TERAPIA FARMACOLOGICA DELL'OBESITA'

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OBIETTIVI DELLA TERAPIA DELL'OBESITA' (OMS)

- Prevenzione dell'aumento di peso
- Il mantenimento del peso idoneo
- Gestione delle comorbilità
  - riduzione dell'insorgenza
  - riduzione dei rischi associati
- Definizione del target ponderale primario

OBESITY:INCREASED MORBIDITY MORTALITY

- Coronary heart disease
- Hypertension
- Diabetes Mellitus
- Hyperlipidaemia
- Perhipheral vascular disease
- Hyperuricemia
- Gallstones , kidney stones
- Sleep apnoea (hypoventilation)
- Musculoskeletal disorders
- Hormone related malignancies
- Menstrual /sexual/reproductive problems
- Venous stasis
- Anaesthesia and surgery

International weight loss mortality risk in never-smoking US white women aged 40-64 years

- 15,069 women (BMI > 27 kg/m^2) with obesity and co-morbid conditions (CHD, hypertension, stroke, diabetes, cancer, or cirrhosis)
- Intentional weight loss of any amount was associated with:
  - 20% reduction in all-cause mortality
  - 30 - 40% reduction in diabetes-associated mortality
  - 40 - 50% reduction in mortality from obesity-related cancer

Williamson et al, *Am J Epidemiol,* 1995

Weight Cycling Syndrome e malattie cardiovascolari

Studi	End Point	Associazione	Significatività
Goteborg Prospective Study	CHD	++	P=0.02
Western Electrical Study	CHD (exitus)	+ in cyclers	P<0,05
MRFIT	CVD		
-Tutti	Exitus	+++	P=0.001
-Non fumatori			
-Fumatori		+++	P=0,001
Framingham Heart Study			
-Uomini	CHD	++++	P<0,0001
	CHD Exitus	++++	P<0,0001
-Donne	CHD	++	P<0,05
	CHD exitus	+++	P<0,005

OBIETTIVI DELLA TERAPIA DELL'OBESITA'

RIDUZIONE DEL PESO CORPOREO

↓

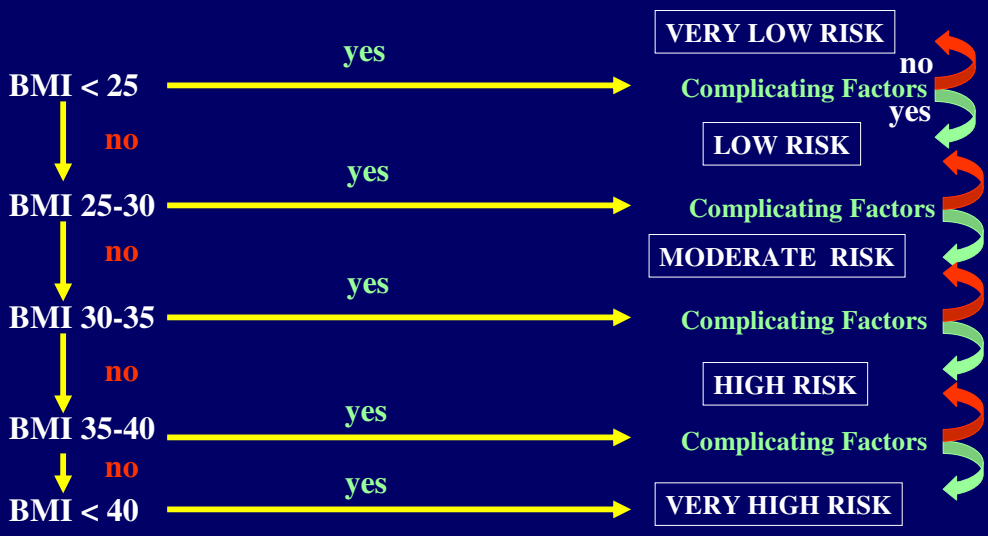
MIGLIORAMENTO DEI FATTORI DI RISCHIO

↓

MIGLIORAMENTO DEGLI "HARD OUTCOMES"
(INFARTO MIOCARDICO, ICTUS, MORTALITA' COMPLESSIVA, ….)

