Terapia farmacologica dell'obesità

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Trento, 31 marzo 2007

Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (NIH '98).

- PHARMACOTHERAPY
- Weight loss drugs approved by FDA may be used as part of a comprehensive weight loss program for patients with BMI > 30, and for patients with a BMI > 27 with concomitant obesity-related risk factors or diseases.
- Evidence Category B.

Terapia Farmacologica

- Orlistat
- Sibutramina
- Rimonabant

PUNTI FONDANTI DELLA MODERNA TERAPIA FARMACOLOGICA DELL'OBESITA'

- EFFETTO SUL MANTENIMENTO DELLA PERDITA DI PESO
- EFFETTO SUI DISTURBI METABOLICI ASSOCIATI
- EFFETTO SUGLI HARD-POINTS (MORTALITA' – MORBIDITA')

Terapia Farmacologica

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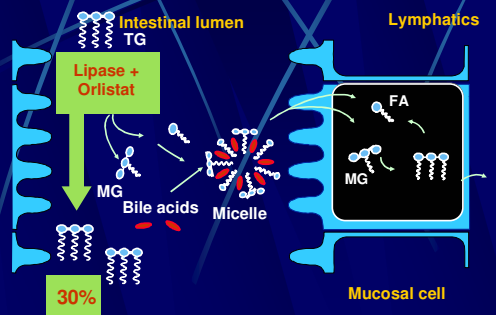
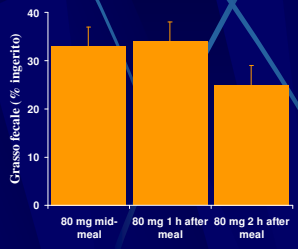
- Rimonabant

Inhibition of fat absorption by Orlistat®

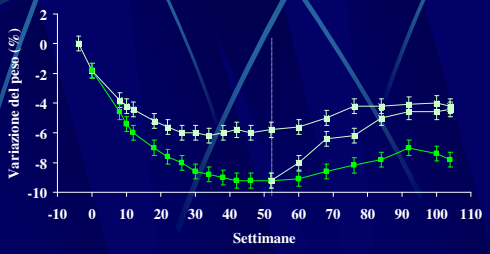


ORLISTAT: ESCREZIONE FECALE DI GRASSI IN RELAZIONE AL TEMPO DI ASSUNZIONE



Hartmann et al. *Br J Clin Pharmacol.* 1993;36:266.

ORLISTAT: Effetto sulla perdita di peso e sul mantenimento a due anni.



Sjostrom et al. Lancet 1998;352:167

ORLISTAT: Ragioni di drop-out

	Placebo	Orlistat
Non cooperazione	7.3	3.2
Eventi avversi	2.6	6.7
Perso dal follow-up	6.1	2.9
Ragioni amministrative	2.6	1.4
Rifiuto del trattamento	2.9	0.9
Fallimento	2.0	0.6
Altro	0.6	2.0
TOTALE	24.1 %	17.7 %

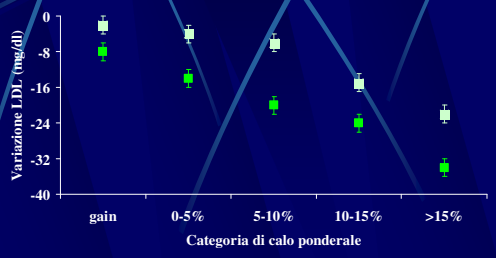
Sjostrom et al. Lancet 1998;352:167

ORLISTAT: Controllo glicemico in pazienti obesi con DM tipo 2

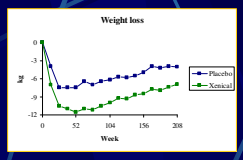
Δ%	Placebo	Orlistat	P
Dose ADO	-9.1%	-22.8%	0.019
Glicemia	8.2%	0.7%	<0.001
HbA1c	0.2%	-0.3%	<0.001
HbA1c (>8%)	-0.1%	-0.5%	<0.001

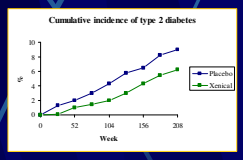
Hollander et al. Diabetes Care 1998;21:1288

ORLISTAT: Effetto specifico sulle LDL a parità di calo ponderale.



XENical in the prevention of diabetes in obese subjects (XENDOS) study





Placebo + Lifestyle (N. 1637): Weight loss = – 4,1 kg. Cumulative incidence of type 2 diabetes = 9.0 %.

Xenical + Lifestyle (N. 1640) : Weight loss = - 6,9 kg. Cumulative incidence of type 2 diabetes = 6.2 %..

