

SEDE DEL CORSO

OFFICINA DEL SAPERE - VIA SAN CARLO DA SEZZE, 18 - LATINA

RELATORI E MODERATORI

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ECM

Il Provider Mytime T. & T. srl n. 2609 ha assegnato 5,9 crediti ECM al programma educativo del corso formativo, secondo criteri uniformi indicati dalla Commissione Nazionale per la Formazione Continua. Il corso è a numero chiuso, per una massima di 50 partecipanti.

PROFESSIONI ACCREDITATE

Professione: Medico Chirurgo

Disciplina: Medicina generale (medici di famiglia)
Pediatrica
Pediatrica di libera scelta
Scienze dell'alimentazione e dietetica

Professione:

Dietista
Infermiere
Infermiere pediatrico
Biologo

SEGRETERIA ORGANIZZATIVA

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CON IL PATRONCINO RICHIESTO DI



Scuola AME "Osteoporosi,
Malattie Ormonali e
Metabolismo Ferrocloridico"

APPROCCIO NUTRIZIONALE: LA DIETA NORMOPROTEICA



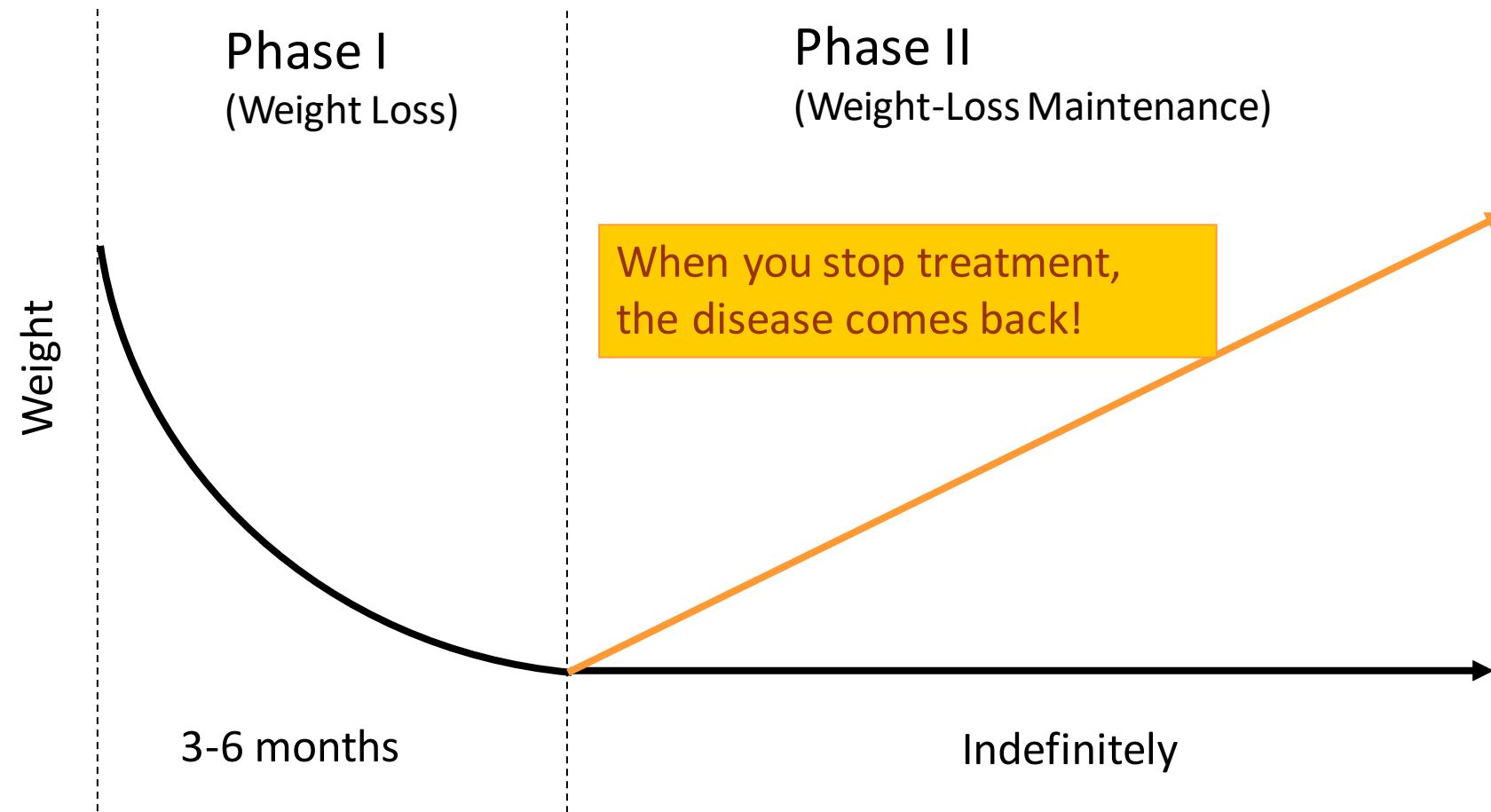
6 MARZO 2015

Responsabile Scientifico
Roberto Cesareo

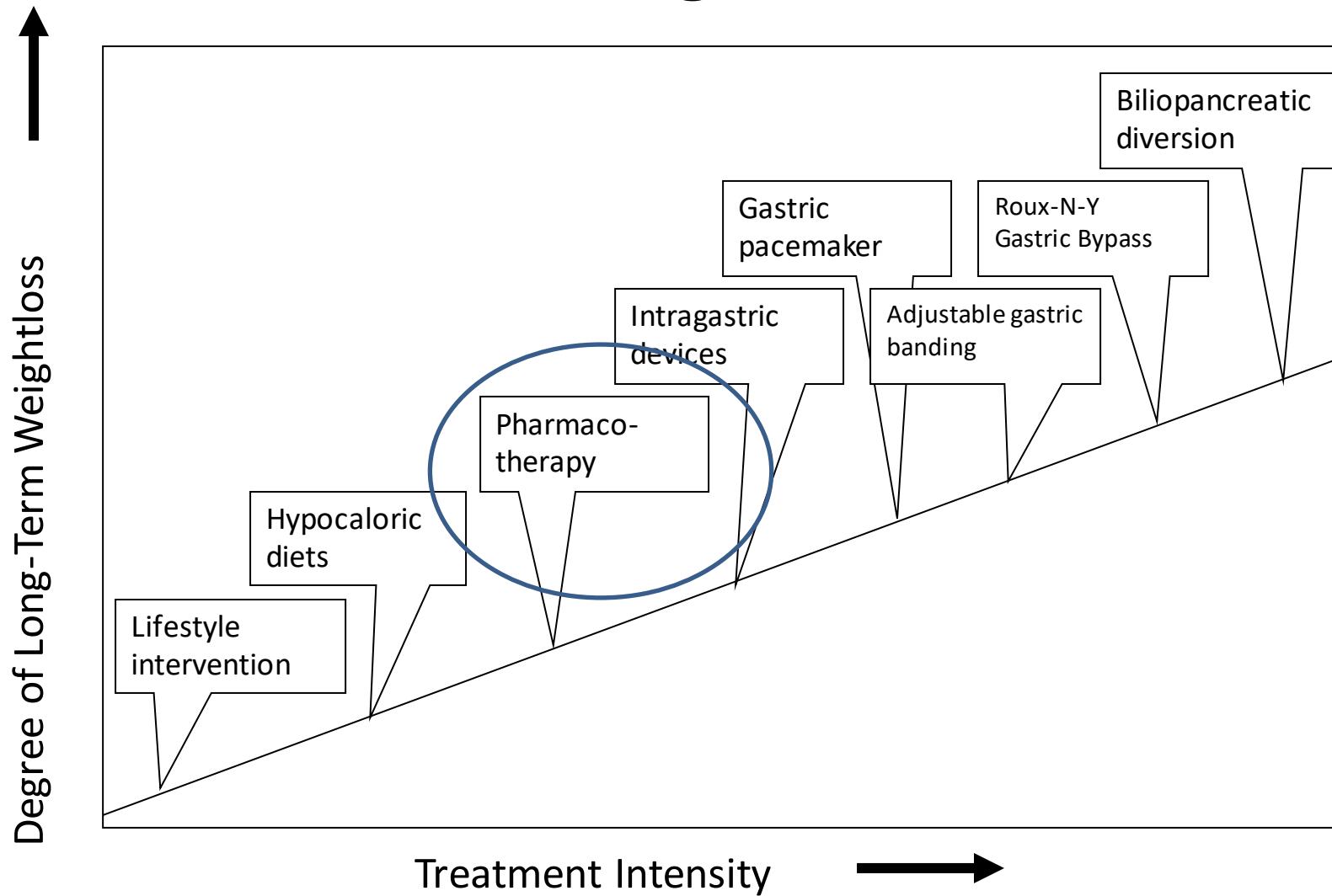
Terapia Farmacologica dell'obesità: Evidence based e dati di efficacia clinica