L'analisi decisionale del trattamento

ALGORITHMS FOR TREATMENT DECISION

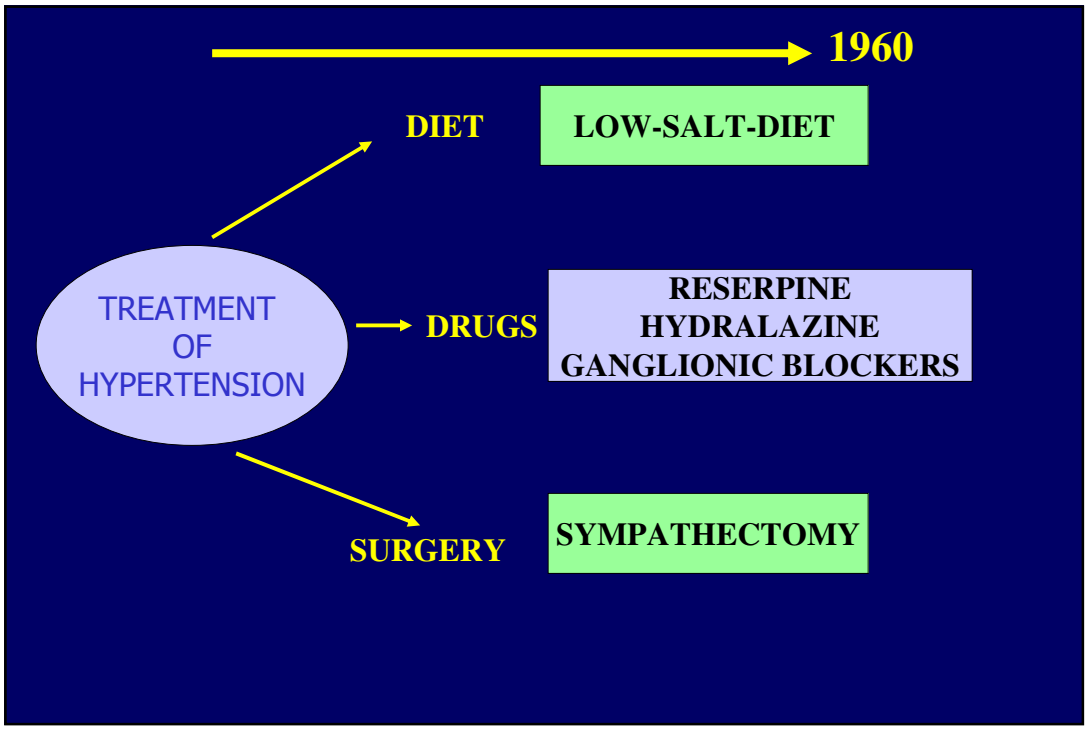


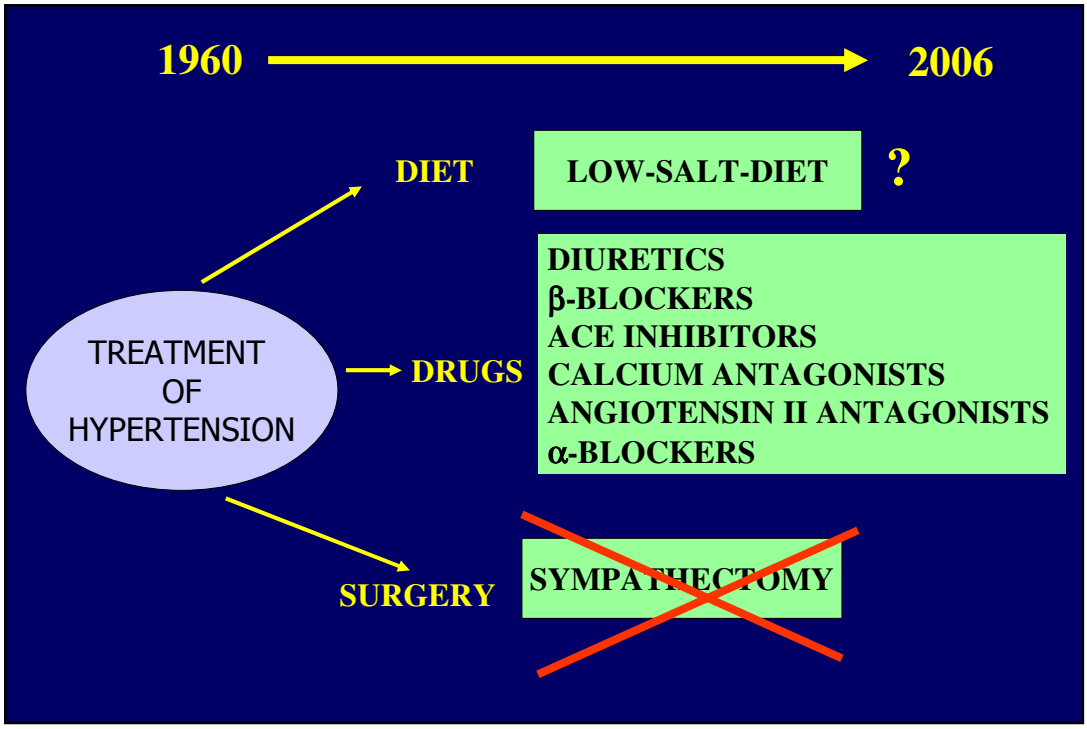
ATP III: The Metabolic Syndrome*

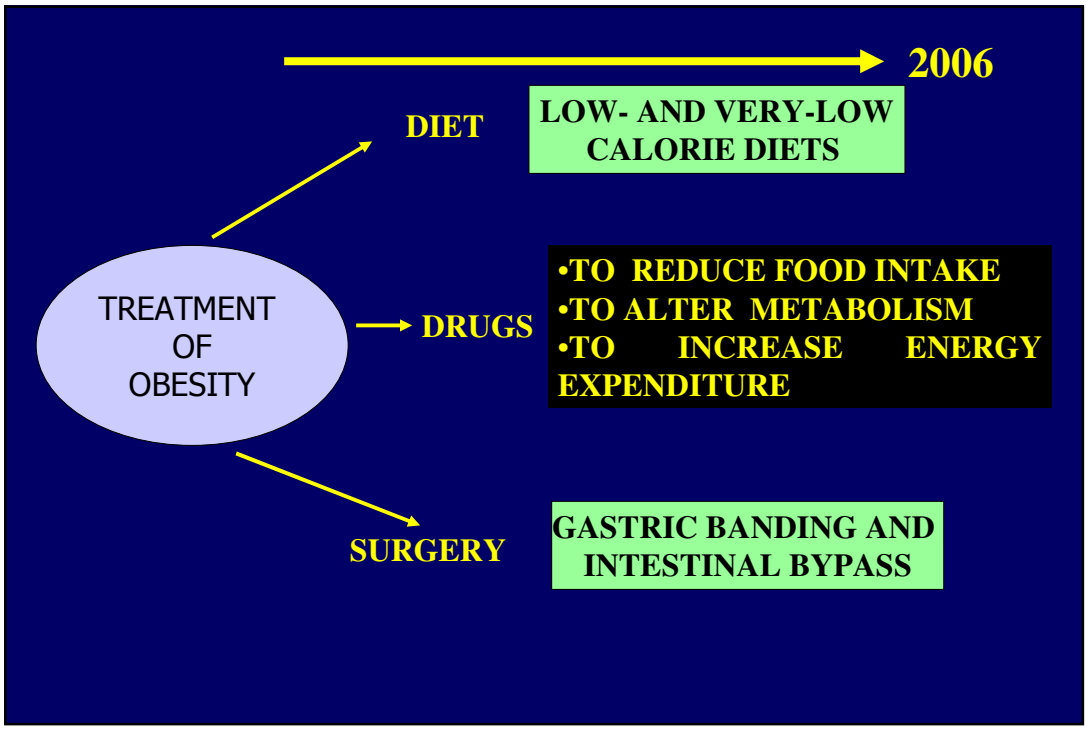
Risk Factor	Defining Level
Abdominal Obesity † (Waist circumference ‡)	
Men	> 102 cm (> 40 inches)
Women	> 88 cm (> 35 inches)
Triglycerides	≥ 150 mg/dL
HDL-C	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood Pressure	≥ 130 / ≥ 85 mm Hg
Fasting glucose	≥ 110 mg/dL

*Diagnosis is established when ≥3 of these risk factors are present.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497




1960
2006
DIET
LOW-SALT-DIET
?
TREATMENT OF HYPERTENSION
DRUGS
DIURETICS
β-BLOCKERS
ACE INHIBITORS
CALCIUM ANTAGONISTS
ANGIOTENSIN II ANTAGONISTS
α-BLOCKERS
SURGERY
SYMPATHECTOMY


2006
DIET
LOW- AND VERY-LOW CALORIE DIETS
TREATMENT OF OBESITY
DRUGS
•TO REDUCE FOOD INTAKE
•TO ALTER METABOLISM
•TO INCREASE ENERGY EXPENDITURE
SURGERY
GASTRIC BANDING AND INTESTINAL BYPASS

STABILIRE UN CRITERIO DI EFFICACIA

FDA (USA)

