6th AME National Meeting
3rd Joint Meeting with the American Association of Clinical Endocrinologists

Verona October 27-29th 2006

Dietary and behavioural treatment: just a hope or real tool?

Claudio Maffeis

Department of Mother & Child, Biology-Genetics, Section of Pediatrics, University of Verona

long-term weight loss maintenance

Definition: “individuals who have intentionally lost at least 10% of their body weight and kept it off at least one year”.

20% of overweight individuals are successful weight losers.

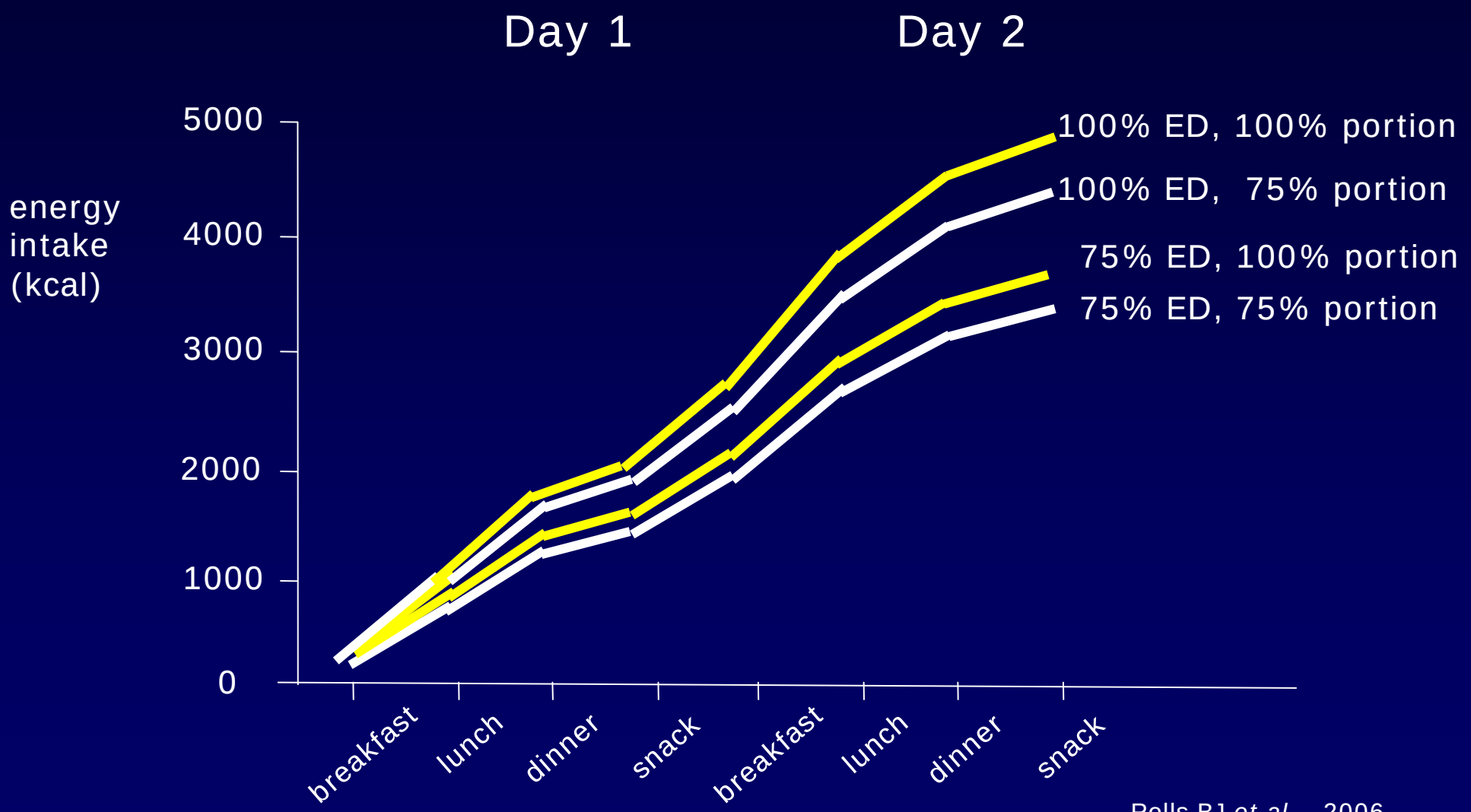
THE NATIONAL WEIGHT CONTROL REGISTRY

diet + physical activity: 89%
diet: 10%
physical activity: 1%

strategies very consistently reported:

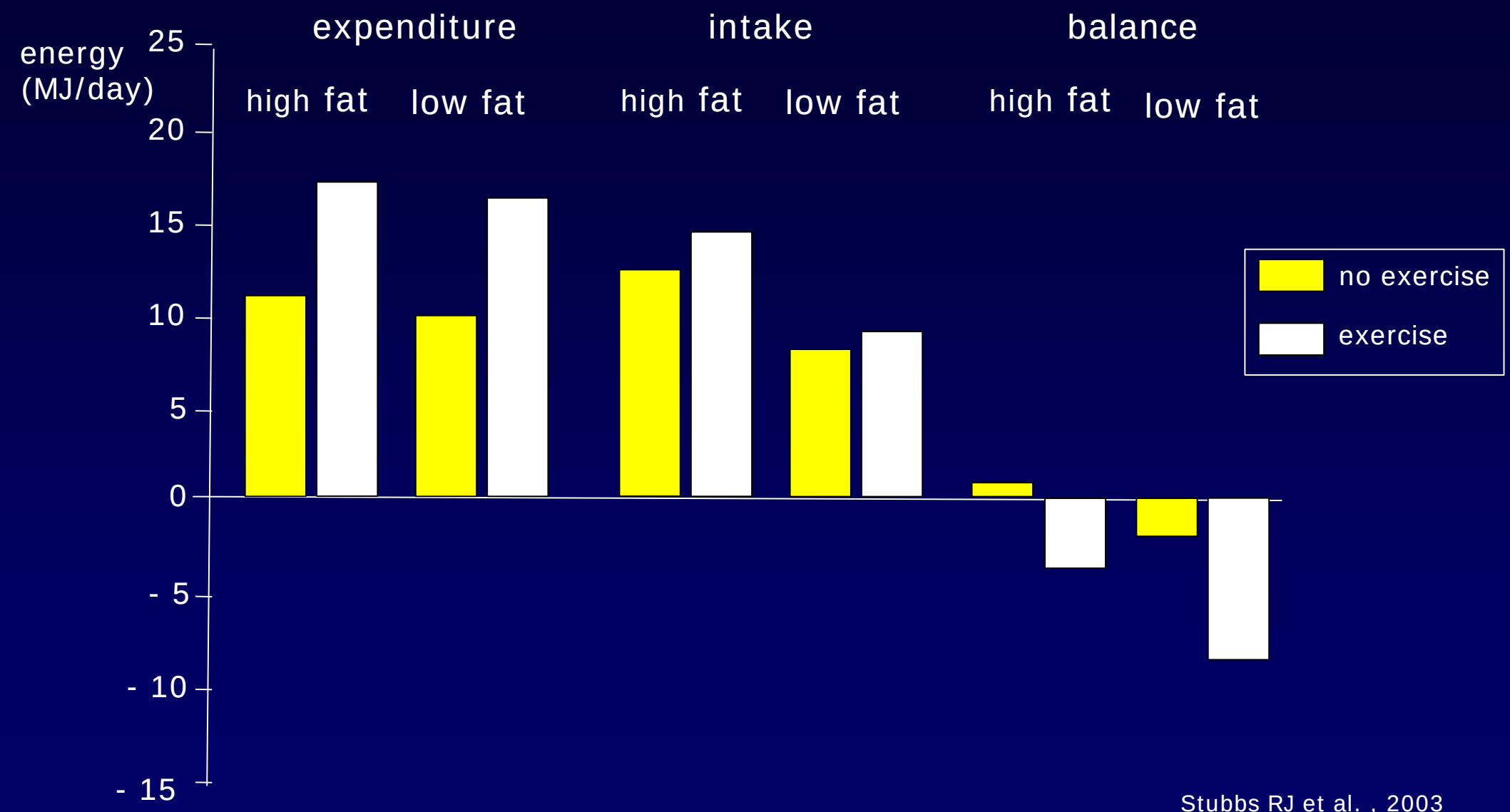
consuming a low-calorie (1800 kcal/day), low-fat (25%) diet
doing high levels of physical activity (3000 kcal/week)
weighing themself frequently
consuming breakfast daily

reduction in portion size and energy density of foods are additive and lead to sustained decreases in energy intake

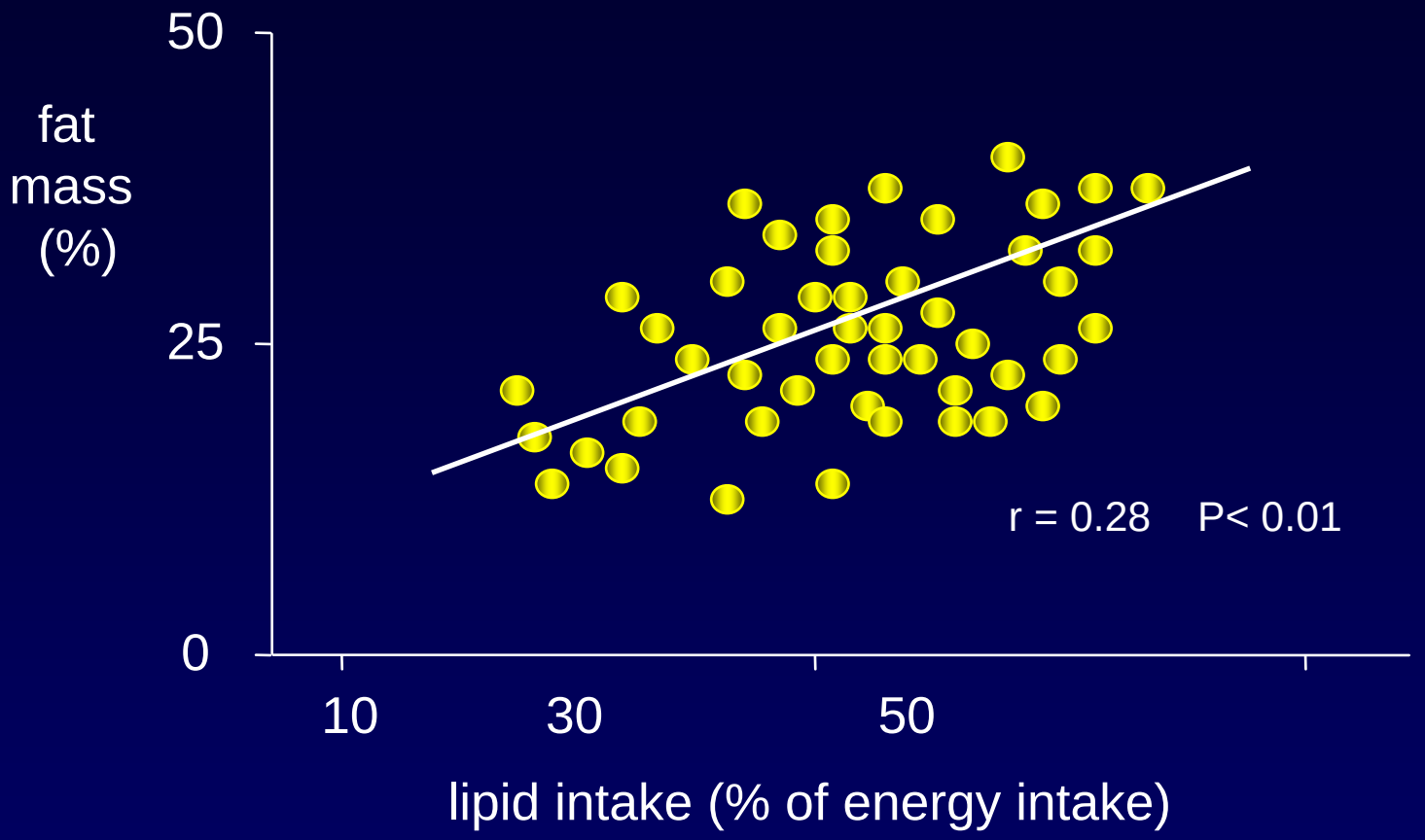


Rolls BJ *et al.* , 2006

rate and extent of compensatory changes in energy intake and expenditure in response to altered exercise and diet composition



Stubbs RJ et al. , 2003

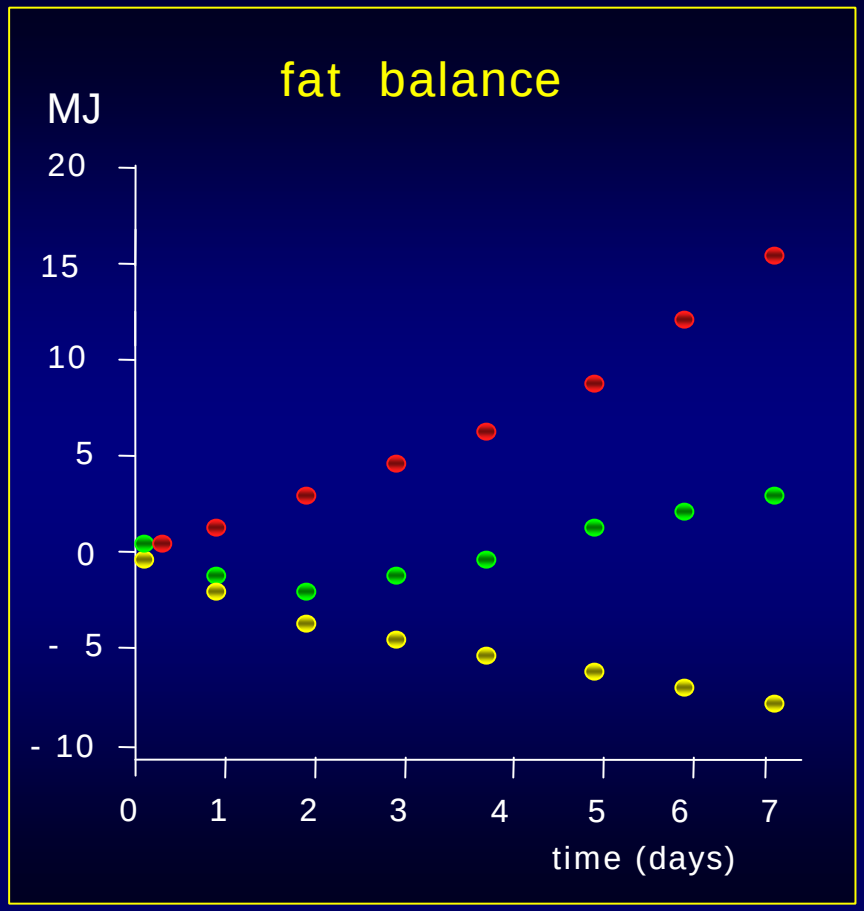


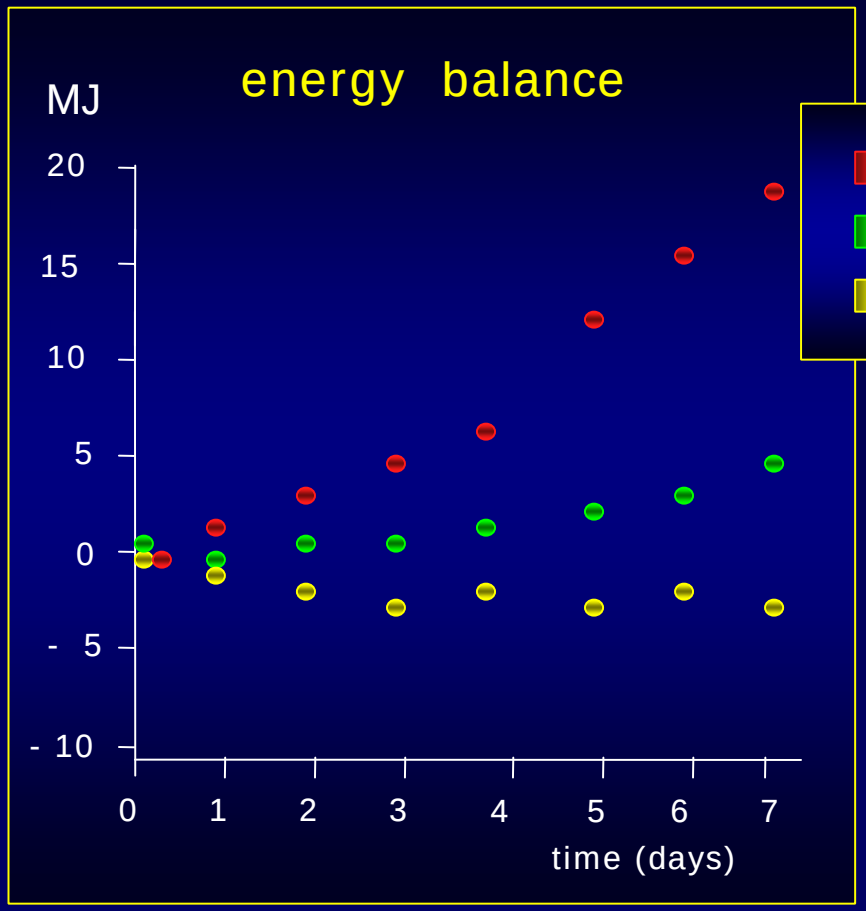
Klesges RC *et al.* AJCN ‘94

Gazzaniga JM, *et al.*AJCN ‘93

Maffeis C *et al.* Int J Obes ‘96

covert manipulation of dietary fat and energy density: effect on substrate flux and food intake in men eating ad libitum

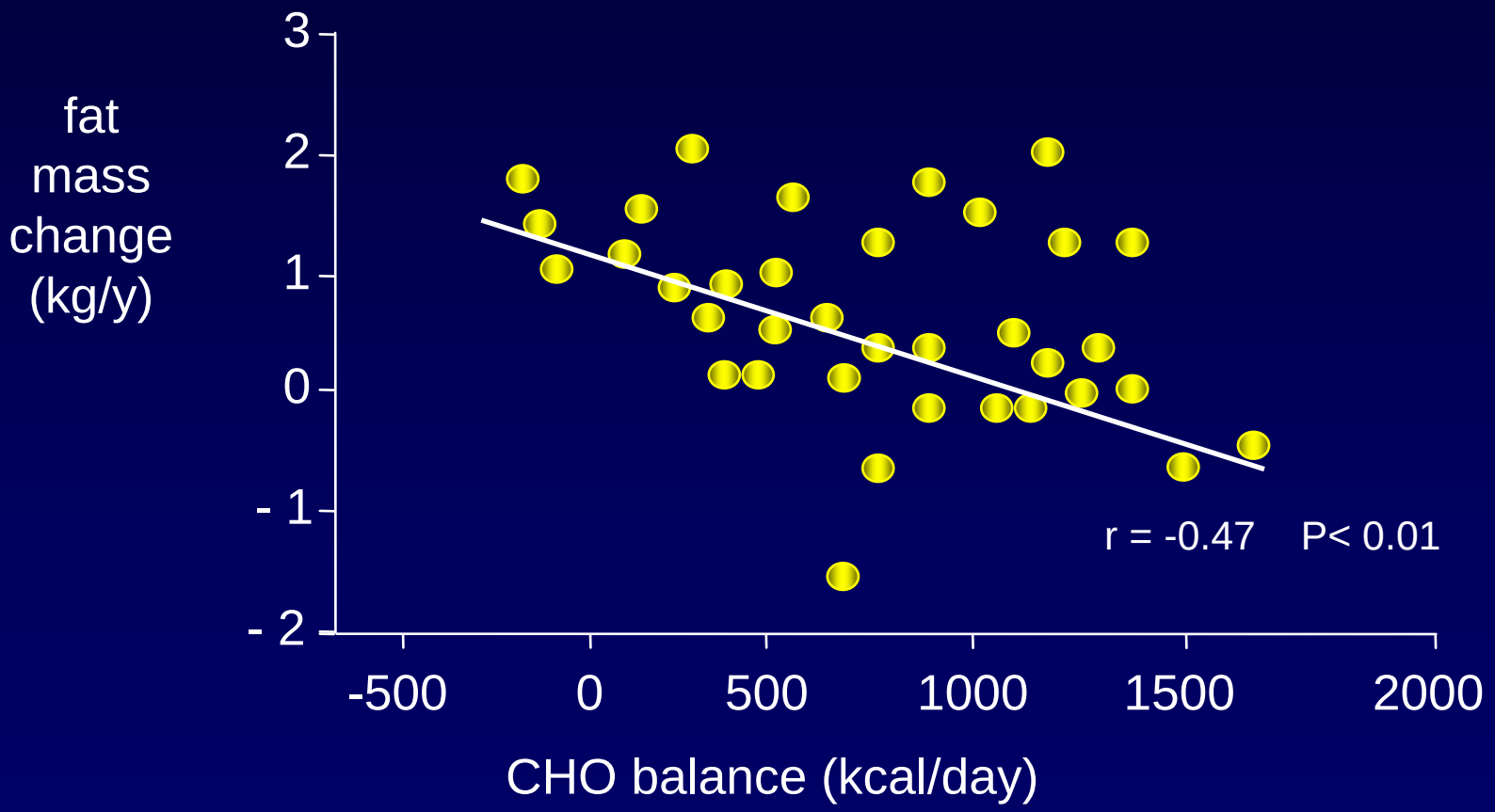




high fat
medium fat
low fat

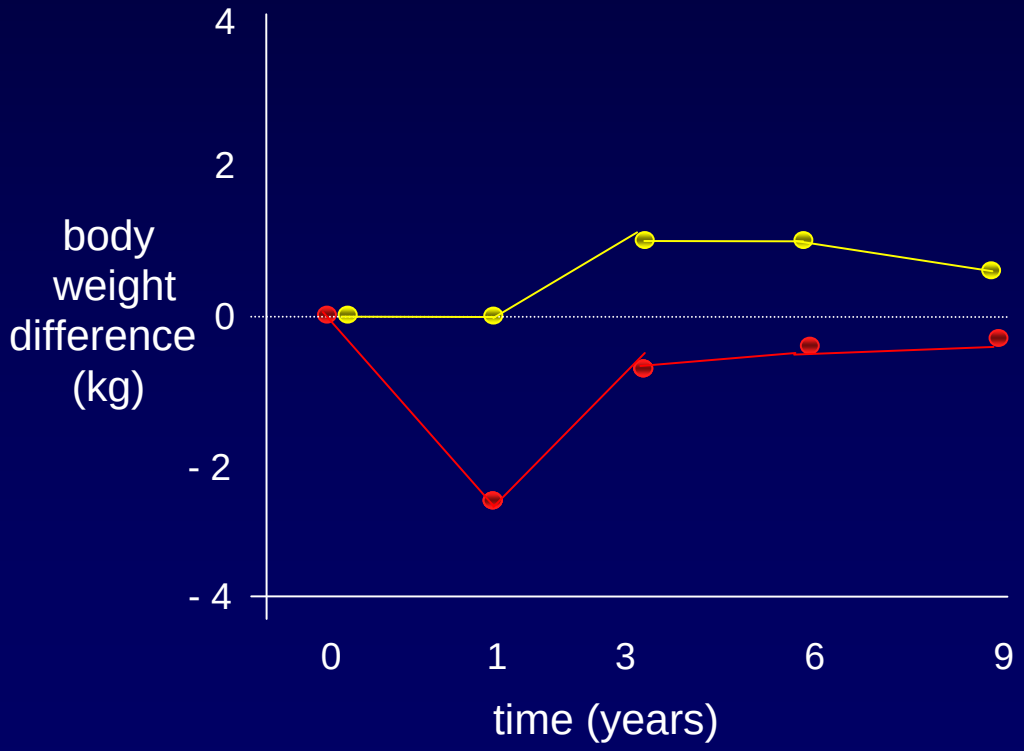
Stubb RJ, *et al*. AJCN 1995; 62:316-29.

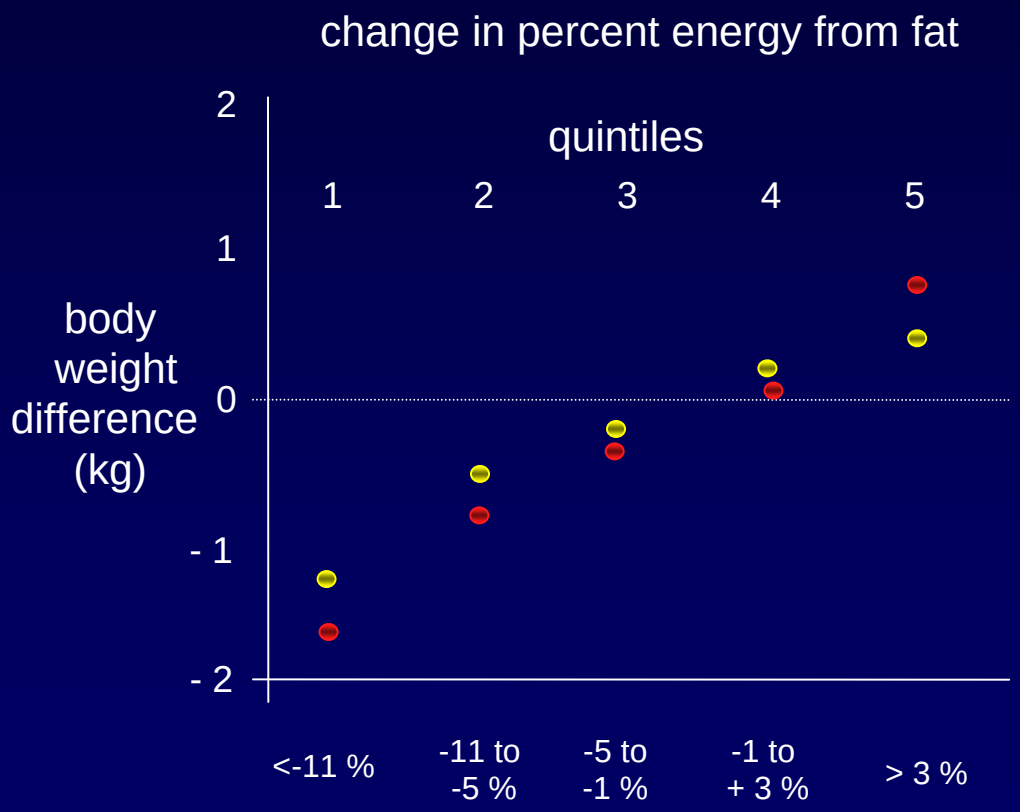
carbohydrate balance predicts weight and fat gain in adults



Eckel RH, *et al.* AJCN 2006

low-fat dietary pattern and weight change over 7 years
The Women'sHealth Initiative Dietary Modification Trial

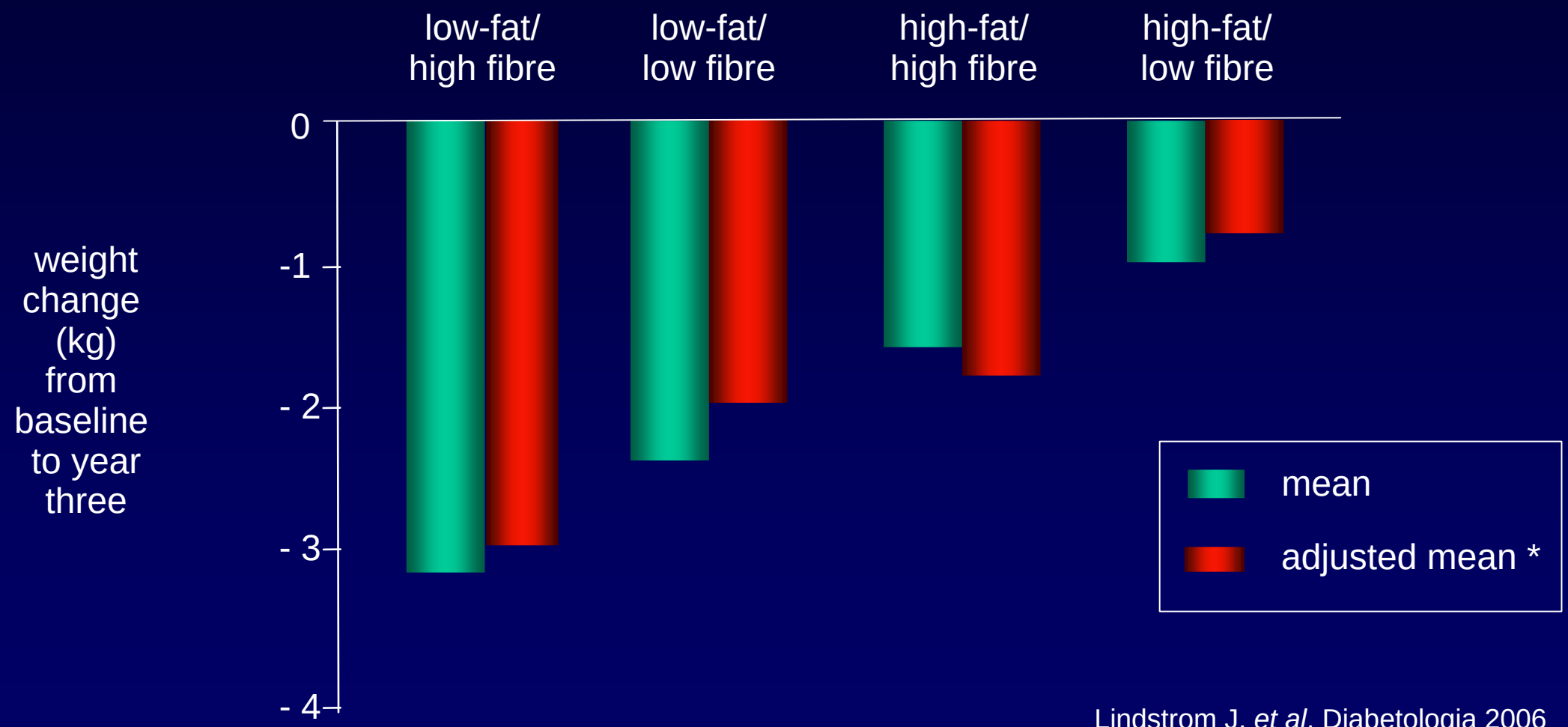




intervention control

Howard BV, *et al*. JAMA 2006

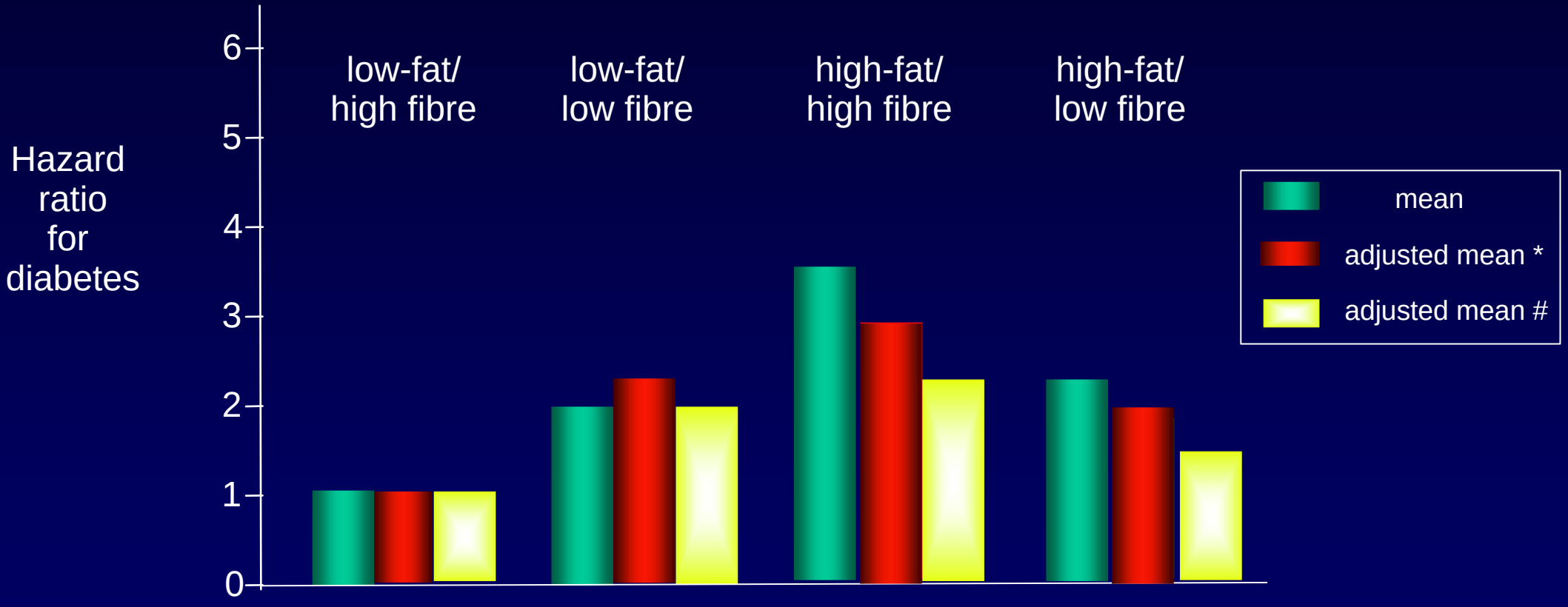
high-fibre, low-fat diet predicts long-term weight loss and decreased type 2 diabetes risk: the Finnish Diabetes Prevention Study



Lindstrom J, *et al*. Diabetologia 2006

* group assignment, age, sex, baseline BW, fat, fibre, VLDL-use, & baseline and follow-up period physical activity

high-fibre, low-fat diet predicts long-term weight loss and decreased type 2 diabetes risk: the Finnish Diabetes Prevention Study

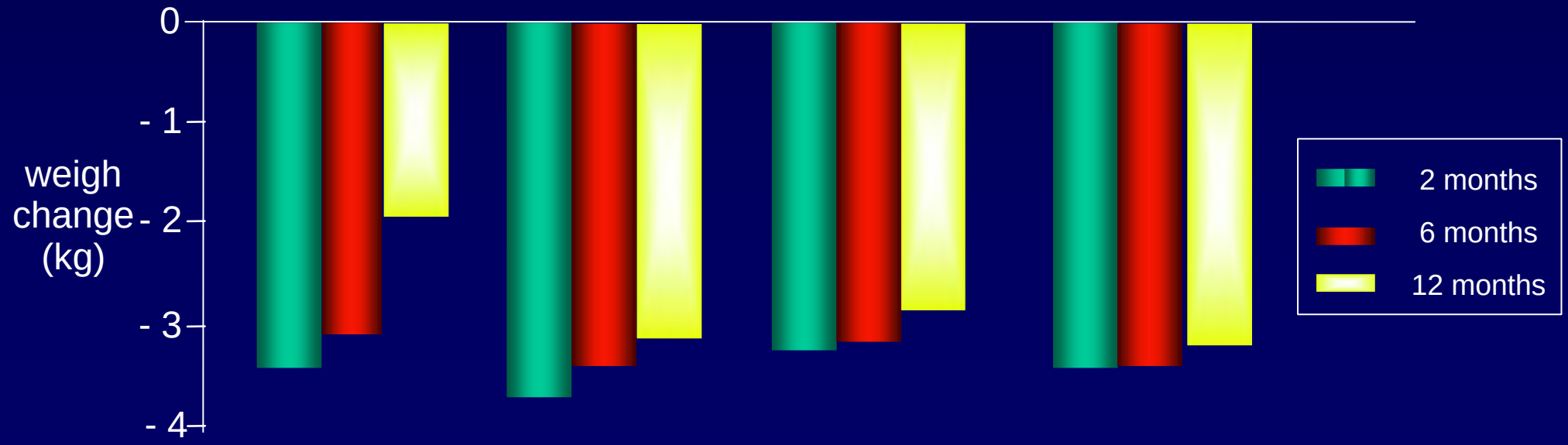


* group assignment, age, sex, baseline BW, fat & fibre intake, baseline 2-h glucose, baseline and follow-up period physical activity
# + weight change

Lindstrom J, *et al*. Diabetologia 2006

Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction

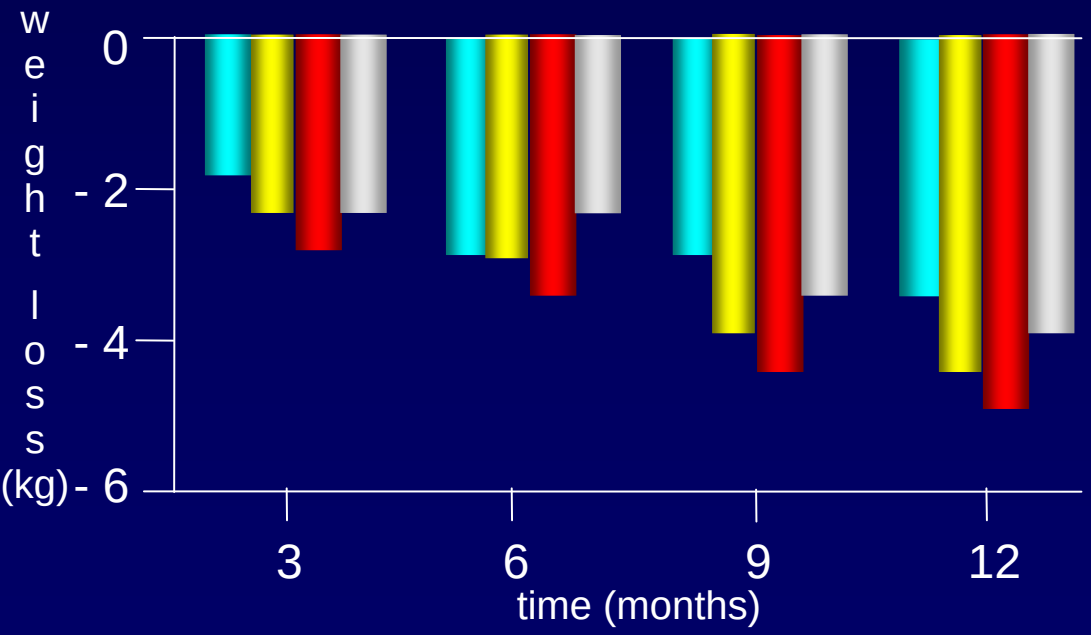
	Atkins (n.40)	Zone (n.40)	Weight Watchers (n.40)	Ornish (n.40)
Energy	1700	1420	1480	1400
CHO (%)	16	45	47	65
Fat (%)	50	34	34	17
Prot (%)	34	21	19	18
Fiber (g)	8	18	15	20

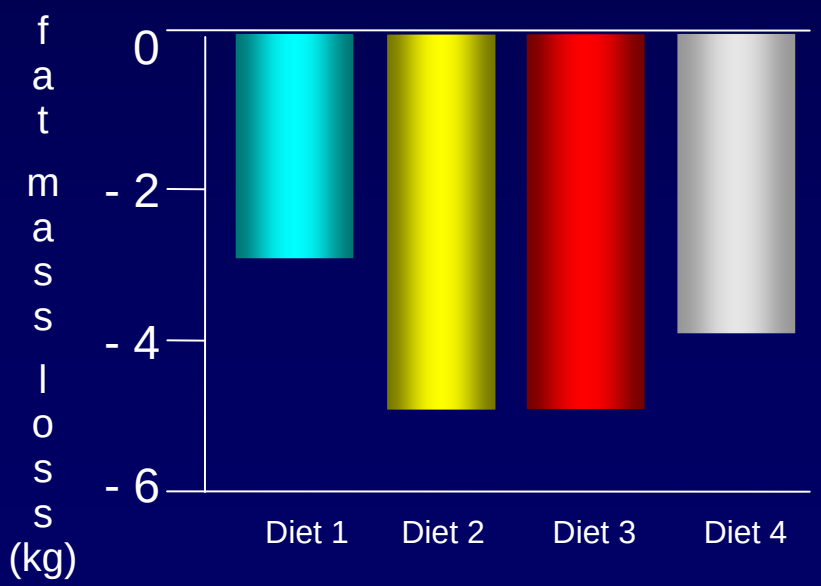


Dansinger ML, *et al*. JAMA 2005

comparison of 4 diets of varying glycemic load on weight loss and cardiovascular risk reduction in overweight and obese adults

	Diet 1 (n.32)	Diet 2 (n.32)	Diet 3 (n.32)	Diet 4 (n.32)
Energy	1300	1300	1300	1300
CHO (%)	56	55	44	44
Fat (%)	29	30	30	30
Prot (%)	15	15	26	26
GI	65	40	68	34
GL (g)	116	65	84	43

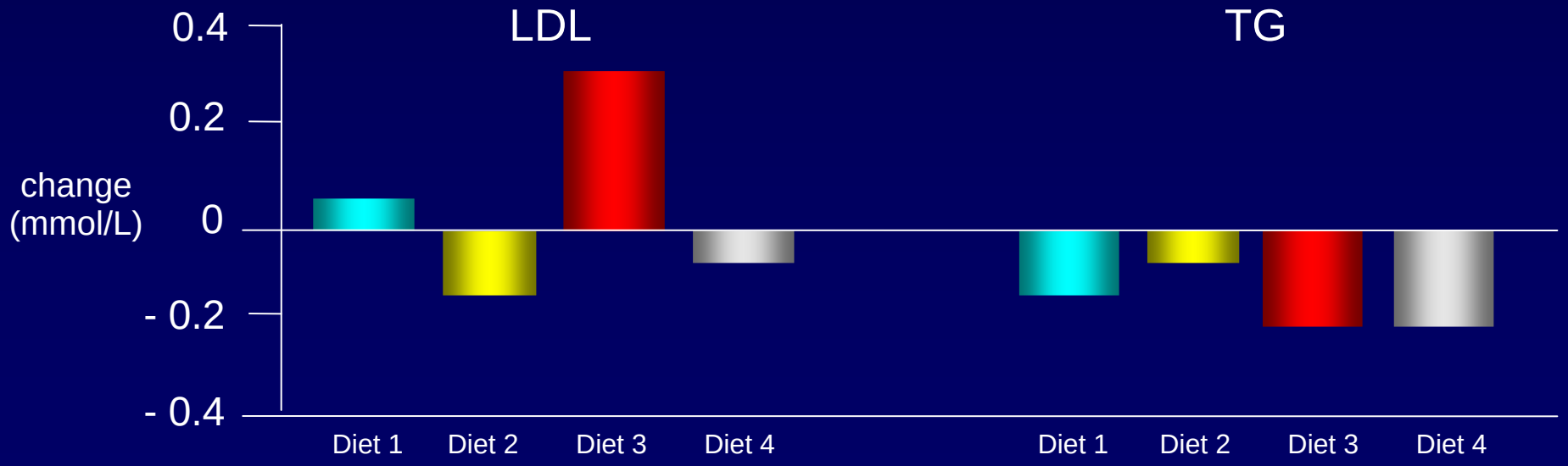




McMillan-Price, *et al*. Arch Intern Med 2006

comparison of 4 diets of varying glycemic load on weight loss and cardiovascular risk reduction in overweight and obese adults

	Diet 1 (n.32)	Diet 2 (n.32)	Diet 3 (n.32)	Diet 4 (n.32)
Energy	1300	1300	1300	1300
CHO (%)	56	55	44	44
Fat (%)	29	30	30	30
Prot (%)	15	15	26	26
GI	65	40	68	34
GL (g)	116	65	84	43



McMillan-Price, *et al*. Arch Intern Med 2006

behavioral treatment of obesity

goal directed - process oriented
advocated small changes

behavioral package	self-monitoring stimulus control problem solving cognitive restructuring slowing eating nutrition education physical activity

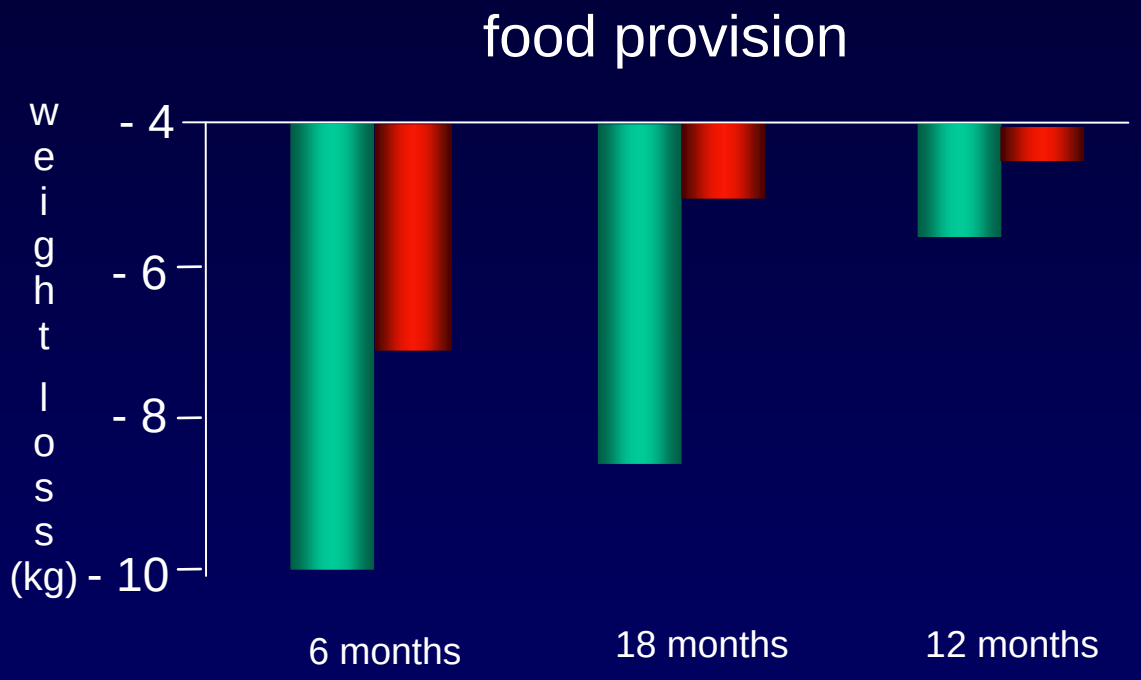
behavioral treatment of obesity

Behavior therapy, when combined with a diet / exercise intervention, increases weight loss compared with diet / exercise alone (-2.3 kg; 95% CI -3.3 to -1.4).