**ROBERTO CESAREO
LATINA**

Phases of Obesity Treatment



Stepped Care Approach to Obesity Management



Characteristics of the ideal Anti-Obesity Drug

- Reduce body weight
- Maintain weight loss
- Well tolerated
- Long-term efficacy
- No rebound effect
- Reduce morbidity
- Reduce mortality

Does weight loss lead to improvement in outcome?

- 10kg loss leads to:
 - Reduction in total cholesterol of 0.25mmol/l
 - Reduction in systolic BP of 6mmHg
 - Reduction in diastolic BP of 3mmHg
- ANY weight loss in people with an obesity related illness leads to:
 - In women - Reduced risk of death, CVD, cancer or diabetes related death
 - In men – Reduced risk of diabetes related death

FDA/EMA

STANCES ON EFFICACY OF ANTIOBESITY DRUG

FDA

- 5% mean weight loss vs placebo at 1 year
- 35% or more the proportion of subjects who lose weight respect to placebo

EMA

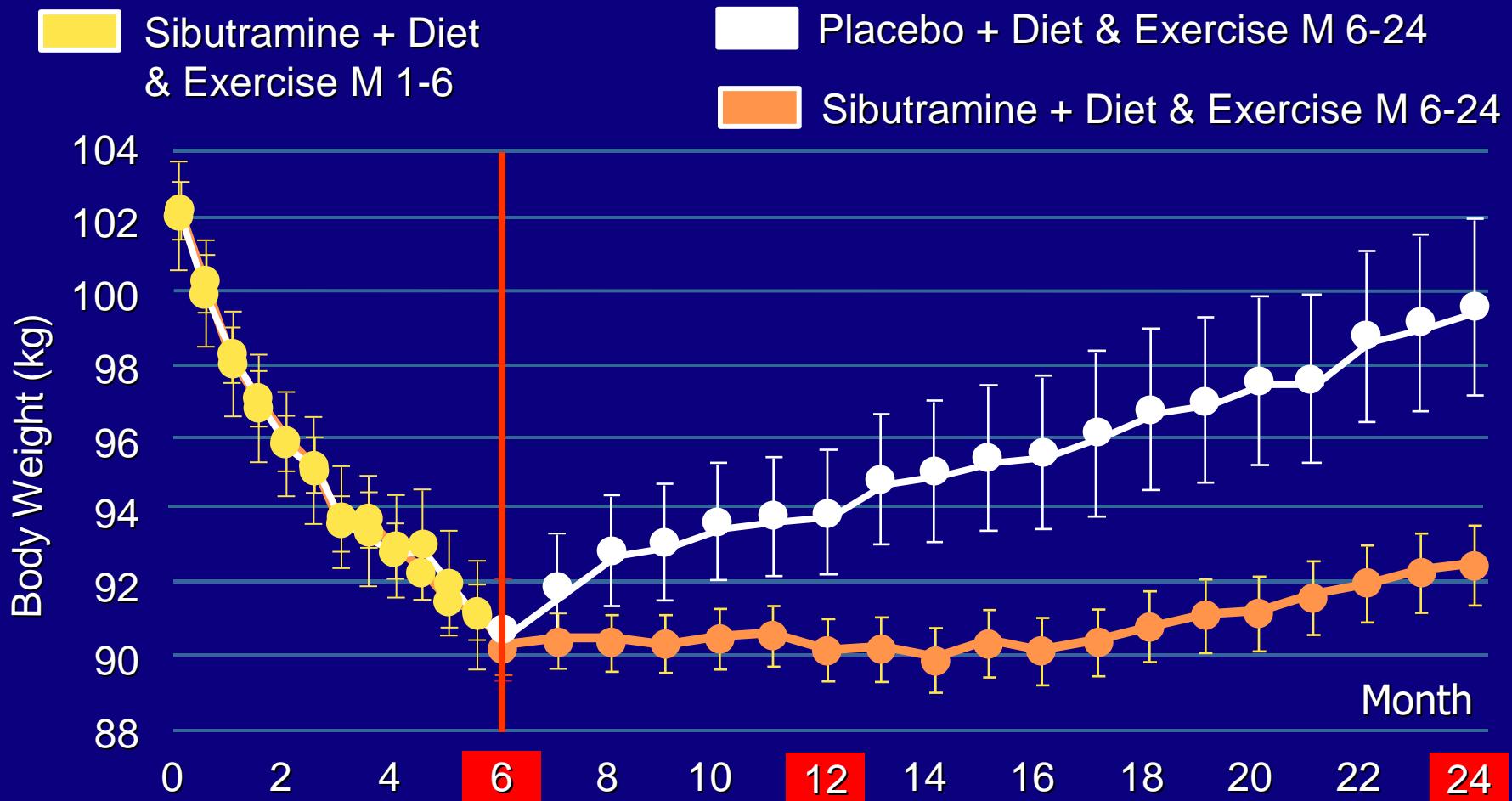
- 10% mean weight loss vs placebo at 1 year
- 50% or more the proportion of subjects who lose weight respect to placebo

OFF LABEL DRUGS

At least 350 drugs are in the pipeline

- Sibutramine
- Rimonabant
- Antidepressant: bupropion, fluoxetine
- Topiramate
- Fentermina
- Metformin

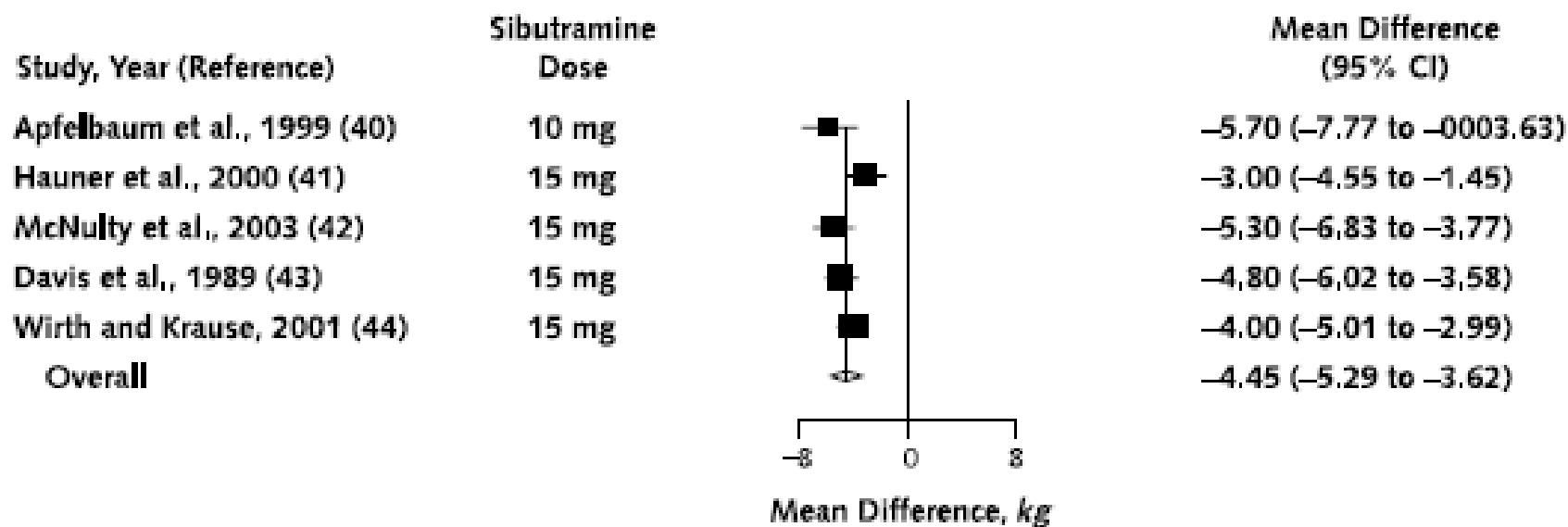
Sibutramine: 2-Year Efficacy Weight Loss and Weight Maintenance