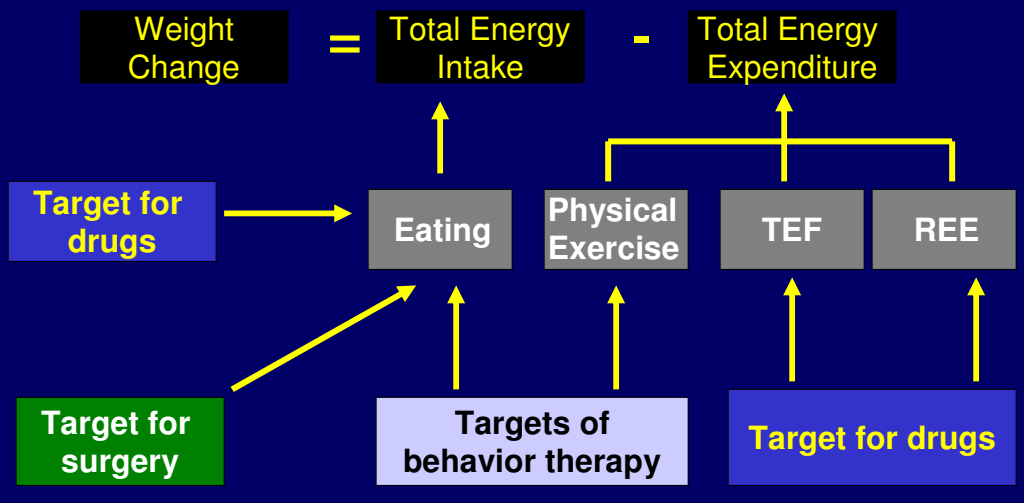
Perdita di peso superiore al 5% rispetto al placebo

CPMP (EU)

Perdita di peso superiore al 10% rispetto al peso di partenza

CPMP= Committee for Proprietary Medicinal Products

TARGETS FOR DRUG TREATMENT AND THE ENERGY BALANCE MODEL



PRINCIPALE MECCANISMO D'AZIONE DEI FARMACI USATI NELLA TERAPIA DELL'OBESITA'

Farmaci	Stimolatori del rilascio			Inibitori del reuptake			Inibitori delle lipasi
	5-HT	NA	DA	5-HT	NA	DA	
Dexamfetamina		√	√				
Fentermina		√	√				
Fenfluramina	√						
Dexfenfluramina	√						
Sibutramina				√	√		
Orlistat							√
Rimonabant	Agonista inverso CB1						

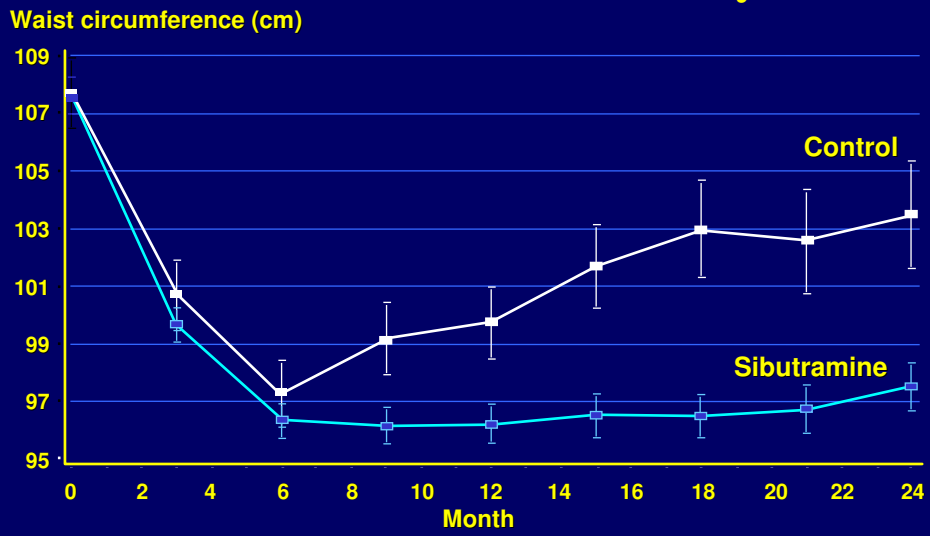
Sibutramine mode of action

- Inhibition of serotonin and noradrenaline reuptake
- Enhancement of satiety
- Increased energy expenditure

STORM Mean bodyweight changes during weight loss and weight maintenance phases over 2 years

NB: Same diet and exercise for both sibutramine and control

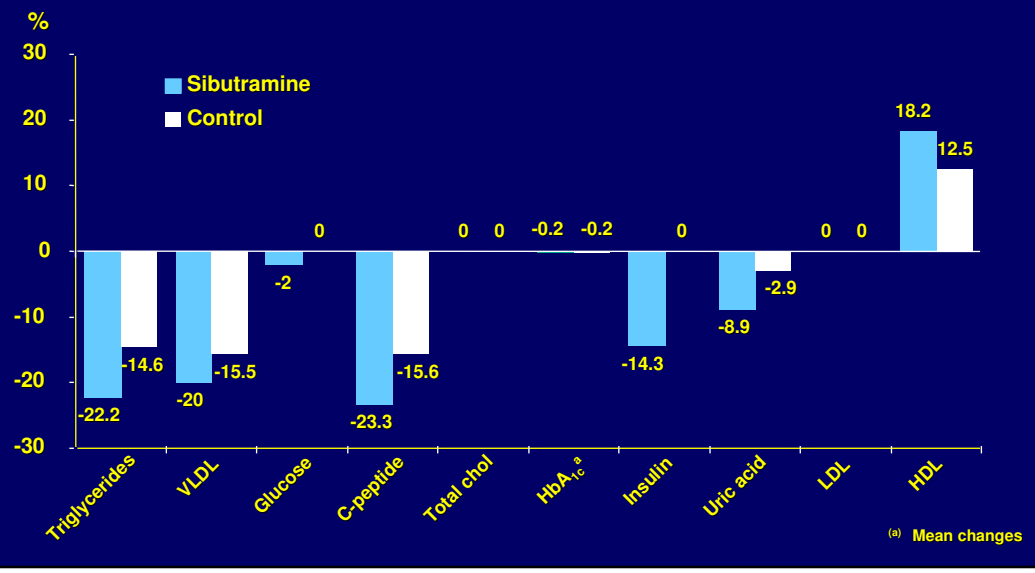
STORM Waist circumference reduction and maintenance over 2 years



NB: Same diet and exercise for both sibutramine and control

STORM

Median % change in metabolic risk factors at 2 years from baseline for sibutramine patients and control group



STORM

Vital sign changes, baseline to end point, control group vs sibutramine all patients

Variable	Database	Baseline	Change from baseline
SBP mmHg	Control	123.7	-2.0
	Sibutramine (All)	126.1	+1.2
DBP mmHg	Control	81.0	-0.7
	Sibutramine (All)	81.2	+3.1
Pulse rate	Control	72.4	0.4
	Sibutramine (All)	72.7	4.4

STORM

Effect of Sibutramine on cardiovascular risk factors

Improved lipid parameters:

- **HDL-cholesterol: ↑ 21%; Triglycerides: ↓ 14.7%; VLDL-Cholesterol: ↓ 13.5%**

Better fat distribution:

- **Waist circumference: ↓ 9.2cm; Waist:hip ratio: ↓ 10%**

Less insulin resistance

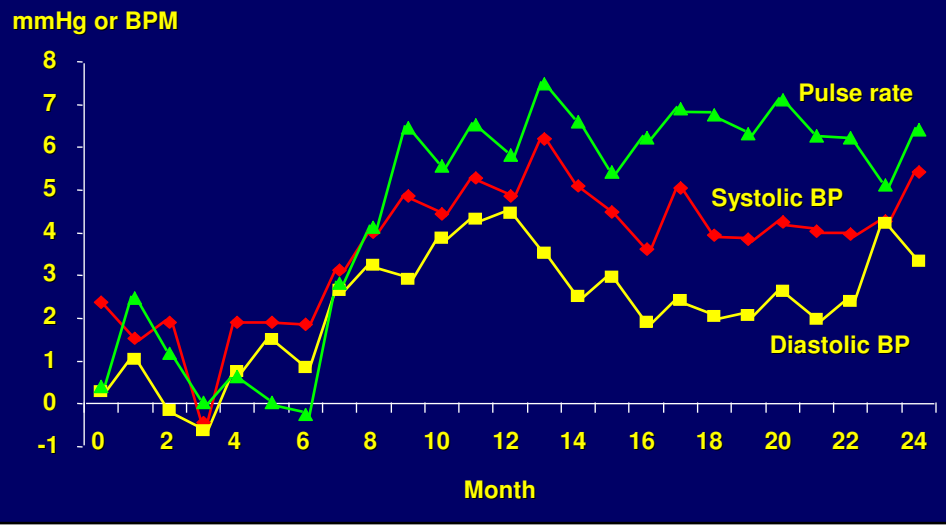
- **Insulin ↓ 14.9%; C-Peptide: ↓ 15.4%**

Small cardiovascular changes

- **BP: ↑ 0.1/2.3mmHg; HR: ↑ 4.1beats/min respectively.**

STORM

Changes in seated vital signs (placebo subtracted) over 2 years (Observed data)



Effect of Sibutramine on Weight Management and Metabolic Control in Type 2 Diabetes

A meta-analysis of clinical studies

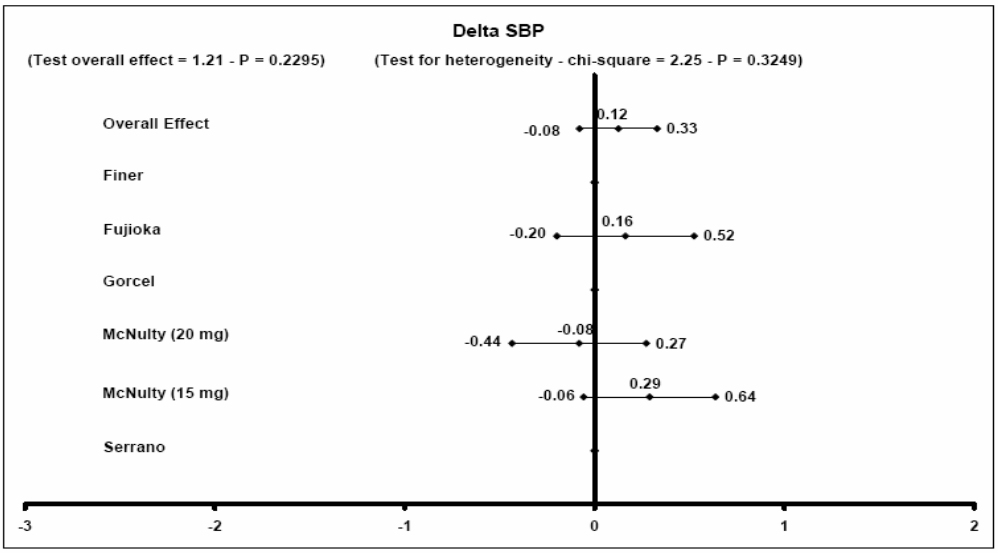
ROBERTO VETTOR, MD
ROBERTO SERRA, MD
ROBERTO FABRIS, MD
CLAUDIO PAGANO, MD
GIOVANNI FEDERSPIL, MD

with the metabolic syndrome increasing the risk of death from all causes as well as cardiovascular disease (3). The U.K. Prospective Diabetes Study provided several

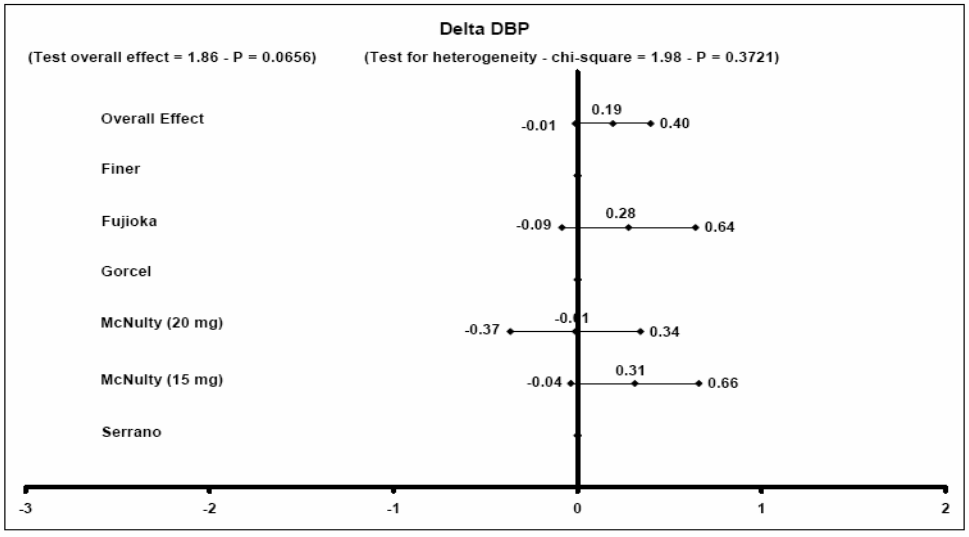
A meta-analysis of RCT on the clinical effectiveness of sibutramine used for the management of obese type 2 diabetes

Age (years)	Sibutramina		Placebo	Durata terapia	Trattamento	Sibutramina		Placebo	
	Dose	N. Pazienti	N. Pazienti	mesi	Antidiabetico	Media	SD	Media	SD
Role of Sibutramine in the treatment of obese Type 2 diabetic patients receiving sulphonylurea therapy (SERRANO)	15 mg	69	65	6	Sulfanilurea	52.9	8.9	54.3	8.3
A randomized trial of Sibutramine in the management of obese Type 2 diabetic patients Treated With Metformin (McNulty)	15 mg	68	64	12	Metformina	49.0	8.2	51.0	8.8
A randomized trial of Sibutramine in the management of obese Type 2 diabetic patients Treated With Metformin (McNulty)	20 mg	62	64		Metformina	48.0	7.9	51.0	8.8
Effects of Sibutramine in Obese female subjects with Type 2 diabetes and Poor Blood Glucose control (Gorcel)	20 mg	29	25	6	Metformina, Sulfanilurea	46.9	6.6	49.3	7.3
Weight loss with Sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus (Fujioka)	5/20 mg	89	86	6	Dieta, Metformina, Sulfanilurea	53.5	10.0	55.0	10.2
Sibutramine is effective for weight loss and diabetic control in obesity with type 2 diabetes: a randomized, double-blind, placebo-controlled study (Finer)	15 mg	47	44	3	Dieta, Insulina, Metformina, Sulfanilurea	53.7	8.4	54.1	7.5
		364	348						