Cognitive-behavior therapy, when combined with a diet / exercise intervention, increases weight loss compared with diet / exercise alone (-4.9 kg; 95% CI -7.3 to -2.4).

Shaw K et al. Cochrane DSR 2005

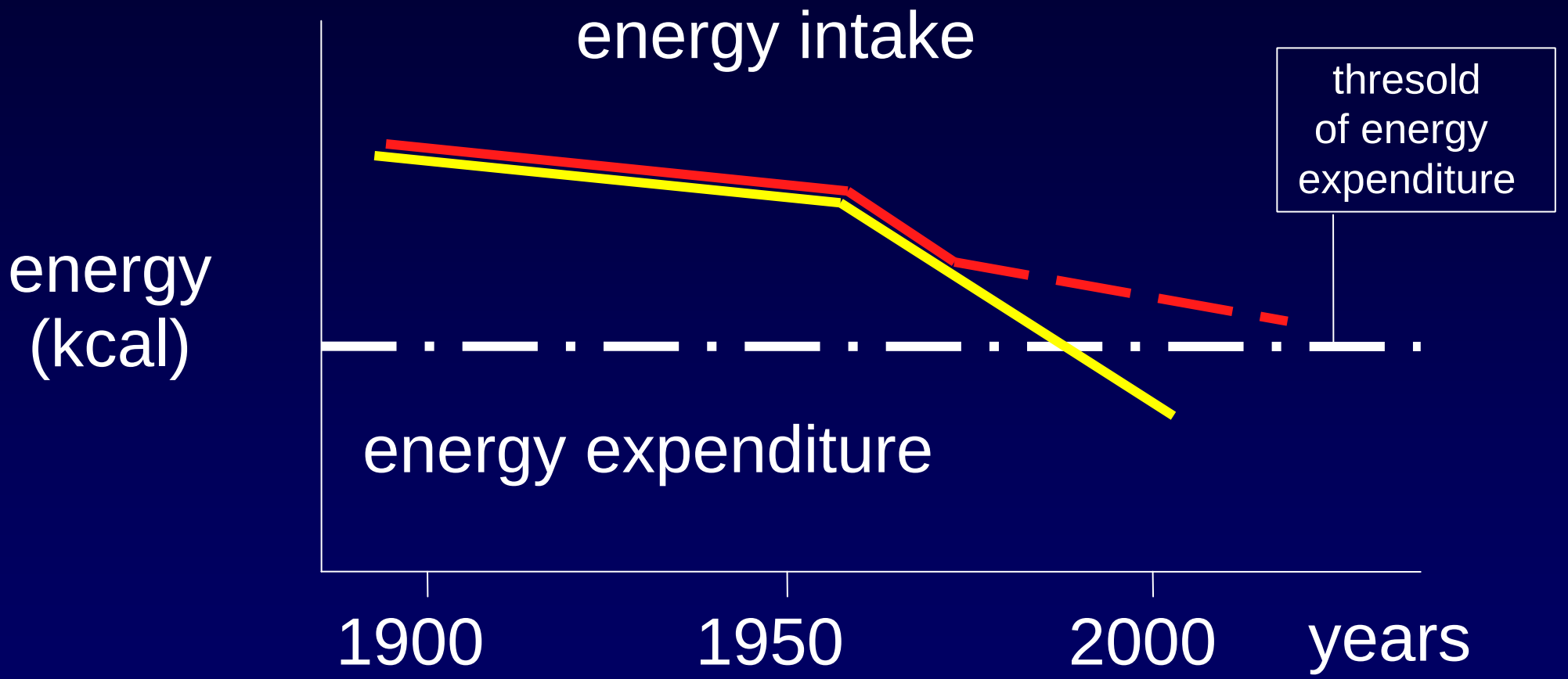
behavioral treatment of obesity
strategies for augmenting outcomes



meal replacement

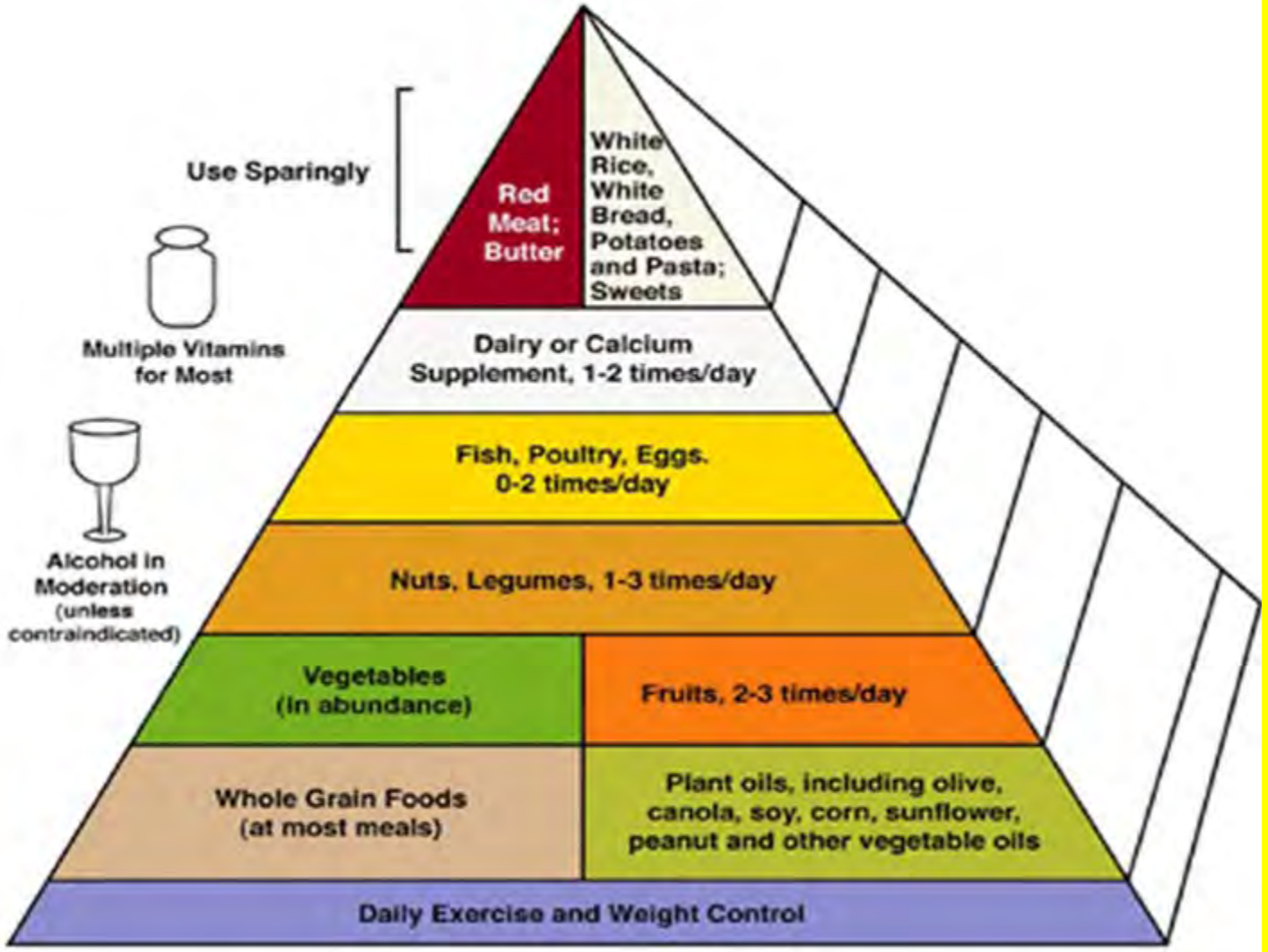
pharmacotherapy

commercial weight loss programs

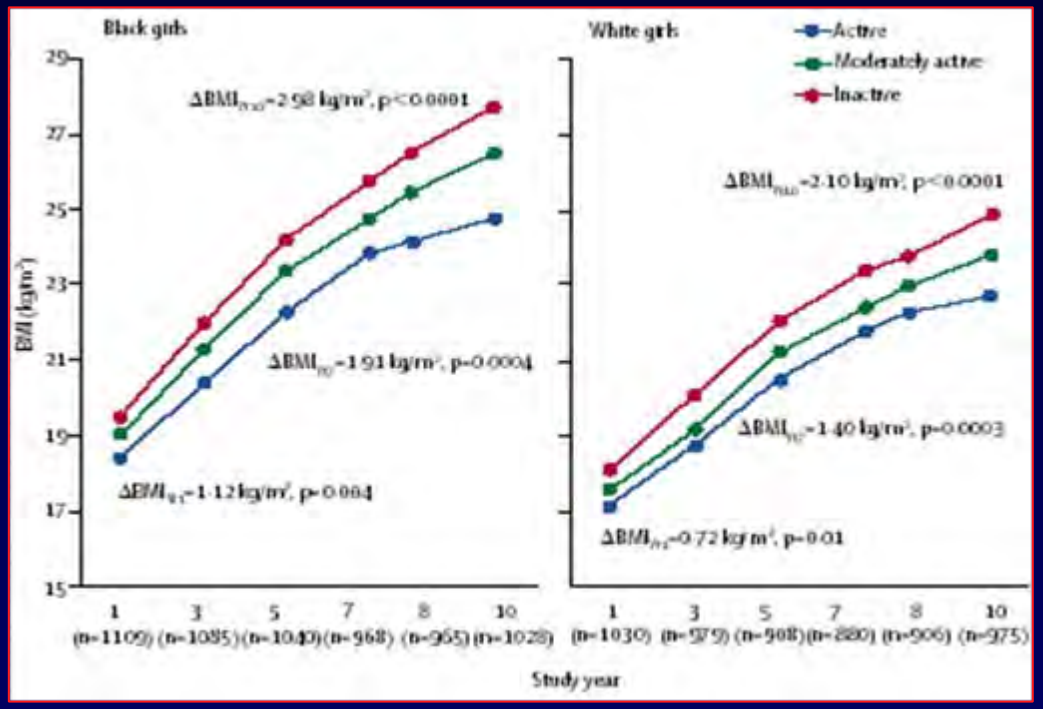


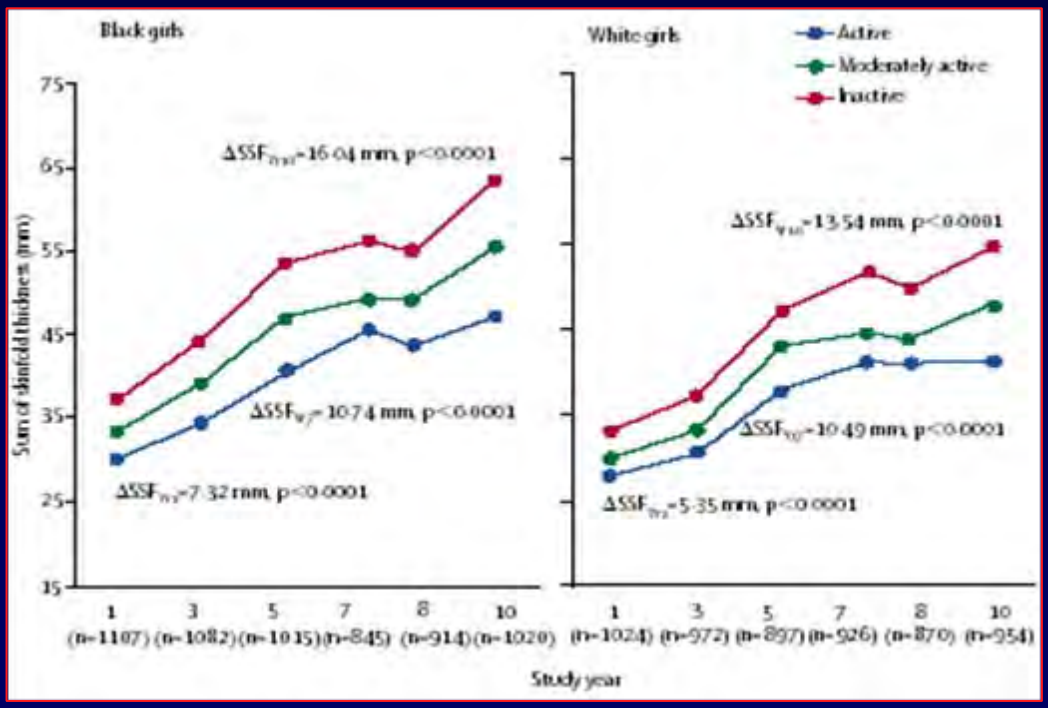
Hill & Wyatt J Appl Physiol , 2005

Healthy Eating Pyramid



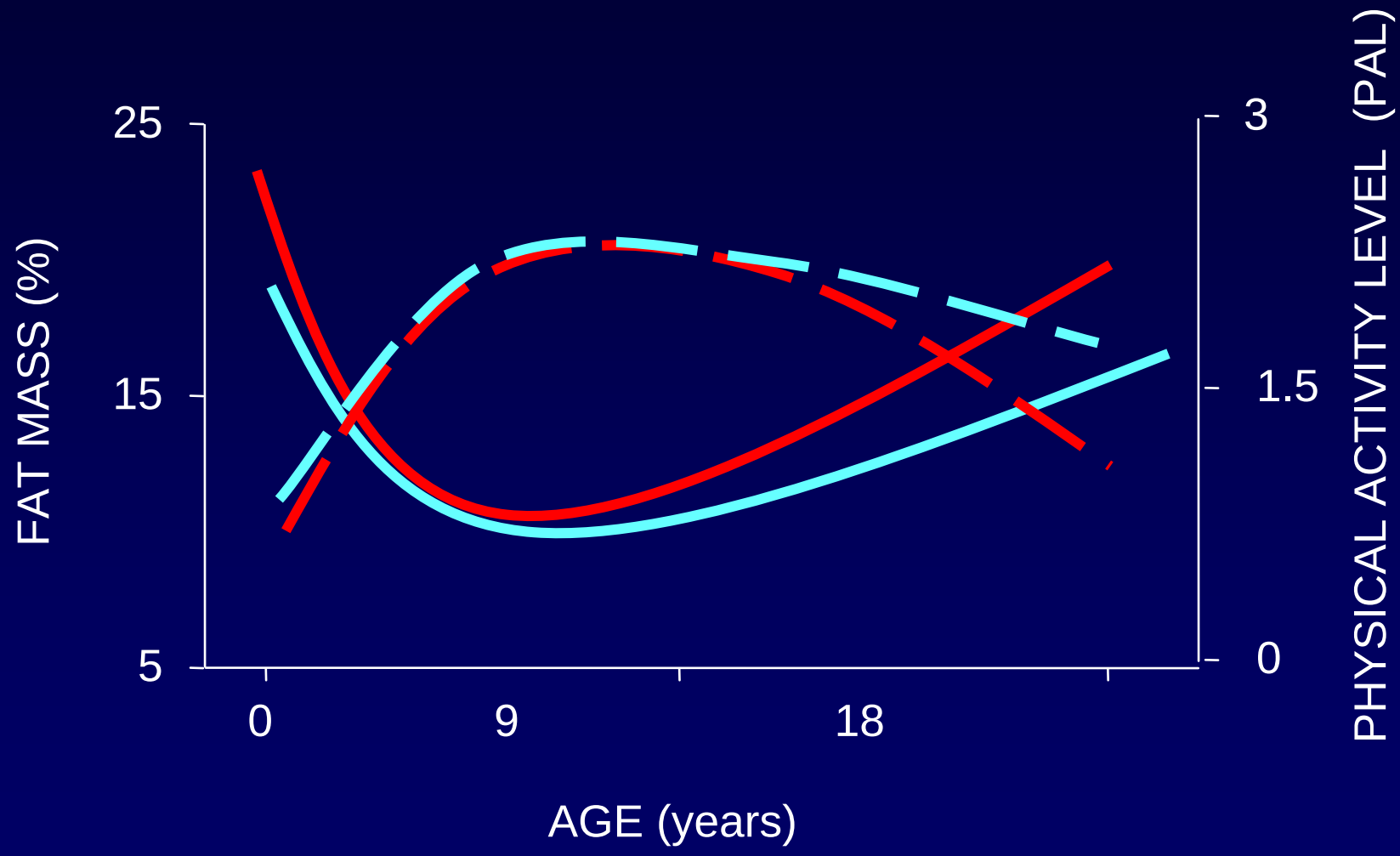
livelli di attività fisica durante l'adolescenza possono influenzare significativamente il BMI e l'adiposità nell'età adulta.



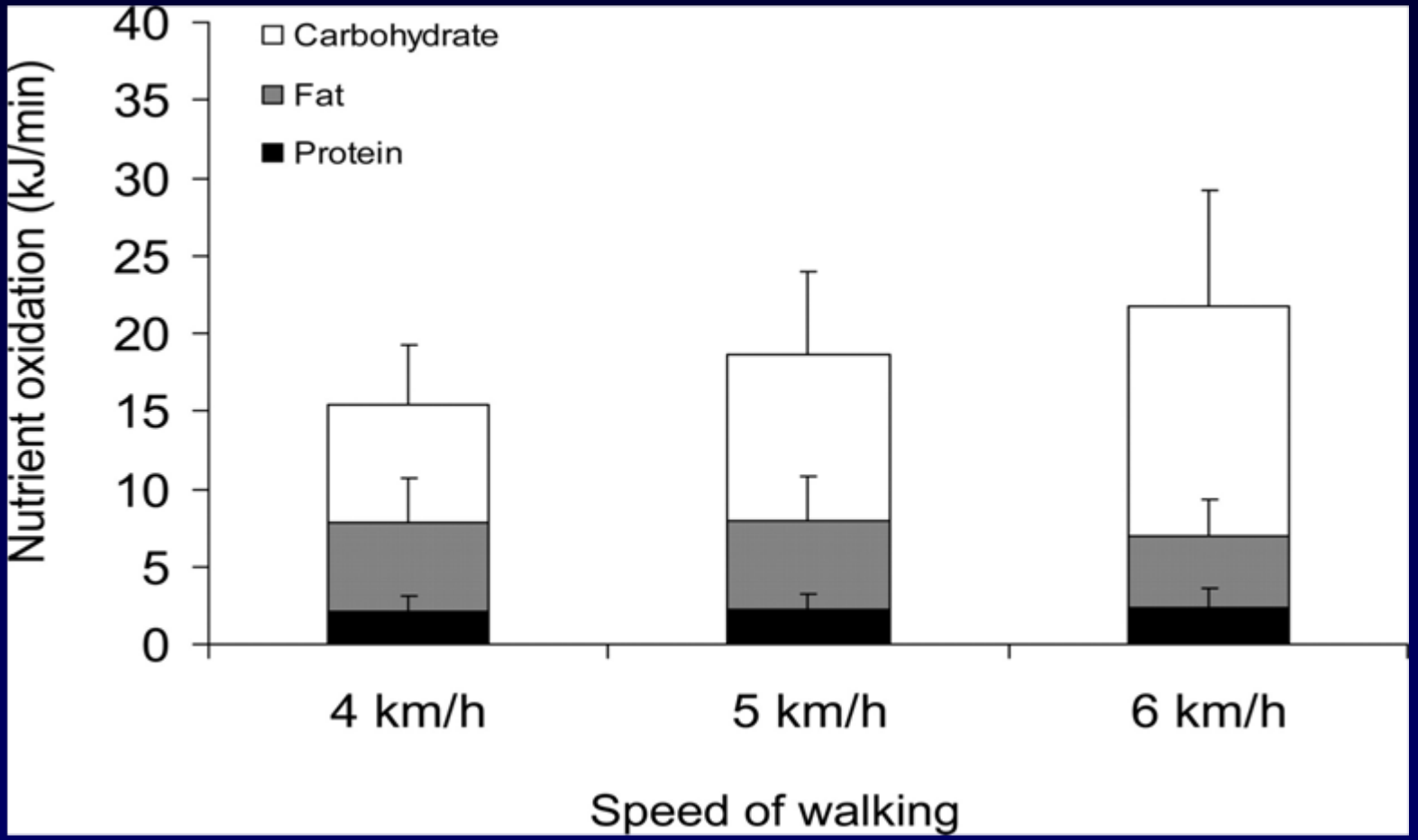


Kimm SYS, *et al* Lancet, 2005

PHYSICAL ACTIVITY AND BODY FAT



Nutrient oxidation measured during walking at speeds of 4, 5, and 6 km/h, respectively, in a group of obese prepubertal children



Maffeis, C. *et al.* J Clin Endocrinol Metab 2005;90:231-236

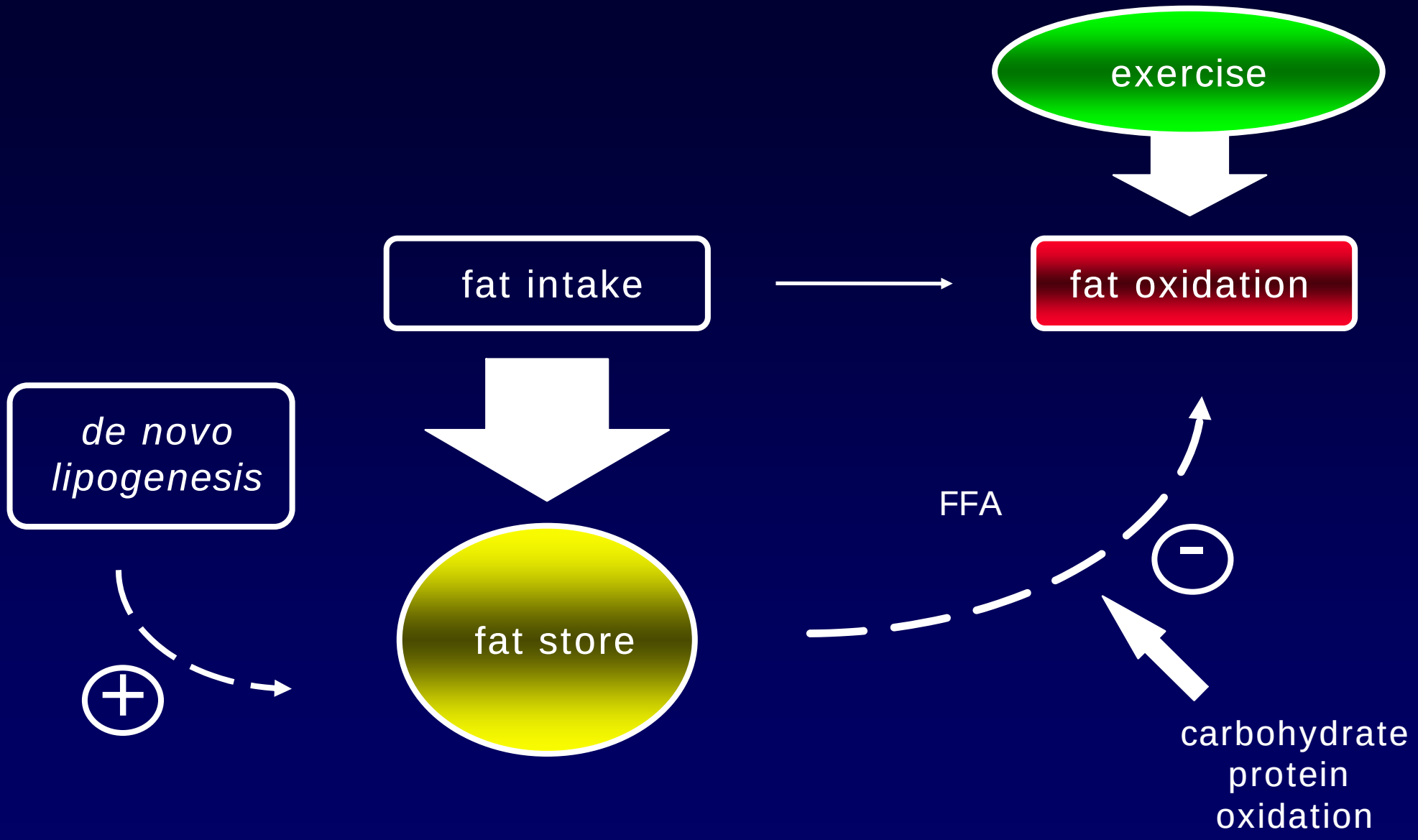
conclusions

Low-calorie, low-fat, (low-GI), high fiber diet is the most effective in the treatment of obesity

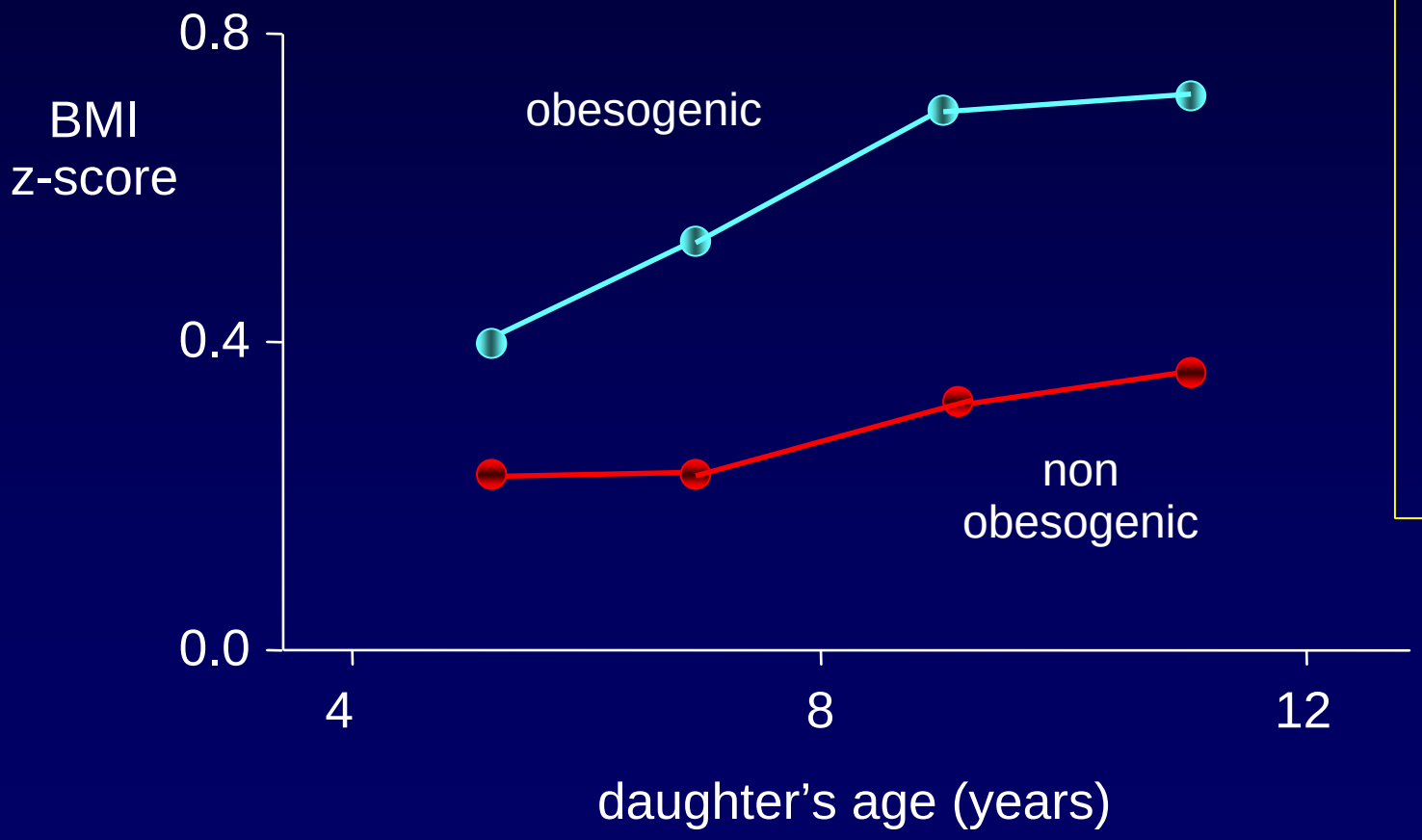
Food provision and meal replacement may be of help

Physical activity (>400 kcal per day) is associated with a better outcome both in the medium- and the long-term

Behavioral and cognitive-behavioral therapy increase the efficacy of diet & physical activity


exercise
fat intake
fat oxidation
de novo lipogenesis
FFA
fat store
carbohydrate
protein
oxidation

association of family environment with children's TV viewing and with low levels of physical activity



Family cluster

Body fat (%)

Fat intake (%)

TV viewing (h/day)

Davidson KK, et al. Obes Res 2005

diet in the managment of weight loss

Low-calorie diets

Low carbohydrate diets

Very-low-calorie diets

Very-low-fat diets

6th AME National Meeting
Italian Association of Clinical Endocrinologists

3 rd Joint Meeting with AACE
American Association of Clinical Endocrinologist

Update in Clinical Endocrinology
Verona, ITALY October 27-29, 2006

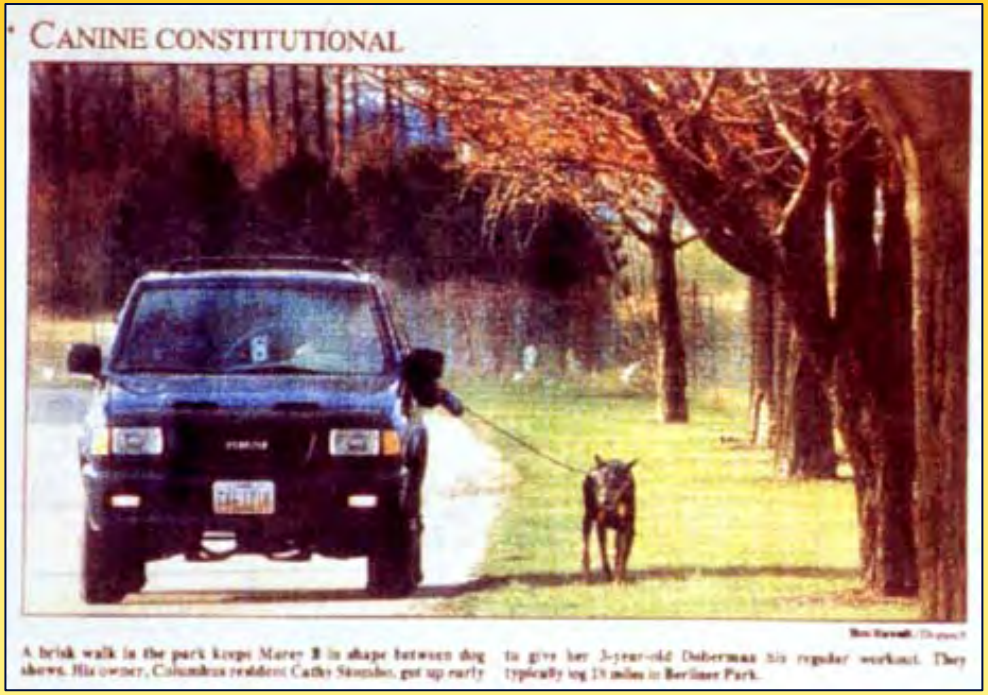
Current Management of Obesity

Drug Therapy: the present

Mauro Maccario

ENDOCRINOLOGIA
e MALATTIE del METABOLISMO
Università di Torino

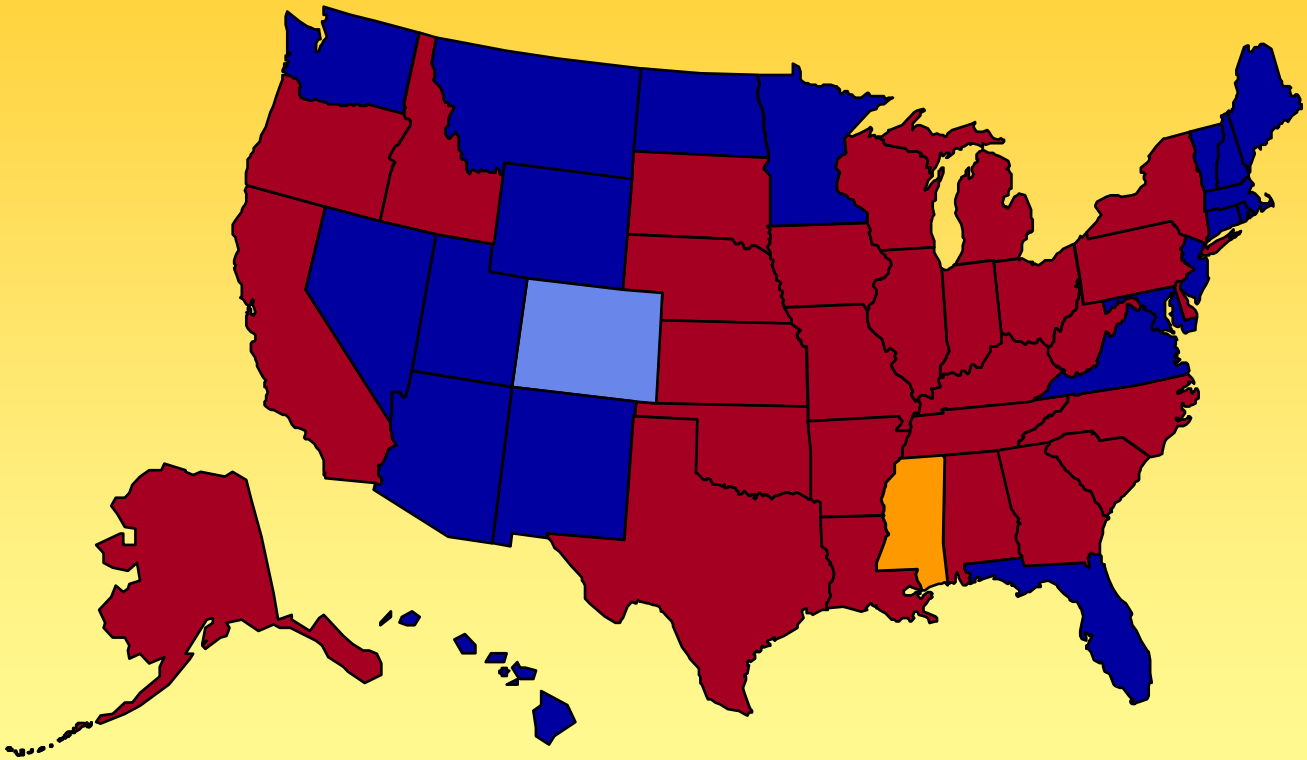
Need of a drug treatment?



- Genetic basis
- One of the major causes of morbidity and mortality in western countries.
- Failure of non-pharmachological treatment

Obesity Trends* Among U.S. Adults

BRFSS, 2001

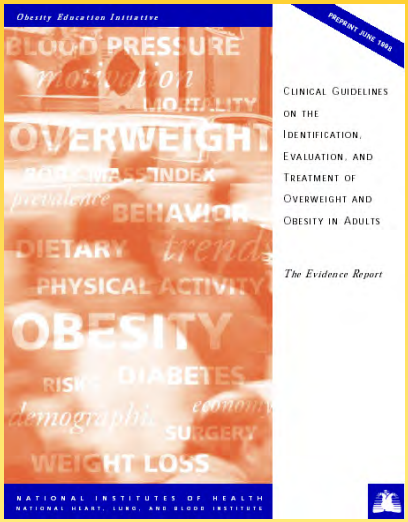


(*BMI ≥30, or ~ 30 lbs overweight for 5′4″ woman)

Source: Mokdad A H, et al. *J Am Med Assoc* 1999;282:16, 2001;286:10.

Evidence Statement: *Weight loss drugs approved by the FDA for long-term use may be useful as an adjunct to diet and physical activity for patients with a BMI of ≥ 30 with no concomitant obesity-related risk factors or diseases, and for patients with a BMI of ≥ 27 with concomitant obesity-related risk factors or diseases. Evidence Category B.*

Need of a drug treatment



In carefully selected patients, appropriate drugs can augment LCDs, physical activity, and behavior therapy in weight loss. Weight loss drugs that have been approved by the FDA for long-term use can be useful adjuncts to dietary therapy and physical activity for some patients with a BMI of > 30 with no concomitant risk factors or diseases, and for patients with a BMI of > 27 with concomitant risk factors or diseases. The risk factors and diseases considered important enough to warrent pharmacotherapy at a BMI of 27 to 29.9 are hypertension, dyslipidemia, CHD, type 2 diabetes, and sleep apnea. Continual assessment by the physician of drug therapy for efficacy and safety is necessary.

AME-AACE, Verona 2006

11. 4. PRINCIPI DELLA TERAPIA FARMACOLOGICA

11. 4. 4. Nei pazienti con IMC compatibile con una condizione di **obesità lieve o moderata**, la terapia farmacologica potrebbe avere uno spazio nell'ambito di un programma terapeutico integrato.

11. 4. 5. In questi pazienti, gli obiettivi dell'associazione del farmaco sarebbero:

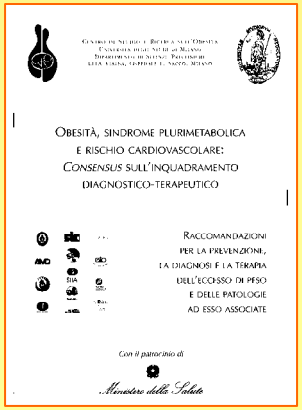
- Riduzione dei fattori di rischio
- Miglioramento della patologia associata
- Facilitare il mantenimento del peso dopo una fase di calo ponderale.

11. 4. 6. Nei pazienti con IMC compatibile con una condizione di **obesità grave,** la terapia farmacologica potrebbe avere uno spazio nell'ambito di un programma terapeutico integrato.

11. 4. 7. In questi pazienti, gli obiettivi dell'associazione del farmaco sarebbero:

- Favorire la compliance alla dieta
- Determinare un effetto "antabuse" verso alcune componenti della dieta
- Facilitare un iniziale calo ponderale che motivi il paziente a proseguire il trattamento
- Facilitare il mantenimento del peso dopo una fase di calo ponderale.

Need of a drug treatment



Need of a drug treatment ICSI 2004

ICSI Health Care Guideline

Prevention and Management of Obesity (Mature Adolescents and Adults)
First Edition/November 2004

Management Recommendations Based on BMI/Risk of Disease

BMI	*18.5-24.9	25-29.9	30-34.9	35-39.9	≥ 40
Risk	Low	Minor	Moderate	High	Severe
N = Nutrition	N	N	N	N	N
P = Physical Activity	P	P	P	P	P
B = Behavioral Management	B	B	B	B	B
M = Medication		M**	M	M	M
S = Surgery				S***	S

* In this group of patients, weight maintenance and prevention of obesity are key issues because a substantial proportion of these patients may become overweight/obese in the future.

** Patients considered for pharmacotherapy should have a BMI > 30 and no concomitant obesity-related risk factors or diseases, or a BMI > 27 with concomitant obesity-related risk factors or diseases.

*** In the presence of significant comorbid conditions, surgery may be indicated for patients with a BMI of ≥ 35.

See also Annotation #2, Table 2, " Comorbid Condition Assessment."

Medications

1. Sibutramine and Orlistat are safe for most patients when carefully monitored by a physician and may be part of a program for weight management or maintenance which should include nutrition and physical activity changes when indicated.
2. Since the short-term use of drugs (< 3 months) has not generally been found to be effective, pharmacotherapy should only be included in the context of a long-term treatment strategy.

Characteristics of an Ideal Drug

- Induces a **dose-related reduction** in body weight, even above 20%
- **Lowers blood pressure** more than can be accounted for by weight loss
- **Lowers blood glucose** more than can be accounted for by weight loss
- **Raises HDL**-cholesterol and lowers triglycerides
- **Reduces visceral fat** more than subcutaneous fat
- Has only **minimal sides effects**
- Cannot be abused
- Is taken only **once** daily
- Does not interact with other drugs
- Is **cheap**

Disappointments..

Date	Drug	Outcome
1893	Thyroid	Hyperthyroidism
1933	Dinitrophenol	Cataracts, neuropathy
1937	Amphetamine	Addiction
1967	Rainbow pills (amphetamines, digitalis, diuretics)	Deaths
1971	Aminorex	Pulmonary hypertension
1997	Fenfluramine/phentermine	Valvular insufficiency
2000	Phenilpropanolamine	Hemorrhagic stroke

Amphetamines derivatives with noradrenergic activity are still available... no longer than 3 months, not in cardiovascular disease, etc..

bollettino d'informazione sui farmaci

Which drug is now available?

Vietate le preparazioni a base di anoressizzanti ad azione centrale

Sulla base del parere espresso dal *Committee for Proprietary Medicinal Products* (CPMP) - presso l'agenzia europea dei medicinali - e delle indicazioni fornite dalla sottocommissione di Farmacovigilanza, si comunica che con Decreto 24 gennaio 2000 (GU n.25 del 1/2/2000) a partire dal 16 febbraio 2000 *"è fatto divieto ai farmacisti di eseguire* ***preparazioni magistrali*** *contenenti fentermina, mazindolo, norpseudoefedrina, fenbutrazato, fendimetrazina, amfepramone (dietilpropione) e propilexedrina e comunque tutte le altre sostanze che da sole o in associazione fra loro o con altre sostanze abbiano lo scopo di ottenere un effetto anoressizzante ad azione centrale, ed i medici sono tenuti ad astenersi dal prescriverle."*

Si ricorda che era già stato vietato l'utilizzo in preparazioni magistrali anche preparate in farmacia di fenfluramina e dexfenfluramina (Decreto 17 settembre 1997; GU n.219 del 19/9/1997) e di pemolina (Decreto 30 ottobre 1998; GU n.281 del 1/12/1998).

Per completezza si riportano brevemente gli estremi dei provvedimenti che hanno portato alla sospensione dell'autorizzazione delle **specialità medicinali** a base di fenfluramina, dexfenfluramina, pemolina, fendimetrazina e amfepramone.