Adapted from: James WPT, et al. *Lancet*. 2000;356:2119-2125.

Meta-Analysis: Pharmacologic Treatment of Obesity

SIBUTRAMINE



The NEW ENGLAND JOURNAL of MEDICINE

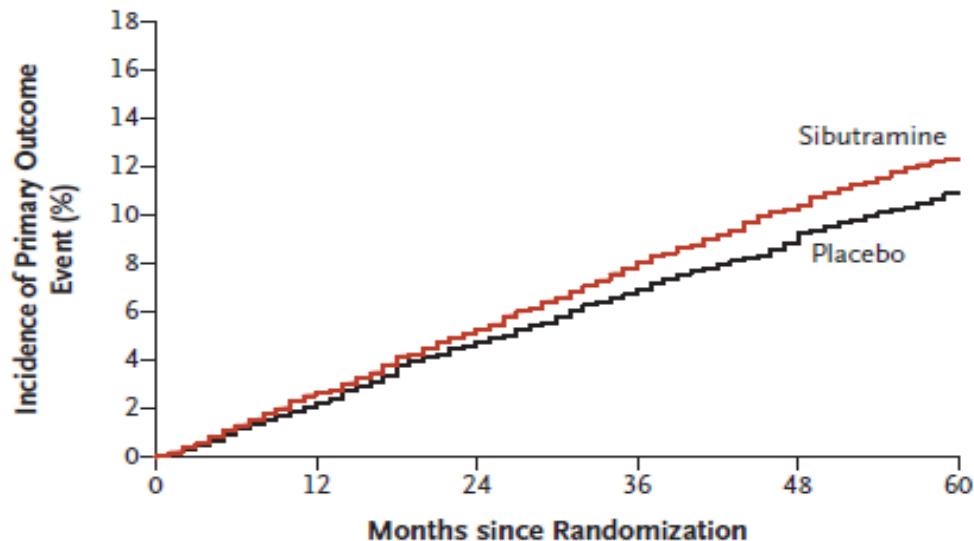
ESTABLISHED IN 1812

SEPTEMBER 2, 2010

VOL. 363 NO. 10

Effect of Sibutramine on Cardiovascular Outcomes in Overweight and Obese Subjects