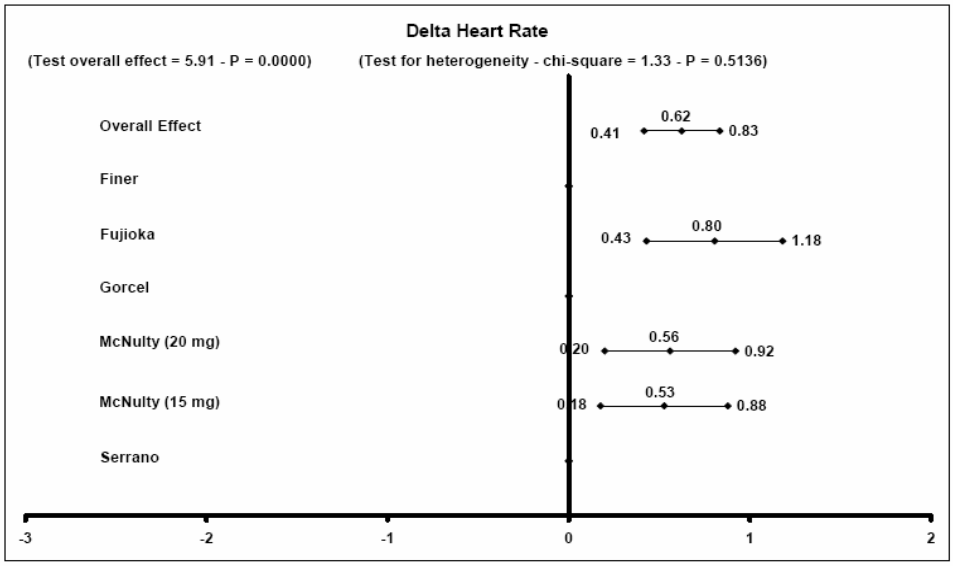
A meta-analysis of RCT on the clinical effectiveness of sibutramine used for the management of obese type 2 diabetes



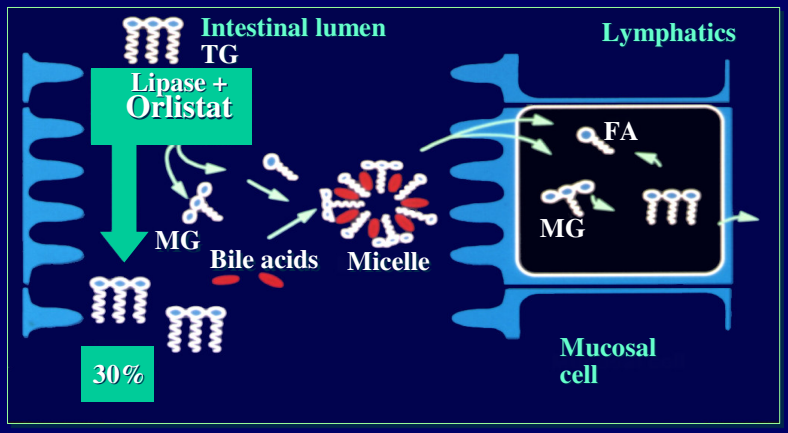
A meta-analysis of RCT on the clinical effectiveness of sibutramine used for the management of obese type 2 diabetes



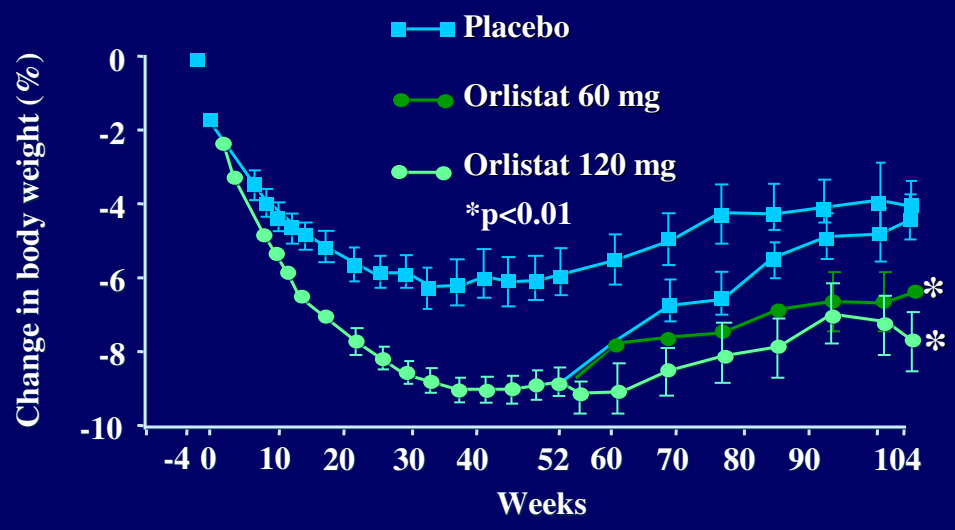
A meta-analysis of RCT on the clinical effectiveness of sibutramine used for the management of obese type 2 diabetes



Inhibition of fat absorption by Orlistat



Change in body weight over 2 years



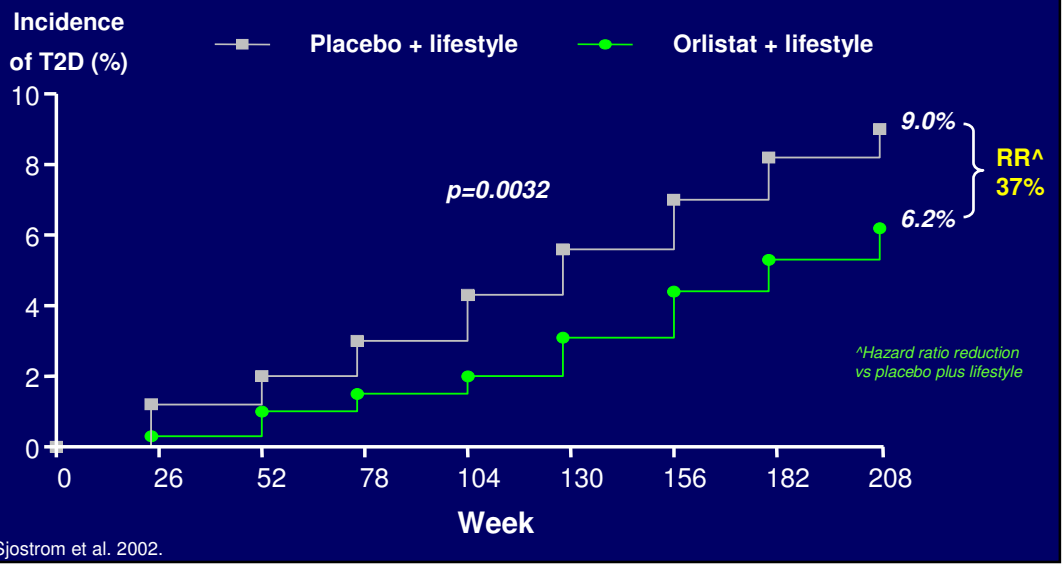
Itt population: NM14185

Effect of Orlistat on fat-soluble vitamins

Vitamin	Initial		52 weeks		104 weeks		Reference range
	Placebo	Orlistat	Placebo	Orlistat	Placebo	Orlistat	
A	2.69	2.58	2.62	2.60	2.21	2.13	1.58-3.97 µmol/L
D	61.97	60.88	74.42	59.55	61.24	52.43	18-121 µmol/L
E	30.12	29.81	28.64	26.04	30.19	27.49	18.1-50.6 µmol/L
ß-carotene	0.34	0.36	0.42	0.28	0.46	0.33	0.09-1.06 µmol/L