- Decreto 17 settembre 1997 (GU n. 219 del 19/9/1997): è sospesa l'autorizzazione delle specialità medicinali a base di fenfluramina (Ponderal, Dima-Fen, Pesos) e dexfenfluramina (Isomeride, Glypolix);
- Decreto 30 ottobre 1998 (GU n.281 del 1/12/1998): è vietata la produzione e l'immissione in commercio di specialità medicinali comunque contenenti pemolina;
- Decreto 16 luglio 1999 (GU n.173 del 26/7/1999): revoca, su rinuncia della specialità Plegine a base di fendimetrazina;
- Decreto 15 novembre 1999 (GU n.275 del 23/11/99): sospensione dell'autorizzazione all'immissione in commercio di specialità medicinali a base di amfepramone (Tenuate Dospan, Linea Valeas).

BOLLETTINO D'INFORMAZIONE SUI FARMACI
Bimestrale del Ministero della Salute
http://www.sanita.it/farmaci/bollettino/bollettino.htm

Which drug is available?

E' vietato utilizzare i seguenti principi attivi principi attivi, sia come medicinali industriali che come galenici magistrali:

AMFECLORAL (1)	AMFETAMINA (1)	AMINOREX (1)
APETINIL (1)	BENZFETAMINA (1)	CICLOEXEDRINA(1)
CLOBENZOREX (1)	CLOFOREX (1)	CLORFENTERMINA (1)
CLORTERMINA (1)	DEXAMFETAMINA (1)	DEXFENFLURAMINA (2)
FENTERMINA (1)	FENFLURAMINA (2)	FENMETRAZINA (1)
FENPROPOREX (1)	MEFENOREX (1)	MEFENTERMINA (1)
d-lMETAMFEPIRAMONE (1)	METAMFETAMINA (1)	PEMOLINA (3)

FENTERMINA (1) - pur essendo esplicitamente indicata nel DM 24 gennaio 2000 l'utilizzazione di tale sostanza rimane a tutt'oggi vietata nelle preparazioni galeniche perché rientrante nel divieto espresso dal DM 13 aprile 1993

MAZINDOLO (1) pur essendo esplicitamente indicata nel DM 24 gennaio 2000 l'utilizzazione di tale sostanza rimane a tutt'oggi vietata nelle preparazioni galeniche perché rientrante nel divieto espresso dal DM 13 aprile 1993

1. D M 13 aprile 1993
2. D M 17 settembre 1997
3. DM 30 ottobre 1998

Which drug is available?

A seguito della sospensione del DM 24 gennaio 2000 è invece possibile eseguire preparazioni magistrali con sostanze aventi un effetto anoressante ad azione centrale non espressamente indicate nell'elenco di cui sopra e in particolare con le seguenti sostanze:

AMFEPRAMONE ("dietilpropione")
FEMBUTRAZATO
FENDIMETRAZINA
NORPSEUDOEFEDRINA
PROPILEXEDRINA
NOREFEDRINA ("FENILPROPANOLAMINA")
BENFLUOREX (esclusivamente nella Metodica Terapeutica Zohoungbogbo-M.T.Z.)

Diethylpropion: can we use it?

Amfepramone (Dietilpropione)

La Circolare FOFI n. 6818 del 12.06.2006 ha riassunto la situazione vigente:

In base a quanto disposto dall'art. 5 del DL 23/1998, convertito con modificazioni nella legge 94/1998, “non è consentita la prescrizione di preparazioni magistrali a base di principi attivi già contenuti in specialità medicinali la cui autorizzazione all'immissione in commercio sia stata revocata o non confermata per motivi non attinenti ai rischi d'impiego del principio attivo". Tuttavia, con decreti in data 15.11.1999, l'autorizzazione all'immissione in commercio delle specialità medicinali che contengono "amfepramone" ("Tenuate Dospan" e "Linea Valeas") è stata soltanto sospesa (ancorché per motivi attinenti ai rischi d'impiego); pertanto, nel caso di specie, non trattandosi di "revoca" ma di "sospensione", non appare ricorrere l'ipotesi preclusiva di cui all'art. 5 della legge 94/1998.
E' pur vero che il Ministero della sanità, con il DM 24.1.2000, aveva comunque espressamente vietato l'esecuzione di preparazioni magistrali contenenti sostanze anoressizzanti, tra le quali era esplicitamente indicato anche l'amfepramone; tuttavia, tale provvedimento è stato sospeso dal TAR Lazio. Si deve pertanto ritenere che, allo stato, sia consentita la prescrizione di preparazioni magistrali a base di "amfepramone", sulla base delle disposizioni contenute nel DM 18.9.1997 come modificato dal DM 30.10.1998, vale a dire con le stesse modalità e negli stessi limiti previsti per la "fendimetrazina"

PHARMACOTHERAPY OF OBESITY: THE PRESENT

Current available anti-obesity drugs for long time treatment:

- **SIBUTRAMINE *(Ectiva, Reductil)***
- **ORLISTAT (*Xenical*)**

Raccomandazioni per la prevenzione, la diagnosi e la terapia dell'eccesso di peso e delle patologie ad esso associate

11. 4. PRINCIPI DELLA TERAPIA FARMACOLOGICA

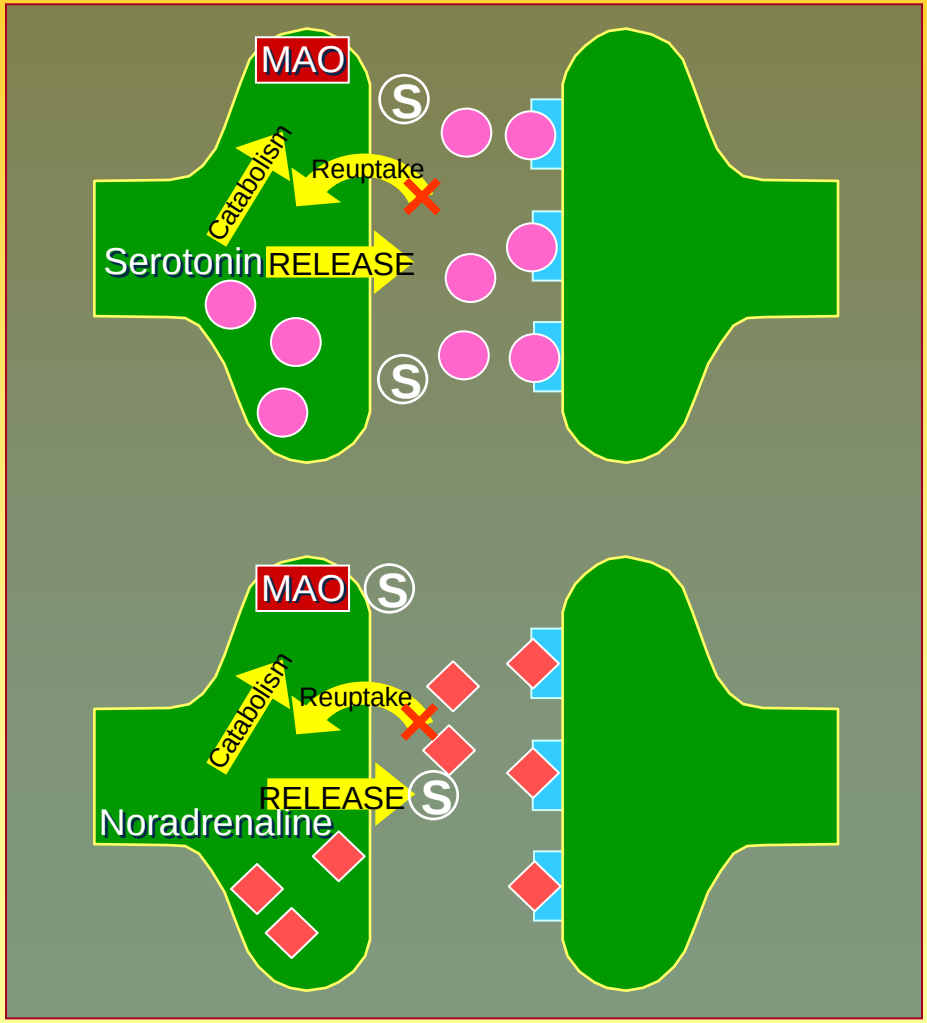
11. 4. 1. I farmaci da impiegare nella terapia farmacologia dell'obesità dovrebbero avere una efficacia confermata in studi eseguiti specificatamente per valutarne il rapporto rischio/beneficio ai dosaggi approvati dall'Autorità Sanitaria. I principi attivi valutati nell'ambito della *Consensus* attualmente disponibili e che rispondono a tali requisiti sono la sibutramina e l'orlistat.

AME-AACE, Verona 2006

Sibutramine: mechanisms of action.

sibutramine blocks serotonin and noradrenaline reuptake

S =sibutramine
◆ =noradrenaline
● =serotonin



Adapted from Ryan et al. Obesity Res. 1995; 3:553S-559S.

AME-AACE, Verona 2006

Mechanism of action for weight loss and toxicity of obesity drugs

Agents	Releasing Agent			Reuptake Inhibitor			Symphato-mimetic activity
	5-HT	NA	DA	5-HT	NA	DA	
Dexamphetamine[1]		√	√				√
Phentermine[1]		√	√				√
Fenfluramine[2]	√						
Dexfenfluramine[2]	√						
Sibutramine				√	√		
Fluoxetine				√			

[1]addiction, hypertension, myocardial toxicity, sudden death

[2]mitral and aortic lesions (5HT2B-R mediated) resembling valvular abnormalities of carcinoid syndrome with serotonin (5-HT) excess

Sibutramine

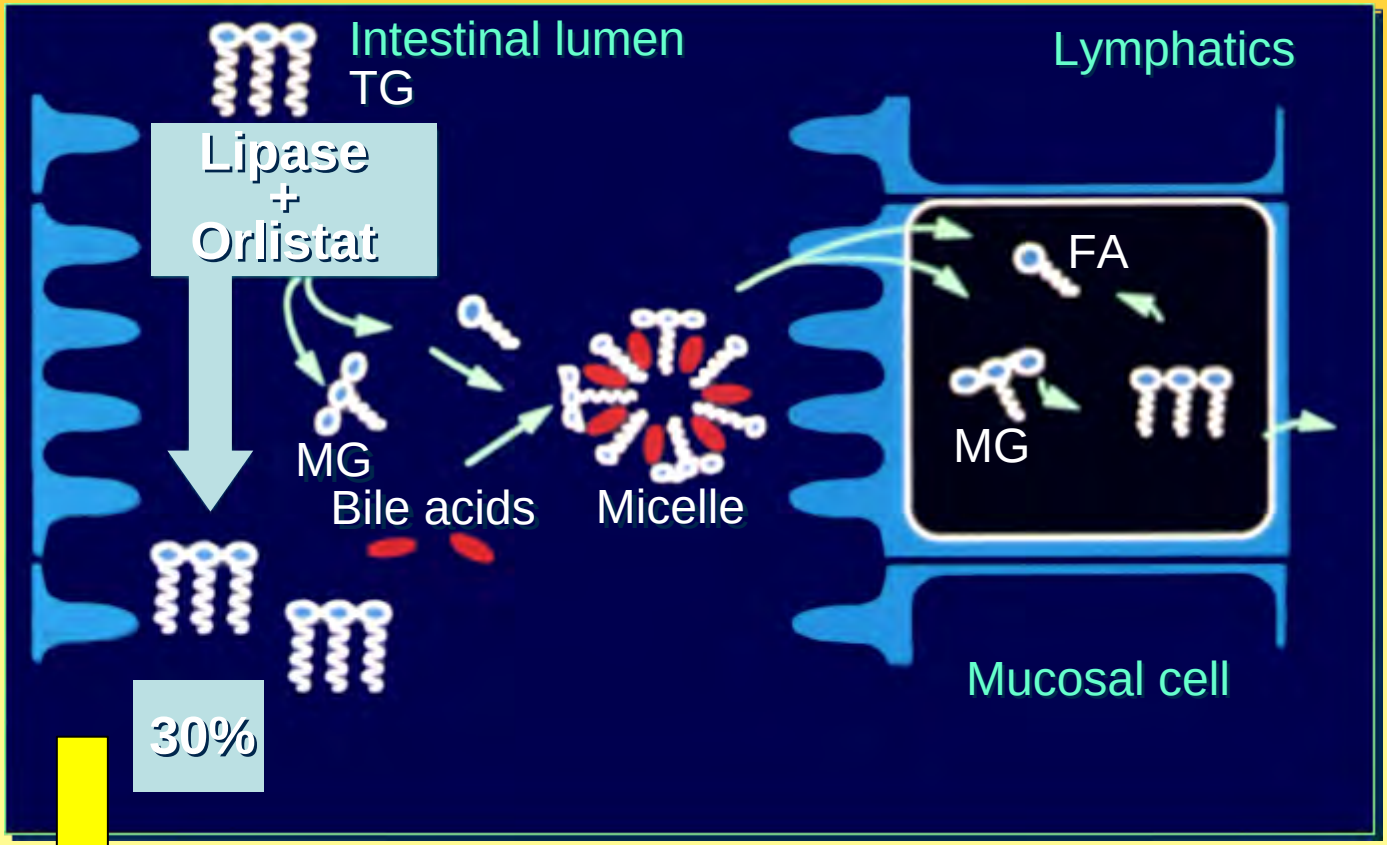
- Unlike fenfluramine and dexfenfluramine, sibutramine does not stimulate 5-HT_{2B}-R. Unlike anphetamine sibutramine does not stimulate adrenergic receptors.
- Sibutramine (at 2-5 times the therapeutic dose) lacks acute abuse potential in comparison with amphetamine.

SIBUTRAMINA
Con il Decreto 7 marzo 2002 del Ministero della Salute (G.U. n. 61 del 13.3.2002) è stata vietata la vendita delle specialità medicinali ad azione anoressizzante contenenti Sibutramina (Reductil, Ectivam Reduxate). Tale sospensione si estende anche alle preparazioni magistrali contenenti lo stesso principio attivo. Con successivo Decreto del 7 agosto 2002 (G.U. n. 201 del 28.08.2002) sono state riammesse al commercio le stesse specialità, ma non le preparazioni magistrali a base di sibutramina. Sono inoltre state introdotte modificazioni al regime di vendita di dette specialità, classificate in fascia c) con prescrizione riservata agli specialisti in cardiologia, diabetologia, endocrinologia, medicina interna e scienza dell'alimentazione. La prescrizione deve essere accompagnata da una scheda informativa che lo specialista deve consegnare al paziente.
La sospensione del DM 24 gennaio 2000 avrà efficacia fino a quando non si pronunci, su istanza di parte, il Consiglio di Stato ovvero fino al momento in cui sarà emanato un eventuale nuovo decreto.

Orlistat: mechanism of action

It is a reversible inhibitor of gastric and pancreatic lipases

Negligible systemic absorption (<1% detected in plasma) and therefore, minimal systemic lipase inhibition



Faecal fast loss at total daily dose of 360 mg orlistat

AME-AACE, Verona 2006

Sibutramine and Orlistat

ORIGINAL INVESTIGATION

The Efficacy and Safety of Sibutramine for Weight Loss

A Systematic Review

Arch Intern Med. 2004;164:994-1003

David E. Arterburn, MD, MPH; Paul K. Crane, MD, MPH; David L. Veenstra, PharmD, PhD

Review Article

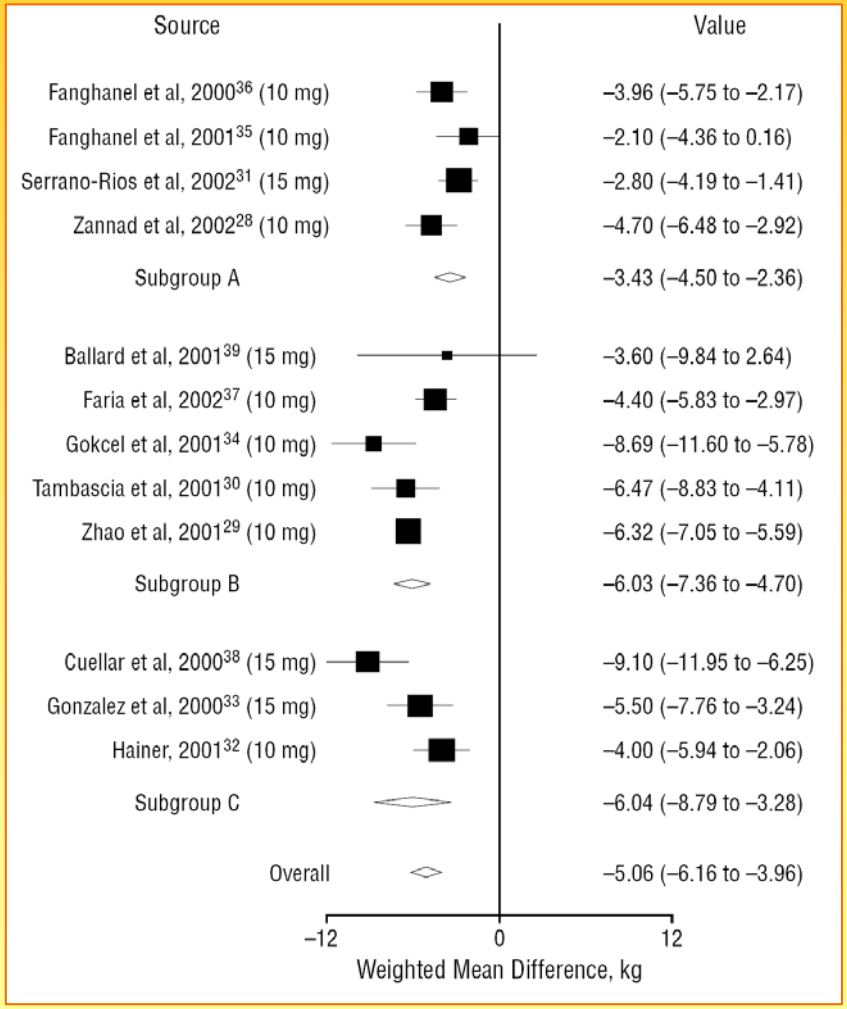
Am J Clin Nutr 2004;80:1461–8

Changes in body weight and serum lipid profile in obese patients treated with orlistat in addition to a hypocaloric diet: a systematic review of randomized clinical trials[1,2]

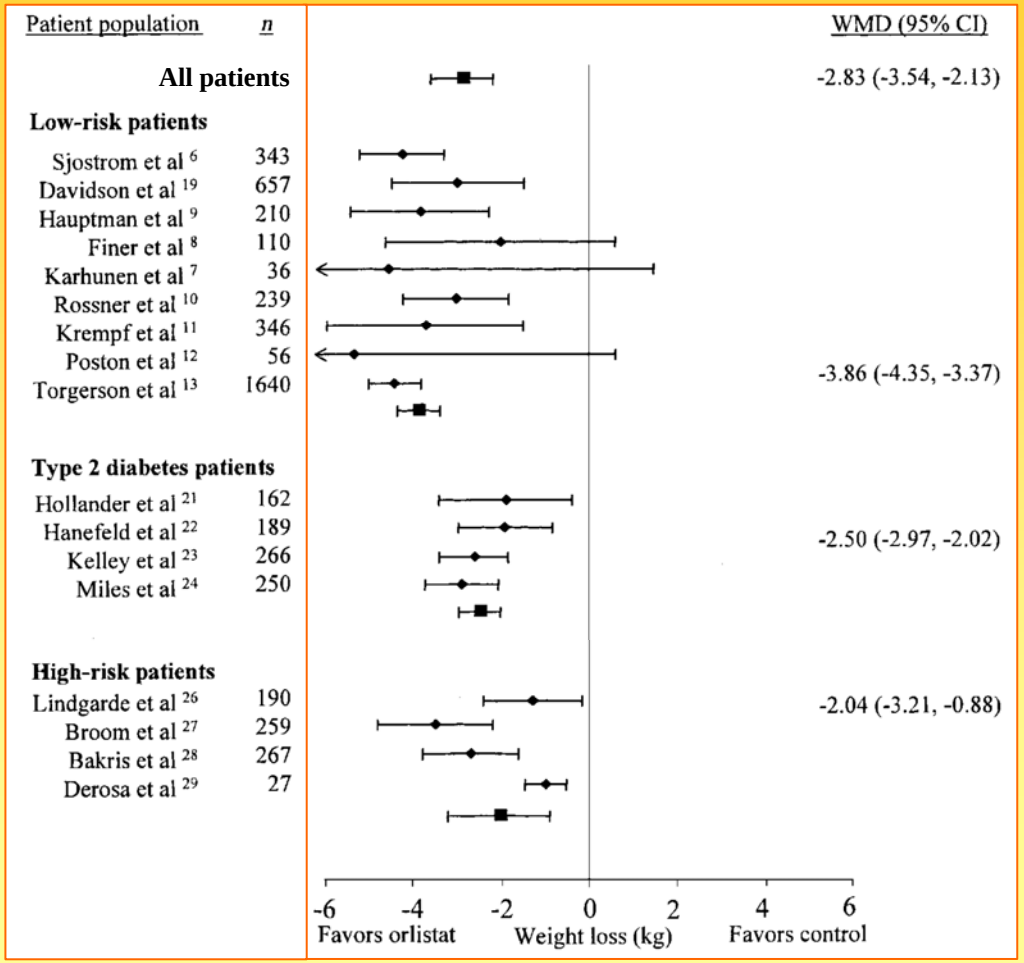
Brian Hutton and Dean Fergusson

Weight Loss

Sibutramine



Orlistat

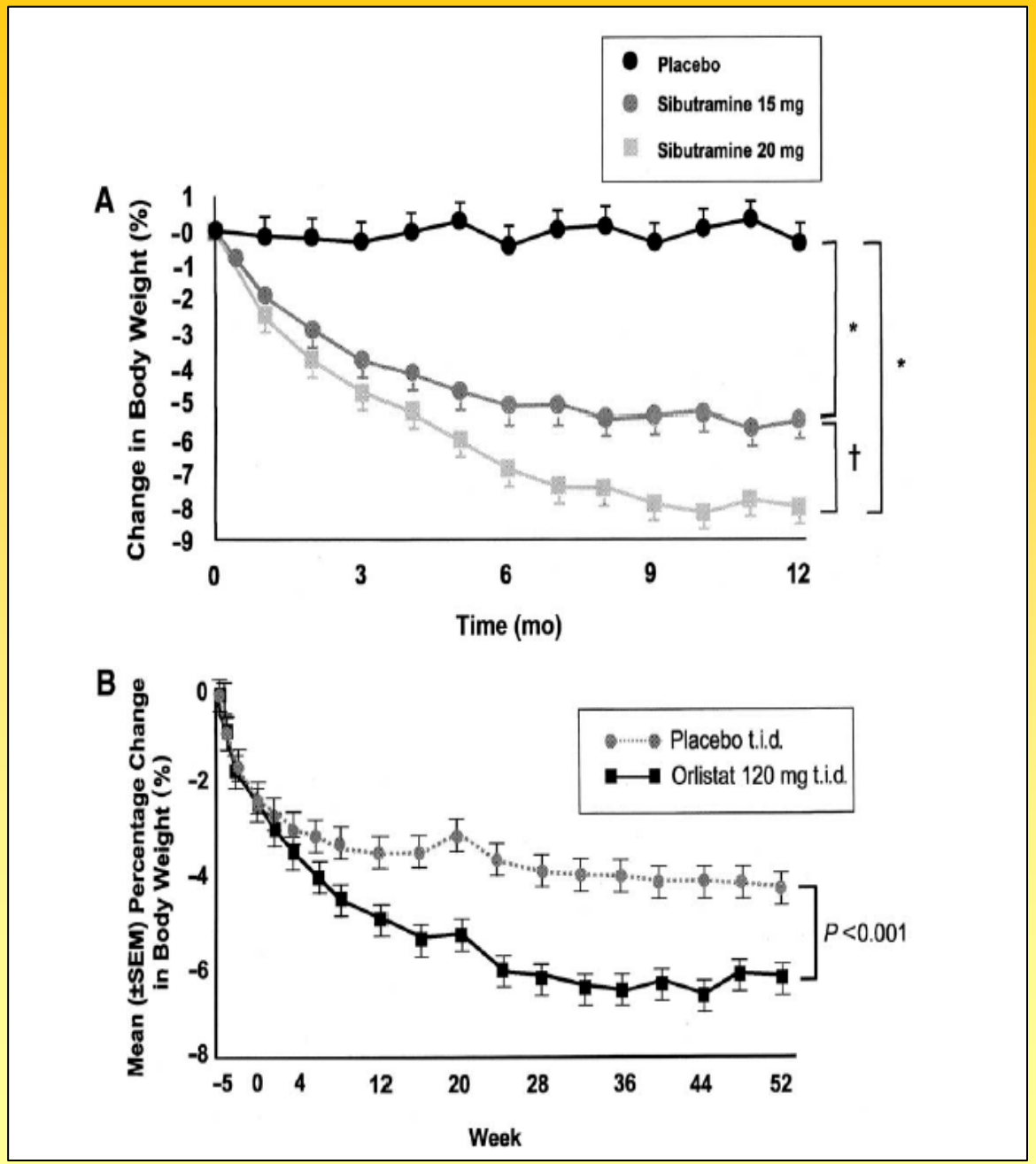


AME-AACE, Verona 2006

Weight Loss

Sibutramine and orlistat in weight loss of obese patients with type 2 diabetes

McNulty et al.,
Diabetes Care, 2003



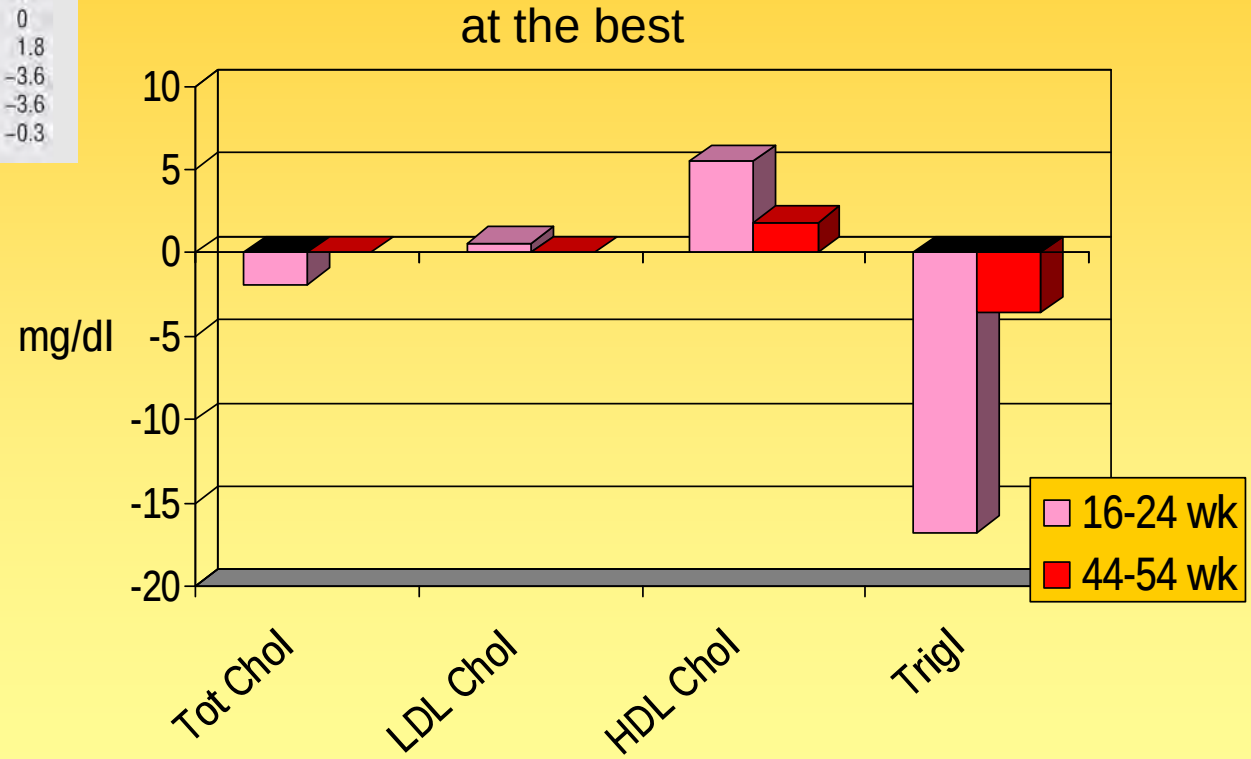
Effects of Sibutramine on Lipids

Table 2. Secondary Cardiovascular and Metabolic Outcomes From High-Quality RCTs of Sibutramine Hydrochloride, 10 to 15 mg/d, vs Placebo, by Treatment Duration*

Secondary Outcome	Treatment Duration, wk		
	8-12	16-24	44-54
Blood pressure, mm Hg			
Systolic	−0.2	−1.6 to 5.6	4.6
Diastolic	1.6	−0.8 to 1.7	2.8
Heart rate, beats/min	1.3	0.75 to 5.9	5.9
Cholesterol level, mg/dL			
Total	NR	−1.9 to 1.8	0
LDL	NR	0.6 to 2.6	0
HDL	NR	1.3 to 5.5	1.8
Triglyceride level, mg/dL	NR	−16.8 to 0	−3.6
Fasting serum glucose level, mg/dL	−19.8	−4.0 to −9.0	−3.6
Glycosylated hemoglobin level, %	−0.4	−0.1	−0.3

*Data are given as mean differences (MDs), sibutramine minus placebo, for a single high-quality RCT or a range of MDs when more than one high-quality RCT was identified.

Arternburn D. et al.
Arch Intern Med.
2004;164:994-1003



Effects of Orlistat on Lipids

Pooled between-group differences in serum lipid changes in 1-y studies[1]

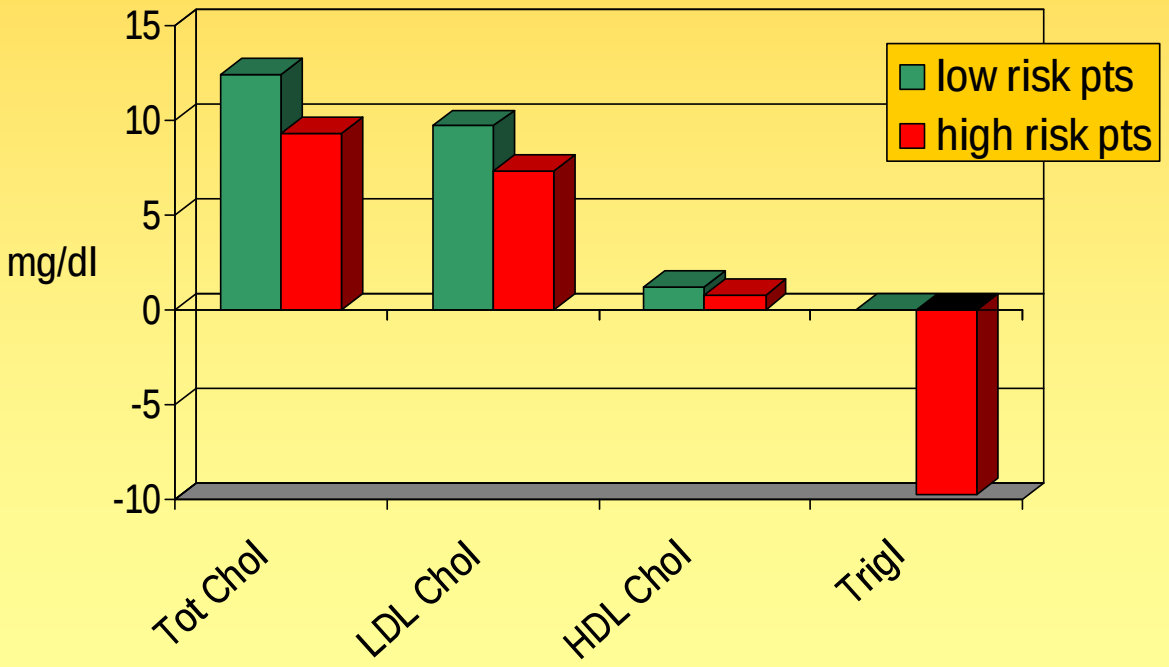
Outcome	Obese, low-risk patients: No. of studies (sample size)	Obese, low-risk patients: WMD, OL − PL (95% CI)	Obese, high-risk patients: No. of studies (sample size)	Obese, high-risk patients: WMD, OL − PL (95% CI)
Total cholesterol (mmol/L)	5 (2679)	−0.32 (−0.39, −0.25)[2]	2 (908)	−0.24 (−0.41, −0.07)[2]
LDL cholesterol (mmol/L)	5 (2679)	−0.25 (−0.31, −0.19)[2]	2 (908)	−0.19 (−0.30, −0.09)[2]
HDL cholesterol (mmol/L)	4 (1799)	−0.03 (−0.06, 0.01)	1 (376)	−0.02 (−0.06, 0.02)
LDL:HDL	4 (1799)	−0.18 (−0.26, −0.11)[2]	1 (532)	−0.15 (−0.30, 0.00)[2]
Triacylglycerols (mmol/L)	3 (1581)	0.00 (−0.17, 0.16)	1 (376)	0.11 (−0.1, 0.32)

[1] OL, orlistat; PL, placebo; WMD, weighted mean difference.
[2] Significant treatment effect favoring orlistat, $P \leq 0.05$.

Brian Hutton and Dean Fergusson

Am J Clin Nutr 2004;80:1461–8.

weighted means



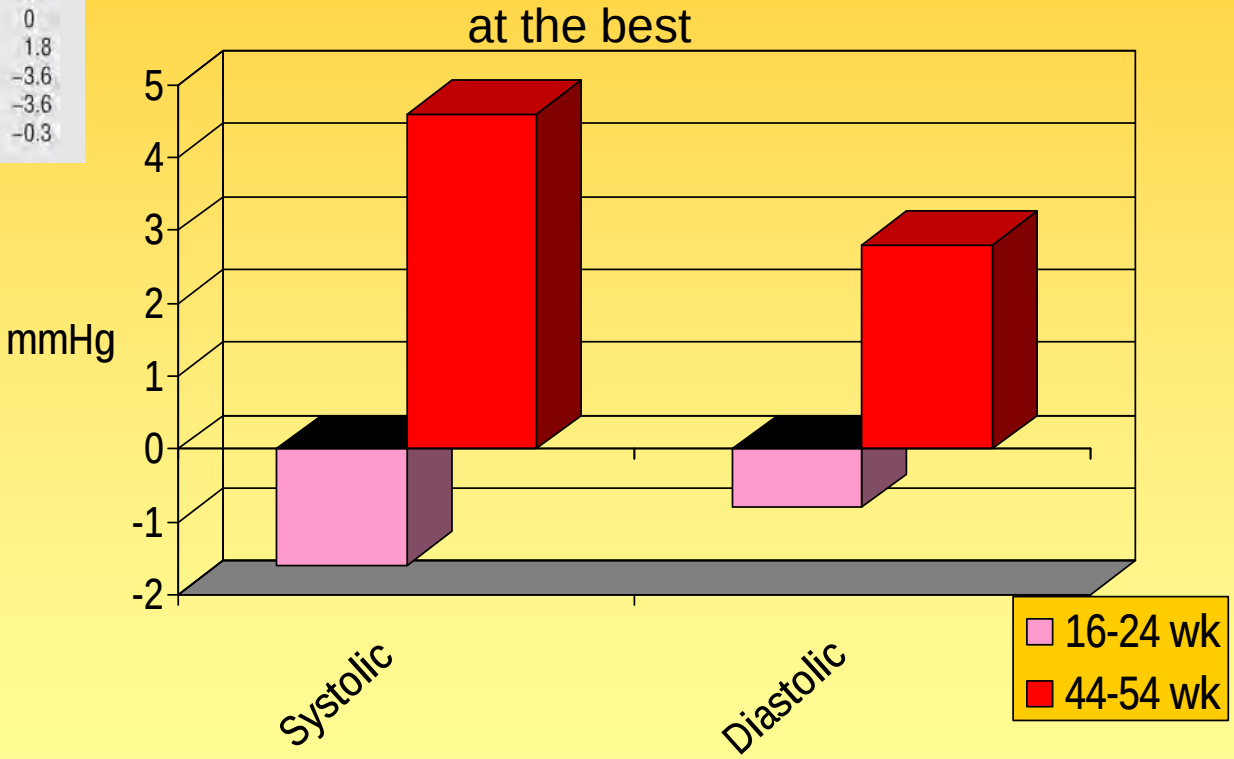
Effects of Sibutramine on Blood Pressure

Table 2. Secondary Cardiovascular and Metabolic Outcomes From High-Quality RCTs of Sibutramine Hydrochloride, 10 to 15 mg/d, vs Placebo, by Treatment Duration*

Secondary Outcome	Treatment Duration, wk		
	8-12	16-24	44-54
Blood pressure, mm Hg			
Systolic	−0.2	−1.6 to 5.6	4.6
Diastolic	1.6	−0.8 to 1.7	2.8
Heart rate, beats/min	1.3	0.75 to 5.9	5.9
Cholesterol level, mg/dL			
Total	NR	−1.9 to 1.8	0
LDL	NR	0.6 to 2.6	0
HDL	NR	1.3 to 5.5	1.8
Triglyceride level, mg/dL	NR	−16.8 to 0	−3.6
Fasting serum glucose level, mg/dL	−19.8	−4.0 to −9.0	−3.6
Glycosylated hemoglobin level, %	−0.4	−0.1	−0.3

*Data are given as mean differences (MDs), sibutramine minus placebo, for a single high-quality RCT or a range of MDs when more than one high-quality RCT was identified.

Arternburn D. et al.
Arch Intern Med.
2004;164:994-1003



Sibutramine – Adverse events

(at 10 mg/d sibutramine)

- **0.3-2.7 mm Hg and 1.6-3.4 increase in systolic and diastolic blood pressure, respectively (2-5%)**
- **2-5 beat/min increase in resting heart rate (1-8%)**
- **headache (31%), dry mouth (16.7%), constipation (10.8%), insomnia (9.4%)**

Adverse effects could be reduced without sacrificing efficacy if sibutramine was given intermittently for 44 wks (12 wks active drug alterning with 7 wks of placebo)

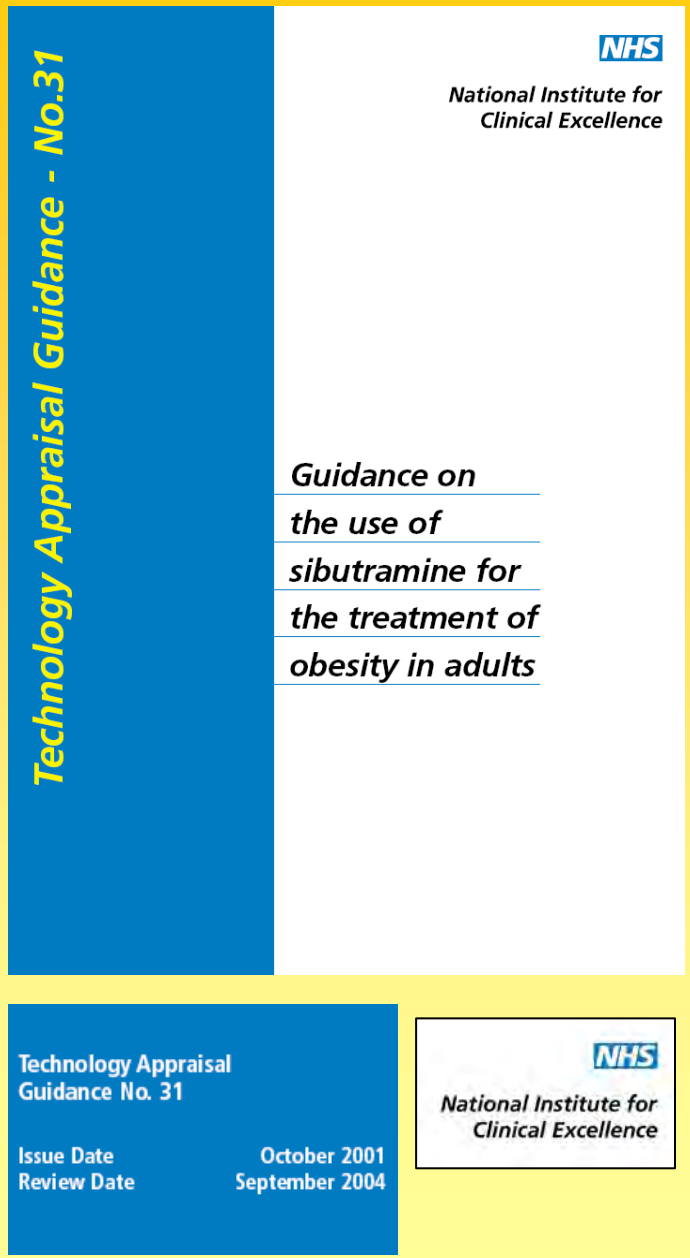
Orlistat: commonly observed adverse events (year 1)

Sjöström L. et al. Lancet 1998, 352; 167-172	Placebo (n=340)		Orlistat (n=343)	
	Incidence %	Withdrawals %	Incidence %	Withdrawals %
Fatty/oily stool	5.0	0.3	**30.9**	0.3
Increased defecation	7.4	0	**20.4**	0.3
Oily spotting	1.2	0	**17.5**	1.2
Faecal urgency	3.5	0	9.6	0.0
Flatulence	2.6	0	7.0	0.0
Faecal incontinence	0.0	0	7.0	1.5
Flatus with discharge	0.0	0	7.0	0.0
Oily evacuation	0.6	0	6.4	0.0
Liquid stools	11.8	0	**14.9**	0.3

Concomitant use of natural fiber (*psyllium mucilloid*) reduce the incidence of these gastro-intestinal effects. Supplementation of fat-soluble vitamins may be prudent to prevent the development of vitamin deficiency syndromes.

Sibutramine

- **Treatment plan**
- **Age 18-65**
- **BMI > 30 (or 27 with comorbidity)**
- **Previous attempts with diet, exercise, etc..**
- **Monitoring of treatment by health care professionals**
- **Starting dose 10 mg/day; may be increased at 15 mg/d after 4 weeks**
- **Continue if weight loss > 2 kg at 4 weeks and >5% initial bw at 3 months**
- **Not recommended (or suspended) if BP is above 145/90 or increases by more than 10 mmHg**
- **Not beyond 12 months**
- **No evidence support coadministration with other drugs**



www.nice.org.uk

Orlistat

Guidance on the Use of Orlistat for the Treatment of Obesity in Adults

NHS
National Institute for Clinical Excellence

www.nice.org.uk

Technology Appraisal Guidance No. 22

Issue Date March 2001
Review Date February 2004

1. Guidance

1.1 Orlistat should only be prescribed for people who have lost at least 2.5 kg in weight by dietary control and increased physical activity alone in the month prior to the first prescription and meet one of the following criteria:

1.1.1 a body mass index (BMI) of 28 kg/m^2 or more in the presence of significant co-morbidities which persist despite standard treatment. (E.g. Type 2 diabetes, high blood pressure and/or high total cholesterol level).

1.1.2 a BMI of 30 kg/m^2 or more with no associated co-morbidities.

Orlistat should only be prescribed for people between the ages of 18 and 75 years.

1.2 When treatment with orlistat is offered, arrangements should be made for appropriate health professionals (see paragraph 7.1) to offer specific concomitant advice, support and counselling on diet, physical activity and behavioural strategies.

1.3 Continuation of this therapy beyond three months should be supported by evidence of a loss of at least a further 5% of body weight from the start of drug treatment.

1.4 Continuation of this therapy beyond six months should be supported by evidence of a cumulative weight loss of at least 10% of body weight from the start of drug treatment.