A Primary Outcome Event



No. at Risk

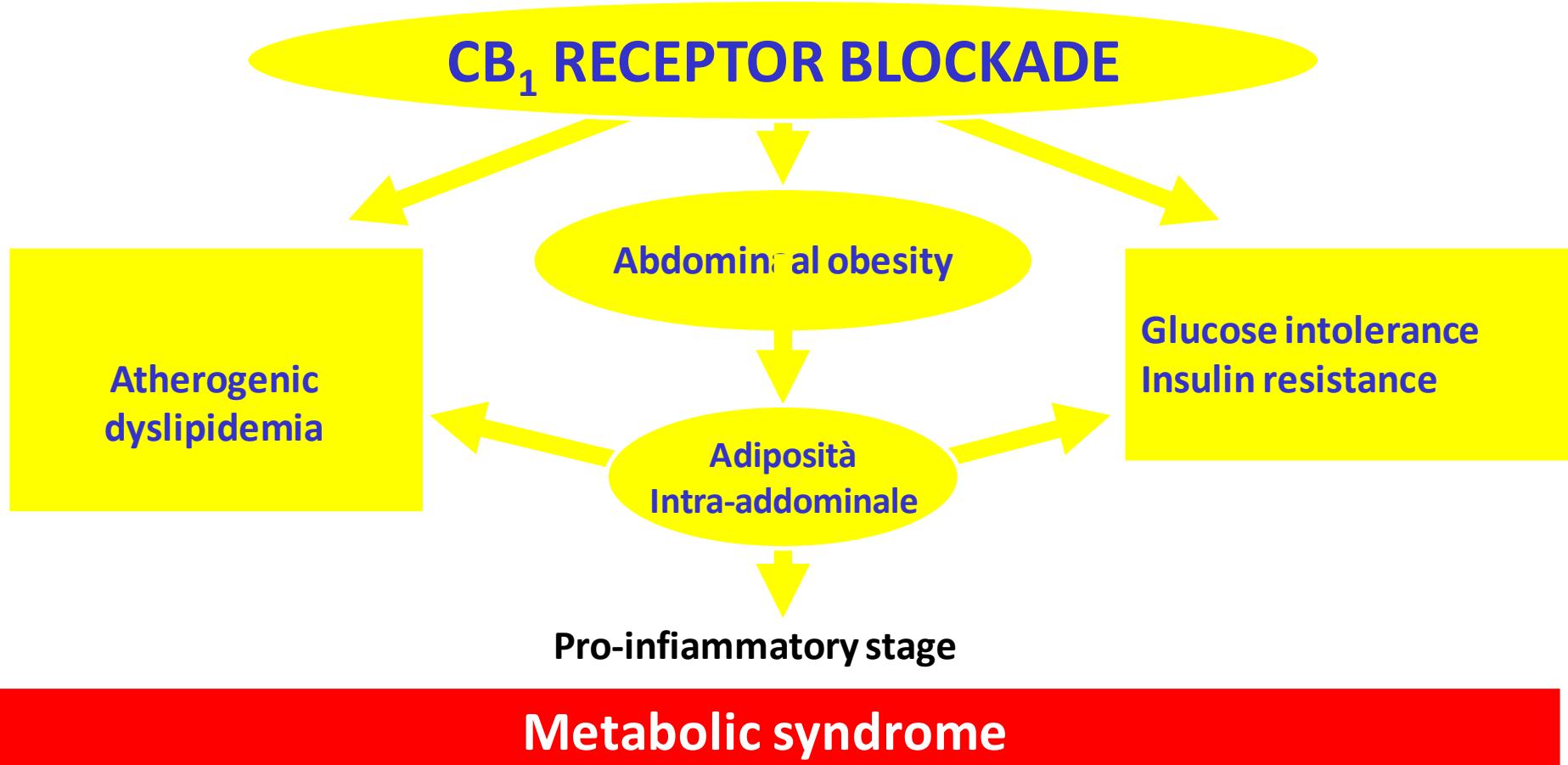
| | | | | | | |
|-------------|------|------|------|------|------|------|
| Placebo | 4898 | 4776 | 4623 | 4482 | 3467 | 1730 |
| Sibutramine | 4906 | 4749 | 4601 | 4427 | 3403 | 1720 |