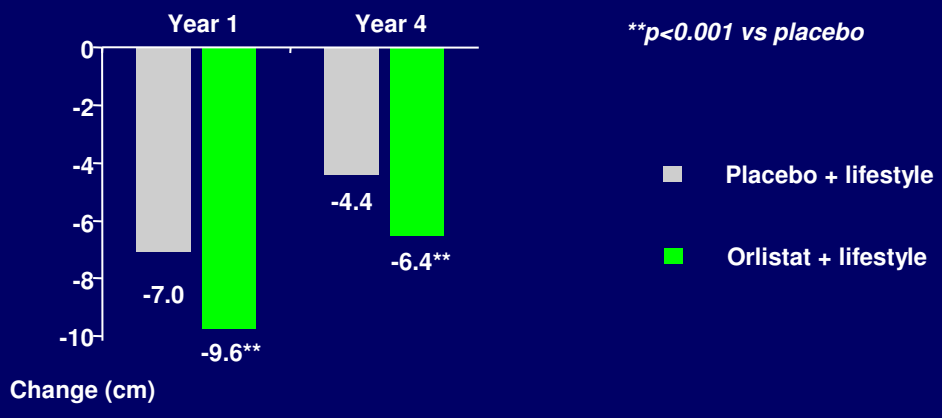
Safety population BM14149

XENDOS results
Cumulative incidence of type 2 diabetes



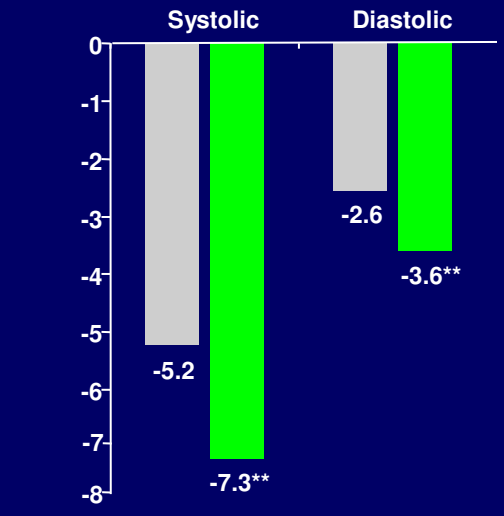
Sjostrom et al. 2002.

XENDOS results
Effect of Orlistat on waist circumferencea



Sjostrom et al. 2002.

XENDOS results
Effect of Orlistat on blood pressure at yr 1



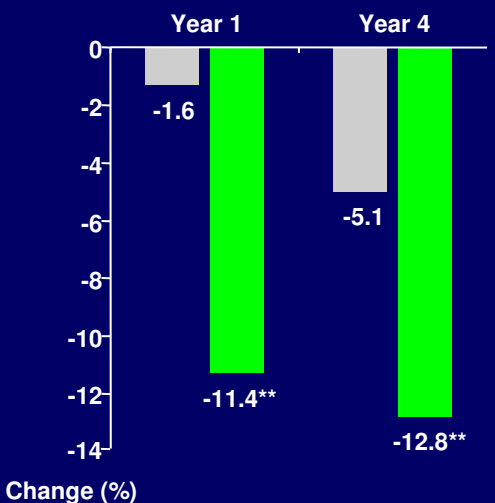
***p<0.001 vs placebo*

Placebo + lifestyle

Xenical + lifestyle

Sjostrom et al. 2002.

XENDOS results
Effect of Orlistat on LDL cholesterol



***p<0.001 vs placebo*

Placebo + lifestyle

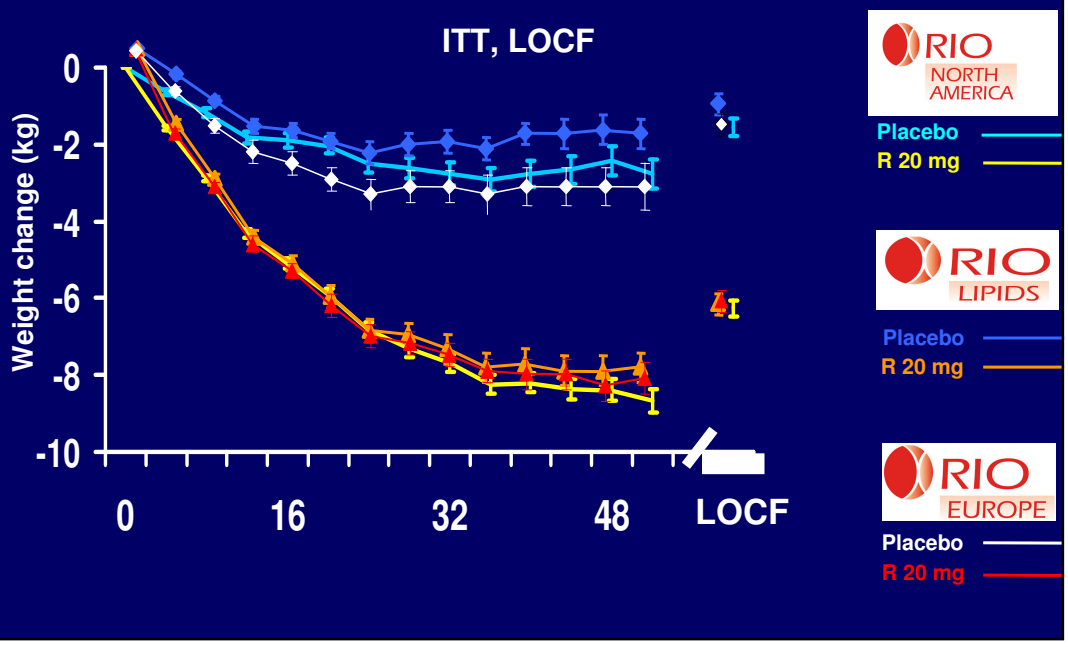
Orlistat + lifestyle

Sjostrom et al. 2002

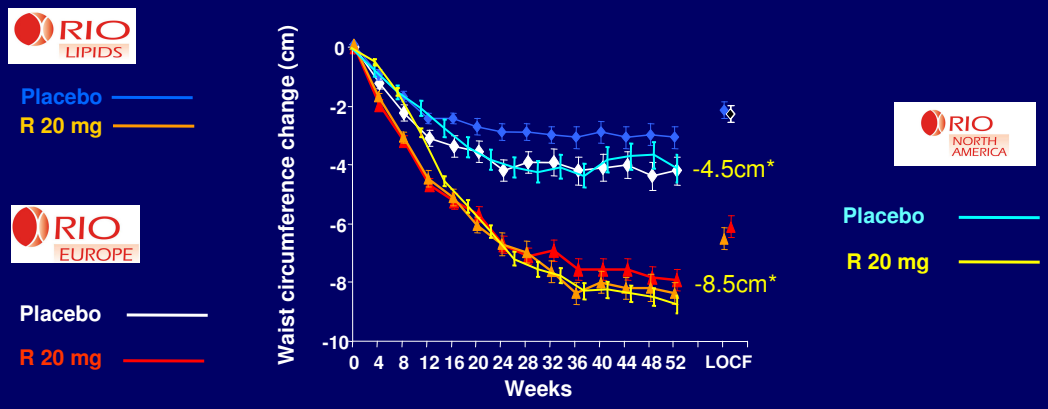
Leptin-regulated endocannabinoids are involved in maintaining food intake