1.5 Treatment should not usually be continued beyond 12 months, and never beyond 24 months.

XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study

A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients

JARL S. TORGERSON, MD, PHD[1]
JONATHAN HAUPTMAN, MD[2]
MARK N. BOLDRIN, MS[2]
LARS SJÖSTRÖM MD, PHD[1]

***Diabetes Care* 27:155–161, 2004**

Orlistat and T2DM

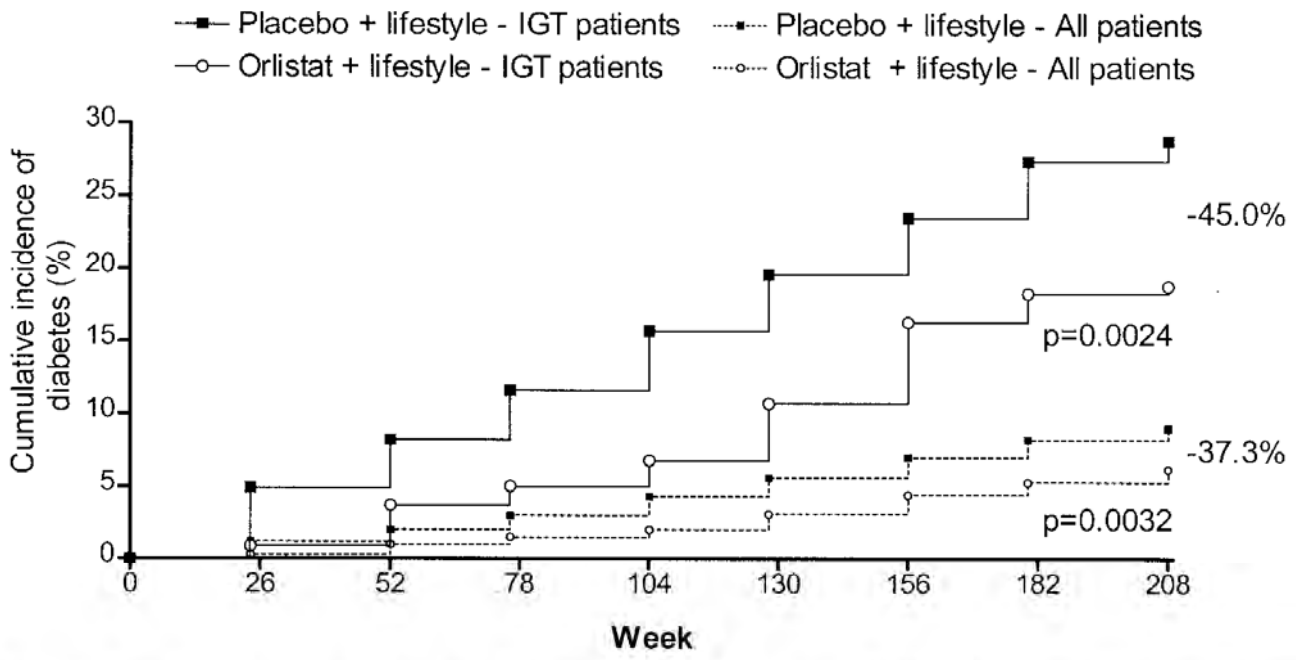


Figure 1—*Cumulative incidence of diabetes by study group in all obese patients (IGT or NGT at baseline) and only in obese patients with IGT at baseline. The decrease in the risk of developing diabetes with orlistat plus lifestyle compared with placebo plus lifestyle is indicated. P values shown are for the log-rank test.*

Royal College of Physicians
Setting higher medical standards

- Royal College of Physicians guidance suggests that:
  - Sibutramine may be more suitable for: frequent snackers, nocturnal eaters, patients with low HDL
  - Orlistat may be more suitable for: patients with impaired glucose tolerance or diabetes, patients with high total/LDL cholesterol, patients with high fat intake who can adhere to a low fat diet, patients who have repeatedly lost and regained weight

Fluoxetine

Evidence Report/Technology Assessment
Number 103, July 2004
Pharmacological and Surgical Treatment of Obesity

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services

www.ahrq.gov

Figure 7. Pooled analysis: fluoxetine, 6 months

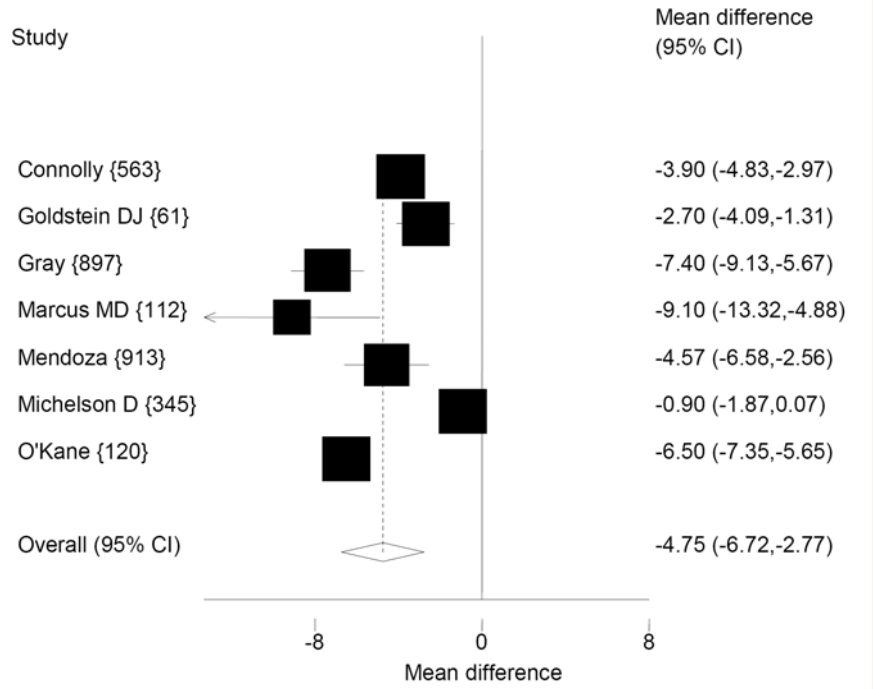
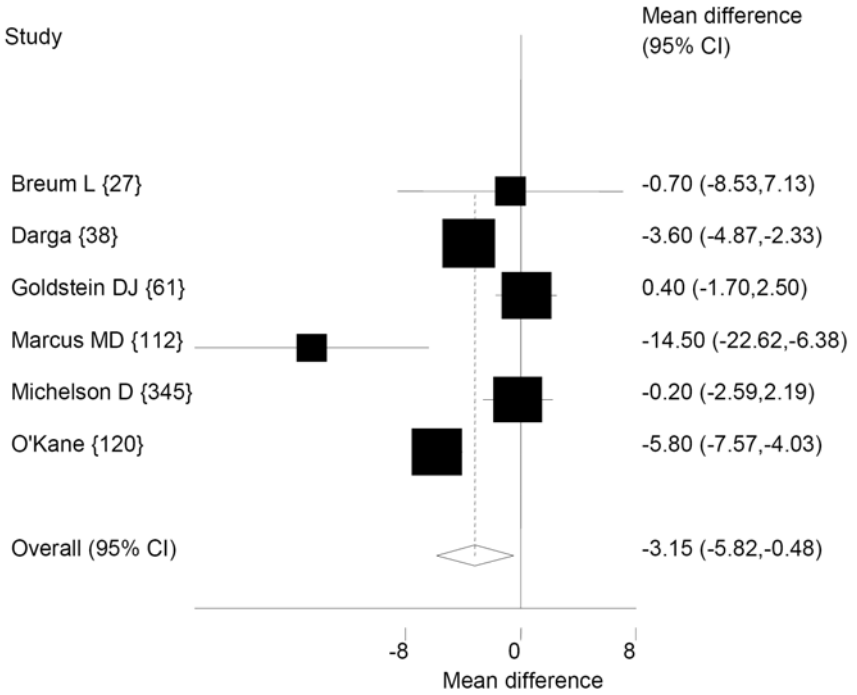


Figure 8. Pooled analysis: fluoxetine, 12 months



‘Natural’ weight loss

AME-AACE, Verona 2006

‘Natural’ weight loss

Giorno & Notte New!

Dimagrisci in 30 giorni!

PER INFORMAZIONI 848.151.717 TARIFFA URBANA

COME FUNZIONA | APPROFONDIMENTI | TESTIMONIALS | VIDEO | ORDINA

Contattaci!

Live chat Offline

Telefono Offline

E-mail

La prima confezione te la regaliamo noi!!!

...risultati garantiti in soli 30 giorni!!!

Come Funziona

1 NUOVA FORMULA PIU' EFFICACE

Si tratta di un integratore alimentare per il **controllo e la diminuzione del peso corporeo** a base di nuovi estratti che hanno un potere blocca grasso e brucia grasso più potente del Chitosano.
Funziona in modo combinato e sinergico con azione giornaliera (New Giorno) dopo i pasti ed azione notturna (New Notte) prima del sonno.
- E' l'evoluzione del prodotto dimagrante più venduto in Italia con **oltre un milione di clienti**;
- Risponde alle esigenze dei clienti in quanto può essere assunto **fino a 30 min dopo i pasti principali**, blocca con le sue nuove componenti **il 30% in più di grassi** rispetto al Chitosano;
-Le componenti principali, Neopuntia Nopal e Bioperine, sono naturali e brevettate.

2 GIORNO

New Giorno è stato ora potenziato con nuovi ingredienti 100% naturali, per un'azione ancora più mirata e concentrata.
La NeOpuntia Nopal® cattura il grasso prima che venga assorbito, eliminandolo poi nell'intestino mentre l'Agro secco di sidro di mele favorisce la diuresi.
NeOpuntia Nopal® è un nuovo ritrovato di origine vegetale ed è stato dimostrato scientificamente che riesca a bloccare fino al 30% in più di grassi rispetto al Chitosano.
L'Agro secco di sidro di mele agisce in sinergia con la NeOpuntia combattendo la ritenzione dei liquidi e quindi favorendo il raggiungimento del peso ottimale.

3 NOTTE

New Notte contiene un insieme di estratti naturali e minerali unici e rivoluzionari che agiscono per bruciare il grasso nel tuo corpo.
Tutto funzionamentre dormi, per cui lascia che New Notte lavori per te andando tranquillamente a letto: tu perdi peso!
L'Agro secco di sidro di mele è un estratto naturale del succo di mela che favorisce l'eliminazione dei liquidi in eccesso.
La Bioperine® è un estratto brevetatto e naturale che deriva dal pepe nero, aumenta la biodisponibilità degli altri ingredienti di New Notte. Specificatamente favorisce l'assimilazione del Fucus, migliorando il consumo energetico corporeo per bruciare calorie e grassi.

ORDINA »

I PRINCIPI ATTIVI

GIORNO

il **Neopuntia Nopal** è una fibra vegetale brevettata, pura e naturale al 100% che viene estratta in maniera completamente naturale e delicata dal Fico d'India (Cactus Opuntia Ficus-Indica). E' un ingrediente nuovo nell'ambito dei prodotti per il dimagrimento che ha la capacità di aggredire e bloccare i grassi introdotti con l'alimentazione, evitandone l'assimilazione.
Come blocca-grassi è il 30% più potente del Chitosano.
l'**Aceto di mele** ha proprietà tonificanti e depurative, quindi aiuta ad eliminare i liquidi in eccesso.
il **Cromo** interviene nel metabolismo degli zuccheri, stimolando l'attività degli enzimi responsabili del metabolismo del glucosio, favorendo quindi una regolare assimilazione dei carboidrati

NOTTE

il **Biopirene** è un' estratta dal Pepe Nero che è brevettata e naturale (utilizzato da sempre nella medicina indiana), è un TERMONUTRIENTE ha cioè la capacità di aumentare la biodisponibilità degli altri ingredienti contenuti nelle compresse notte, favorendo la loro assimilazione da parte dell'organismo, migliorando il consumo energetico corporeo e contribuendo quindi a bruciare più calorie e di conseguenza a tenere sotto controllo il peso. L'azione del Fucus e dell'Aceto di Mele è potenziata dall'azione della BIOPERINE.
l'**Aceto di mele** ha proprietà tonificanti e depurative, quindi aiuta ad eliminare i liquidi in eccesso.
il **Fucus** (E.S. 0,1% in Iodio (15%)) E' ricco di iodio, che favorendo il metabolismo basale, aiuta a bruciare calorie e quindi a controllare il peso.

E PER PERDERE PESO PIÙ VELOCEMENTE...
New Giorno & Notte funziona ancora meglio se lo associ ad una dieta equilibrata e variata e ad un po' di esercizio fisico: basta infatti una camminata veloce per bruciare un bel po' di calorie!

‘Natural’ weight loss ?

Capturia - .. "*la modalità d'uso era semplicissima: dovevo semplicemente prendere 60 gocce al giorno diluite in acqua. Tutto qui!*" […] *Dopo 3 giorni* […] *avevo perso 3 chili* […] *avevo mangiato come sempre di tutto* […]*. Dopo 2 settimane avevo perso 10 Kg* […]*. Nel giro di un mese avevo perso 15 chili* […] *Senza sforzi,* ***senza seguire diete drastiche****.. Sono passati circa 6 mesi da quando ho iniziato il trattamento e le posso garantire che* ***non ho ripreso nemmeno un etto****. Il mio peso si è semplicemente stabilizzato e nonostante mangi di tutto, continuo a non ingrassare* […], *senza medicinali e senza sforzi*. […] "…**trattamento 100% naturale** e senza effetti secondari“..

Solubel - .. l'Istituto di ricerca Bioline è venuto a conoscenza di una sbalorditiva scoperta che ha portato a un nuovo trattamento dimagrante" e ne è sottolineata la particolare proprietà "di invertire l'effetto delle calorie […] anziché trasformare le calorie in grassi, le calorie vengono sia bruciate ed eliminate per vie naturali che trasformate in energia […] senza alcuna controindicazione".

QuickDiet *– … Le persone che l'hanno provato, sono così entusiaste, soprattutto perché la diminuzione di peso si ottiene senza limitazioni di cibo senza medicinali, senza sport o massaggi*". *Quickdiet*" a base di estratto di Nopal [*altro nome del fico d'india* n.d.r.] "*Non è un'illusione* ***è serio e scientificamente provato****. E ASSOLUTAMETE SICURI: chiunque prova il trattamento Quickdiet dimagrisce* [perché] ***stimola il metabolismo e distrugge i grassi***".

"Capturia" contiene tarassaco, malva, tiglio, betulla e pilosella; "Solubel" contiene ananas, mango, scorza di limone e schisandra; "QuindkDiet" contiene alga fucus, rosa canina, garcinia, nopal e glucomannano.

AUTORITA' GARANTE
DELLA CONCORRENZA E DEL MERCATO

..nota del 28 settembre 2005, l'Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione (di seguito anche INRAN):

Alghe fucus – … in essi si possono trovare tracce di ***arsenico e metalli pesanti*** che vengono normalmente metabolizzati dall'alga... gli estratti da fucus possono avere un'azione lassativa. L'azione di stimolo sul metabolismo di questi preparati deriva dalla presenza in essi di ***iodio*** che, in molti casi, ne è il principio attivo più importante.

Gambo di Ananas – E' presente in questo frutto un complesso enzimatico, la bromelina, che risulta avere alcune proprietà farmacologiche. Queste proprietà includono ***l'inibizione dell'aggregazione piastrinica, l'attività fibrinolitica***, effetti antinfiammatori ed aumento delle capacità esfolianti.. i preparati a base di gambo d'ananas dovrebbero essere utilizzati con estrema cautela per i soggetti con ulcera peptica o affetti da patologie che riguardano il sistema coagulante e piastrinico o per somministrazione in concomitanza di farmaci anticoagulanti.

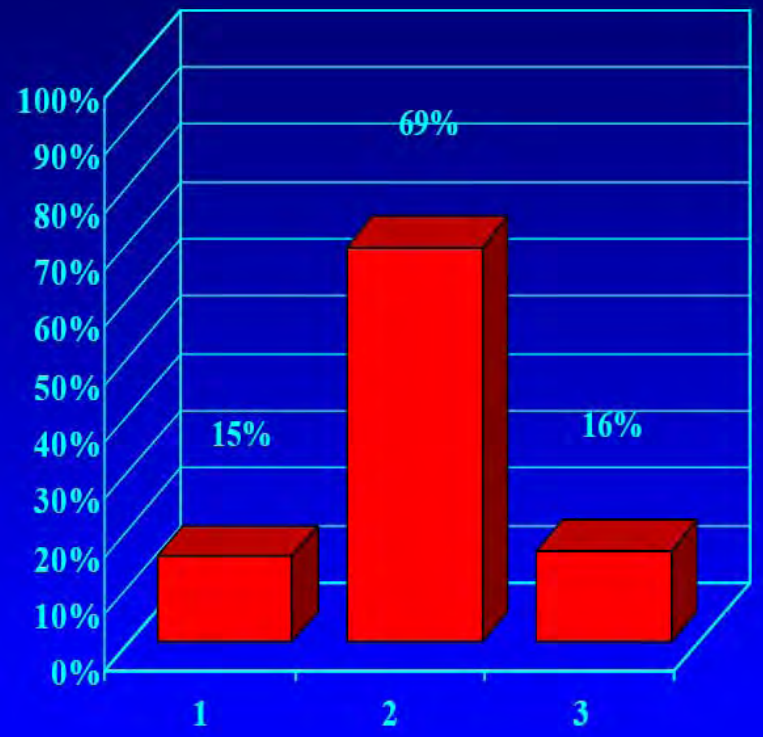
Glucomannano – ..polisaccaridi caratterizzati da una elevata affinità per l'acqua e da un elevato grado di viscosità; .. capacità sequestrante nei confronti di molti nutrienti. Se consumato in dosi eccessive può provocare ***disturbi intestinali, quali distensione addominale per produzione di gas e diarrea***.

Tarassaco – Gli estratti di Tarassaco vengono comunemente utilizzati nella medicina orientale, per le proprietà salutistiche ad essi attribuiti, quali ***l'effetto diuretico***, di promozione di funzioni epatiche e come stimolante per l'appetito.

Is thyroid hormone still used for treatment of obesity?

Nella vostra pratica clinica quanti pazienti con ipotiroidismo subclinico mettete in terapia con tiroxina?

1 .La minoranza
2. La maggioranza
3. Circa metà



A.M.E.

Congresso Nazionale

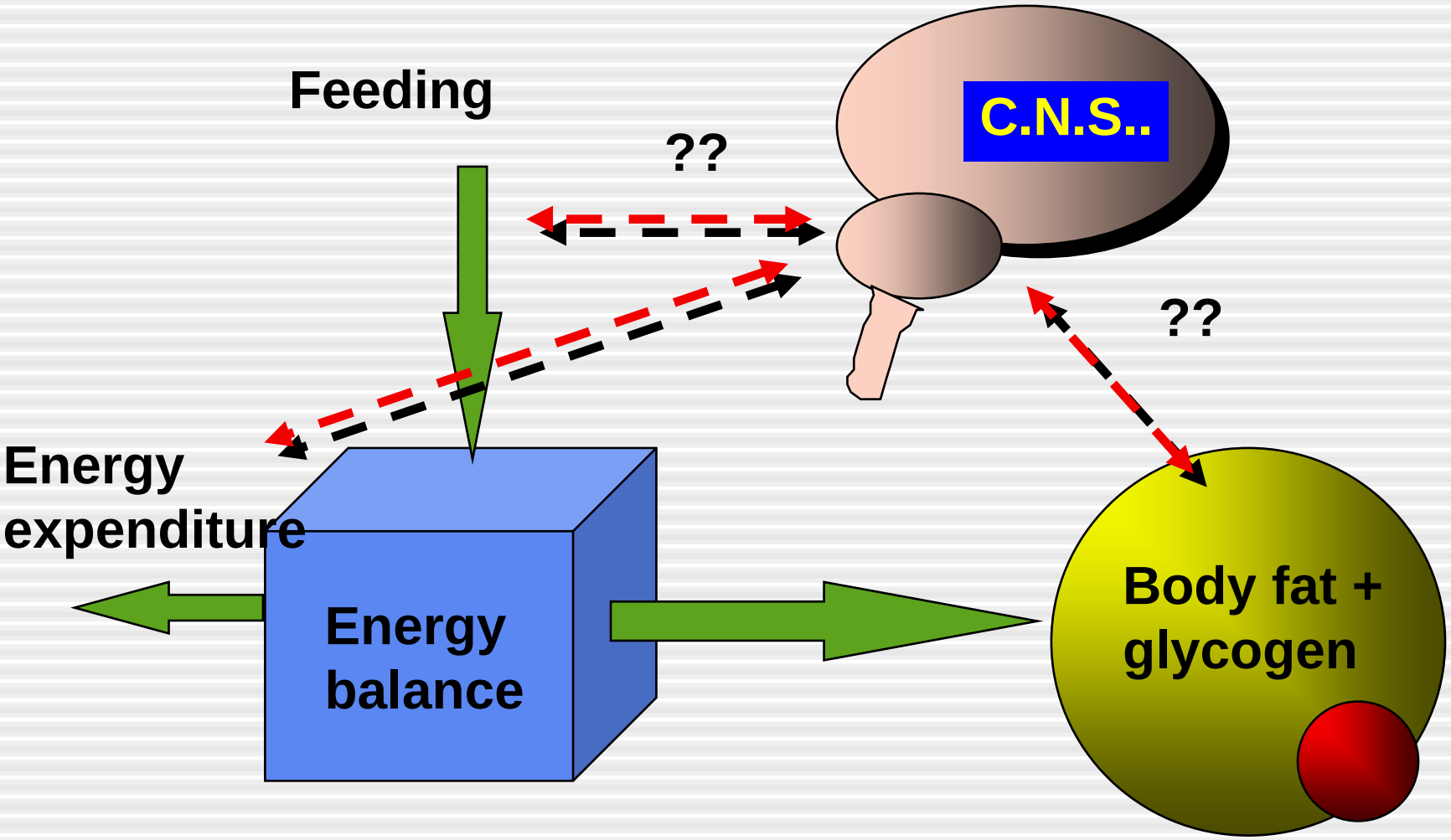
Pescara 2005

Drugs for obesity: the future

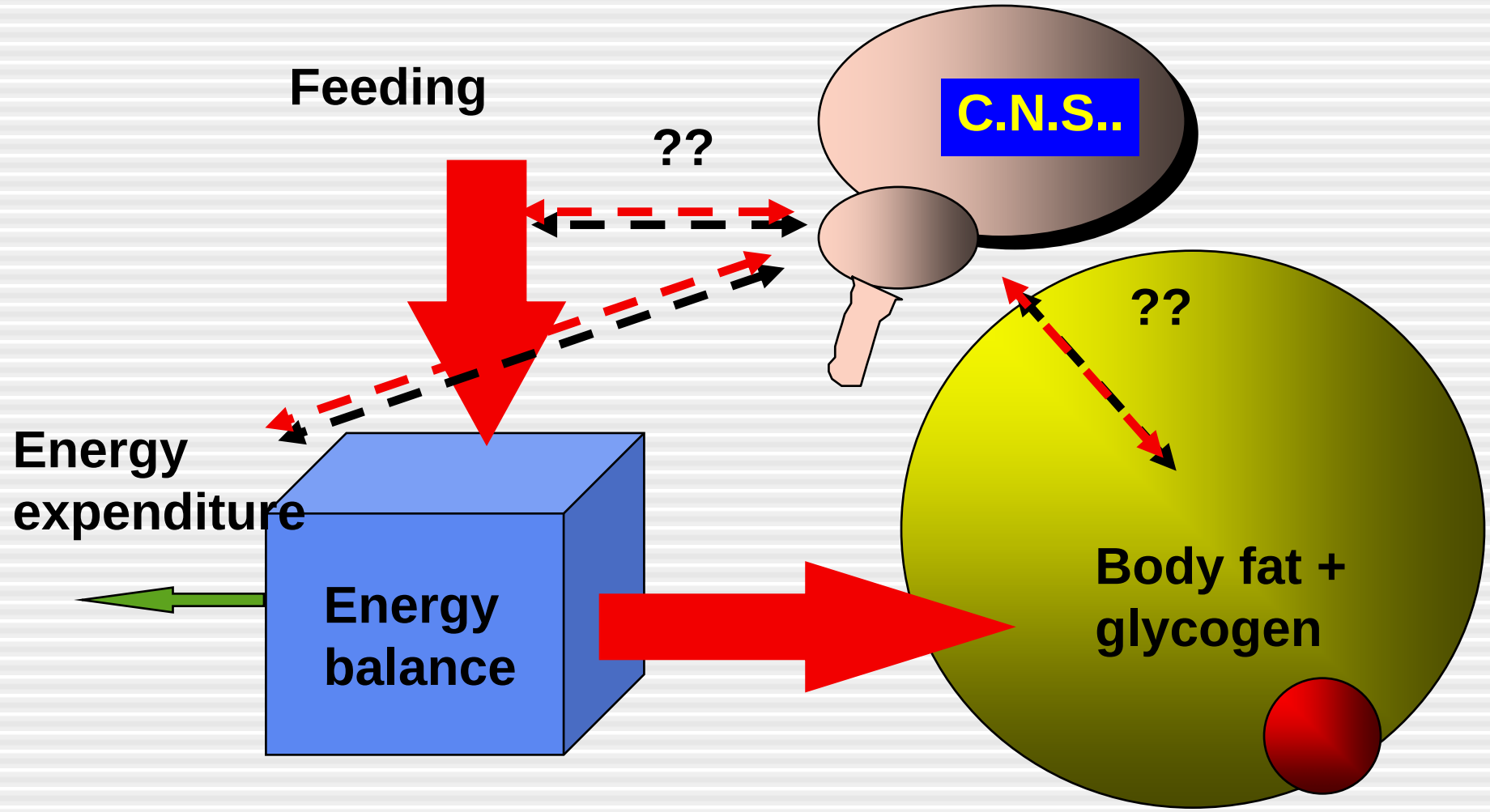
Vincenzo Bacci MD FACE

Policlinico Umberto I University Hospital - Rome

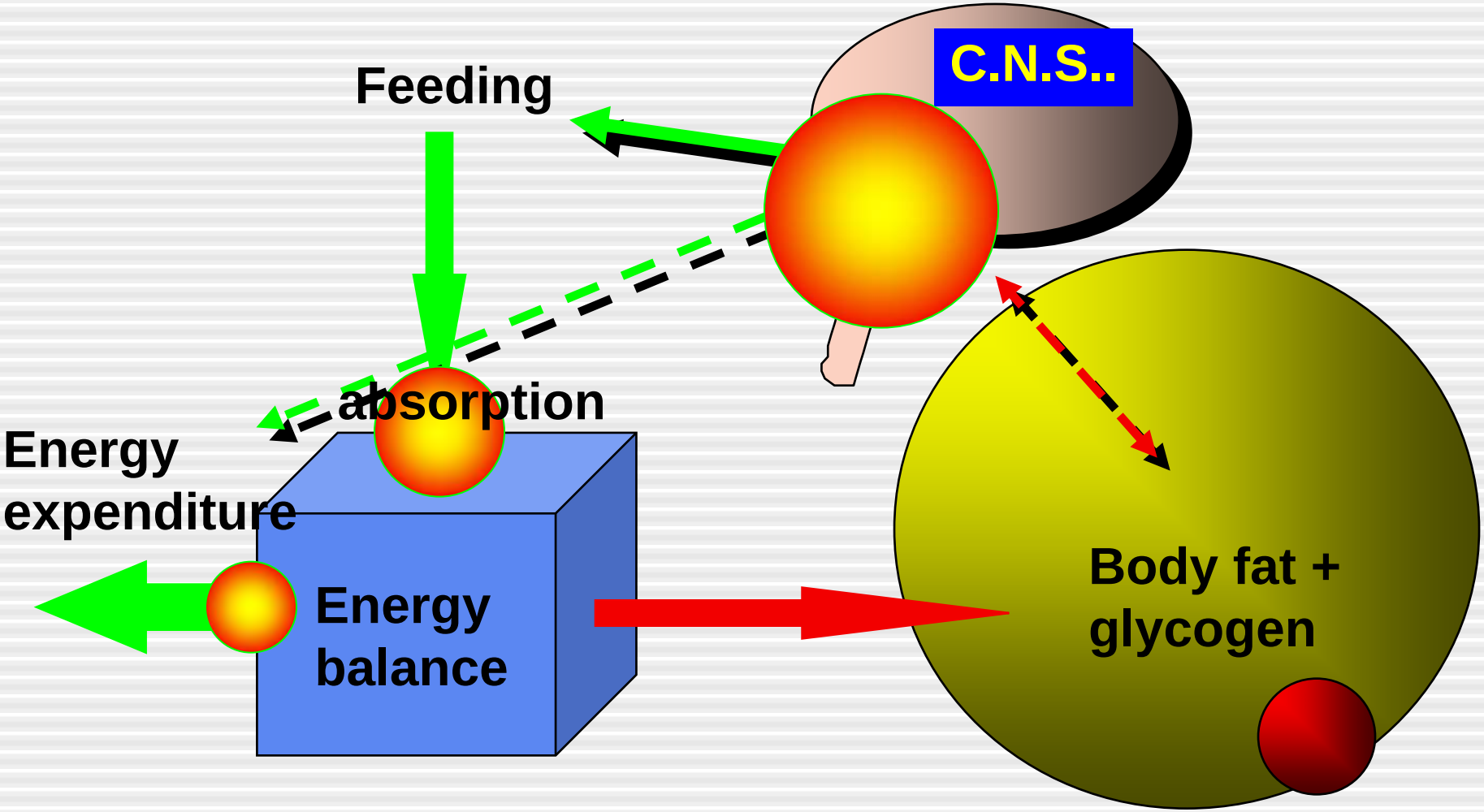
Basic model of energy storage regulation



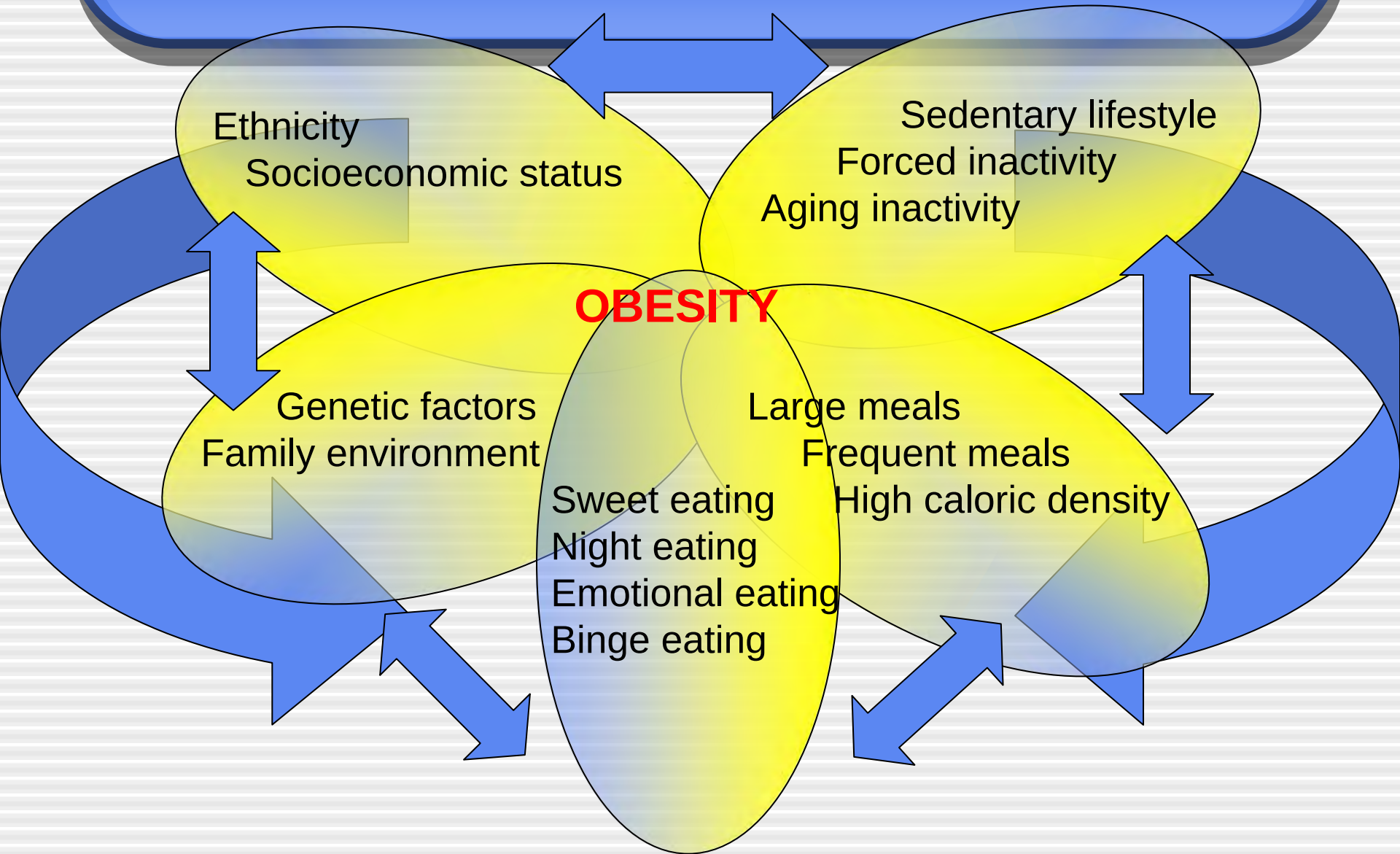
Basic model of positive energy balance - obesity



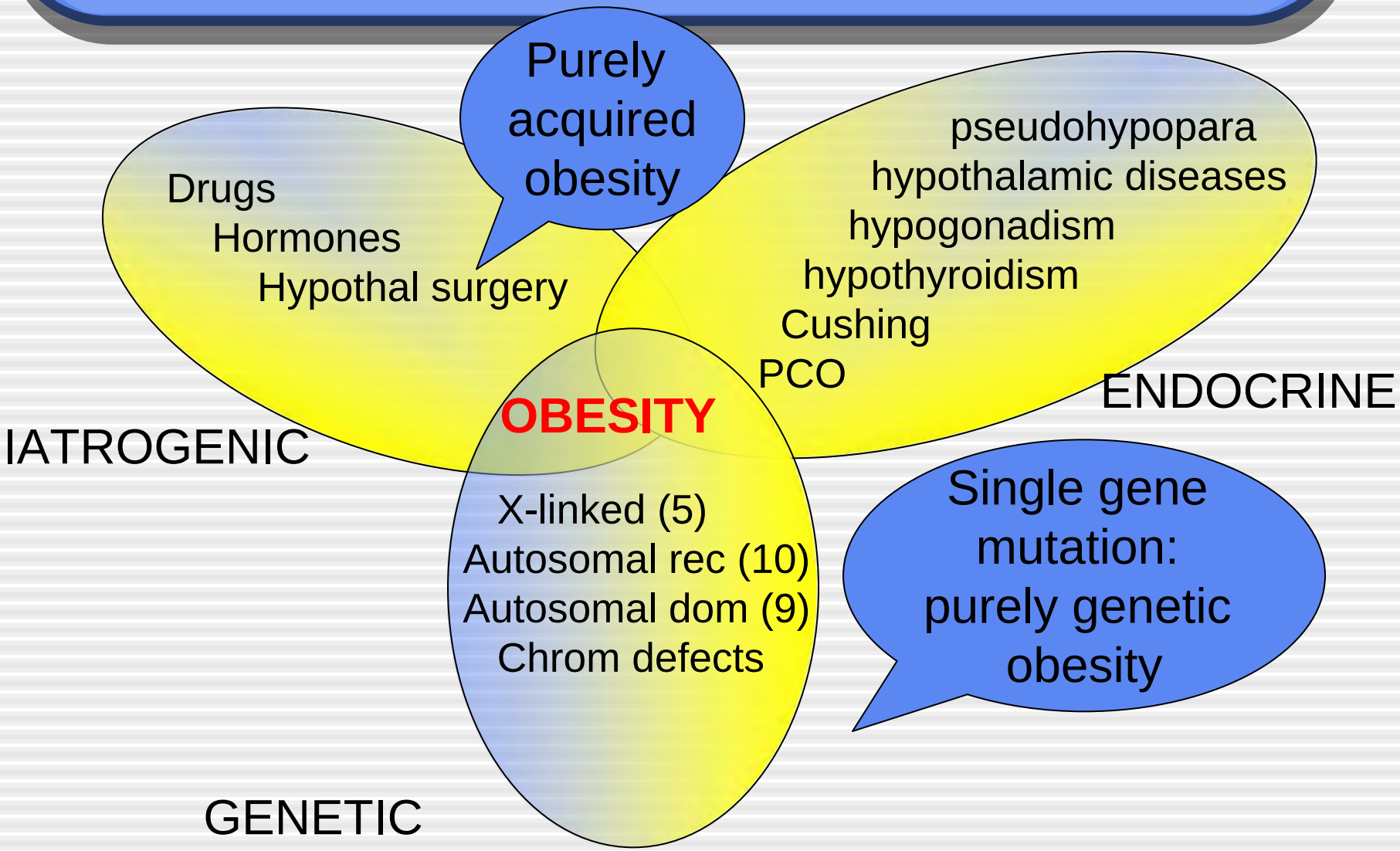
Obesity drugs targets



Pathogenesis of obesity



Pathogenesis of obesity -2



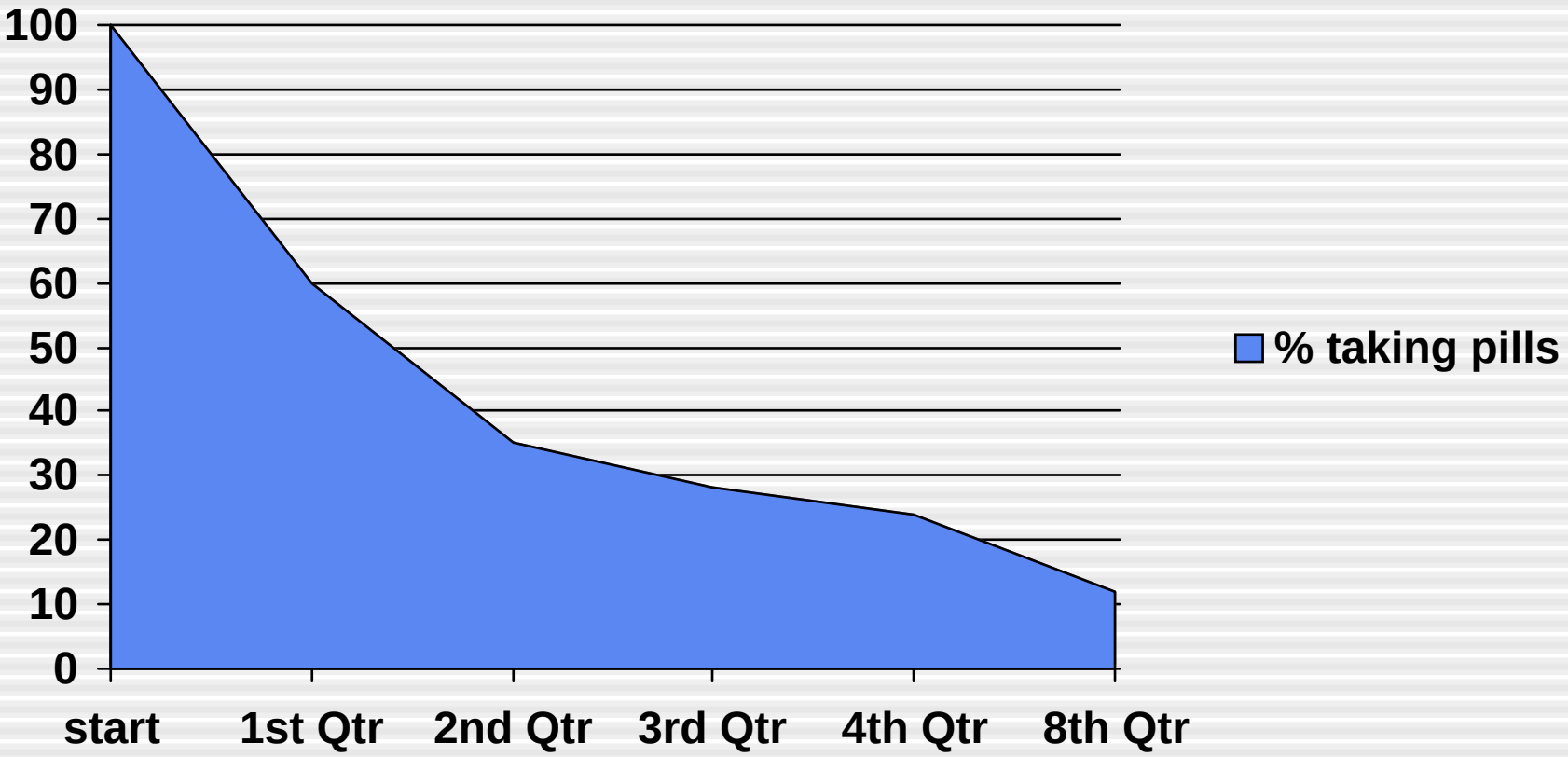
Obesity drug market trends: key factors

- **Safety/tolerance concerns**
- **Marketing difficulties:**
  - **Drugs cannot give an athletic look**
  - **Drugs can be only part of a complex treatment strategy**
- **Economic considerations**
  - **Drugs are often not reimbursed**

Drug Reimbursability

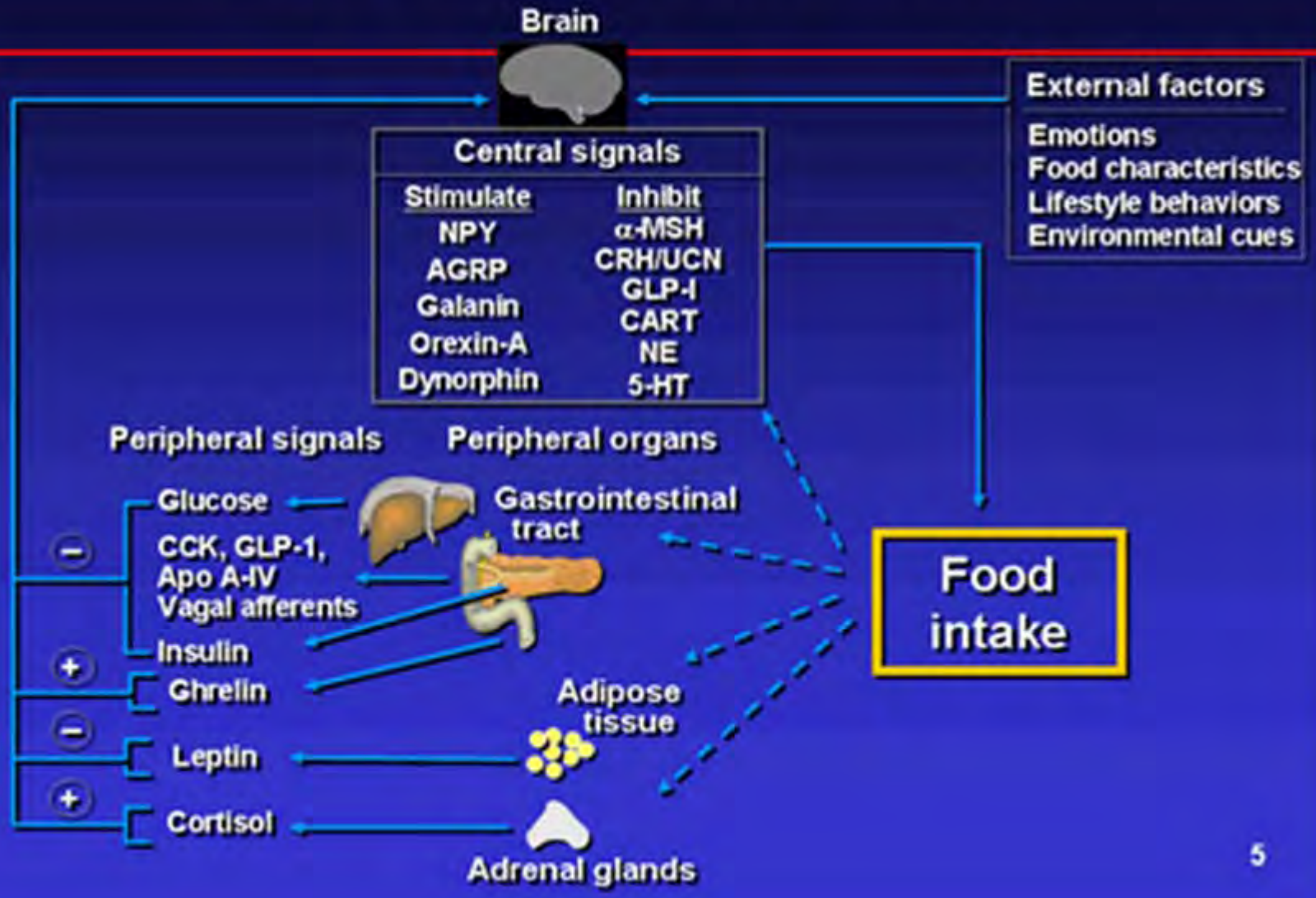
Country	Reimb.	notes
Denmark	yes	guidelines
France	no	
Germany	no	
Italy	no	Class C
Spain	no	Annex 2
Sweden	yes	
Switzerland	yes	
UK	yes	guidelines
USA	partial	Limited indications; not covered by Medicare/Medicaid