SCOUT TRIAL

| Study Group † | Placebo (% of patients) | Sibutramine (% of patients) | Hazard Ratio (95% Confidence Interval) | p-value |
|-------------------------------|----------------------------|--------------------------------|---|---------|
| DM Only Group | | | | |
| Total patients (n) | 1,178 77 | 1,207 79 | 1.010 <i>(0.737, 1.383)</i> | 0.951 |
| Cardiovascular Events* | (6.5%) | (6.5%) | | |
| CV Only Group | | | | |
| Total patients (n) | 793 66 | 759 77 | 1.274 <i>(0.915, 1.774)</i> | 0.151 |
| Cardiovascular Events* | (8.3%) | (10.1%) | | |
| CV + DM Group | | | | |
| Total patients (n) | 2,901 346 | 2,906 403 | 1.182 <i>(1.024, 1.354)</i> | 0.023++ |
| Cardiovascular Events* | (11.9%) | (13.9%) | | |

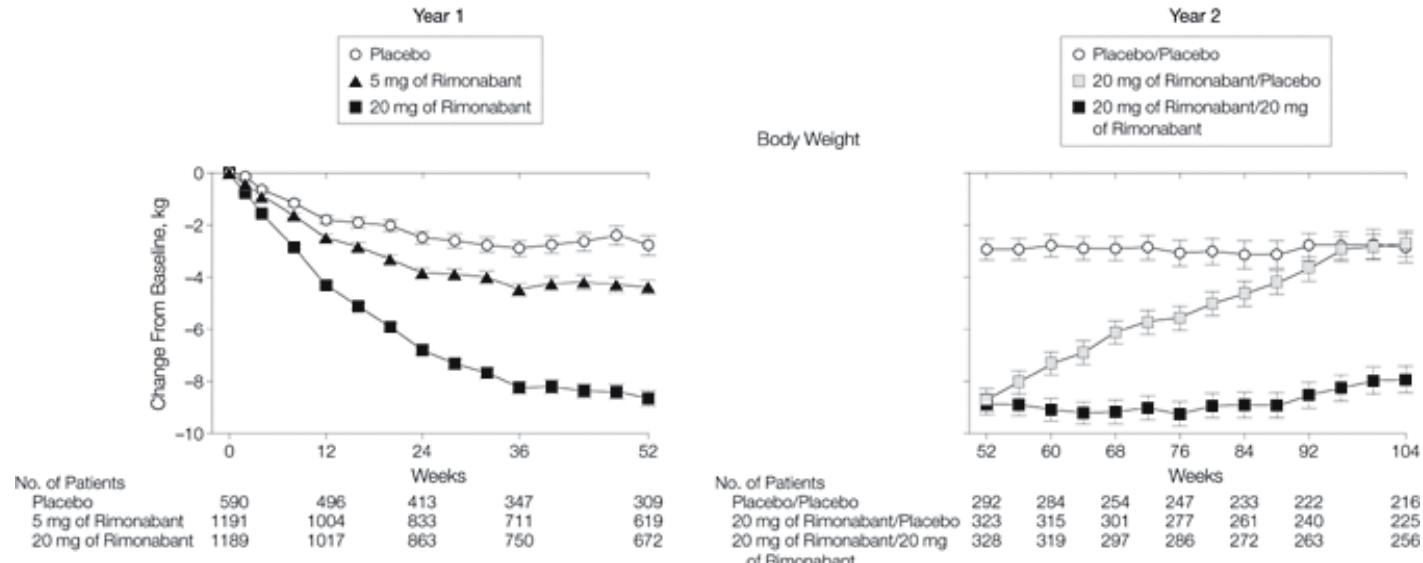