RR REDUCTION = 37 %

Torgerson et al. Diabetes Care 2004;27:155

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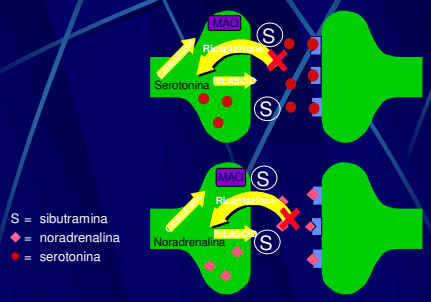
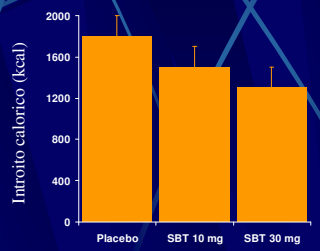
SIBUTRAMINA : MECCANISMO D'AZIONE



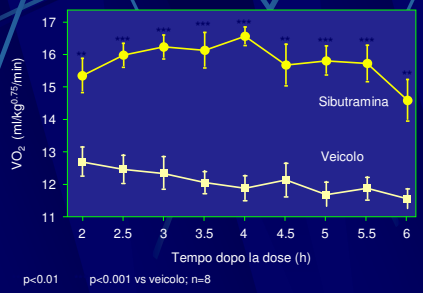
Adattata da Ryan et al. *Obesity Res.* 1995;3: 553S.

SIBUTRAMINA: RIDUZIONE DELL'INTROITO DI CIBO IN DONNE OBESE NON A DIETA



Rolls BJ et al. *Obesity Res.* 1998;6:1.

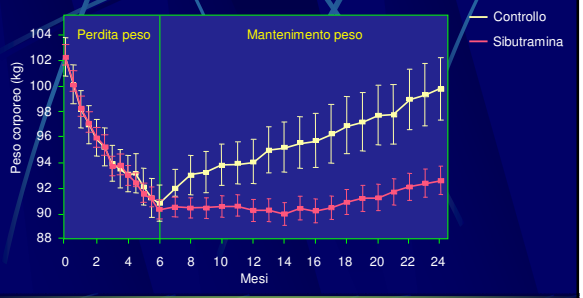
SIBUTRAMINA: EFFETTI SUL CONSUMO DI OSSIGENO (VO_2) NEL RATTO



p<0.01 p<0.001 vs veicolo; n=8

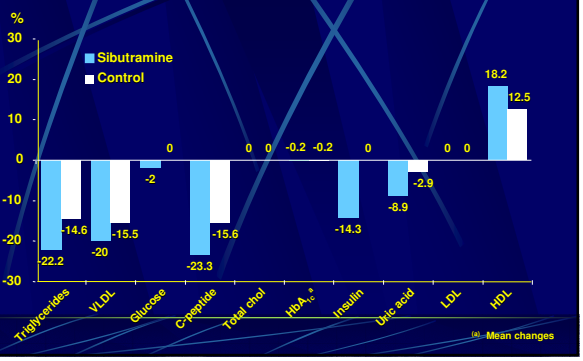
Connoley et al., *Br. J. Pharmac.* 1995;114:388P

STORM: Sibutramine Trial of Obesity Reduction and Maintenance



James et al. Lancet 2000;356:2119

STORM: % change in metabolic risk factors at 2 years for sibutramine patients and control group



[a] Mean changes

SIBUTRAMINA: MODIFICAZIONI DELLA PRESSIONE ARTERIOSA E FREQUENZA CARDIACA RISPETTO AL BASALE

Gruppo dose	Categoria perdita peso	Modificazione media dal basale		
		PAS (mmHg)	PAD (mmHg)	FC (bpm)
Placebo	Tutti i pazienti	-1.6	-1.6	-0.3
Sibutramina 10 mg	Tutti i pazienti	+0.1**	+0.1***	+3.6***
	<5% o aum. peso	+1.2***	+0.6***	+3.2***
	≥5% perd. peso	-1.3	-0.3**	+3.6***
	≥10% perd. peso	-2.7	-1.0	+3.5***
Placebo	Tutti i pazienti	-0.2	-0.2	+0.2
Sibutramina 15 mg	Tutti i pazienti	+1.0*	+1.0***	+4.6***
	<5% o aum. peso	+2.2**	+1.8***	+4.9***
	≥5% perd. peso	-0.1	+0.2	+3.9***
	≥10% perd. peso	-1.0	-0.9	+2.6***

*p<0.05 ; ** p<0.01; *** p<0.001 confrontati con l'intero gruppo placebo

SCOUT: Sibutramine Cardiovascular OUtcome Trial.