Compliance and duration of drug therapy for obesity



UK pts clinical record data, IMS Disease analiser

Regulation of Food Intake

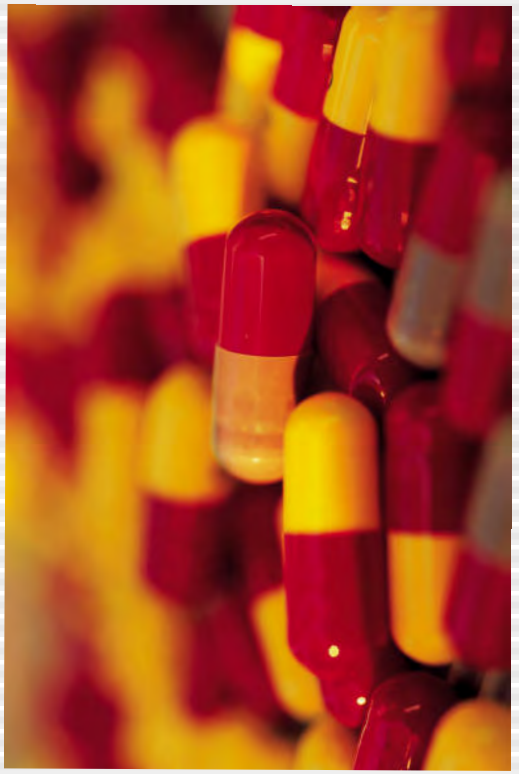


Obesity future drugs

- **Over 100 molecules are in various stages of preclinical and clinical development.**

Timeframe of new drugs development

- Basic research 2-3 yrs
- Pre-clinical development 2-3 yrs
- Clinical phase I 1 yr
- Clinical phase II 1-2 yrs
- Clinical phase III 2-3 years



Potential agonists 1

- **Adiponectin**
- **MSH/MC4R (*MSH/ACTH 4–10*)**
- **Apolipoprotein A-IV**
- **Brain-derived neurotrophic factor/TrkB receptor**
- **CCK/CCK-A receptor (*CCK A and B agonists*)**
- **Ciliary Neurotrophic factor (*Axokine*)**
- **Cocaine- and amphetamine-regulated transcript (CART)**
- **GLP-1(glucagon-like peptide-1) (*longer-acting GLP-1 agonist: exendin-4*)**

Korner & Aronne, JCEM 2004

Potential agonists 2

- **Human GH fragment *(AOD9604)***
- **Insulin mimetics**
- **Leptin; leptin receptor (*leptin analogues - LY 355101*)**
- **Oxyntomodulin**
- **PYY (*PYY 3-36*)**
- **Phosphatidylinositol 3-kinase**
- **Somatostatin**
- **Beta3, serotonin (*APD355*), norepinephrine, dopamine receptors *(sibutramine: inhibition of serotonin, norepinephrine, dopamine reuptake)***

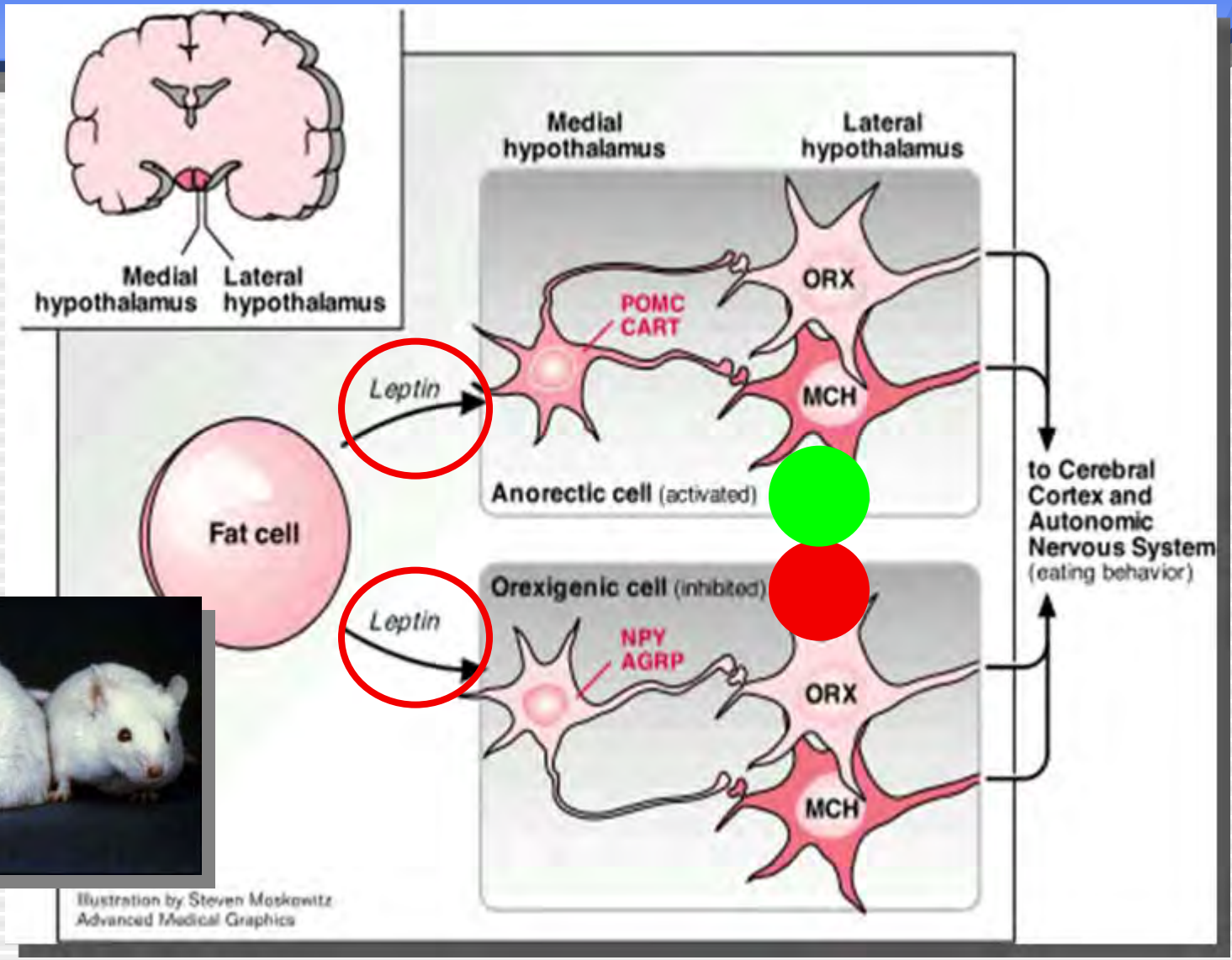
Potential antagonists 1

- **Endocannabinoid receptor CB1 (*antagonists*: *Rimonabant, CP945 598, SLV 319*)**
- **Acetyl CoA carboxylase 2**
- **Agouti-related protein**
- **11 betaHSD1(**11 beta-hydroxy-steroid dehydrogenase type 1- peripheral adipose tissue level)
- **Central CPT1**
- **CRH receptor**
- **DP-IV**
- **Fatty acid synthase (*inhibitor: cerulenin*)**
- **Galanin**

Potential antagonists 2

- **GIP**
- **Ghrelin**
- **Histamine receptor**
- **MCH**
- **NPY (*NPY receptor 1 and 5 blockers*)**
- **Orexin A and B**
- **Suppressor of cytokine signaling-3**
- **Thyrosine phosphatase IB**
-

Leptin


Medial hypothalamus
Lateral hypothalamus
Medial hypothalamus
Lateral hypothalamus
POMC
CART
ORX
MCH
Leptin
Fat cell
Anorectic cell (activated)
to Cerebral Cortex and Autonomic Nervous System (eating behavior)
Orexigenic cell (inhibited)
Leptin
NPY
AGRP
ORX
MCH
Illustration by Steven Moskowitz
Advanced Medical Graphics

Leptin

- **Basic problem: relative leptin resistance and hyperleptinemia in most of obese individuals**
- **High dose leptin therapy: unacceptable local adverse reactions**
- **longer-acting form of pegylated leptin produced additional weight loss in severely, but not moderately, energy-restricted subjects**

Lubina JA et al JAMA 1999
Hukshorn CJ et al ,. Int J Obes Rel Met Dis 2002
and Am J Clin Nutr 2003 77:771–776

Leptin 2

- Central leptin resistance may involve suppressor of cytokine signaling-3
- suppressor of cytokine signaling-3 inhibitors may be an approach to overcome leptin resistance.

Bjørbæk C, et al. Mol Cell 1:619–625 1998

Leptin 3

- During weight loss there is a decline in leptin concentrations that may hamper the ability to maintain weight loss.
- administrations of low replacement dose leptin may reverse this phenomenon
- Leptin could be useful as adjunct maintenance therapy

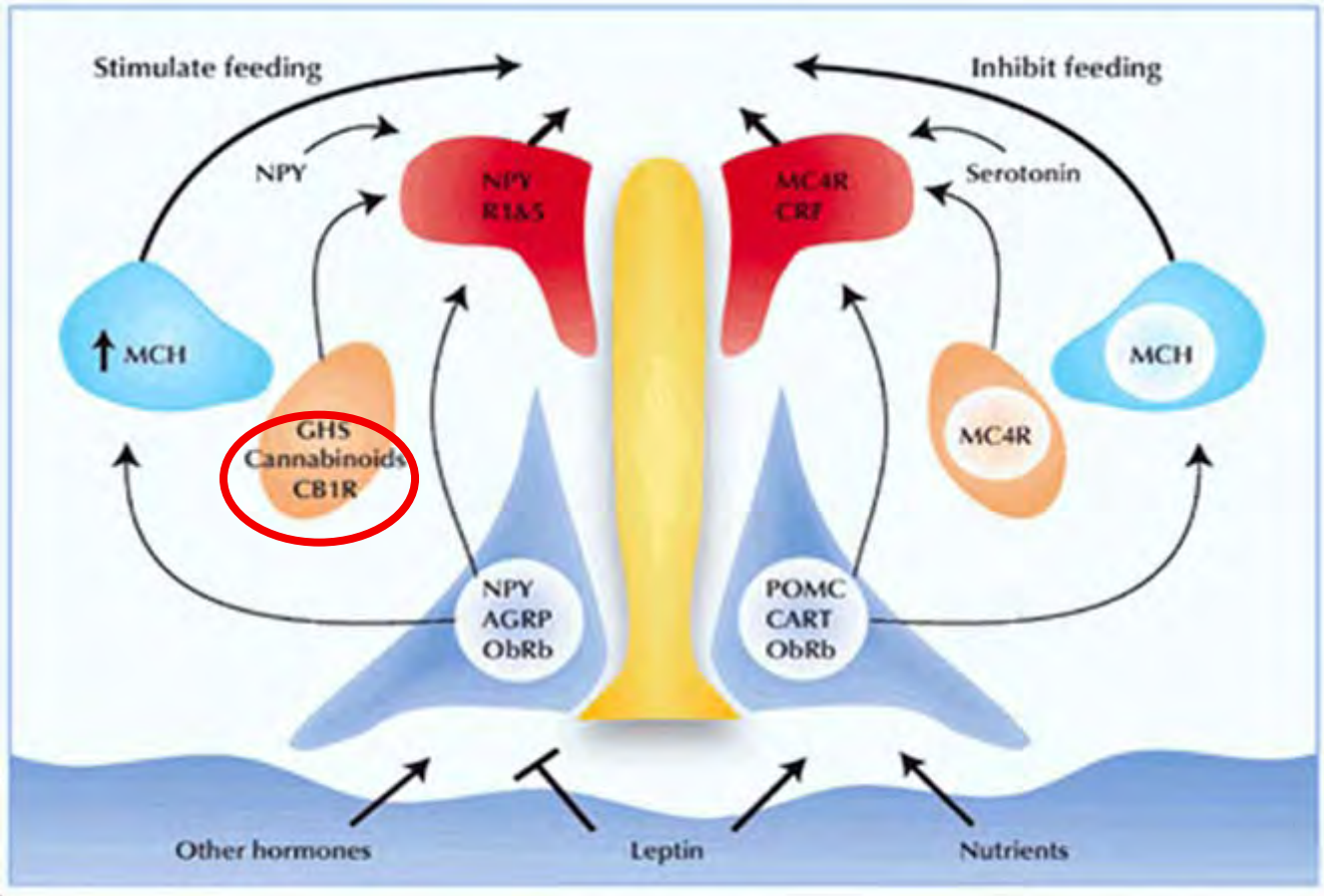
Rosenbaum M, et al 2002 JCEM 87:2391–2394 2002
Chan JL, et al J Clin Invest 111:1409–1421 2003

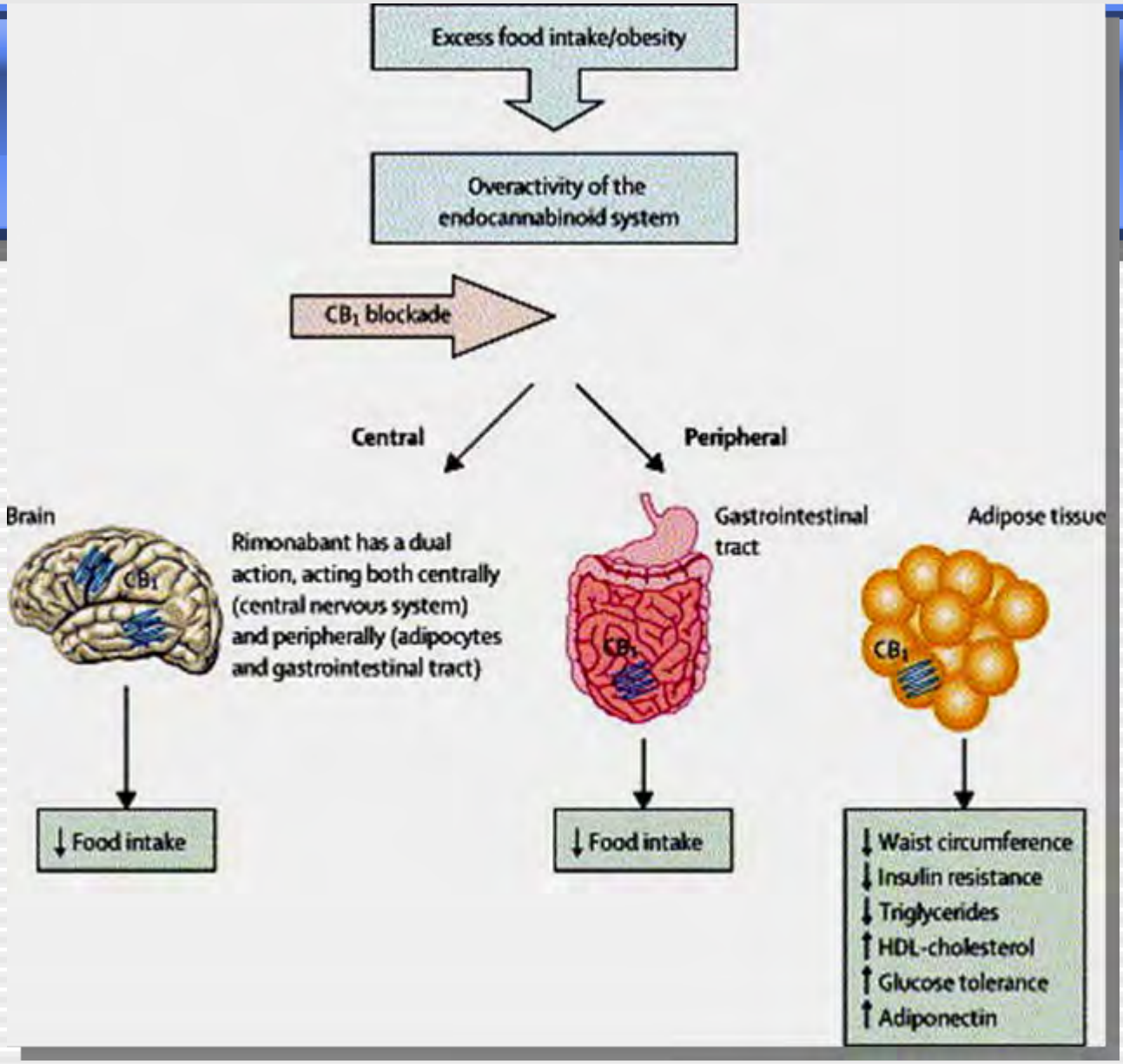
Cannabinoid research

- **1964 Isolation of Δ-9 THC, the active constituent of Cannabis sativa**
- **1988 High-affinity cannabinoid binding site discovered in rat brain**
- **1990 Cloning of the rat G-protein–coupled CB1 receptor**
- **1991 Cloning of the human CB1 receptor**
- **1992 Discovery of anandamide, the first endogenous cannabinoid**
- **1993 Cloning of the peripheral CB2 receptor**
- **1994 Characterization of the first selective CB1 receptor blocker, rimonabant**
- **2004 RIO-Lipids, RIO-Europe 1 year, STRATUS-US (smoke), and RIO-NA studies presented**
- **2005 RIO-Europe and RIO-Lipids published RIO-Diabetes study presented**
- **2006 RIO-NA study published**

Modified from Despres Gelfand and Cannon

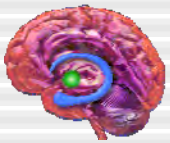
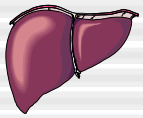
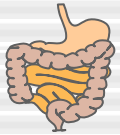
Cannabinoid receptor





Van Gaal, Lancet 2005

Sites of CB_1 receptor and effects of CB_1 blockade

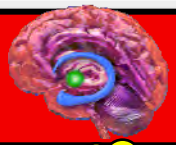
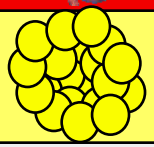
Site of Action	Mechanism(s)	Addresses
 Hypothalamus / Nucleus accumbens	↓ Food intake	Body weight Intra abdominal adiposity
Adipose tissue	↑ Adiponectin ↓ Lipogenesis	Dyslipidemia Insulin resistance
 Muscle	↑ Glucose uptake	Insulin resistance
 Liver	↓ Lipogenesis	Dyslipidemia Insulin resistance
 GI tract	↑ Satiety signals	Body weight Intra abdominal adiposity

DiMarzo 2001; Ravinet Trillou et al 2003; Cota et al 2003; Pagotto et al 2005; Van Gaal et al 2005; Liu et al 2005; Osei-Hyiaman et al 2005

Cannabinoid antagonists - Rimonabant

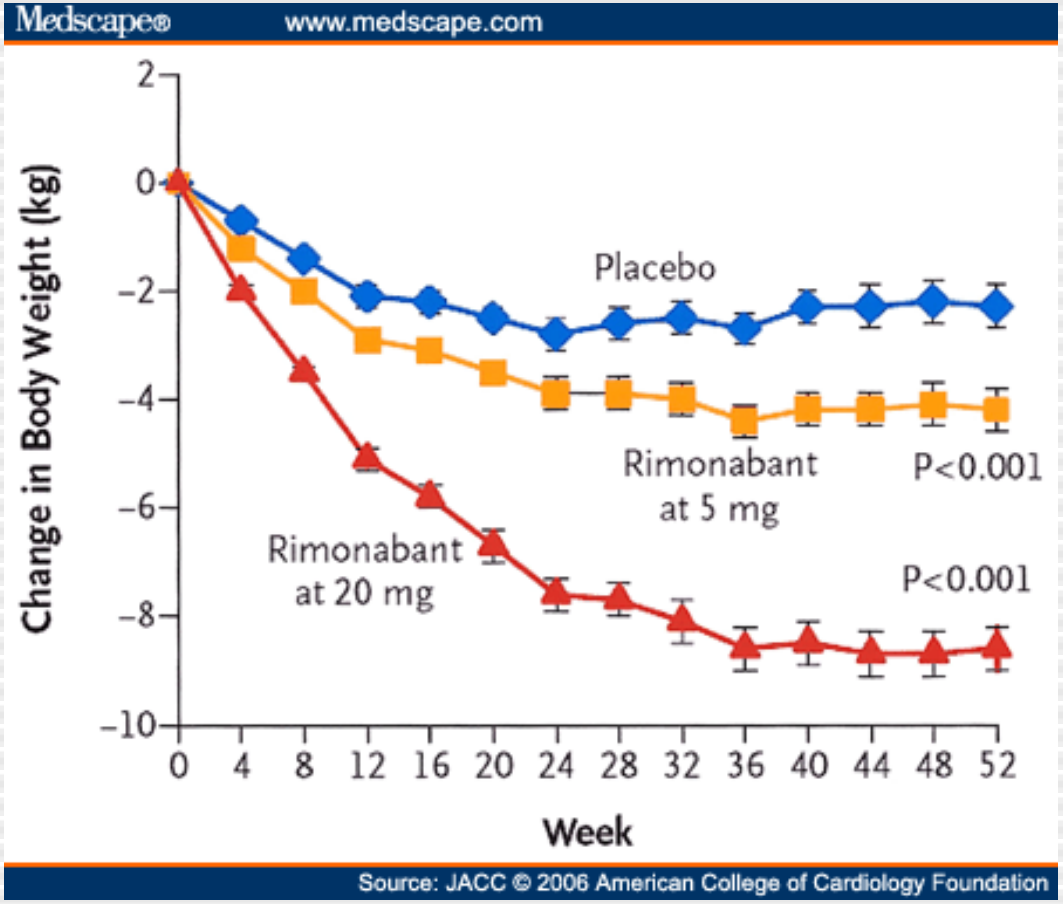
- Acomplia ® Sanofi- Aventis
- CB1 cannabinoid receptor blocker
- Available in 2007
- Impressive pharmacological properties (weight and comorbidities) *but*
- Side effects (leading to discontinuation in RIO-Europe in 14.5% vs 9.2% in placebo)
  - Depression up to 3.7%
  - Nausea up to 13%
  - Diarrhea up to 7%

Rimonabant effects

Central blockade (hypothalamus) 	**Decreased food intake**
Peripheral blockade (adipose tissue) 	**Decreased abdominal fat (waist circumference)**
	↑ Adiponectin
	↓ Triglycerides
	↑ High-density lipoprotein
	↓ Small, dense low-density lipoprotein
	↓ C-reactive protein
	↓ Insulin resistance

Eli V. Gelfand, Christopher P. Cannon, J Am Coll Cardiol. 2006;47(10):1919-1926.

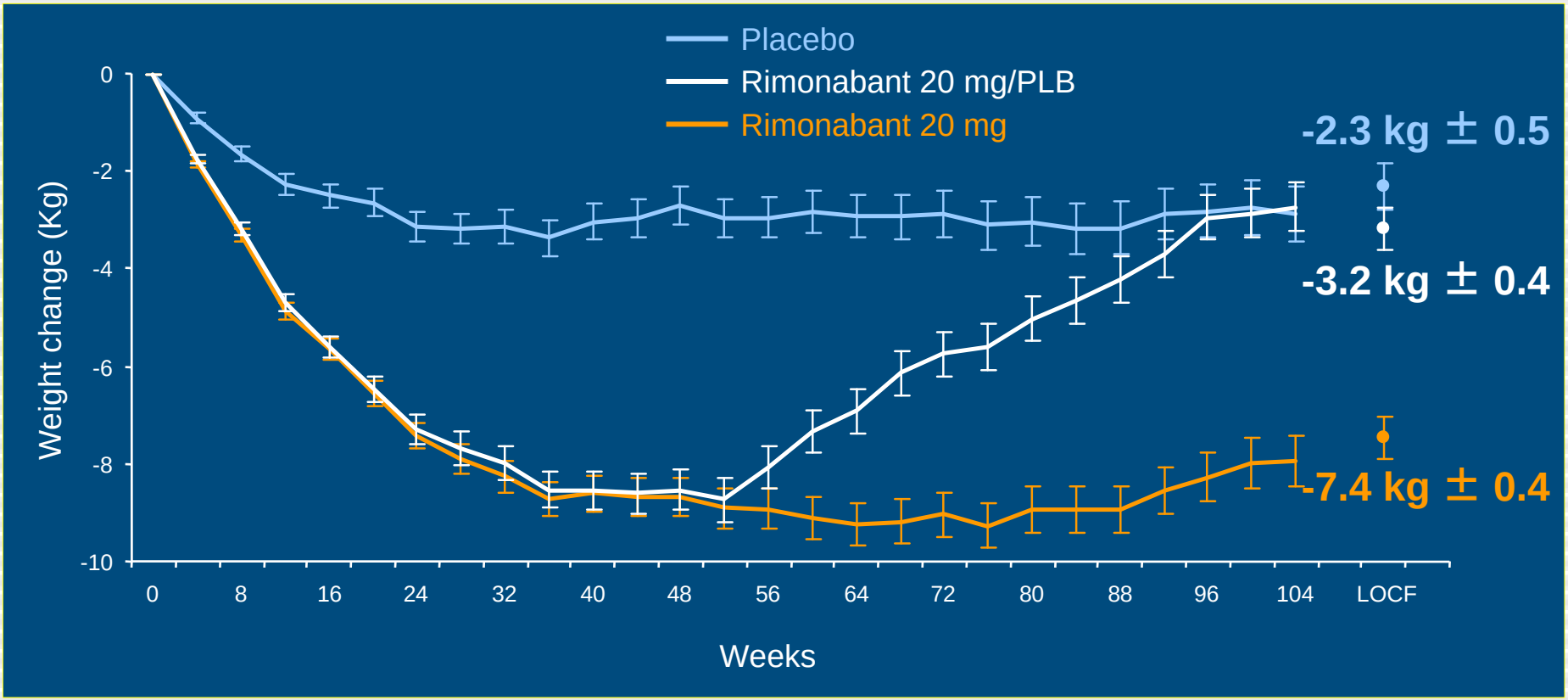
Rimonabant effect on weight at 1 year



Despres JP, Golay A, Sjostrom L. N Engl J Med 2005;353:2121-2134. (from RIO-Lipids)

RIO~NA: Prevention of Weight Regain by Chronic Therapy

ITT, LOCF

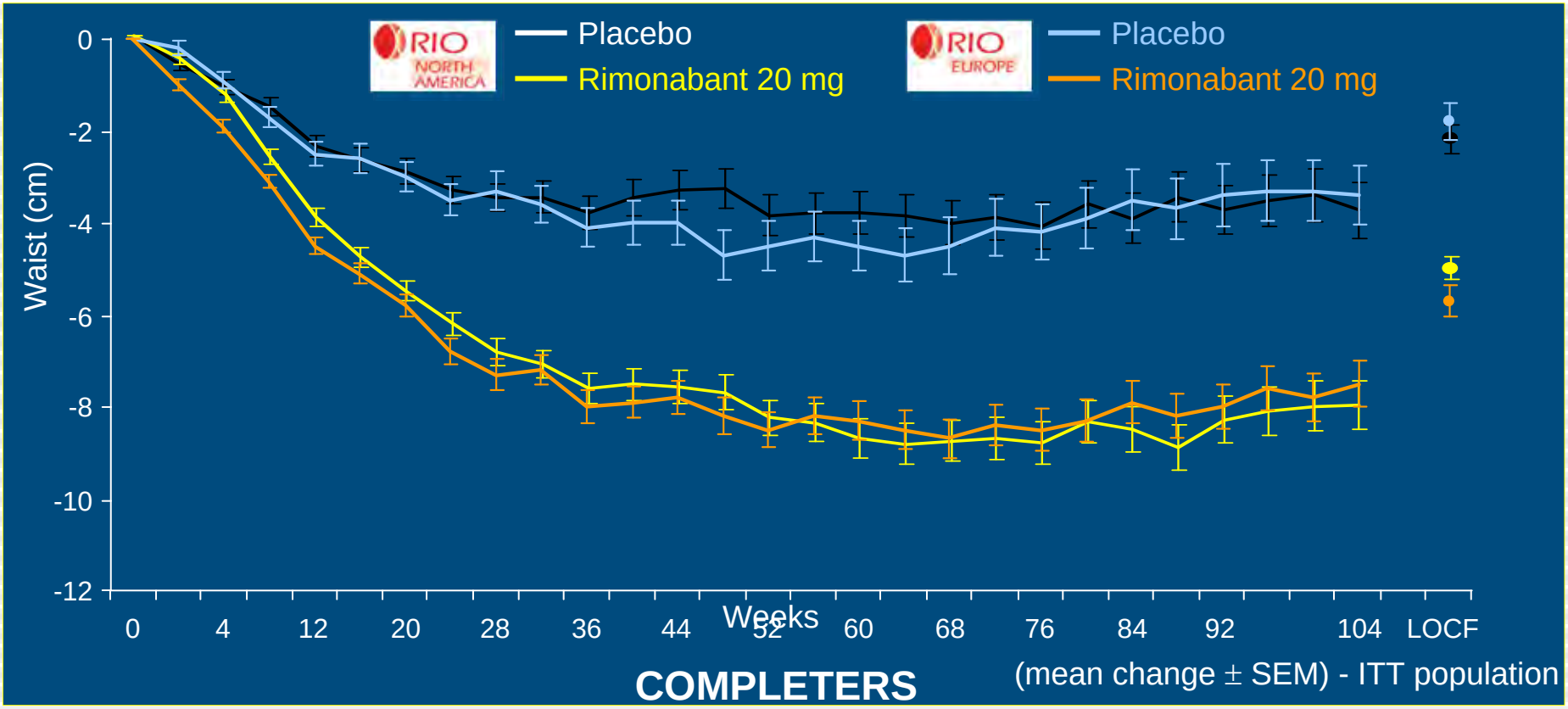


Weight (kg) Change from Baseline over 2 Years (Mean +/- SEM)

X. Pi-Sunyer, Circulation 2005:111(13);1727.

Consistent WC Changes in RIO Studies

ITT, LOCF



RIO~NA

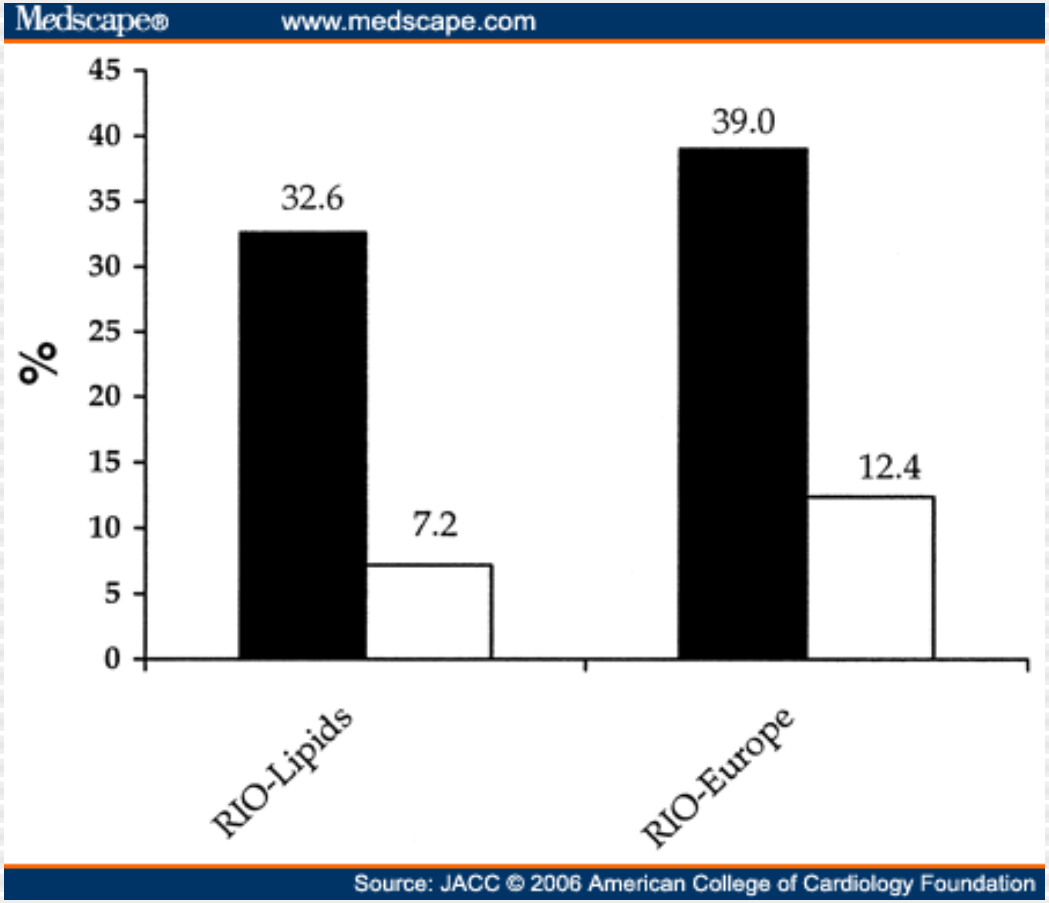
20 mg v. placebo: -4.2 cm (*p*<0.001)

RIO~EU

20 mg v. placebo: -4.1 cm (*p*<0.001)

Van Gaal L., . Presented at the ACC congress, March 2005, presentation 410-13

Rimonabant: weight loss >10%



Percentage of subjects achieving >10% weight loss at one year with rimonabant (solid bars) 20 mg/day versus placebo (open bars) in the first two RIO) trials among those completing the study.

RIO - Europe weight loss

Therapy duration	Rimonabant 5 mg	Rimonabant 20 mg	placebo
1 year	- 3.4 kg	- 6.6 kg	- 1.8 Kg
2 years	- 1.6 Kg	- 7.2 kg	- 2.5 Kg

Mean weight change in completers (63% and 61%)

RIO - Europe side effects

Side effect	Rimonabant 5 mg	Rimonabant 20 mg	placebo
nausea	6%	14%	5%
dizziness	8%	9%	5%
diarrhea	7%	8%	5%
vomiting	2%	5%	2%

Other cannabinoid antagonists

- **CP945 598** - Pfizer
- CB1 cannabinoid receptor blocker
- Expected in 2009
- **SLV 319** - Bristol Myers Squibb
- CB1 cannabinoid receptor blocker
- Phase 1-2

Fat malabsorption: OTC orlistat

- **Alli ® GSK**
- Half-strenght tablets
- Currently in pre-registration for OTC dispensation
- Expected to capture 40% of brand volume within 12 months of launch

IMS therapy forecast

Fat malabsorption: Cetilistat (ATL 92)

- **Alizyme ® Takeda**
- Fat absorption blocker
- Phase 3
- Expected in 2008
- Side effects:
  - Diarrhea - apparently less severe than orlistat

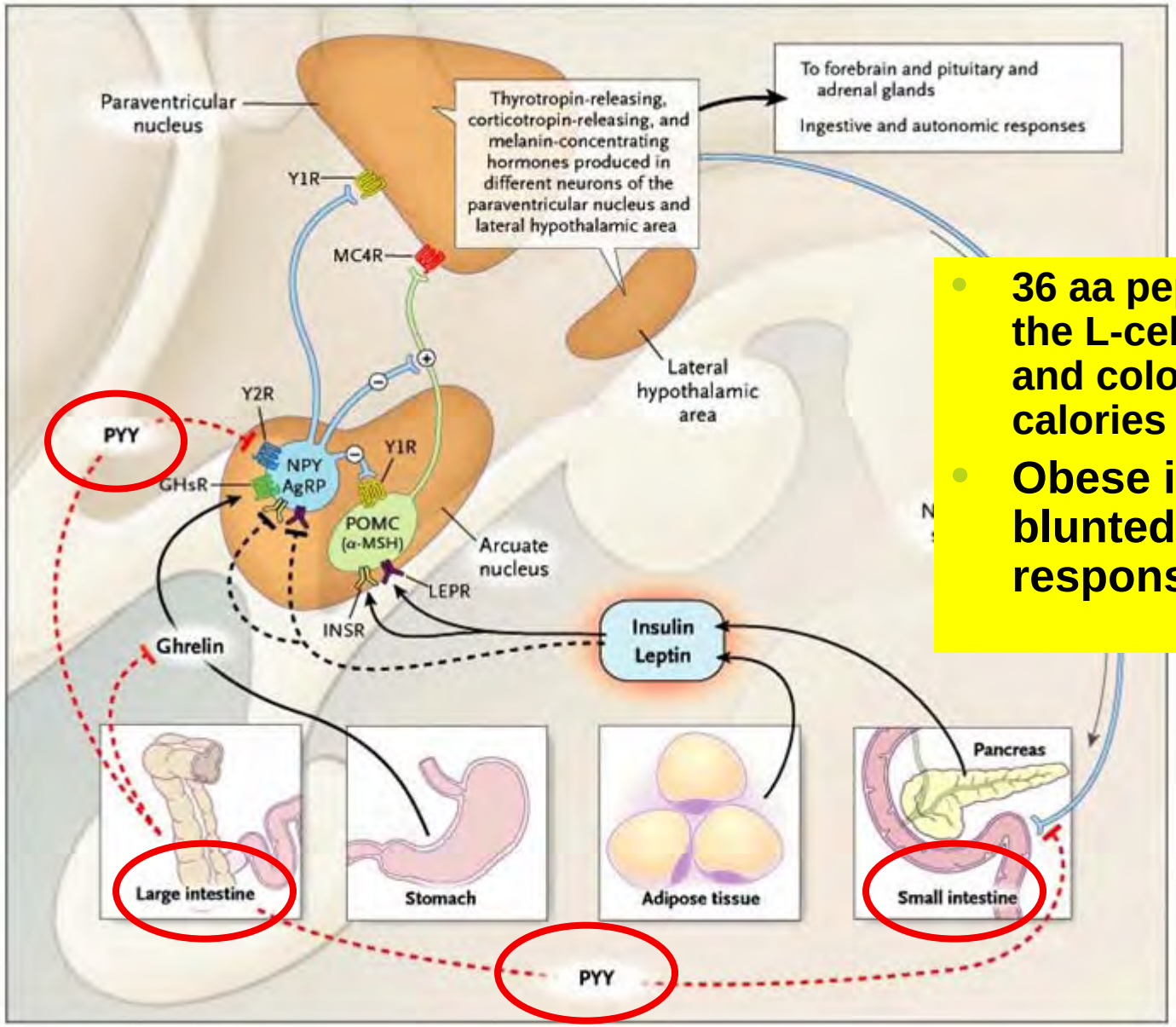
GH analogs

- **AOD9604 - Metabolic Pharmaceuticals**
- GH analog
- Phase 2 trias
- Side effects:
  - Gastrointestinal at high doses

Serotoninergics

- **APD355 - Arena**
- Hypothalamic serotoninergic
- Satiety stimulation
- Phase 2 trials
- Side effects:
  - Nausea
  - headache

PYY

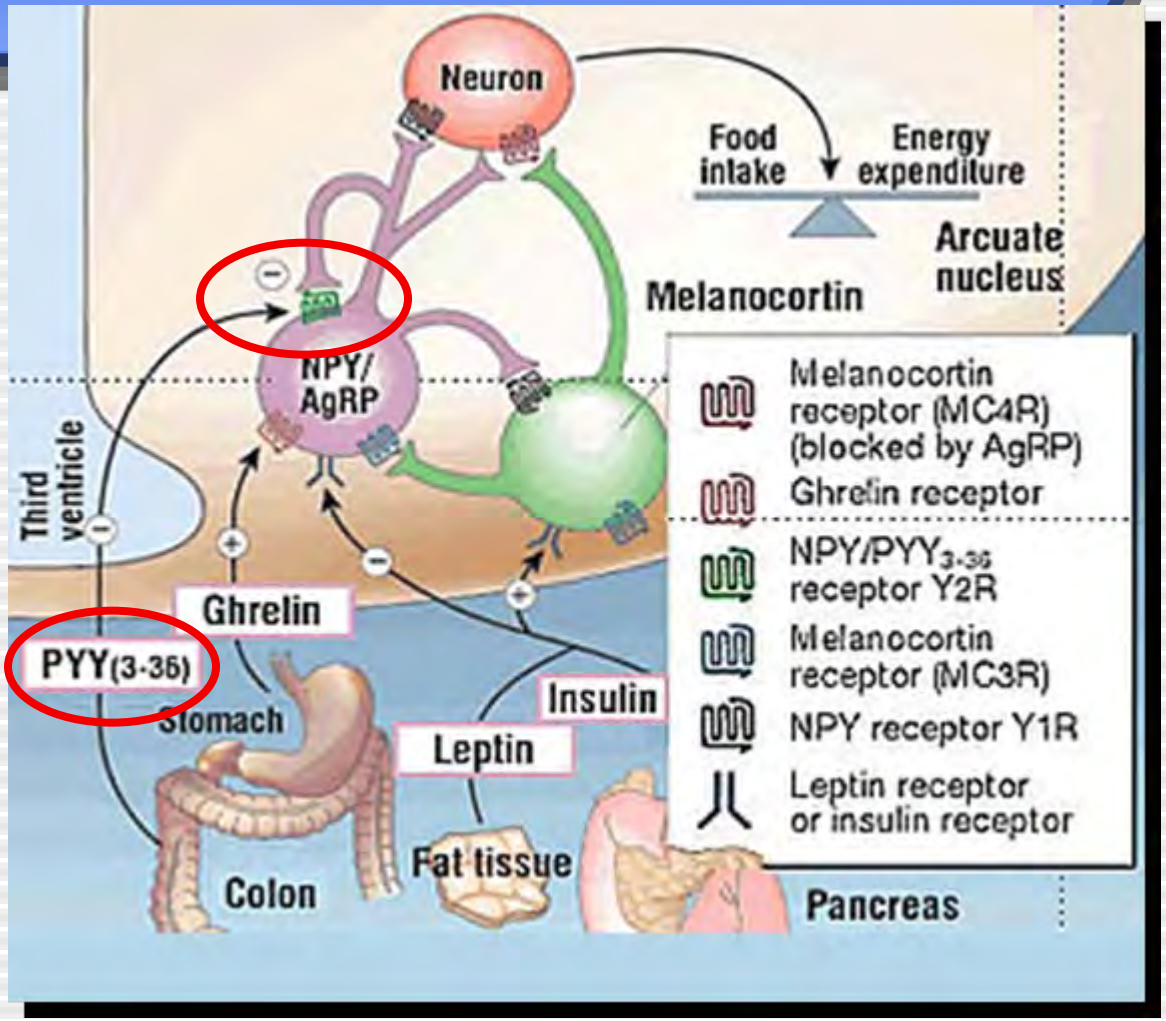


- **36 aa peptide released by the L-cells of GI tract (ileum and colon) in proportion to calories ingested**
- **Obese individuals have a blunted postprandial response**

Chaudhri, JCEM 2006

PYY

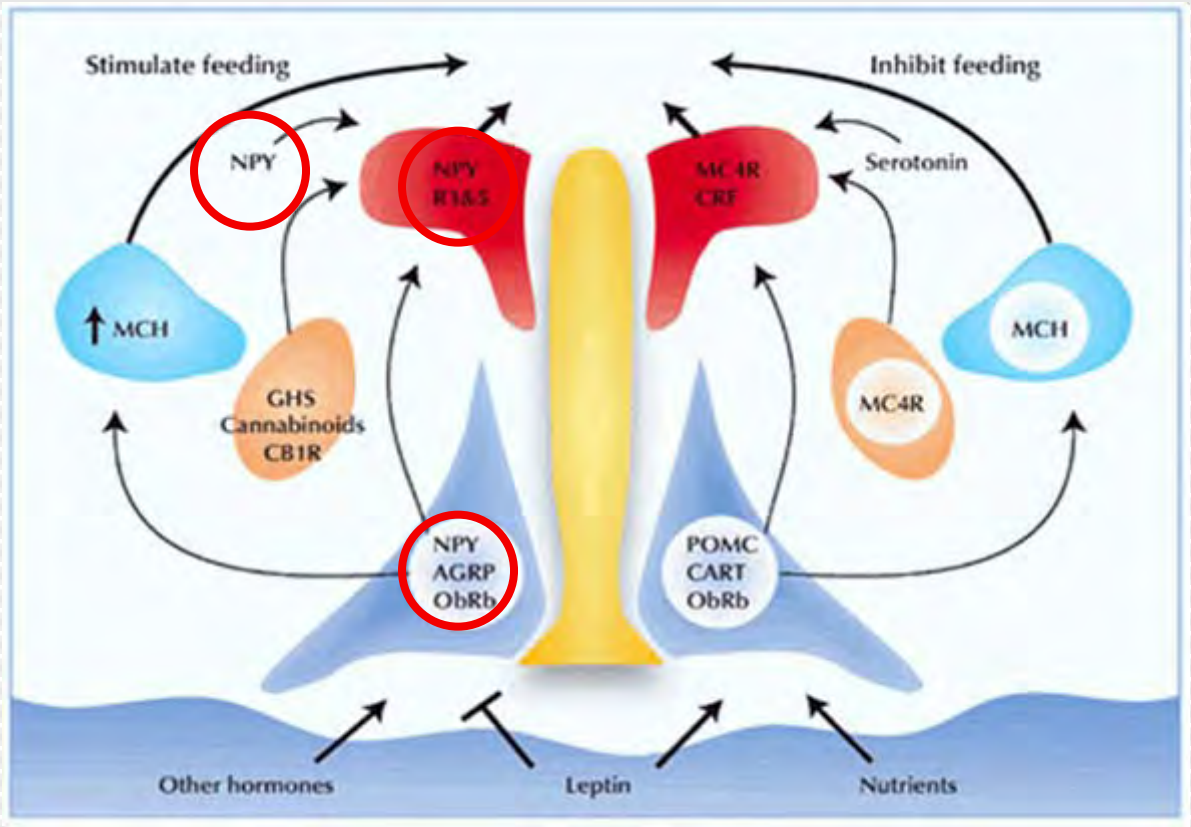
- Receptor Y2 highly expressed on NPY neurons of ARC nucleus of hypothalamus
- PYY reduces food intake in part through the auto-inhibitory NPY receptor Y2R.