Di Marzo V., et al *Nature* 410, 822 - 825, 2001

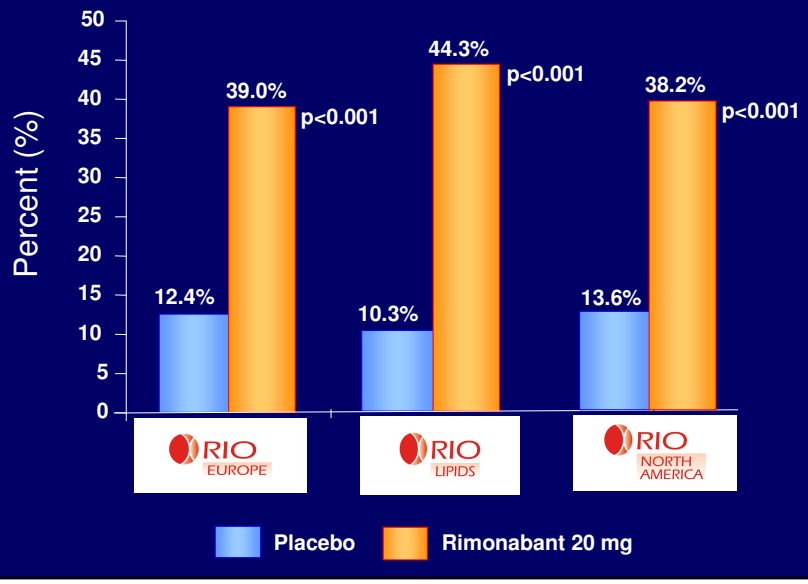
Consistent Weight Change at 1 Year



Consistent Changes in Waist Circumference
Completers



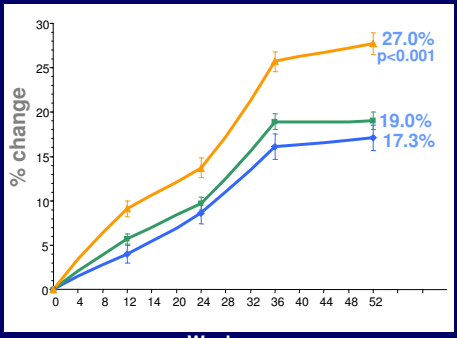
Weight loss ≥10% at 1-year
Completers



Change in HDL-cholesterol and triglycerides: RIO-Europe

RIO EUROPE

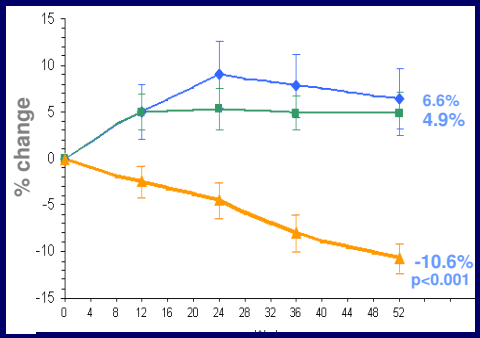
HDL-cholesterol



ITT LOCF

Placebo : 13.4%
5 mg : 16.2% (p=0.048 vs placebo)
20 mg : 22.3% (p<0.001 vs placebo)

Triglycerides



ITT LOCF

Placebo : 8.3%
5 mg : 5.7% (ns vs placebo)
20 mg : - 6.8% (p<0.001 vs placebo)

Placebo Rimonabant 5 mg Rimonabant 20 mg

RIO-Europe → Serious Adverse Events

	Placebo (n=305)	Rimonabant 5 mg (n=603)	Rimonabant 20 mg (n=599)
Any serious adverse event	23 (7·5%)	45 (7·5%)	52 (8·7%)
Respiratory disorders	0	0	2 (0·3%)
Psychiatric disorders	1 (0·3%)	2 (0·3%)	9 (1·5%)
Nervous system disorders	3 (1·0%)	7 (1·2%)	3 (0·5%)
Ear disorders	0	0	1 (0·2%)
Cardiac disorders	0	2 (0·3%)	2 (0·3%)
Vascular disorders	0	2 (0·3%)	3 (0·5%)
Gastrointestinal disorders	3 (1·0%)	3 (0·5%)	2 (0·3%)
Hepatobiliary disorders	3 (1·0%)	5 (0·8%)	1 (0·2%)
Musculoskeletal and connective disorders	6 (2·0%)	13 (2·2%)	10 (1·7%)
Renal and urinary disorders	0	2 (0·3%)	2 (0·3%)
Reproductive system and breast disorders	1 (0·3%)	2 (0·3%)	3 (0·5%)
Investigations	1 (0·3%)	0	1 (0·2%)
Injury, poisoning, and procedure complications	4 (1·3%)	5 (0·8%)	4 (0·7%)
Neoplasms: benign, malignant, and unspecified	2 (0·7%)	5 (0·8%)	7 (1·2%)
General disorders	0	0	1 (0·2%)

Data are proportions of patients with at least one serious event.

Table 6: Serious adverse events by system organ class during the double-blind period of the trial

Discontinuation due to Serious Adverse Events

	Placebo (n=305)	Rimonabant 5 mg (n=603)	Rimonabant 20 mg (n=599)
Any adverse event leading to discontinuation	28 (9·2%)	50 (8·3%)	87 (14·5%)
Psychiatric disorders	16 (5·2%)	18 (3·0%)	42 (7·0%)
Depressed mood disorders	9 (3·0%)	14 (2·3%)	22 (3·7%)
Anxiety	1 (0·3%)	0	6 (1·0%)
Agitation	2 (0·7%)	0	3 (0·5%)
Sleep disorders	0	2 (0·3%)	1 (0·2%)
Nervous system disorders	2 (0·7%)	8 (1·3%)	10 (1·7%)
Headache	0	2 (0·3%)	4 (0·7%)
Dizziness	0	2 (0·3%)	2 (0·3%)
Hypoaesthesia	0	0	2 (0·3%)
Gastrointestinal disorders	0	5 (0·8%)	21 (3·5%)
Nausea	0	1 (0·2%)	14 (2·3%)
Vomiting	0	0	4 (0·7%)
Diarrhoea	0	0	3 (0·5%)
Dyspepsia	0	0	2 (0·3%)
Flatulence	0	2 (0·3%)	0
Cardiac disorders	3 (1·0%)	2 (0·3%)	5 (0·8%)
Palpitations	1 (0·3%)	0	2 (0·3%)

According to the Medical Dictionary for Regulatory Activities in at least two patients in any treatment group (one patient may report several events). Only main system organ classes are presented.