- 9000 obese and overweight patients with high CV risk.
- Reduction in myocardial infarction, stroke and cardiovascular mortality.

Padwal & Majumdar. Lancet 2007;369:71-77

Terapia Farmacologica

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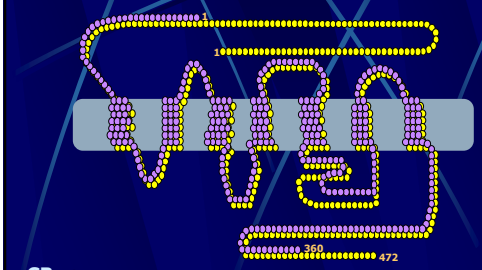
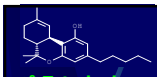
Cannabinoid Receptors



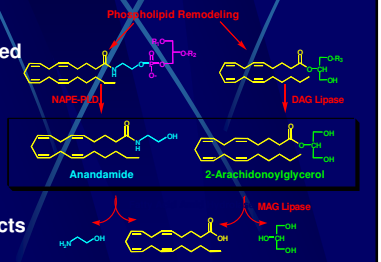
CB_1 1990: *(Matsuda et al)*

CB_2 1993: *(Munro et al)*

ENDOCANNABINOIDS



Δ^9-Tetrahydrocannabinol
1964: *(Gaoni and Mechoulam)*



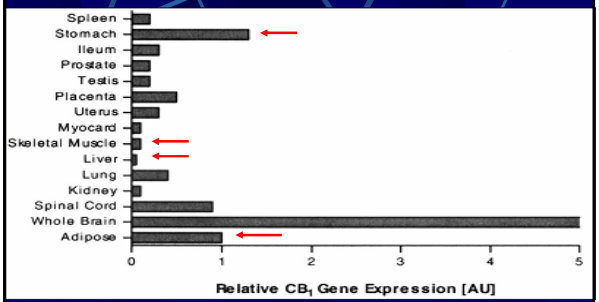
Phospholipid-derived precursors

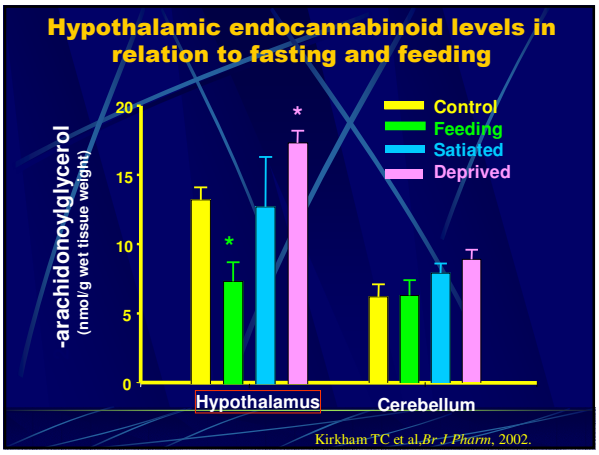
Endocannabinoids

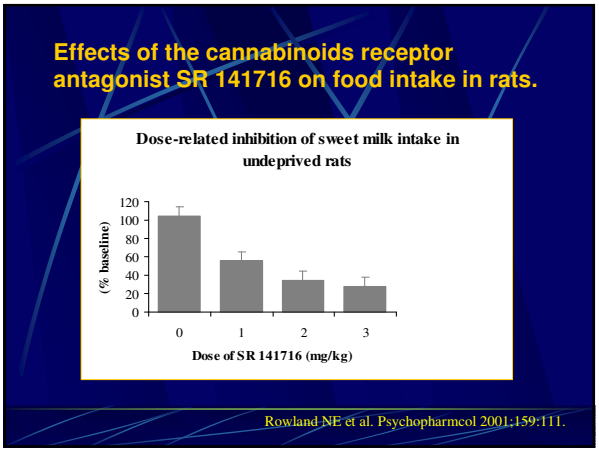
Degradation products

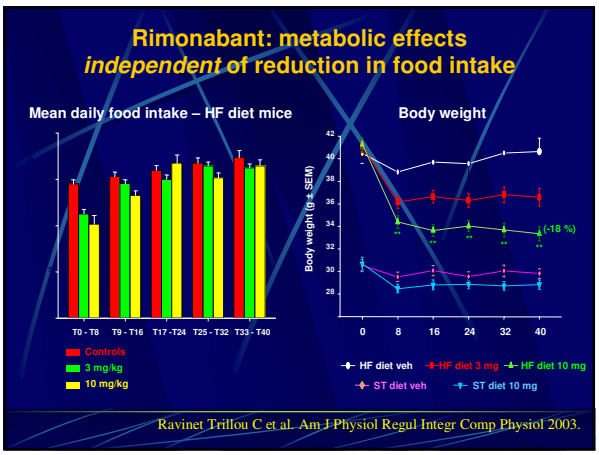
are produced on demand from the cell membrane
are immediately metabolized after their action