Chaudhri, JCEM 2006

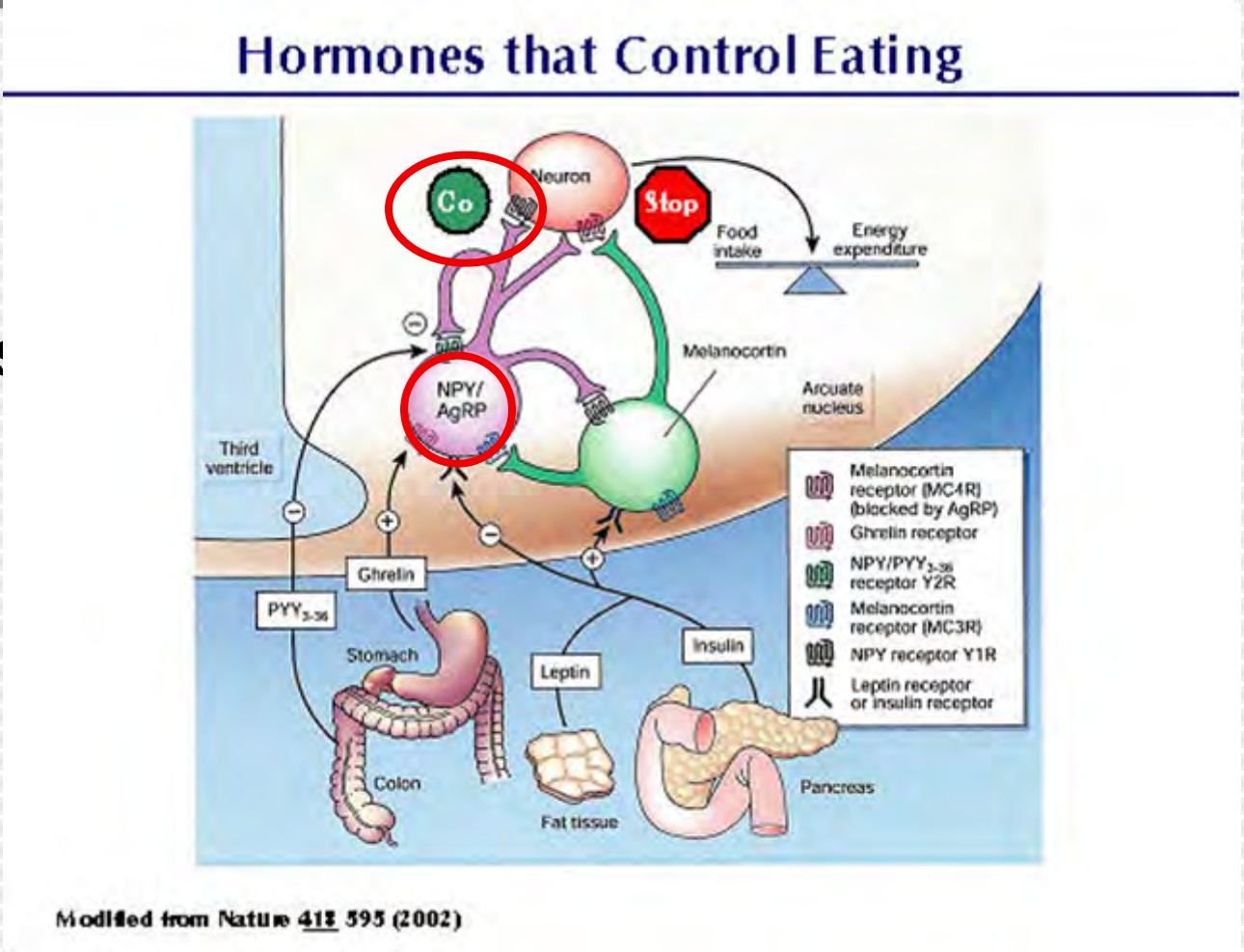
NPY

- **Neuropeptide Y is one of the most potent stimulators of food intake, predominantly carbohydrate intake**

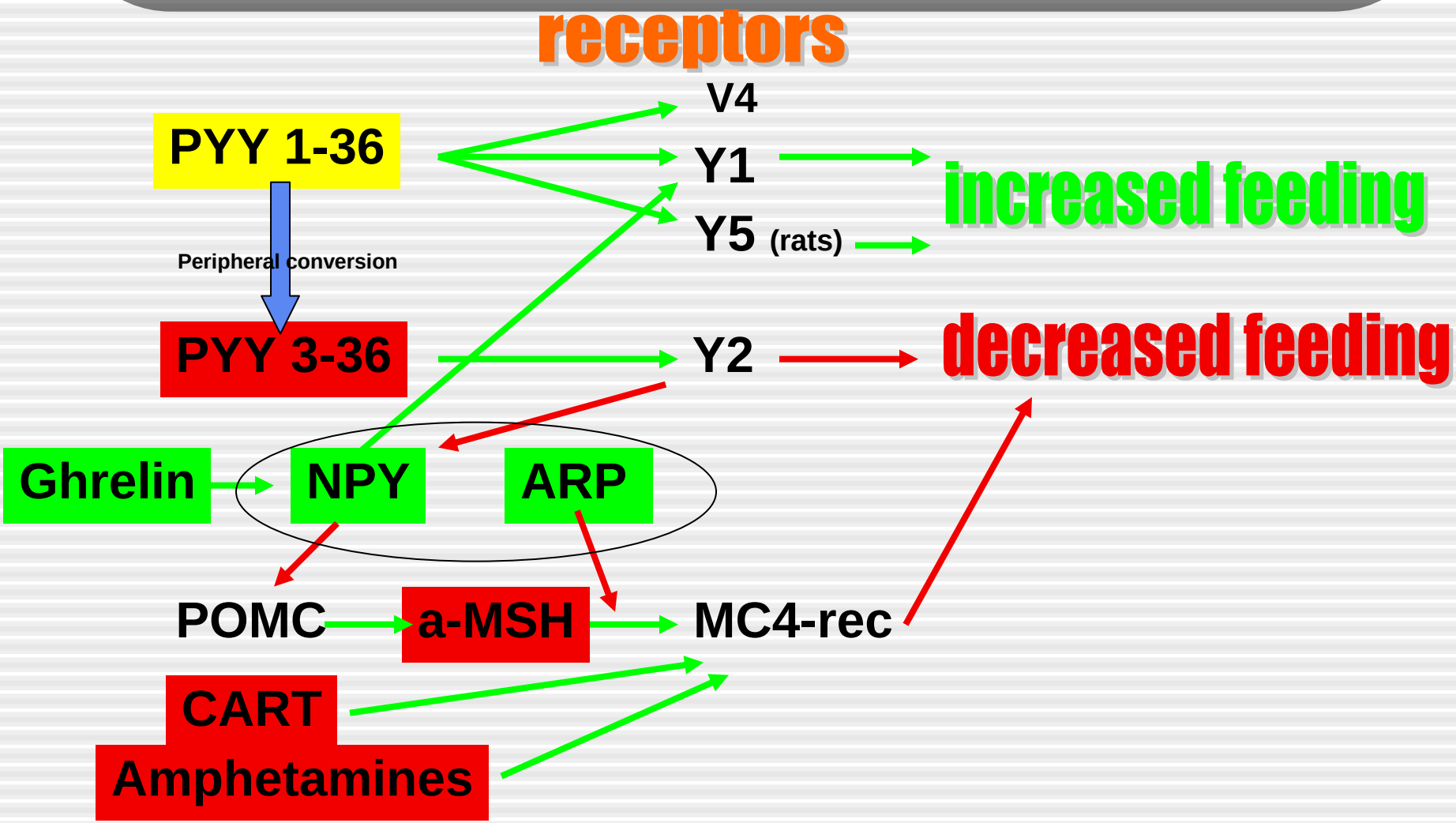


NPY

- **Structurally related to PYY, binds to same receptor family**
- **Much more abundant in CNS expressed in ARC cells**



PYY- NPY actions



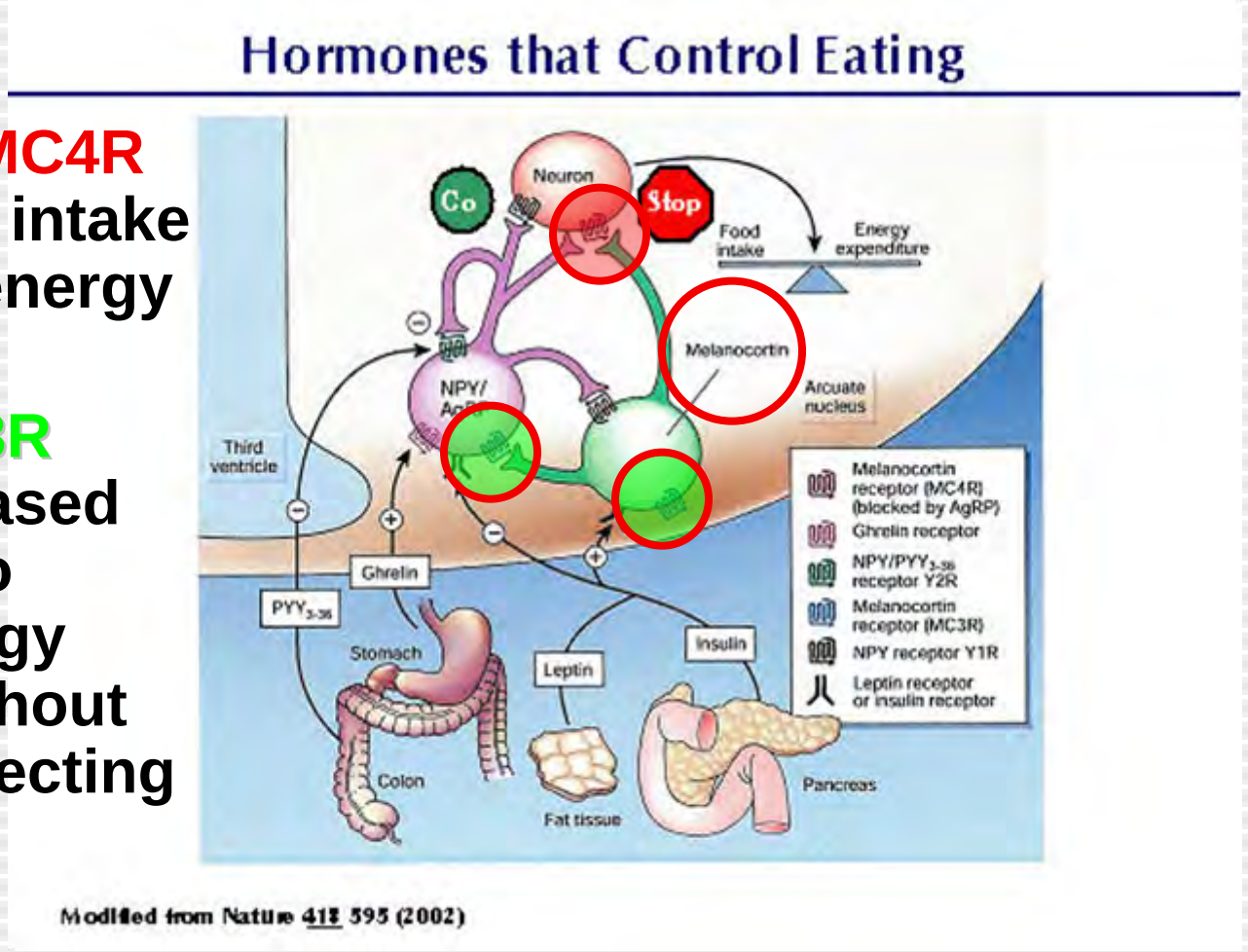
NPY - PYY agonists

- A single infusion of PYY in lean and obese subjects, reduced appetite and food consumption by approximately 30% 2 h after the infusion
- Clinical trials of intranasal administration of PYY are under way
- PYY3-36 - Agonist developed by Merck

Batterham RL 2002 Nature, 2003 N Engl J Med

Melanocortin receptors

- Stimulation of MC4R decreases food intake and increases energy expenditure.
- Deletion of MC3R results in increased adiposity due to decreased energy expenditure without significantly affecting food intake.



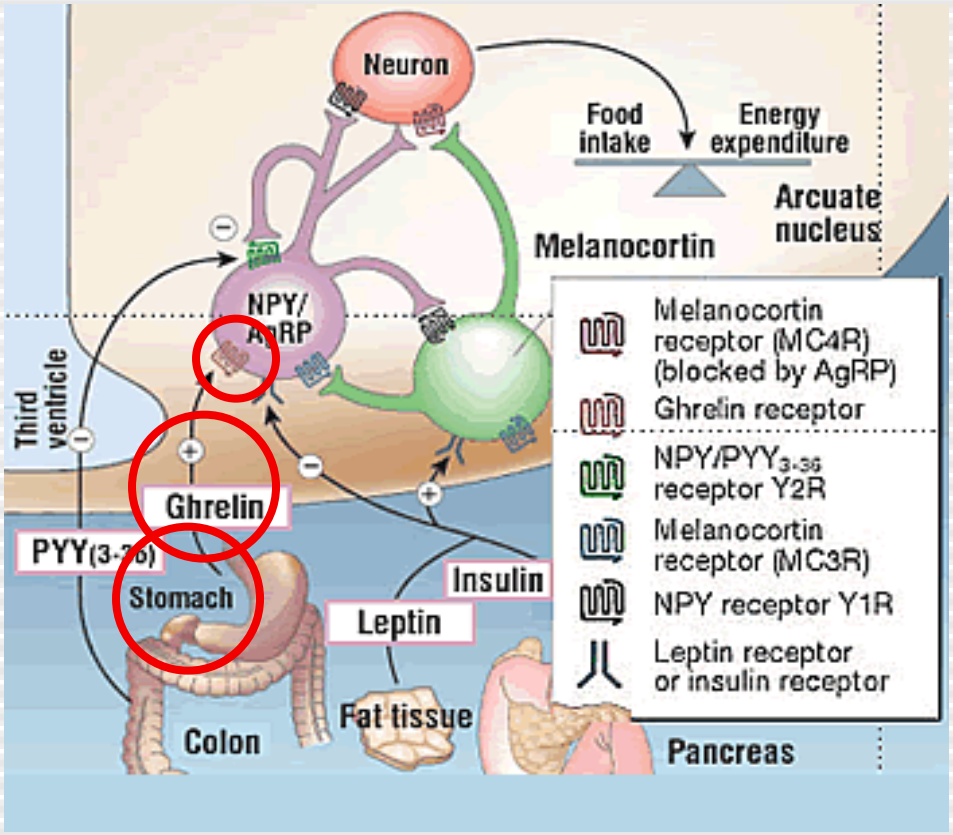
MC4R agonists

- Intranasal treatment with an MC4R agonist, MSH/ACTH 4–10, reduced body weight by 0.79 kg when administered to normal weight humans for 6 weeks
- MSH/ACTH 4–10, did not change the body weight of two obese individuals with proopiomelanocortin deficiency due to loss of function mutations of the proopiomelanocortin gene

Fehm HL, 2001 J Clin Endocrinol Metab 86:1144–1148
Krude H 2003 J Clin EndocrinolMetab 88:4633–4640

Ghrelin

- two major effects; it stimulates GH secretion and increases food intake in rodents and humans by activating the NPY/AGRP-expressing neurons
- in man, produces a 28% increase in food intake, when given iv and weight gain in animals over several days
- However, Ghrelin null animals do not have significantly altered body weight
- Ghrelin agonists have a potential role for treatment of obesity



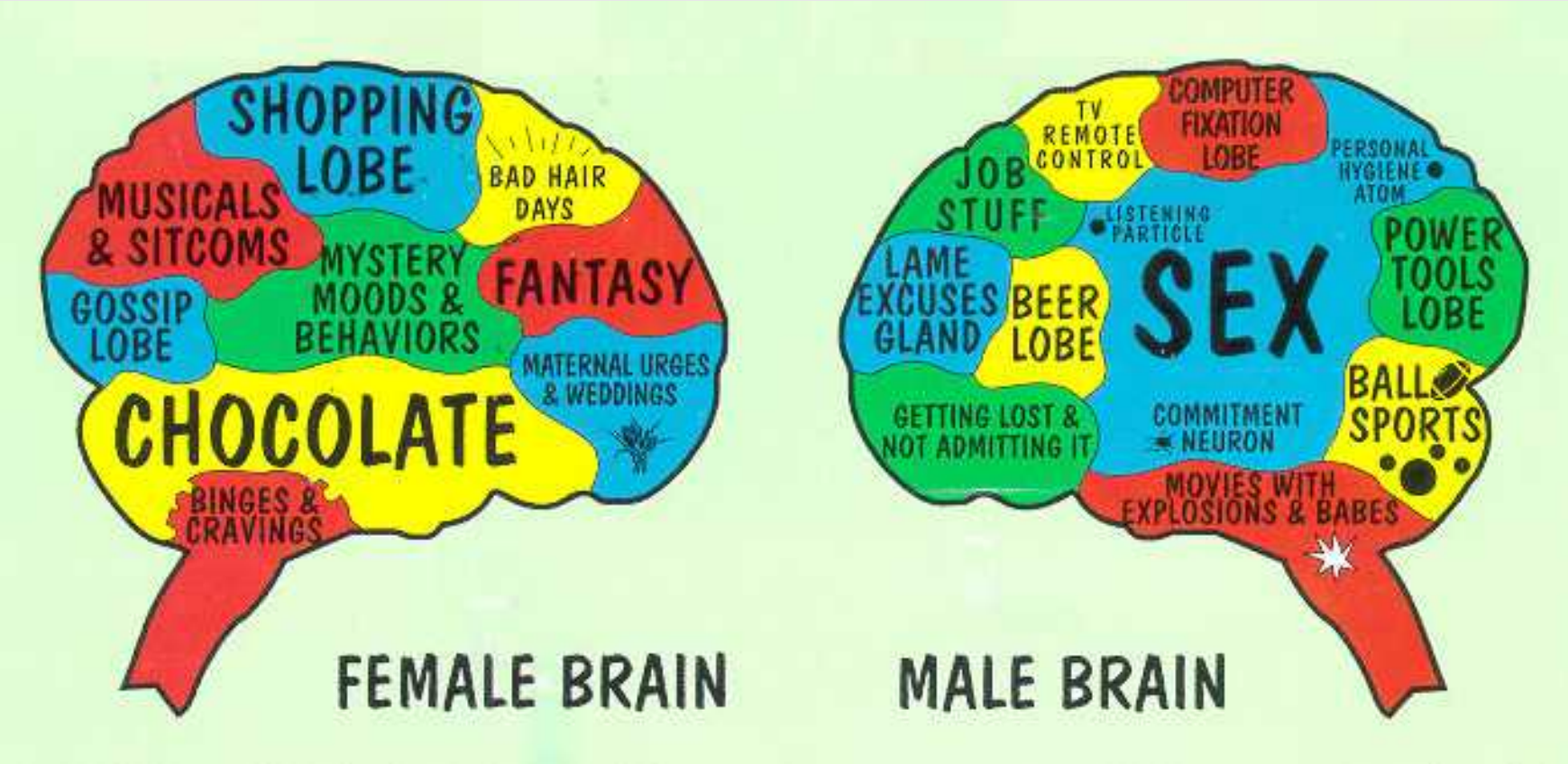
Ciliary Neurotrophic Factor

- Recombinant Human Ciliary Neurotrophic Factor
- **Axokine ®, Regeneron Pharmaceuticals**, 2nd generation CNTF
- Phase III trials for obesity therapy

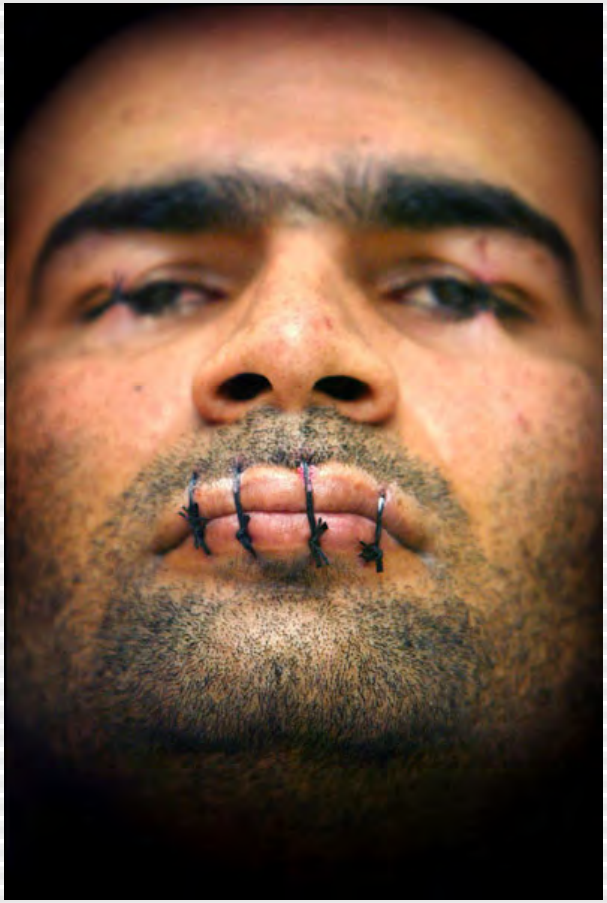
Ciliary Neurotrophic factor 2

- In a trial, the efficacy of Axokine for obesity treatment was limited by the development of antibodies in two thirds of the subjects.
- Patients injected with Axokine lost 2.8 kg compared with a loss of 1.2 kg in patients receiving placebo after 1 yr
- the 30% of participants who did not develop antibodies lost 5.7 kg.

Human brain is complex…



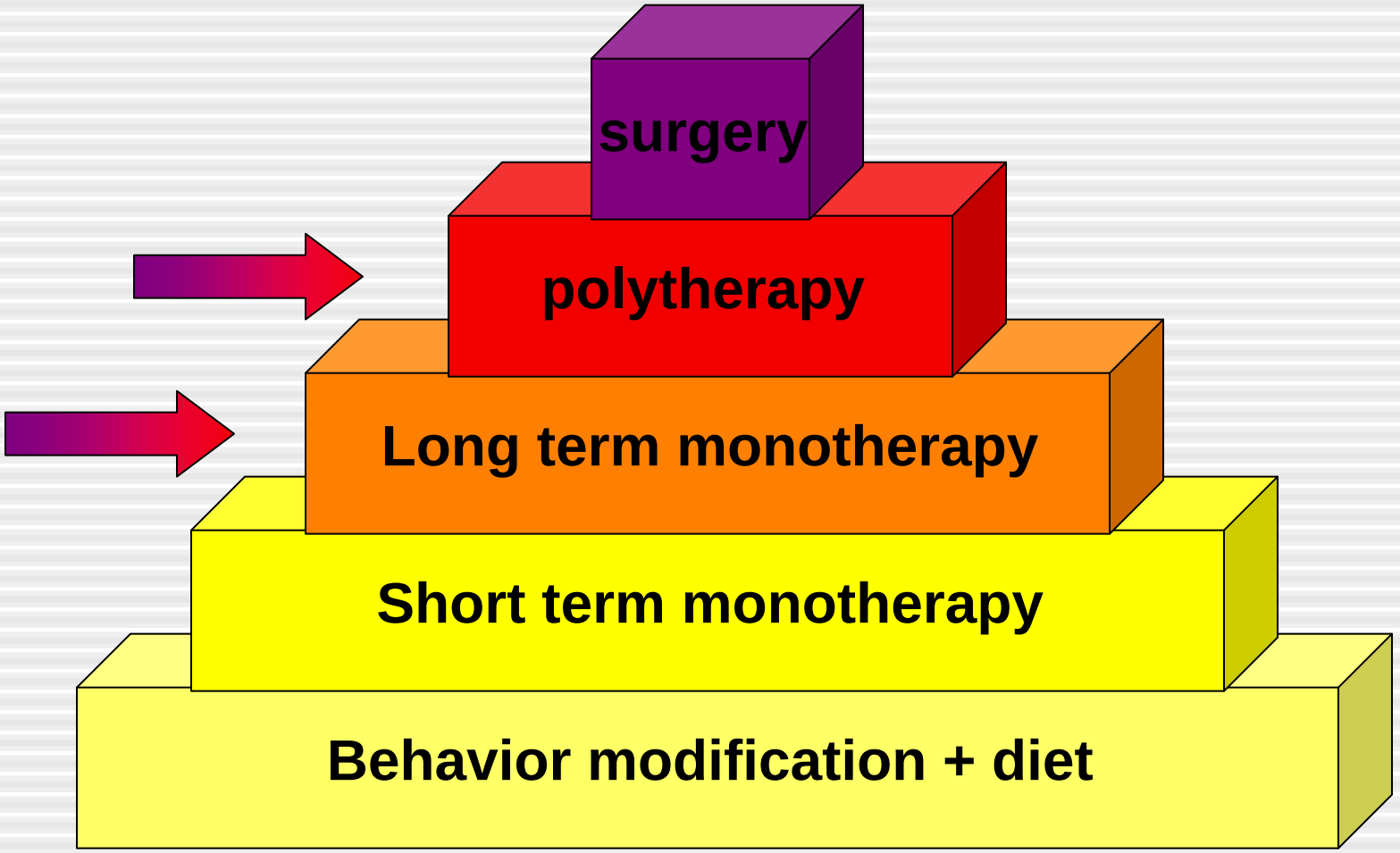
The ultimate solution will not be simple……



Obesity pharmacotherapy: a view of the future

- We should realize that the current obesity epidemics may offset medical progresses leading to improved longevity
- Almost certainly there will never be a "magic bullet" to correct obesity
- Stepwise treatment from lifestyle modifications to monotherapy to multiple drugs for long-term use (as for diabetes or hypertension) will become available and will be the standard approach

Stepwise approach



Obesity pharmacotherapy: a view of the future

- Possible obstacles may be development of neutralizing antibodies, down-regulation of the targeted receptors, and the activation of multiple counterregulatory mechanisms
- For severe obesity drugs should be at least in part covered by public health reimbursement
- Continuing progress of surgical techniques will still provide an effective tool for resistant cases but should hopefully become less important

Thank you for your attention!

VI AME National Meeting
III Joint Meeting with AACE
Update in Clinical Endocrinology

BARIATRIC SURGERY: WHEN, HOW AND RESULTS

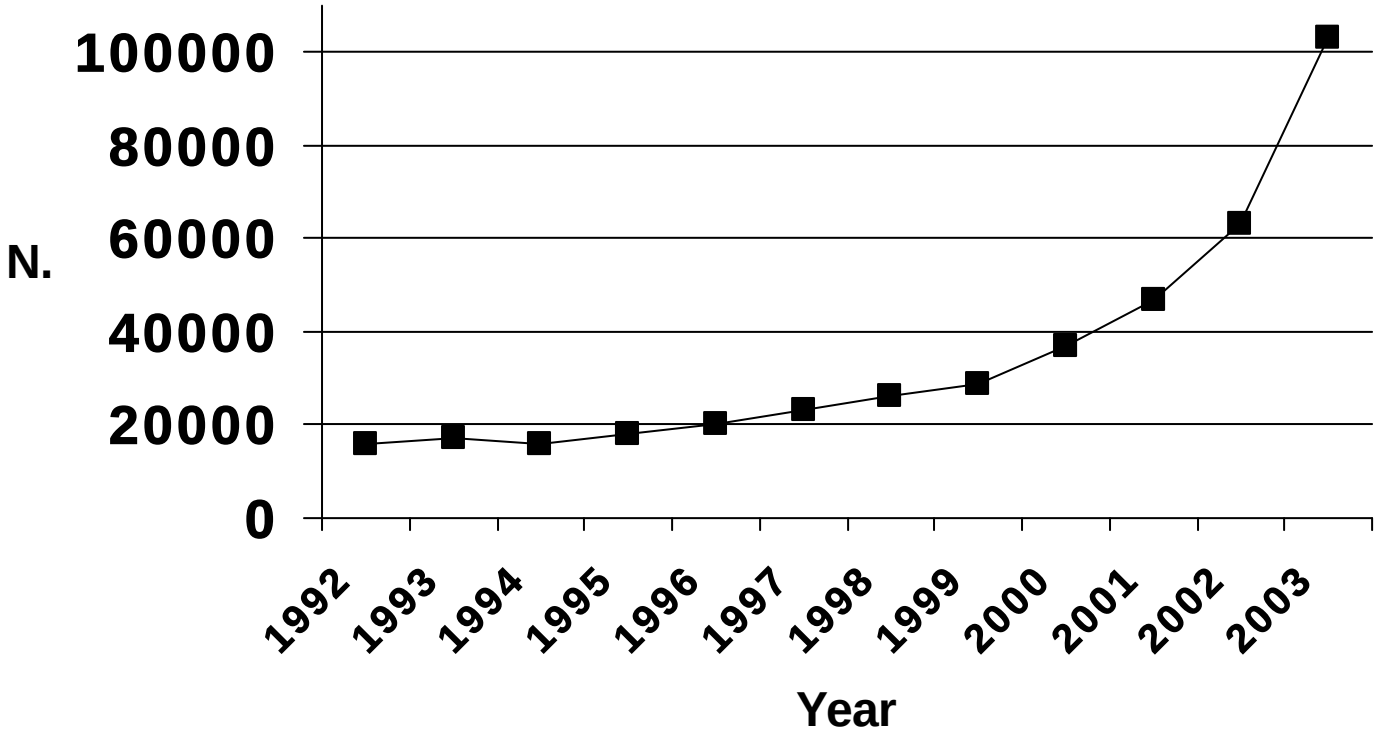
Franco Favretti

Dipartimento di Chirurgia
Ospedale Regionale S. Bortolo Vicenza

Servizio Terapia Medica e Chirurgica dell'Obesità
Università degli Studi di Padova

Verona, 27 Ottobre 2006

Estimated Number of Bariatric Operations performed in the United States, 1992-2003 (data from ASBS).



Steinbrook R. NEJM 2004;350:1075.

Indications to bariatric surgery (NIH Consensus Development Conference Statement) Bethesda, March 25-27, 1991.

- BMI > 40 kg/m^2
  (BMI > 35 kg/m^2 if complicated obesity).
- Age : 18-60 years.
- Longstanding obesity (> 5 years).
- Previous failure of medical therapy.
- Able to participate to long-term follow-up.

Am J Clin Nutr 1992;55:615S

Contraindications to bariatric surgery (NIH Consensus Development Conference Statement) Bethesda, March 25-27, 1991.

- Treatable secondary obesity.
- Very high anaesthesiological risk.
- General conditions reducing life-expectancy.
- Severe psychiatric illnesses.
- Alcohol or drug abuse.
- Bulimia Nervosa.

Am J Clin Nutr 1992;55:615S

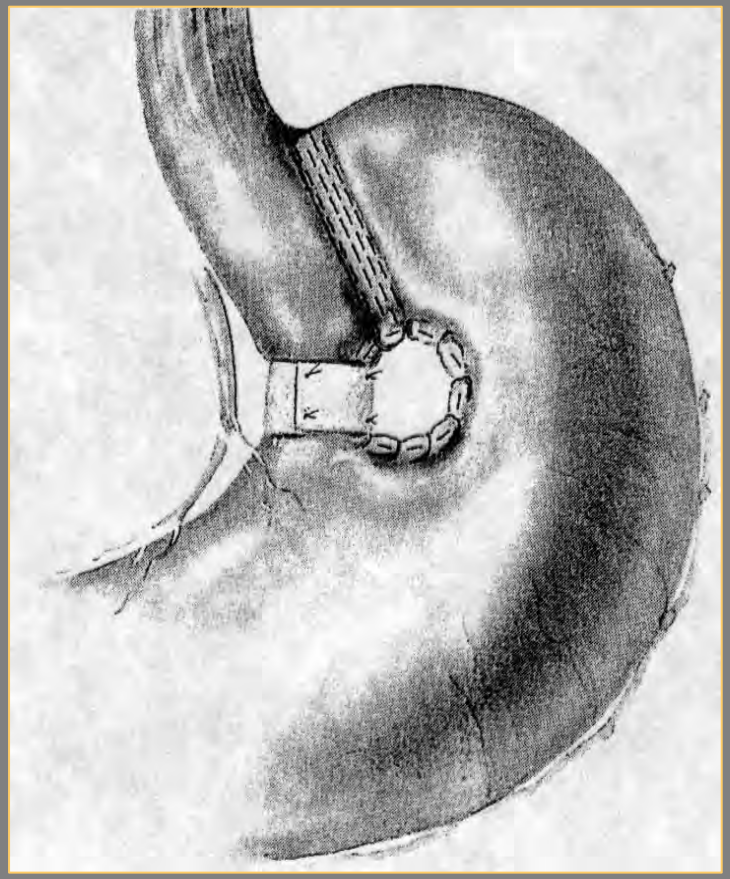
TERAPIA CHIRURGICA: OPZIONI

- Restrizione gastrica:
  - Gastroplastica Verticale
  - Bendaggio Gastrico Regolabile

- Restrizione gastrica + by-pass duodeno-digiunale:
  - Bypass gastrico

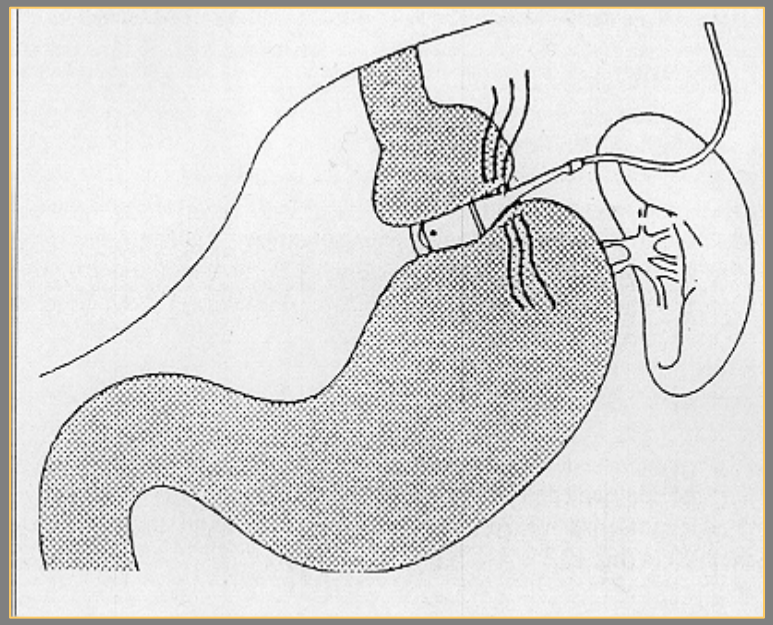
- Restrizione gastrica + malassorbimento:
  - Diversione bilio-pancreatica
  - Duodenal switch

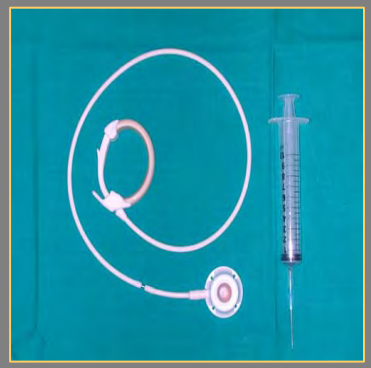
Gastroplastica Verticale

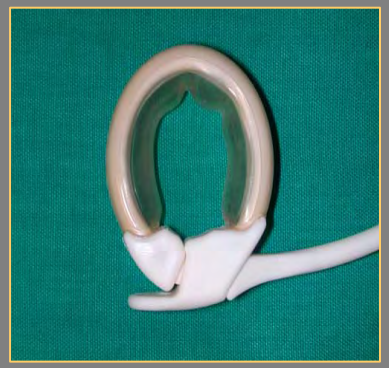


- Vomito frequente
- Esofagite
- Erosione – Stenosi Stoma
- Deiscenza sutura gastrica
- Fistola gastro-gastrica
- Recupero ponderale

Bendaggio Gastrico Regolabile

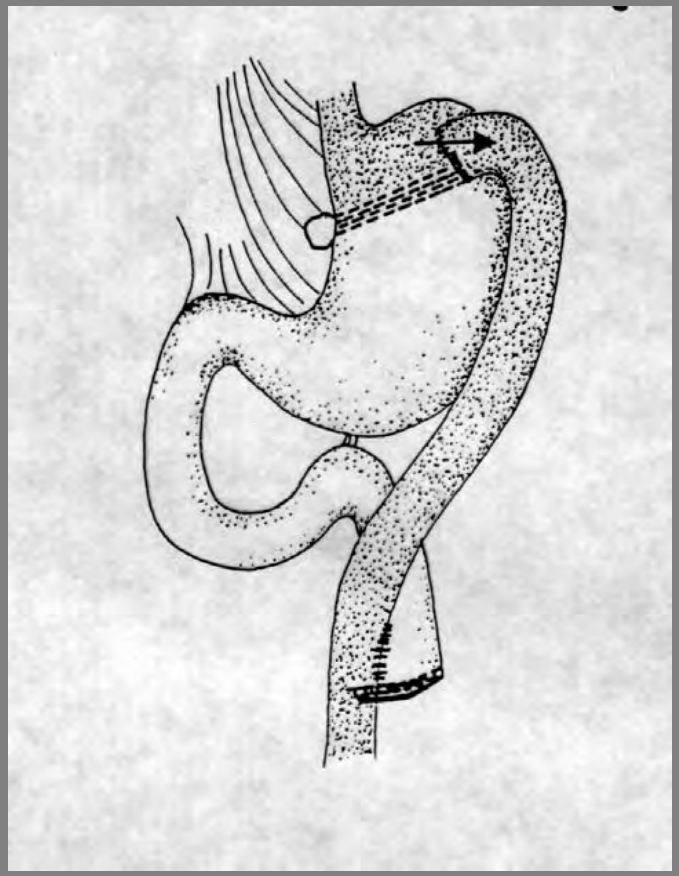






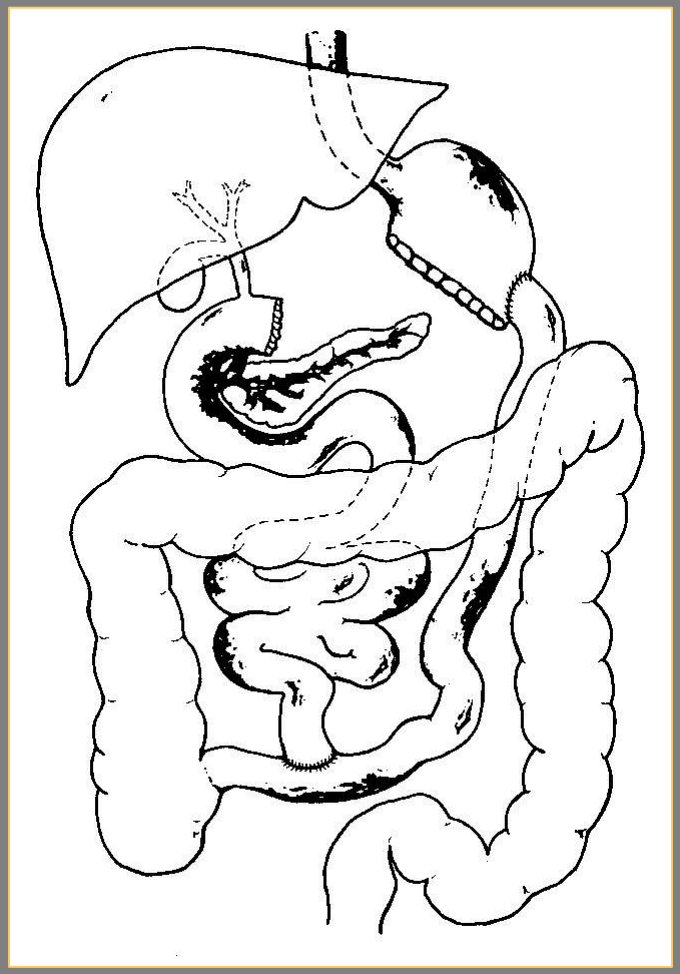
- Vomito
- Esofagite
- Stenosi Stoma
- Dilatazione tasca
- Erosione
- Recupero ponderale

Bypass Gastrico



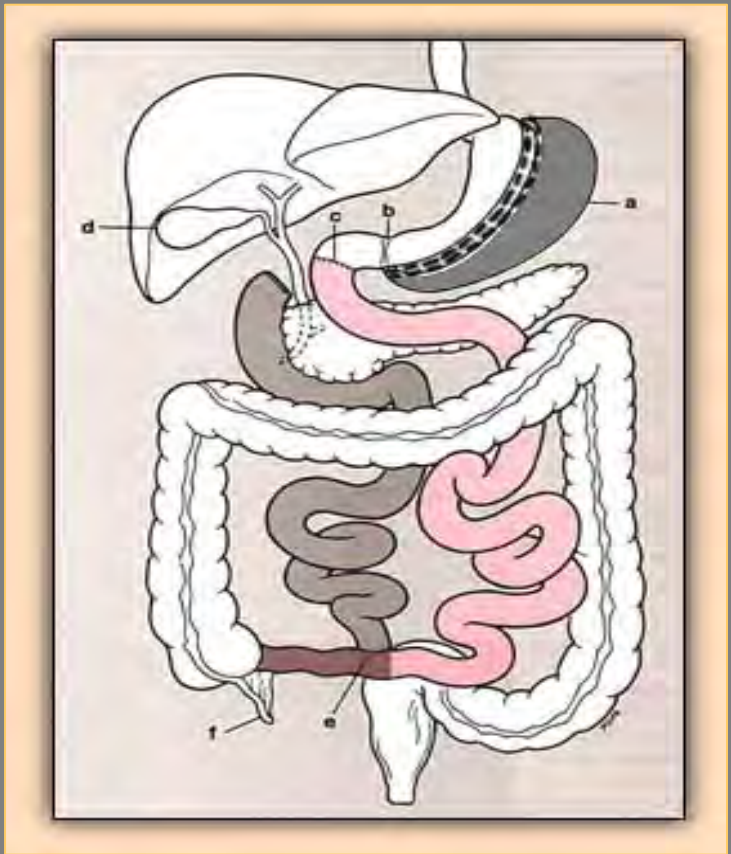
- Esofagite
- Dumping Syndrome
- Deficit di ferro
- Vit B12,A,D,E, acido folico
- Ulcera peptica
- Occlusione dell’Outlet
- Occlusione intestinale