Table 7: Patients reporting adverse events leading to discontinuation

Table 3. Adverse Events.

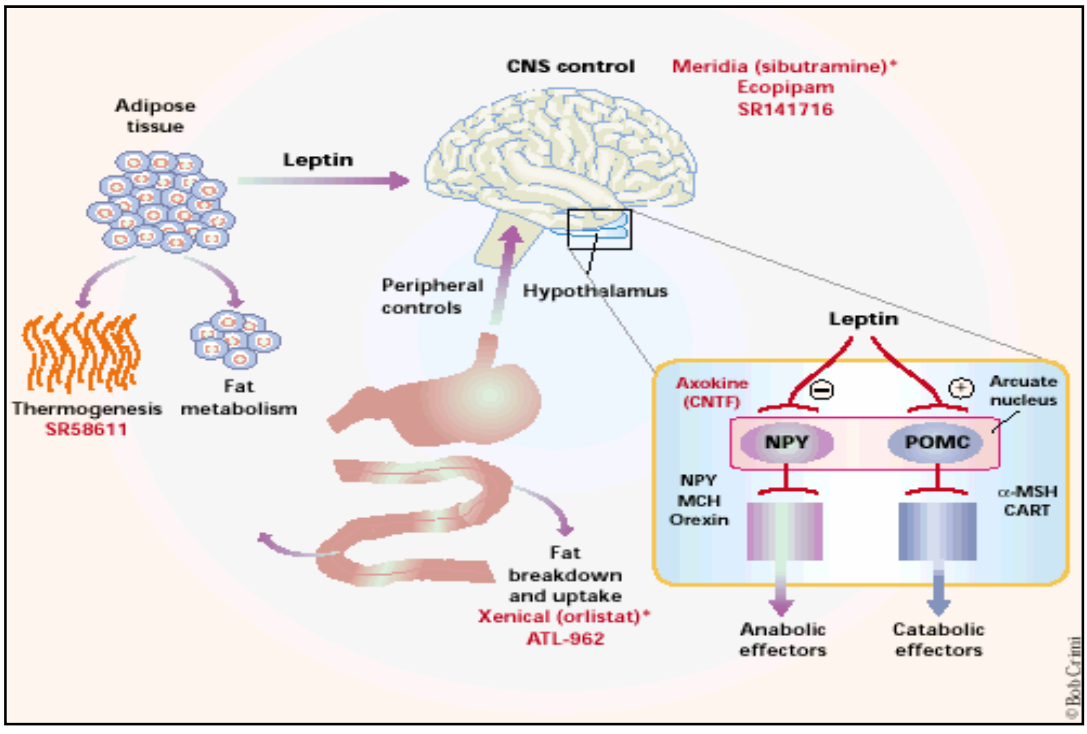
Event	Placebo Group (N=342)	5-mg Rimonabant Group (N=345)	20-mg Rimonabant Group (N=346)
Adverse events — %*			
Nasopharyngitis	21.6	26.4	19.4
Headache	15.8	15.4	15.3
Nausea	3.2	7.2	12.7
Dizziness	6.7	8.4	10.4
Influenza	5.3	6.1	9.5
Upper respiratory tract infection	9.9	8.7	8.7
Anxiety	3.8	2.9	8.7
Back pain	10.2	9.6	7.2
Diarrhea	4.1	6.4	7.2
Gastroenteritis	6.4	4.3	6.6
Insomnia	2.6	4.1	6.4
Arthralgia	9.6	7.0	5.5
Serious adverse events — no. (%)†			
Infections and infestations	1 (0.3)	1 (0.3)	2 (0.6)
Surgical and medical procedures	1 (0.3)	0	0
Immune system disorders	2 (0.6)	0	0
Psychiatric disorders	1 (0.3)	1 (0.3)	1 (0.3)
Nervous system disorders	2 (0.6)	0	2 (0.6)
Eye disorders	0	1 (0.3)	0
Cardiac disorders	0	2 (0.6)	1 (0.3)
Vascular disorders	1 (0.3)	0	0
Gastrointestinal disorders	1 (0.3)	3 (0.9)	1 (0.3)
Hepatobiliary disorders	0	2 (0.6)	0
Musculoskeletal and connective-tissue disorders	1 (0.3)	4 (1.2)	2 (0.6)
Renal and urinary disorders	0	0	1 (0.3)
Reproductive system and breast disorders	0	2 (0.6)	1 (0.3)
Investigations	0	0	1 (0.3)
Injury, poisoning, and procedural complications	0	0	1 (0.3)
Neoplasms: benign, malignant, and unspecified (including cysts and polyps)	0	3 (0.9)	2 (0.6)

RIO-Lipids

Table 3. (Continued.)

Event	Placebo Group (N=342)	5-mg Rimonabant Group (N=345)	20-mg Rimonabant Group (N=346)
Discontinuation — no. (%)‡			
Patients who discontinued participation	24 (7.0)	29 (8.4)	52 (15.0)
Reason for discontinuation			
Psychiatric disorders			
Depression	2 (0.6)	6 (1.7)	10 (2.9)
Anxiety	2 (0.6)	1 (0.3)	6 (1.7)
Major depression	0	2 (0.6)	2 (0.6)
Irritability	2 (0.6)	1 (0.3)	2 (0.6)
Aggression	0	1 (0.3)	2 (0.6)
Depressed mood	0	0	2 (0.6)
Sleep disorder	0	0	2 (0.6)
Insomnia	2 (0.6)	1 (0.3)	0
Nervous system disorders			
Dizziness	0	2 (0.6)	3 (0.9)
Amnesia	0	0	2 (0.6)
Headache	3 (0.9)	1 (0.3)	0
General disorders			
Fatigue	3 (0.9)	0	2 (0.6)
Gastrointestinal disorders			
Nausea	0	2 (0.6)	4 (1.2)
Dyspepsia	0	1 (0.3)	2 (0.6)
Upper abdominal pain	0	0	2 (0.6)
Vascular disorders			
Hypertension	1 (0.3)	2 (0.6)	1 (0.3)
Infections and infestations			
Pneumonia	2 (0.6)	0	0

RIO-Lipids



Alcune considerazioni finali

1. La terapia farmacologica dell'obesità è efficace
2. I farmaci attualmente disponibili sono gravati da effetti collaterali e controindicazioni non dissimili da altre classi di farmaci.
3. Nonostante la terapia farmacologica dell'obesità si sia dimostrata efficace nel ridurre i fattori di rischio (ipertensione, dislipidemia, etc), pochi pazienti sono in trattamento farmacologico per l'obesità e molti pazienti sono in trattamento farmacologico per i fattori di rischio separatamente.