GLP-1) receptor isolated from the lizard *Heloderma suspectum*

has longer biological activity than GLP-1

stimulation of insulin secretion

It was recently
approved for the treatment of type 2 diabetes

Twice daily subcutaneous administration of exenatide in patients with type 2 diabetes led to a dose-dependent weight loss of 1.8 $\pm$ 0.3 kg over 28 days, 2.8 $\pm$ 0.5 kg over 30 weeks, and 4.7 $\pm$ 0.3 kg over 2 years

D. P. Bradley et al, *Nutrition* 2010

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Central Mechanisms

	Pharmacological Actions	Mechanisms of action	Adverse events
Topiramato, Zonisamide (JCEM 2004)	antiepileptic inhibiting the reuptake of 5HT,norepinephrine, and dopamine	anorectic weight loss	paresthesias, somnolence, and difficulty with memory
Bupropione (Ann Intern Med 2005)	antidepressant inhibiting the reuptake of 5HT and dopamine	anorectic weight loss	insomnia
Rimonabant (Acomplia) * Taranabant	Endocannabinoid Receptor Blockers (CB1) smoking cessation	anorectic >thermogenesis	psychiatric effects
AOD9604 AOD 9401	specific metabolic domain responsible for the lipolytic/antilipogenic activity of the hGH	lipolytic/antilipogenic activity	in obese rats

* NOTA INFORMATIVA AIFA
31 Ottobre 2008
I Medici non devono effettuare o rinnovare alcuna prescrizione di ACOMPLIA.

CONCLUSIONS

CONCLUSIONS

Childhood obesity is not only a cosmetic problem. Many adverse health effects associated with adult obesity are already being seen in obese adolescents in which a significant increase in the cardiovascular risk has been observed, probably due to obesity-metabolic disarrangement, but also other co-morbidities such as nonalcoholic fatty liver disease, idiopathic intracranial hypertension, sleep apnea, and orthopedic abnormalities.

CONCLUSIONS

Pharmacotherapy as a strategy for managing overweight, obese and extremely obese adolescents remains controversial.

Although newer drugs are years away from clinical use, the hope for research Investmentsmade to date is translation into safe and effective anti-obesity drugs in the future. The search for novel drug treatments for obesity in childhood and adolescents is, therefore, both legitimate and necessary.


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