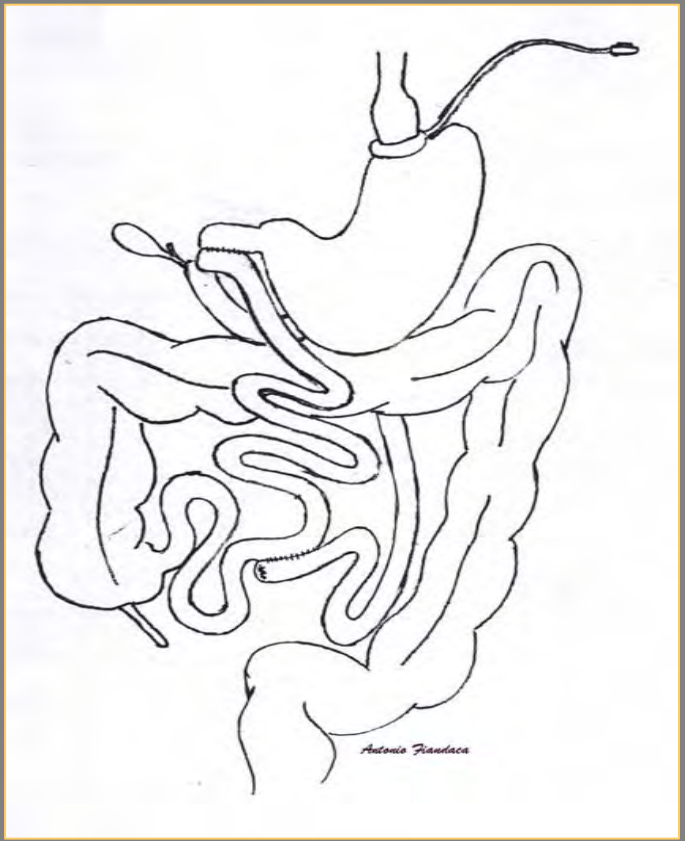
Diversione Biliopancreatica



- Ulcera dello Stoma
- Occlusione Intestinale
- Pancreatite acuta
- Diarrea - Steatorrea
- Anemia sideropenica
- Neuropatia
- Encefalopatia Wernicke
- Malnutrizione proteica
- Demineralizzazione

Duodenal Switch





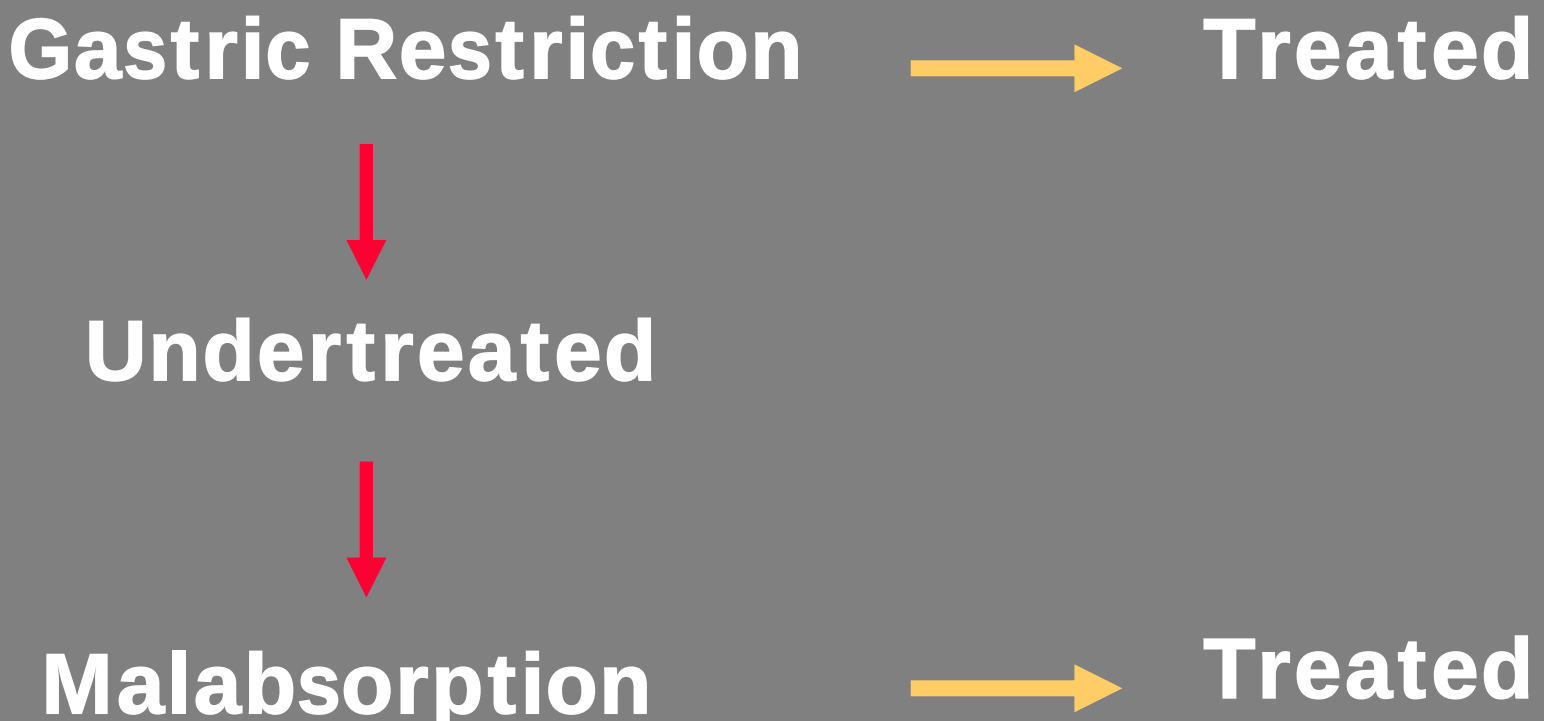
Weight Loss and Risk Score in Lap Band (LAGB), Vertical Banded Gastroplasty (VBG) and Roux-en-Y Gastric Bypass (RYGB): A Systematic Literature Review.

(64 studies LAGB; 57 studies comparative procedure)

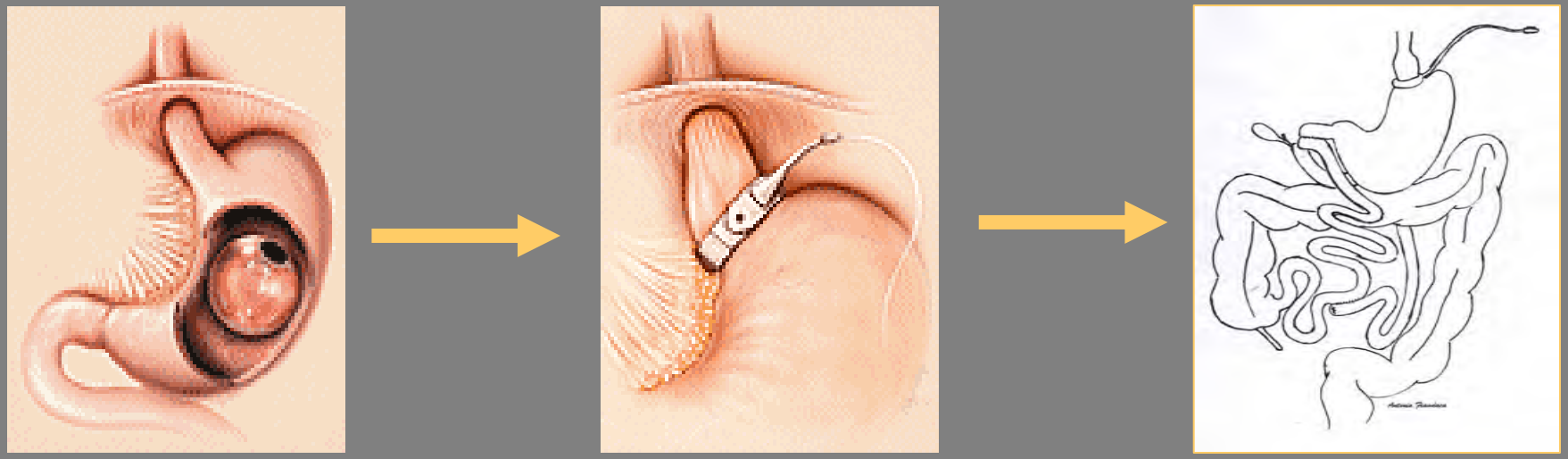
	N. of patients	Mortality rate	Morbidity rate	% Excess Weight Loss	
				0-2 years	2-4 years
LAGB	5780	0.05%	11.3%	↑ ↑	↑ ↑
VBG	2858	0.31%	25.7%	↑ ↑ ↑	↑ ↑
RYGB	9258	0.50%	23.6%	↑ ↑ ↑	↑ ↑

Chapman AE
Laparoscopic Adjustable Gastric Banding in the Treatment of Obesity: A Systematic Literature Review
Surgery 135; 326-351, 2004

BARIATRIC SURGERY
Sequential Treatment



TERAPIA CHIRURGICA SEQUENZIALE



Sequential Treatment of Obesity

Aim of the Treatment:

Improvement of Results:

- ↓ *"Overtreatment"*
- ↓ *Morbidity*
- ↓ *Mortality*

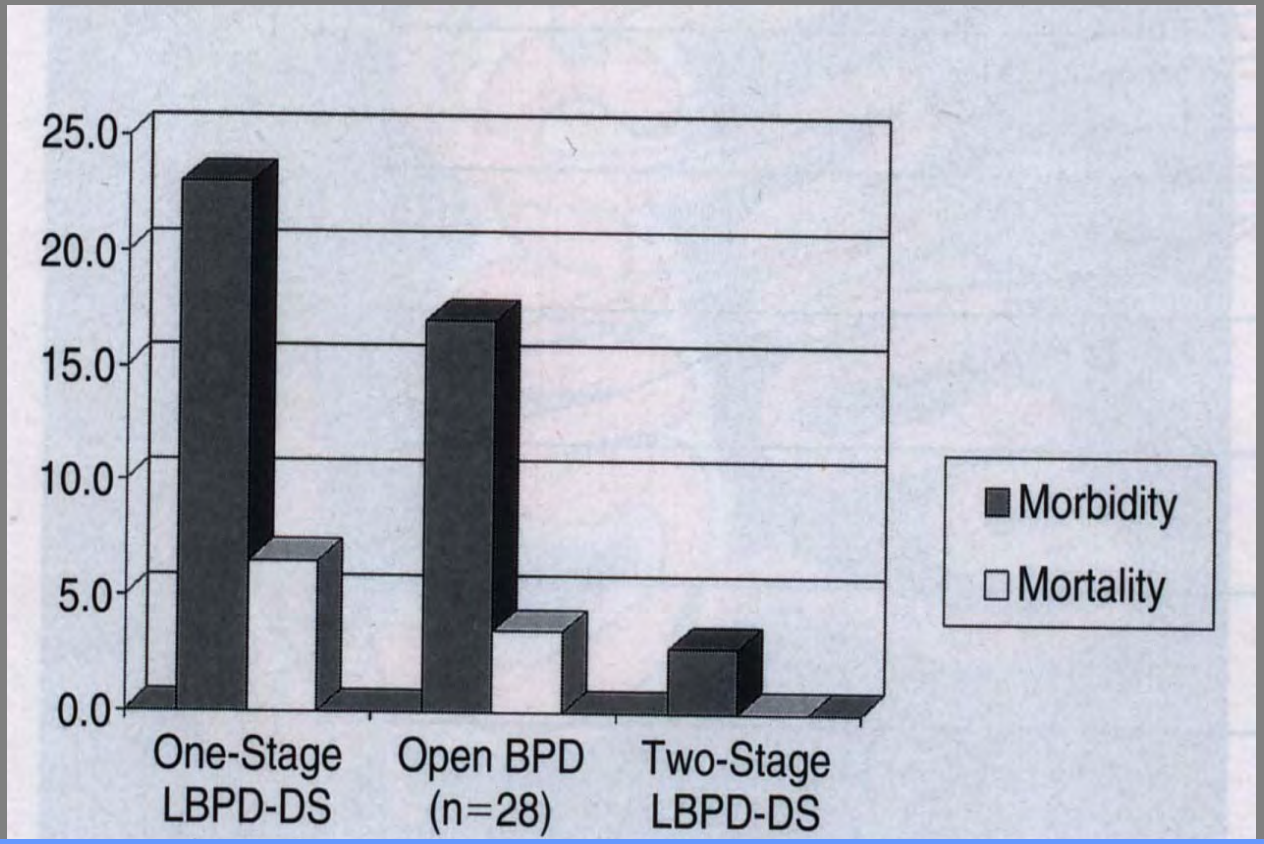
Kral John G

"…staged operation might be the solution to the problem of selecting and appropriate bariatric operation since it was not possible to predict which patients would be well served by pure gastric restrictive operation and which patients would need the addition of malabsorption…"

National Institute of Health (NIH)
Consensus Development Conference on Gastrointestinal Surgery for Severe Obesity 1991

Gagner Series

Morbidity and mortality percentages according to open BPD-DS, Laparoscopic BPD-DS, and Two Stage Laparoscopic BPD-DS



Gagner M, Inabnet W B, Pomp A

Laparoscopic Sleeve Gastrectomy with Second Stage Biliopancreatic Diversion and Duodenal Switch in the Super Obese

Laparoscopic Bariatric Surgery. Lippincot Williams & Wilkins 2004

Quality of life

+

Risk/benefit

=

step by step approach

or

sequential treatment of obesity

LAP BAND: Padua Series

September 1993/March 2006

1851 pts.
(1385 female, 466 male)

Mortality: 0

Follow-up Rate: 90.4%

Very Large, Very Long-Term Study Demonstrating the Safety and Efficacy of Lap Band for Morbid Obesity

- *Up to 12 Years Follow-up (1993-2005)*
- *1791 Consecutive Patients*
- *One Surgical Team*
- *91% Follow-Up*

Laparoscopic Gastric Banding for 1800 Patients: 12 Years Results

Patient Characteristics

- *75.1% Female, 24.9% Male*
- *Mean Age: 38.7 Years*
- *Mean Body Weight: 127.7 ± 24 kg*
- *Mean BMI: 46.2 ± 7.7*
- *Baseline Co-Morbidities: 71% of Patients*

Methods

- ***Dissection***
  - *77.8% Perigastric*
  - *21.4% Pars Flaccida*
  - *0.8% Combined Approach*

- ***11.9% Simultaneous Procedures Performed***
  - *2.4% Hiatal Hernia Repair*
  - *7.8% Cholecystectomy*
  - *1.7% Other Procedure*

Lap Band Outcome Measures

- *Mortality*
- *Resolution/Improvement in Co-Morbidities*
- *Conversion to Laparotomy*
- *Short-Term Complications*
- *Long-Term Complications*
- *Weight Loss*
- *Impact on Life Expectancy*

Results

- ***Mortality: 0 (0/1791 over 12 Years)***
- ***1.7 Conversion Rate***

Laparoscopic Gastric Banding for 1791 Patients: 12 Years Results

Major Complications Requiring Reoperation (106/1791 pts.; Sept 1993-Dec 2005)

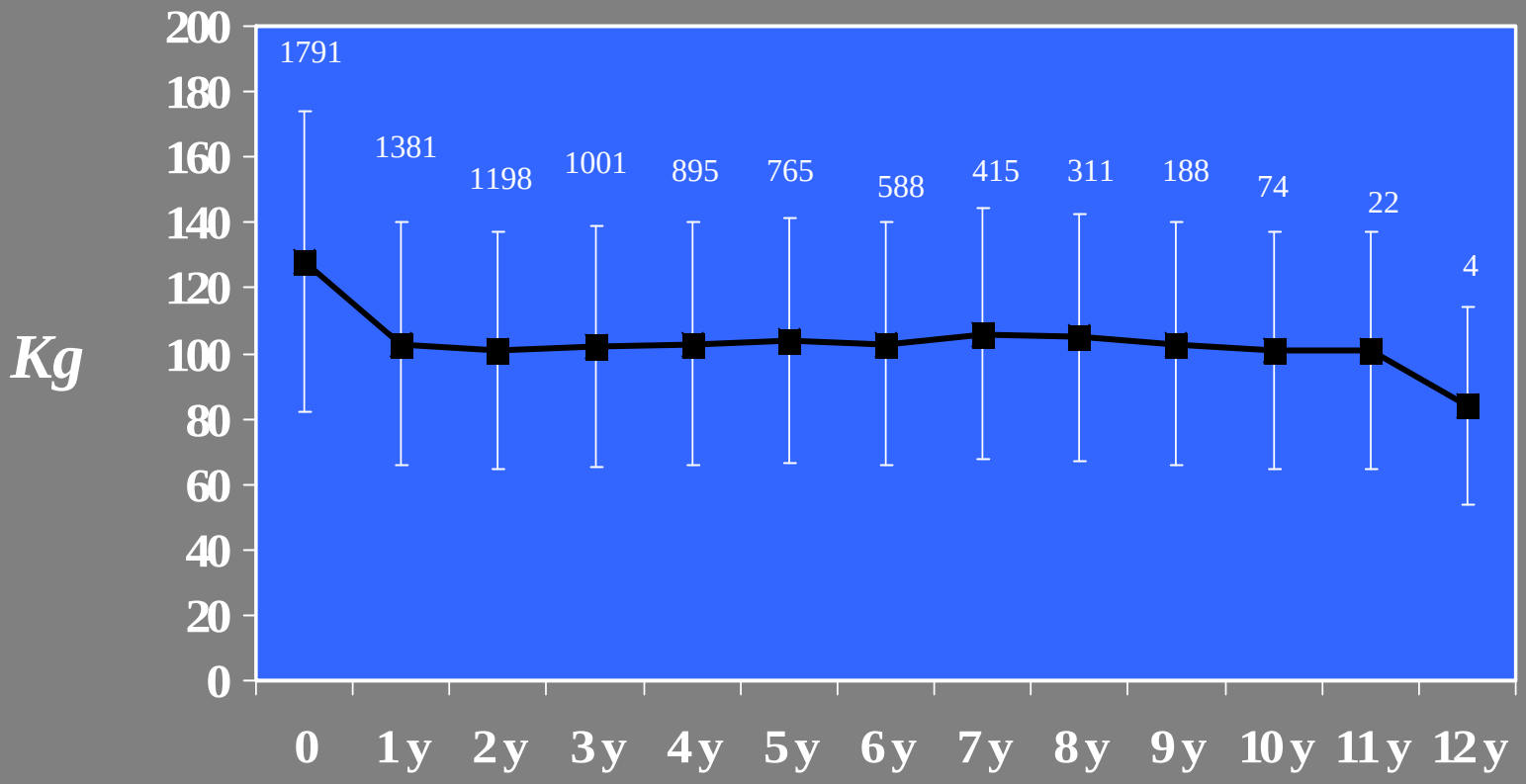
Complications	Number	Rate of Complications	Reoperation	Number	Rate of Reoperation
Stomach Slippage + Pouch Dilatation	*70*	*3.9%*	• *Removal* • *Repositioning*	*20* *50*	*1.1%* *2.8%*
Erosion	*16*	*0.9%*	*Removal*	*16*	*0.9%*
Psychological Intolerance	*14*	*0.7%*	*Removal*	*14*	*0.7%*
Miscellaneous (HIV, Infections, Microperforation)	5	0.27%	Removal	5	0.27%
Gastric Necrosis	1	0.05%	Gastrectomy	1	0.05%
Total	***106***	***5.9%***	***Total***	***106***	***5.9%***
Unsatisfactory Results (Lack of Compliance)	*41*	*2.3%*	• *BPD* • *Removal* • *"BandInaro"*	*5* *12* *24*	*0.27%* *0.7%* *1.3%*

Minor Complications Requiring Reoperation

11.2% Port Reoperation – 200 patients

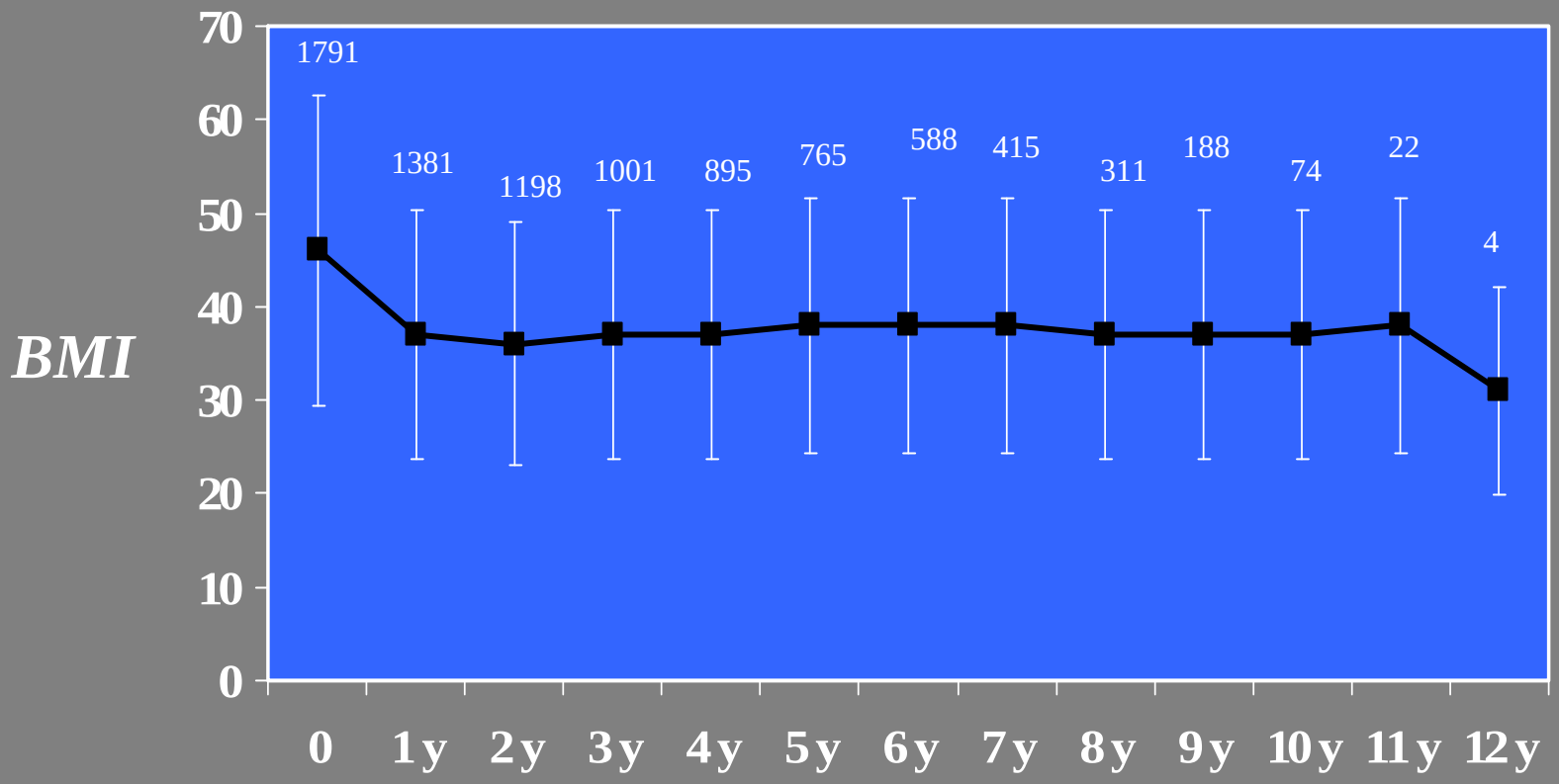
Laparoscopic Gastric Banding for 1800 Patients: 12 Years Results

Results (Kg)



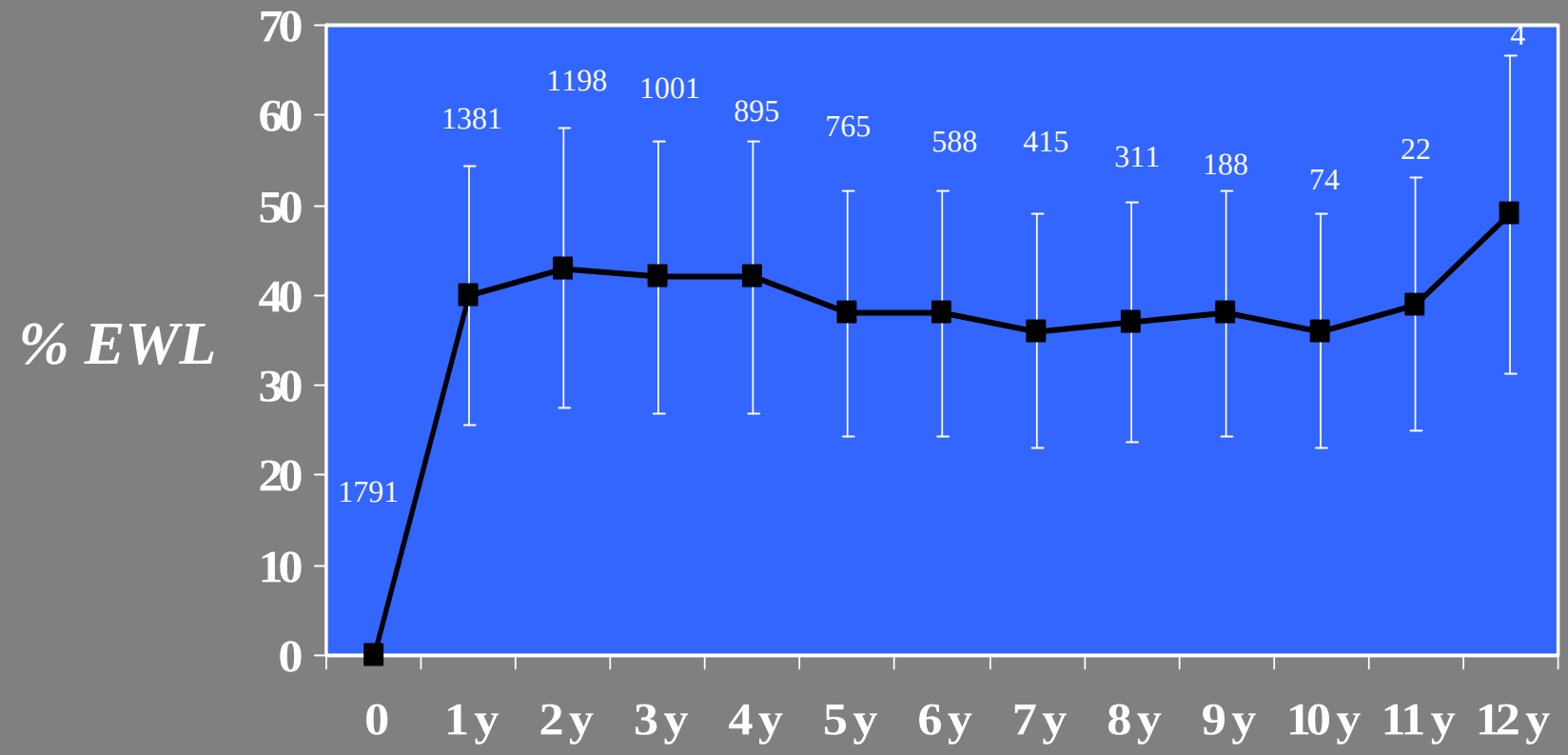
Laparoscopic Gastric Banding for 1800 Patients: 12 Years Results

Results (BMI)



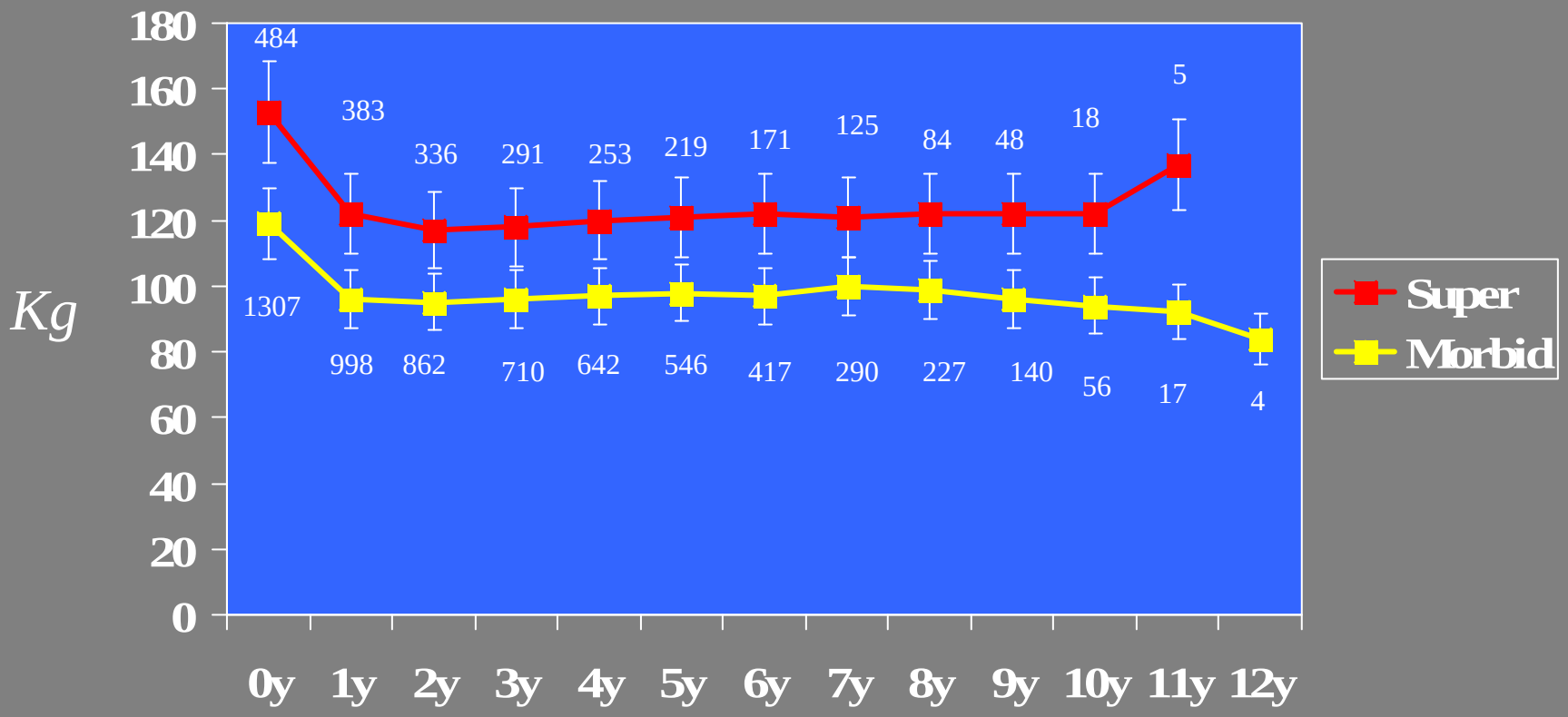
Laparoscopic Gastric Banding for 1800 Patients: 12 Years Results

Results (% EWL)



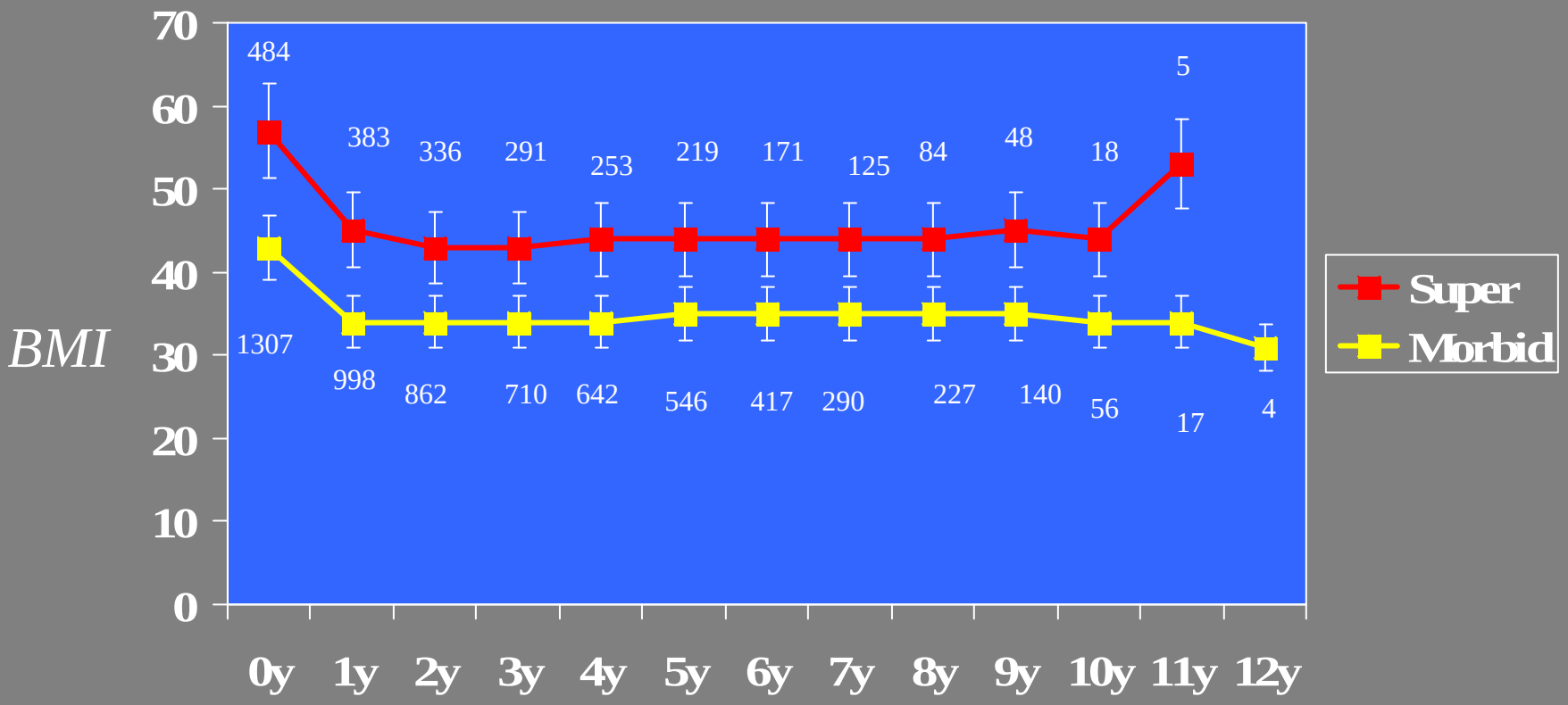
Laparoscopic Gastric Banding for 1800 Patients: 12 Years Results

Results in Super e Morbid Obese (BMI)



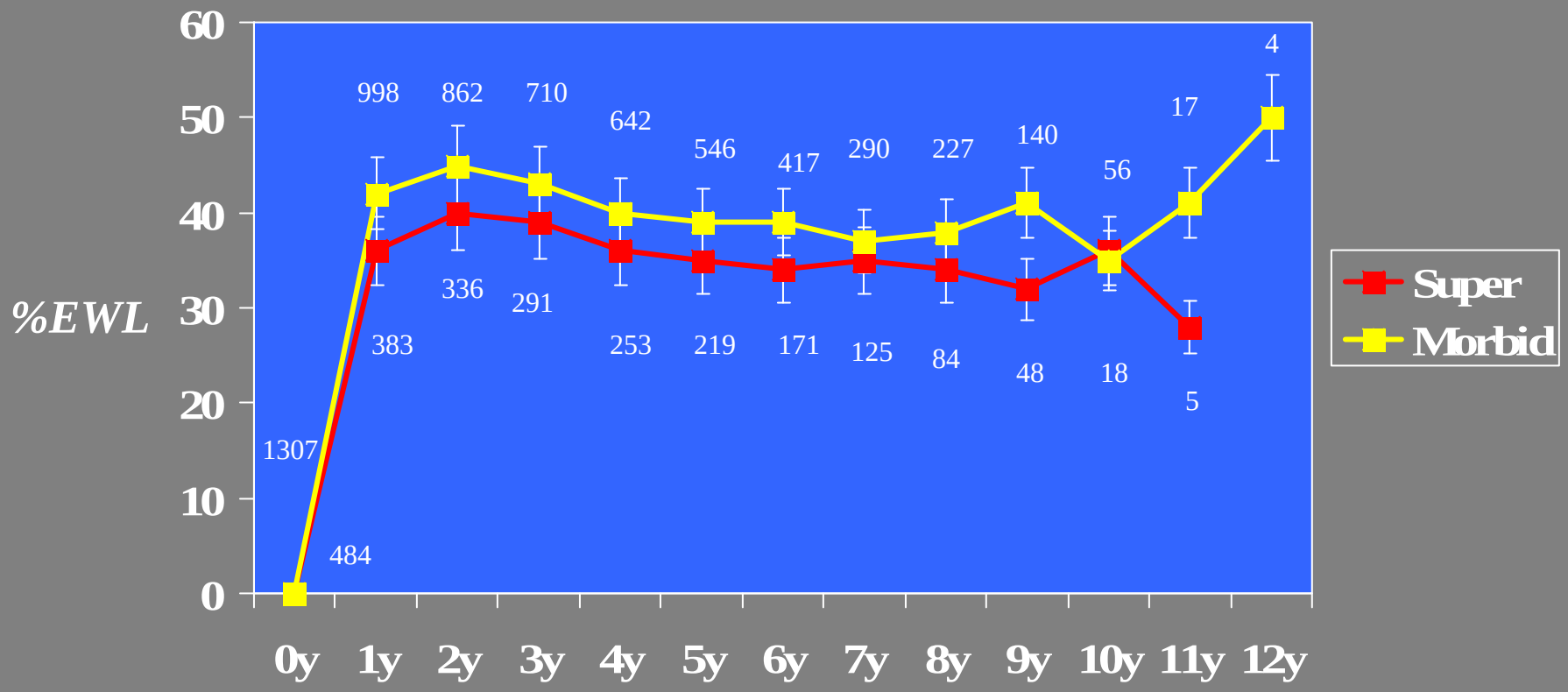
Laparoscopic Gastric Banding for 1800 Patients: 12 Years Results

Results in Super e Morbid Obese (BMI)

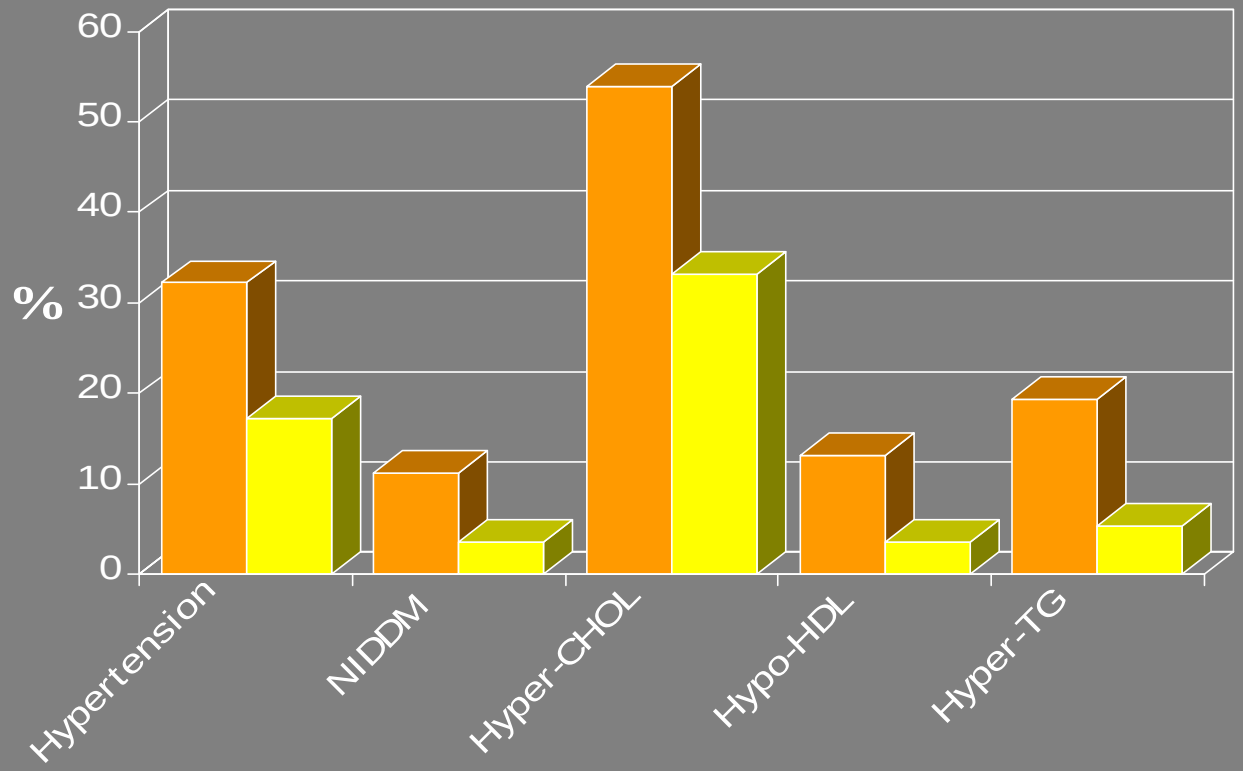


Laparoscopic Gastric Banding for 1800 Patients: 12 Years Results

Results in Super e Morbid Obese (% EWL)

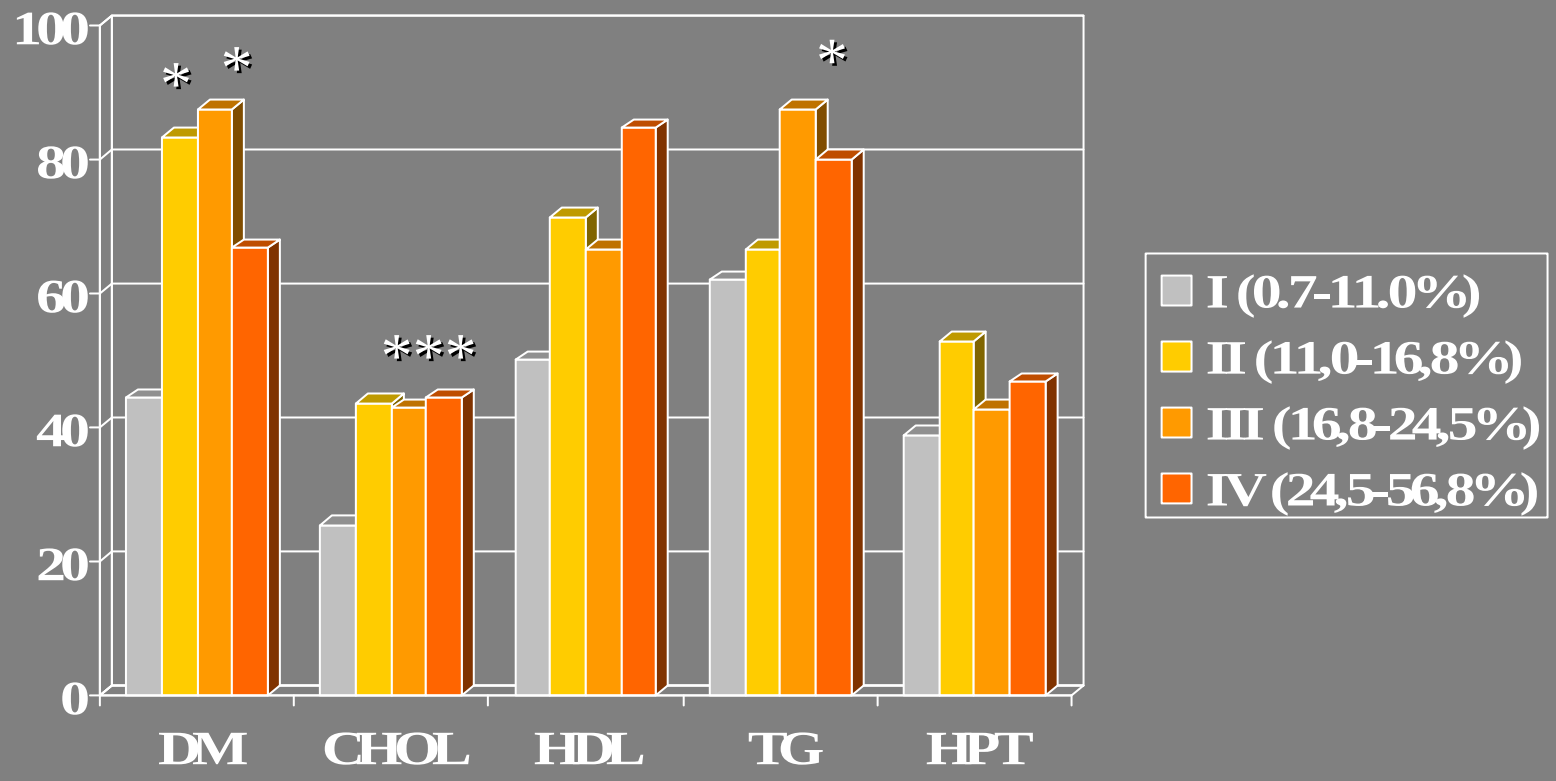


Prevalence of metabolic abnormalities in 650 morbid obese patients before and 1 year after LAP-BAND™.