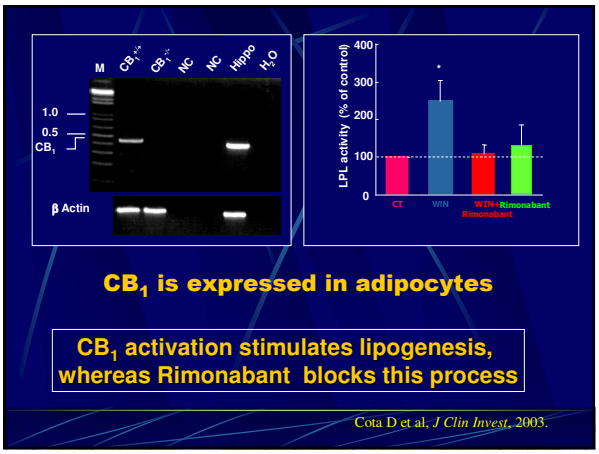
CB1 gene expression




Hypothalamic endocannabinoid levels in relation to fasting and feeding
-arachidonoylglycerol
(nmol/g wet tissue weight)
20
15
10
5
0
*
*
Control
Feeding
Satiated
Deprived
Hypothalamus
Cerebellum
Kirkham TC et al, *Br J Pharm*, 2002.


Effects of the cannabinoids receptor antagonist SR 141716 on food intake in rats.
Dose-related inhibition of sweet milk intake in undeprived rats
(% baseline)
120
100
80
60
40
20
0
0
1
2
3
Dose of SR 141716 (mg/kg)
Rowland NE et al. Psychopharmcol 2001;159:111.


Rimonabant: metabolic effects *independent* of reduction in food intake
Mean daily food intake – HF diet mice
T0 - T8
T9 - T16
T17 -T24
T25 - T32
T33 - T40
Controls
3 mg/kg
10 mg/kg
Body weight
Body weight (g ± SEM)
42
40
38
36
34
32
30
28
(-18 %)
0
8
16
24
32
40
HF diet veh
HF diet 3 mg
HF diet 10 mg
ST diet veh
ST diet 10 mg
Ravinet Trillou C et al. Am J Physiol Regul Integr Comp Physiol 2003.

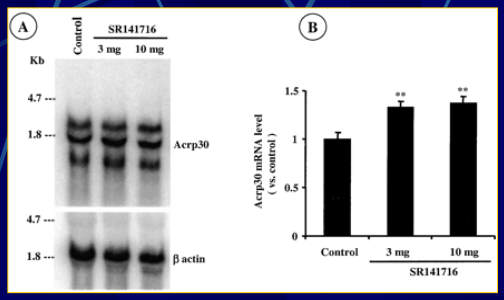


CB_1 is expressed in adipocytes

CB_1 activation stimulates lipogenesis, whereas Rimonabant blocks this process

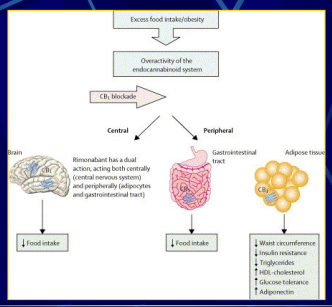
Cota D et al, *J Clin Invest*, 2003.

Effects of SR 141716 on Acrp30 expression in obese (fa/fa) rat adipose tissues.



Bensaid M et al. Mol Pharmacol. 2003 63:908.

Rimonabant, the first CB1 blocker
A multi-impact drug

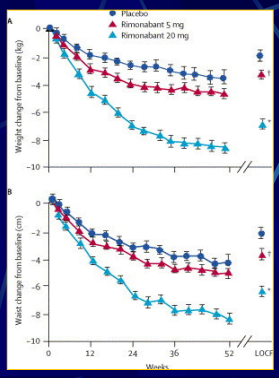


Van Gaal LF et al. Lancet 2005;365:1389.

Rimonabant In Overweight/Obesity

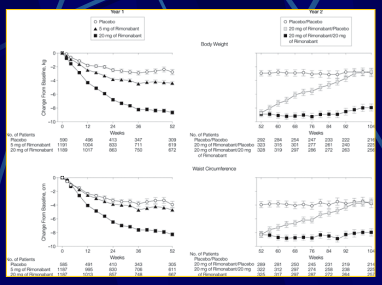
Obese or overweight with/without comorbidities (excluding diabetes)	**3040**	1+1 year Re-randomized
Obese or overweight with/without comorbidities (excluding diabetes)	**1507**	2 years
Obese or overweight with untreated dyslipidaemia (excluding diabetes)	**1033**	1 year
Obese or overweight with type 2 diabetes	**1047**	1 year

RIO – EUROPE

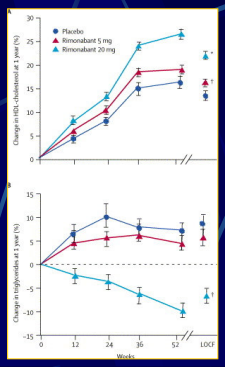


Van Gaal LF et al. Lancet 2005;365:1389.

RIO – NORTH AMERICA



Pi-Sunyer FX et al. JAMA 2006;295:761



RIO – EUROPE

PREVALENCE OF METABOLIC SYNDROME IN COMPLETERS

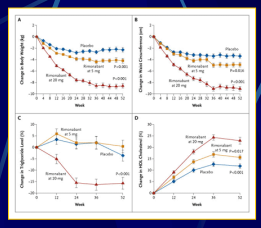
PLACEBO	**38.9→25.7%**
RMN 5 mg	**42.3→27.6%**
RMN 20 mg	**44.9→15.8%**

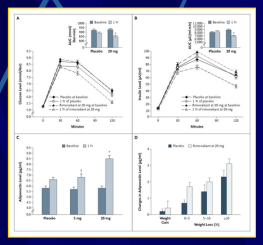
Change from baseline (%)

PLACEBO	**33.9%**
RMN 5 mg	**34.8%**
RMN 20 mg	**64.8%**

Van Gaal LF et al. Lancet 2005;365:1389.

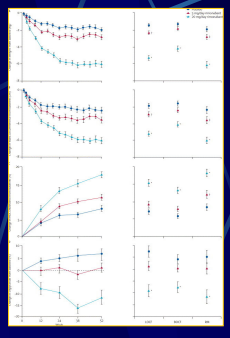
RIO – LIPIDS

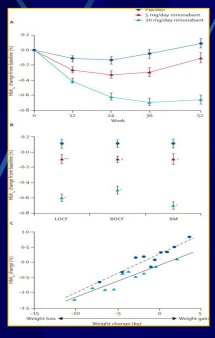




Despres JP et al. N Engl J Med. 2005;353:2121

RIO – DIABETES





Scheen AJ et al. Lancet 2006;368:1660.

RIO programme pooled 1-year overall safety

	Placebo	Rimonabant 5 mg	Rimonabant 20 mg
	N=1254	N=2162	N=2164
Subjects with any adverse event	82.5%	83.0%	86.1%
Subjects with any serious adverse event	4.1%	5.0%	5.6%
Deaths	n=1	n=2	n=1
Subjects discontinued due to adverse event	7.7%	8.9%	13.6%

Pooled year 1 data: RIO-LIPIDS, RIO-EUROPE, RIO-NORTH AMERICA

RIO programme pooled 1-year overall safety: AEs leading to discontinuation

	Placebo (N=1254) n (%)	Rimonabant 5 mg (N=2162) n (%)	Rimonabant 20 mg (N=2164) n (%)
Psychiatric disorders	40 (3.2)	79 (3.7)	146 (6.7)
Depressed mood disorders	19 (1.5)	48 (2.2)	63 (2.9)
Anxiety	5 (0.4)	8 (0.4)	24 (1.1)
Irritability	2 (0.2)	4 (0.2)	10 (0.5)
Nervous system disorders	14 (1.1)	25 (1.2)	46 (2.1)
Headache	5 (0.4)	7 (0.3)	10 (0.5)
Dizziness	1 (<0.1)	4 (0.2)	14 (0.6)
Gastrointestinal disorders	5 (0.4)	18 (0.8)	49 (2.3)
Nausea	1 (<0.1)	5 (0.2)	29 (1.3)

According to MedDRA code, 0.5% in any rimonabant group: in the 3 main system organ class.

CRESCENDO: Comprehensive Rimonabant Evaluation Study of Cardiovascular ENDpoints and Outcomes.

- 17000 obese participants.
- Reduction in myocardial infarction, stroke and cardiovascular mortality.

Padwal & Majumdar. Lancet 2007;369:71-77