Busetto, Favretti et al.

Percent of patients with diabetes, dyslipidaemia or hypertension at baseline with normalisation 1 year after LAP-BAND™, according to quartiles of % Weight Loss.



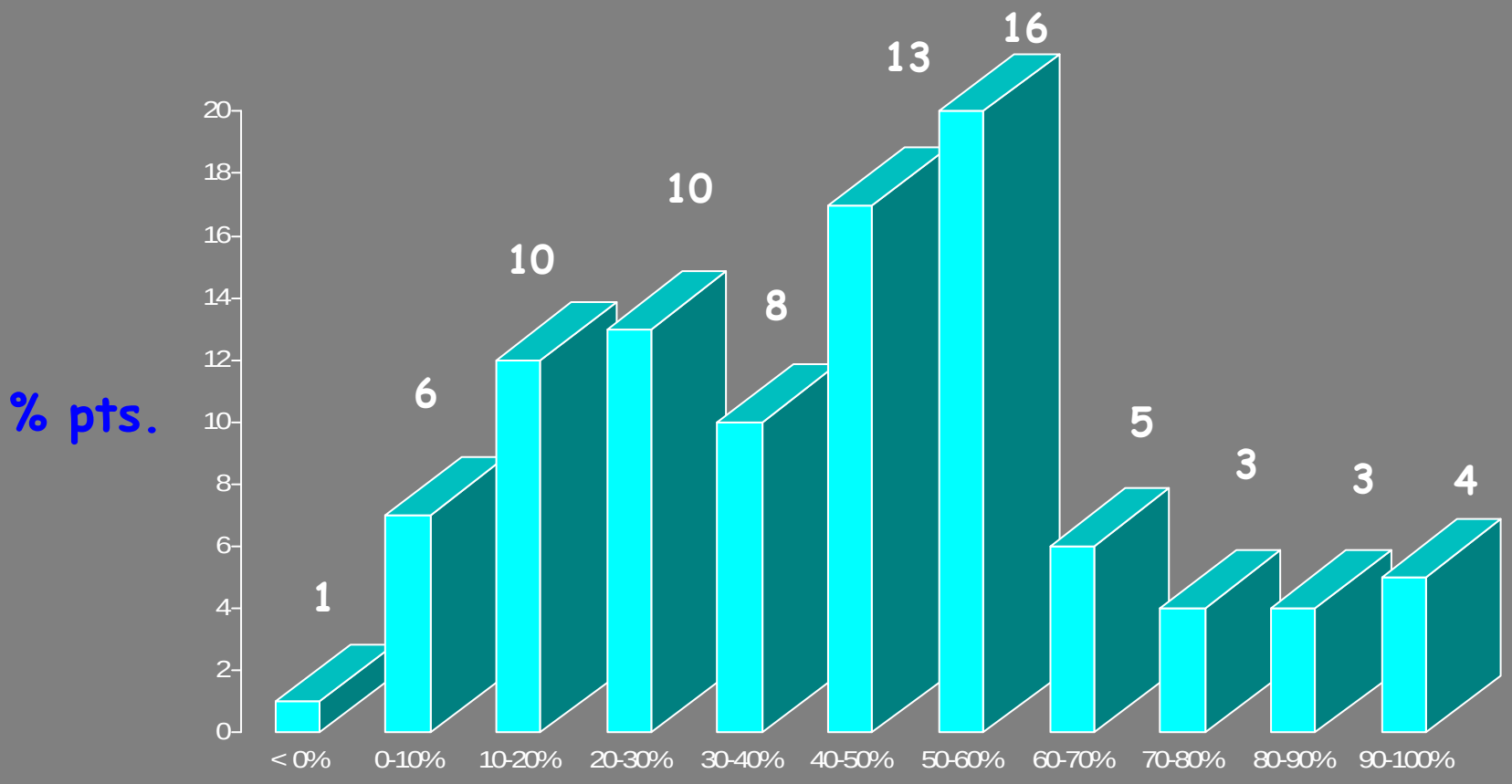
Busetto, Favretti et al.

Laparoscopic Gastric Banding for 1791 Patients: 12 Years Results

- *LAP-BAND is safe and effective in the short, medium and long term*
- *Weight loss is stable over 12 years*
- *In experienced hands the complication rate is low*
- *Intensive follow-up and regular adjustments are of paramount importance*
- *Impact on Life Expectancy*
- *LAP-BAND is our First Choice Operation*

LAP BAND™

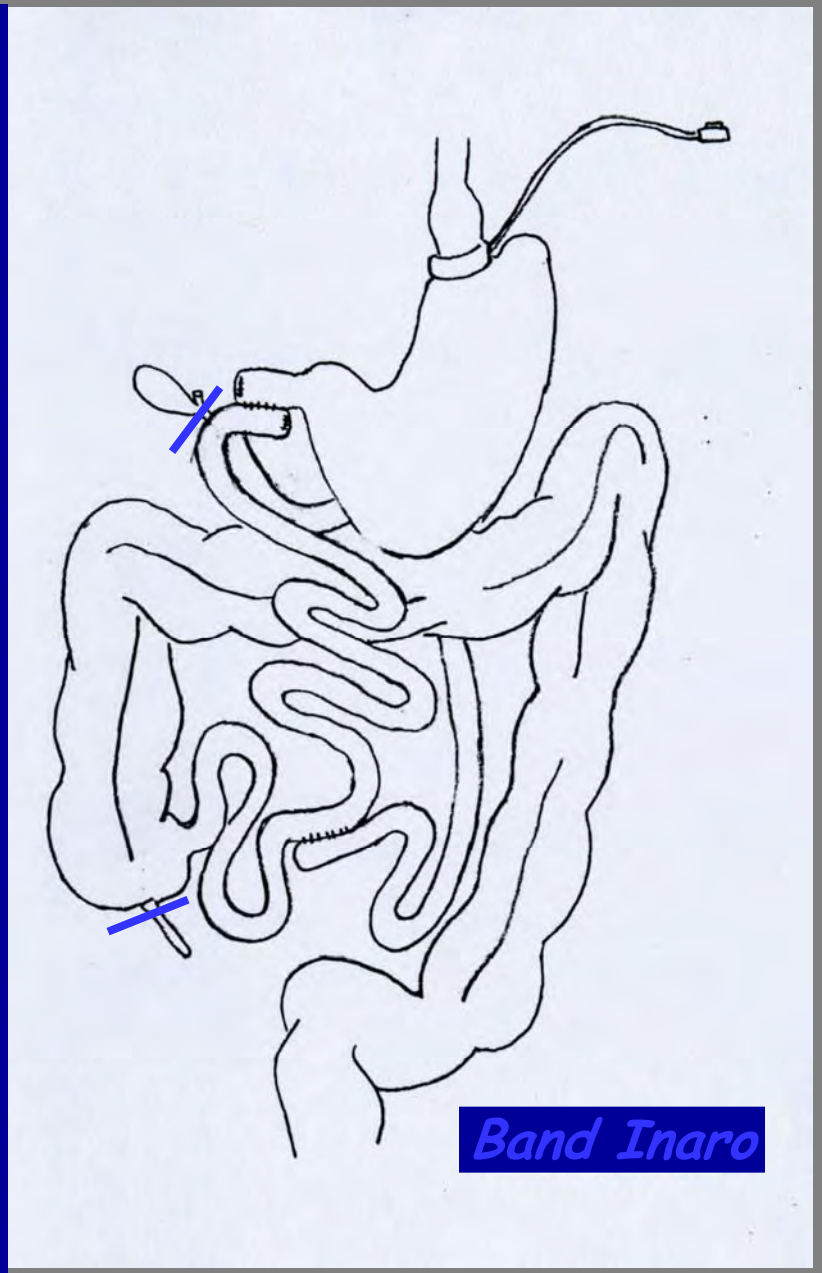
% EWL Distribution at 10 years follow-up: 79 pts.



Lap Band + Scopinaro

Band-Inaro

- Digestive loop = 200 cm.
- Common loop = 50 cm
- Bilio-pancreatic loop = remainder of small intestine



Lap Duodenal Switch with Gastric Preservation and Restriction (Bandinaro)

ANNEAU GASTRIQUE
ET DÉRIVATION BILIO-PANCRÉATIQUE PAR LAPAROSCOPIE

G.B. Cadière, F. Favretti, J. Himpens, G. Segato, E. Capelluto

Bruxelles - BELGIQUE

Le journal de Coelio-Chirurgie - N° 38 - Juin 2001

Lap Duodenal Switch with Gastric Preservation and Restriction (Band-Inaro)

Obesity Surgery, 7, 30–33 1997

Biliopancreatic Diversion with Transitory Gastroplasty Preserving Duodenal Bulb: 3 Years Experience

C. Vassallo; L. Negri; A. Della Valle; M. Salvaneschi; C. Vegezzi; A. Griziotti; C. Dono; P. Mussi; M. G. Bausardo; P. Pietrobono.

Interdisciplinary Centre of Obesity, Surgical Division, Stradella's Hospital, Stradella (PV), Italy

Sequential Treatment

Padua series: May 1993/ January 2006: 59 pts.

4 pts. VBG (open) → BPD DS open

22 pts. ASGB (open) → LASGB+BPD-DS (BANDINARO) open

2 pts. ASGB (open) → LASGB+BPD-DS (BANDINARO) laparoscopy

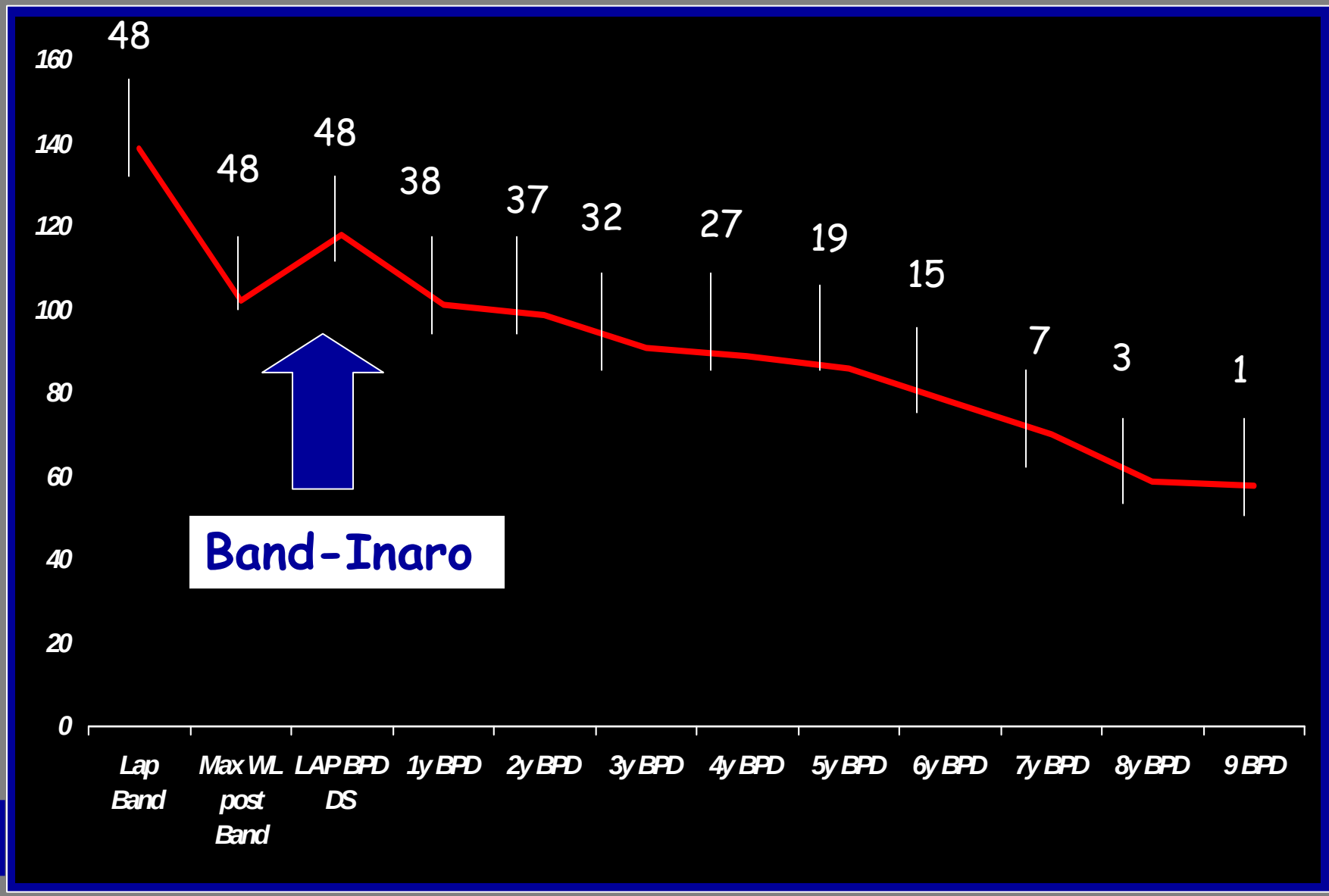
31 pts.LASGB (Laparoscopy) → BANDINARO

- Laparoscopy 28
- Conversion 1
- Open 2

Padua total series: May 1993/ January 2006: 59 pts.

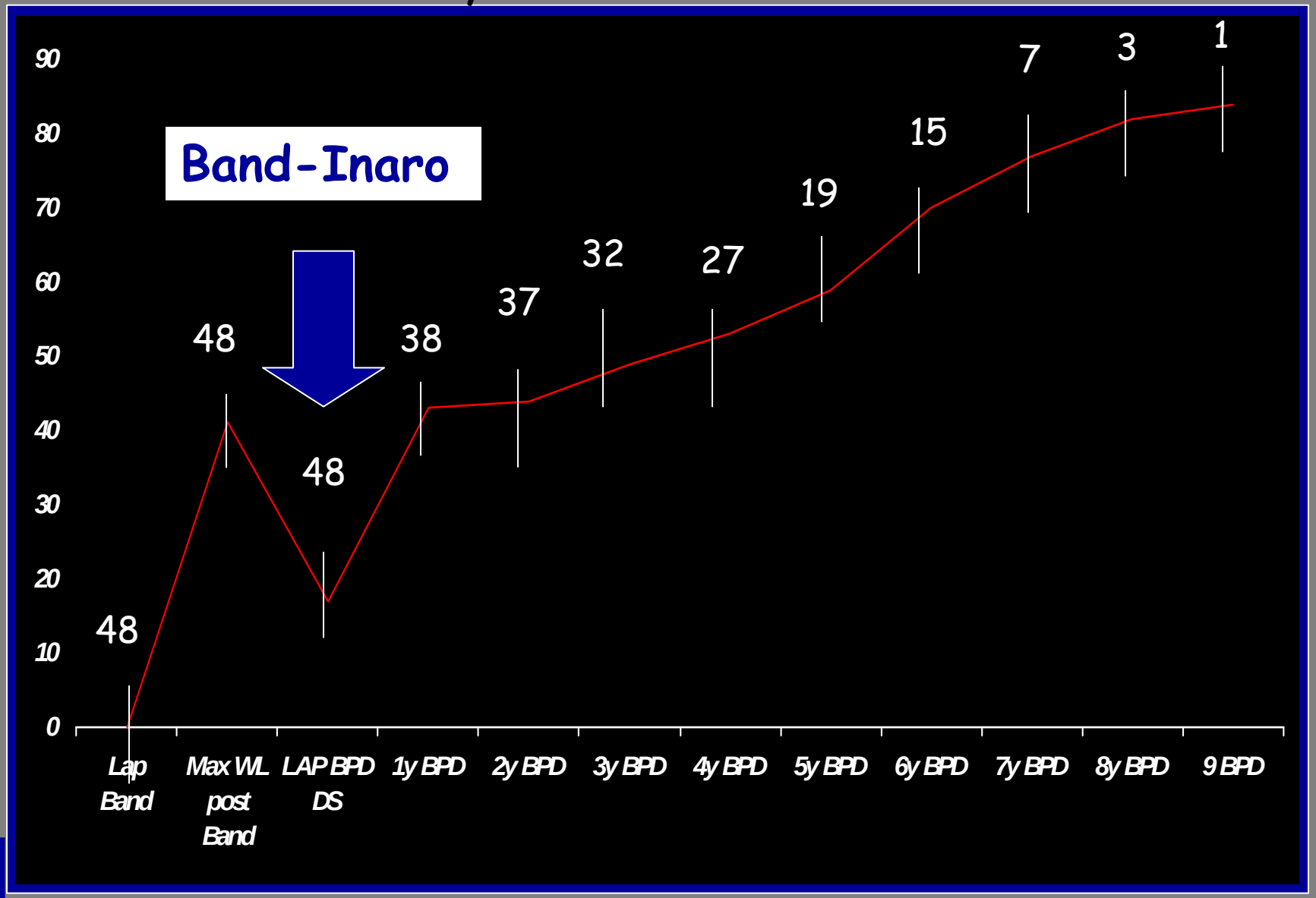
Mean Weight Loss (Kg) in a subset of 48 pts (open + laparoscopic series)

May 1993/June 2005



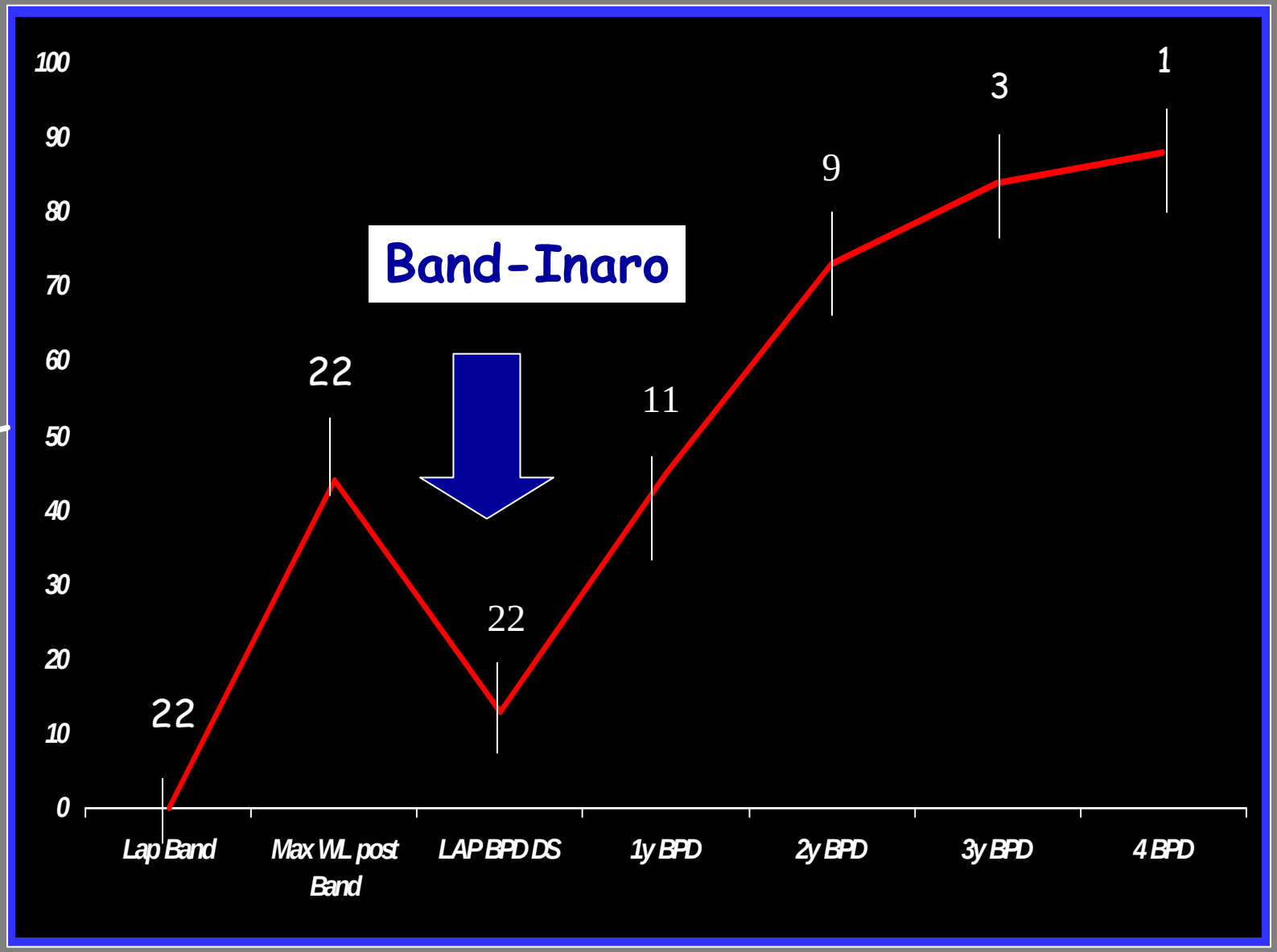
Padua total series: May 1993/ January 2006: 59 pts.

% EWL in a subset of 48 pts (open + laparoscopic series)
May 1993/June 2005



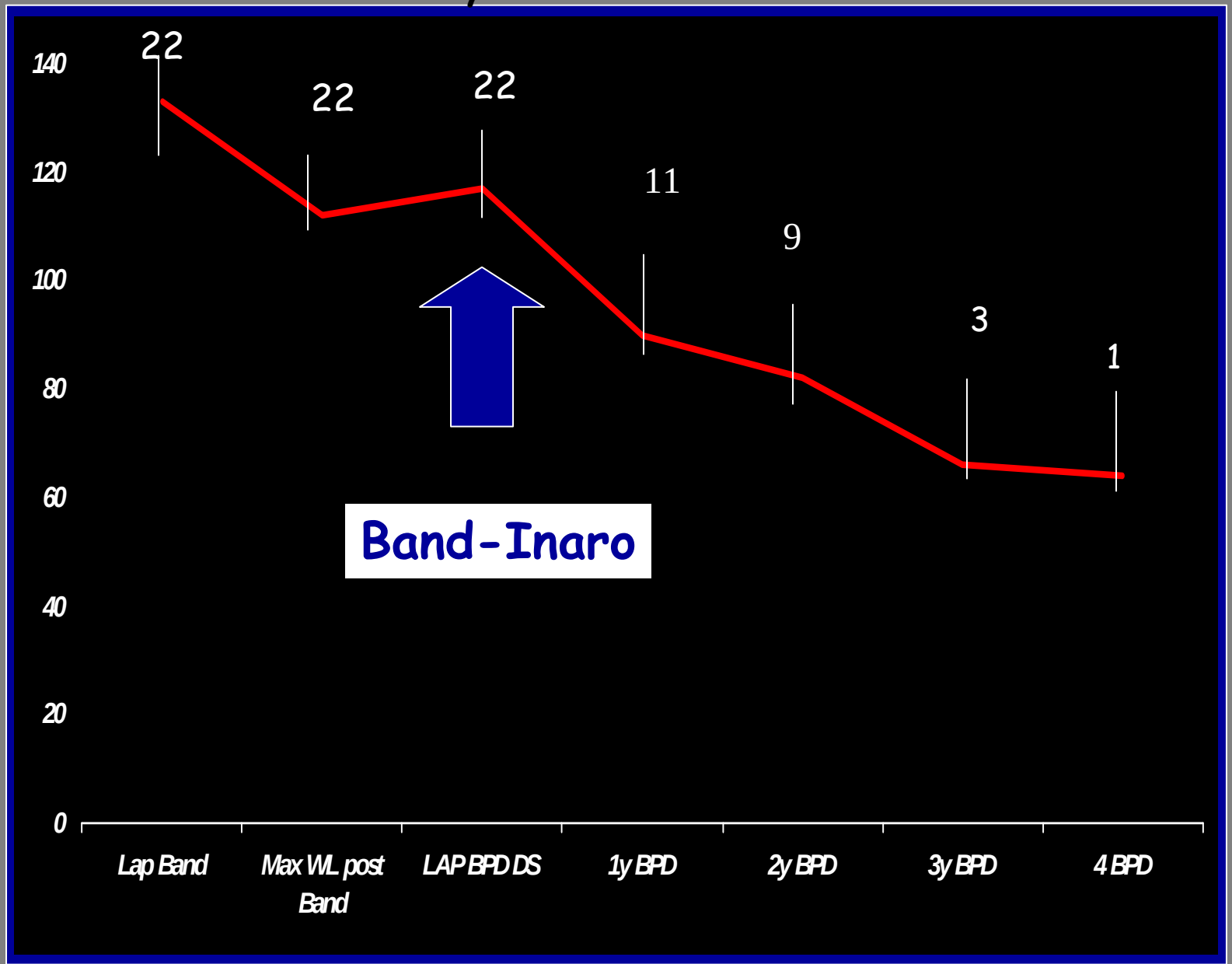
Padua total series: May 1993/ January 2006: 59 pts.

% EWL in a subset of 22 pts (laparoscopic series)
May 1993/June 2005



Padua total series: May 1993/ January 2006: 59 pts.

Mean Weight Loss (Kg) in a subset of 22 pts (laparoscopic series) May 1993/June 2005



Padua total series: May 1993/ January 2006: 59 pts.

Subset of 39 pts (open + laparoscopic series)

May 1993/June 2005

Biochemistral Data

	Pre-op	Post-op
Months of Follow-up		**38.8±29.0 (3-96)**
Glycemia, mg/dl	**96.3±15.8**	**88.5±21.9**
Total Cholesterol, mg/dl	**193.3±49.9**	**133.3±26.*** **
HDL Cholesterol, mg/dl	**45.1±13.0**	**48.5±11.8**
Trygliceredes, mg/dl	**136.3±85.8**	**97.2±47.4***
AST, U/l	**31.7±41.7**	**26.0±11.7**
ALT, U/l	**40.3±36.7**	**34.6±24.8**
Proteins, g/dl	**72.3±4.4**	**69.3±5.5**
Albumin, g/dl	**41.1±3.6**	**39.6±5.8**
Hemoglobin, g/dl	**13.2±1.3**	**11.6±1.6*** **
MCV, ftl	**82.1±8.6**	**81.9±8.3**
Iron, mcg/dl	**68.7±31.1**	**37.1±25.9****

Student's t-test for Couplet data: * = p<0.05; ** = p<0.01; *** = p< 0.001.

Bandinaro

Effects and Metabolic Complication

❖ Bowel movement (daily)	4.4±3.2 (range: 2-16)
❖ Anemia (WHO Criteria: M<13.0 and F<12.0 g/dl)	50.0% of pts
❖ Secondary HyperParathyroidism (PTH>normal range)	61.1% of pts
❖ Low albuminemia (Albuminemia < 30g/dl)	0.0 % of pts

Bandinaro

Surgical Complication

Open Bandinaro

- 1 pancreatitis (requiring reoperation)
- 1 internal hernia (requiring reoperation)

Laparoscopic Bandinaro

- 3 duodenum-ileal fistulas (not requiring reoperation)
- 1 bleeding of gastro-colic ligament (requiring reoperation)
- 1 case of mortality (myocardial infarction)

Bandinaro

Conclusion

- Increased respect for anatomy and function
- Good results (weight loss and complication)
- Second choice/remedial surgery
- Sequential surgery

Bariatric Surgery

Future characterized by:

- Major impact of Quality of Life and Risk/Benefits Analyses Concepts
- Step by Step approach/Sequential Therapy of Obesity

TOTAL MORTALITY IN MORBID OBESE PATIENTS TREATED WITH LAPAROSCOPIC ADJUSTABLE GASTRIC BANDING: A FOLLOW-UP STUDY

L. Busetto[1], M. Mazza[1], D. Mirabelli[2], M.L. Petroni[3], G. Segato[1], M. Chiusolo[2], F. Favretti[1], F. Merletti[2], F. Balzola[3], G. Enzi[1].

[1] Servizio Terapia Medica e Chirurgica dell'Obesità, University of Padova, Italy
[2] Epidemiologia dei Tumori, University of Torino, Italy
[3] Istituto Auxologico Italiano, Piancavallo, Italy

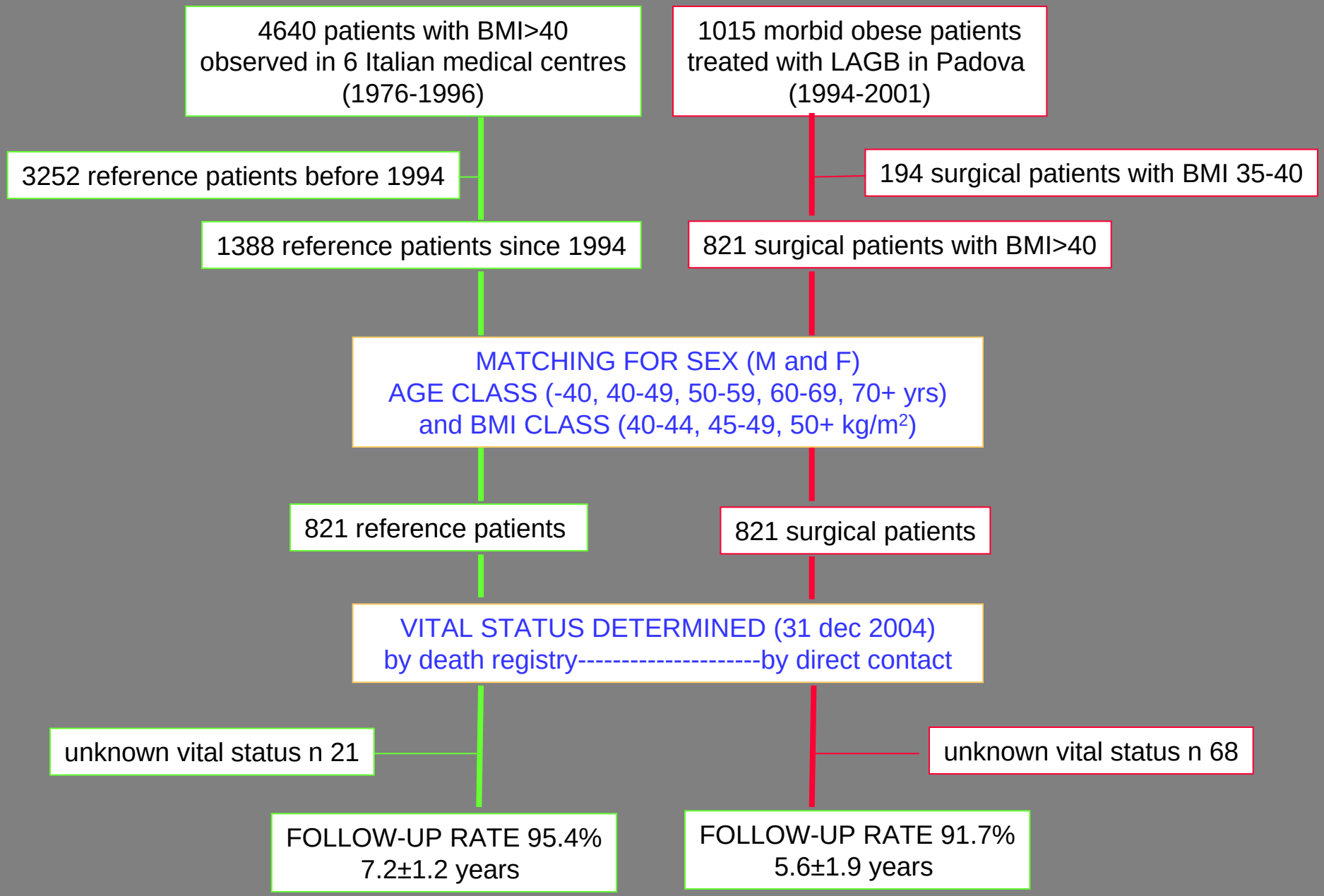
Project: “Mortality in obese patients treated with gastric banding: a follow-up study".

Bariatric surgery cohort:
Padova series 1994-2001
1015 LAGB patients

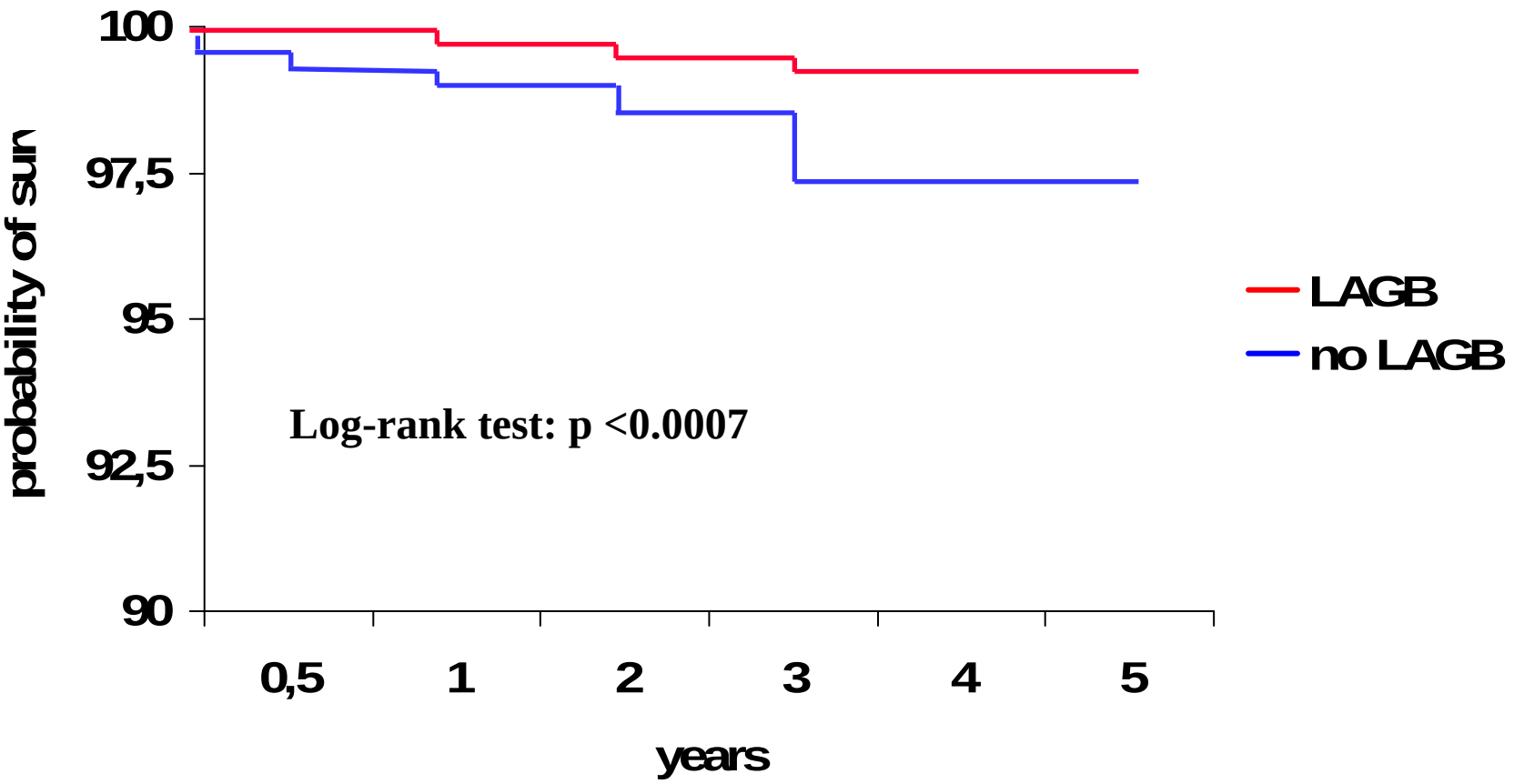
MORTALITY STUDY (total and cause-specific mortality)

FOLLOW UP 3-11 YRS / mean follow-up 5-6 yrs

Matched reference cohort:
GISGO cohort
4732 patients with BMI >40


4640 patients with BMI>40
observed in 6 Italian medical centres
(1976-1996)
1015 morbid obese patients
treated with LAGB in Padova
(1994-2001)
3252 reference patients before 1994
194 surgical patients with BMI 35-40
1388 reference patients since 1994
821 surgical patients with BMI>40
MATCHING FOR SEX (M and F)
AGE CLASS (-40, 40-49, 50-59, 60-69, 70+ yrs)
and BMI CLASS (40-44, 45-49, 50+ kg/m2)
821 reference patients
821 surgical patients
VITAL STATUS DETERMINED (31 dec 2004)
by death registry----------by direct contact
unknown vital status n 21
unknown vital status n 68
FOLLOW-UP RATE 95.4%
7.2±1.2 years
FOLLOW-UP RATE 91.7%
5.6±1.9 years

Kaplan-Meier estimates of survival.



Recorded cases of death: Surgical cohort N. 8 Reference cohort N. 36

Results of Multivariate (Cox) Survival Analysis.

		Hazard Ratio of Death (95% CI)	
- SEX:	Female	1.00	
	Male	3.14	(1.72 – 5.73)
- AGE:	- 40 yrs.	1.00	
	40 - 49	3.50	(1.32 – 9.26)
	50 - 59	5.04	(1.89 – 13.41)
	60 - 69	7.69	(2.67 – 22.16)
- BMI :	40 - 44 kg/m^2	1.00	
	45 - 49	1.07	(0.44 – 2.60)
	50 +	2.19	(1.07 – 4.49)
- TREATMENT:	Reference	1.00	
	LAGB	**0.38**	**(0.17 – 0.85)**

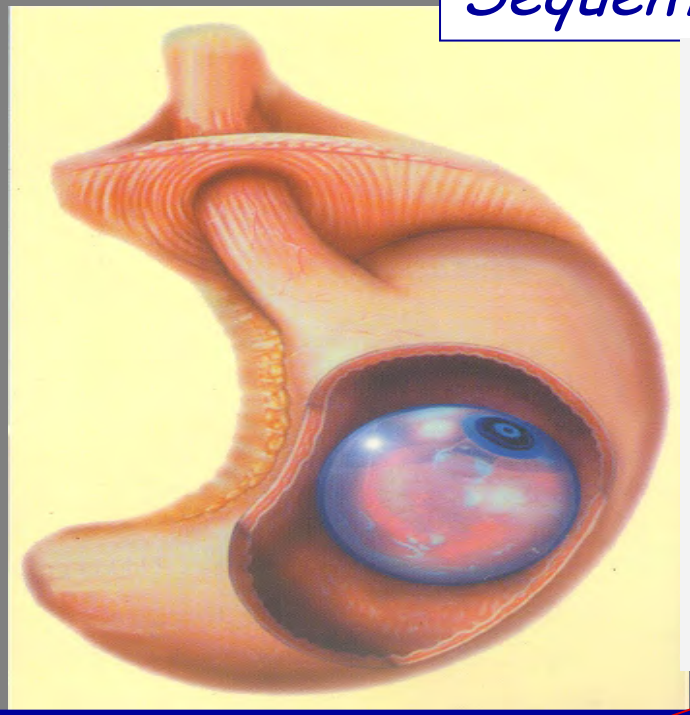
CONCLUSION

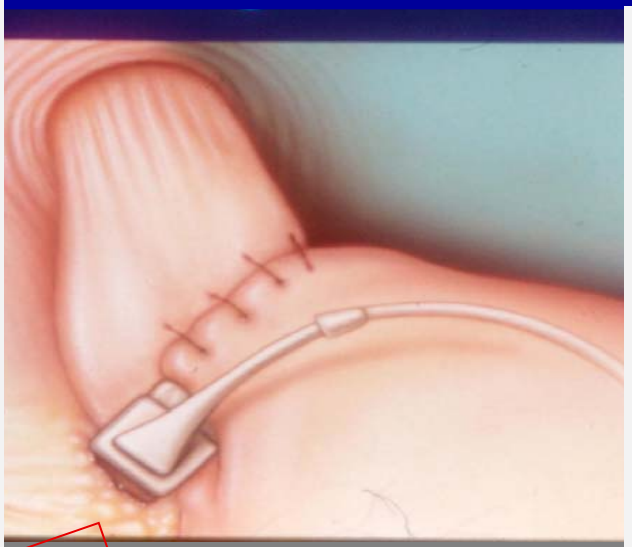
- This follow-up study seems to demonstrate that the 5-year total mortality rate was lower in morbid obese patients treated with LAGB than in matched reference patients observed at medical centres.
- However, to major points remain to be solved:
  1. Follow-up rate was lower in the LAGB group and an additional number of deaths could have happened in the members of the surgical cohort with unknown vital status.
  2. Differences in total mortality between the two cohorts may be due to some difference in baseline clinical status that remains undetected in our study.

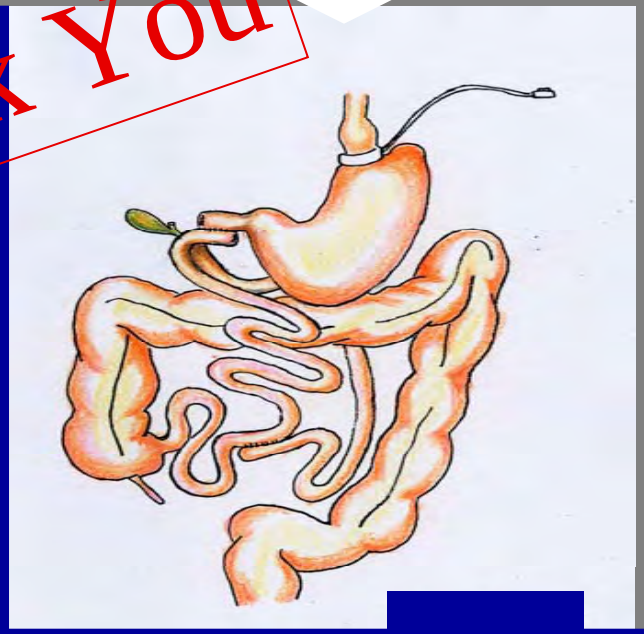
Chirugia Bariatria : gold standards

- Selezione multidisciplinare dei pazienti (chirurgo, obesiologo, psicologo, ...).
- Team chirurgico con esperienza in più di una tecnica operatoria.
- Supporto nutrizionale post-operatorio.
- Follow up multidisciplinare routinario.
- Committment al follow up a lungo termine.
- Trattamento rapido delle complicanze.

Sequential treatment







Thank You