Rimonabant

CB₁ blockade reduces multiple
cardiometabolic risk factors



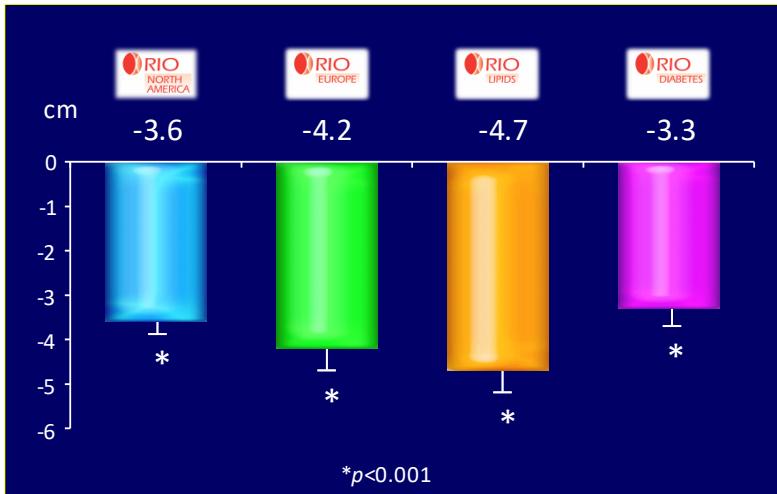
Rimonabant

- Cannabinoid-1 receptor blocker
 - Reduces overactivation of the central & peripheral endocannabinoid system
- 3045 pts with BMI>27 and HTN or dyslipidemia
- 4-wk single blind placebo + diet run-in
 - Randomized to 5 mg daily, 20 mg daily, or placebo for 1 year
 - Treated pts re-randomized to placebo or continued rimonabant for 2nd year
- High drop out rate~ 50% in all groups
- Most common side effect was nausea (11.2% vs 5.8%)

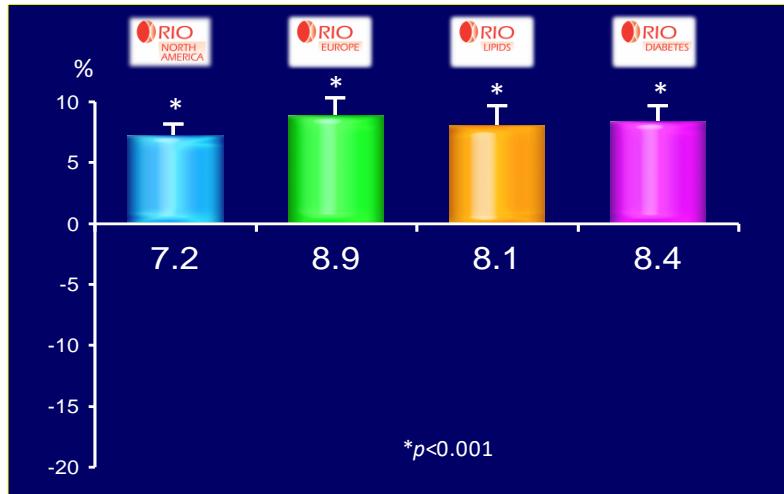


Metabolic parameters Rimonabant and metabolic syndrome

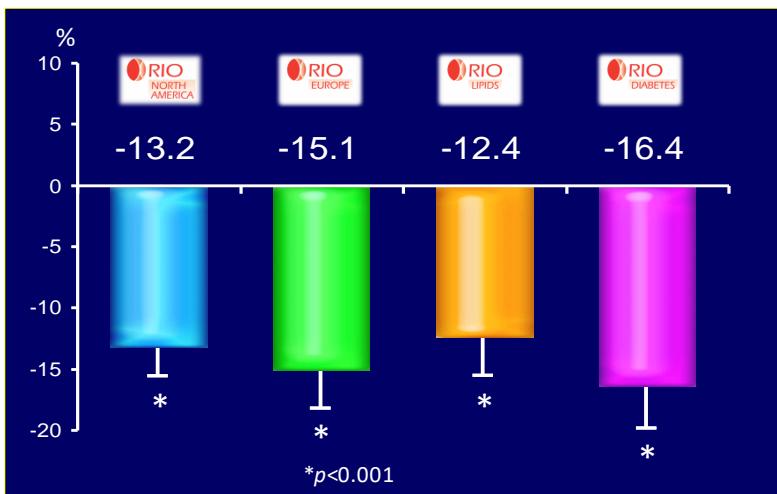
Circonferenza vita (cm)



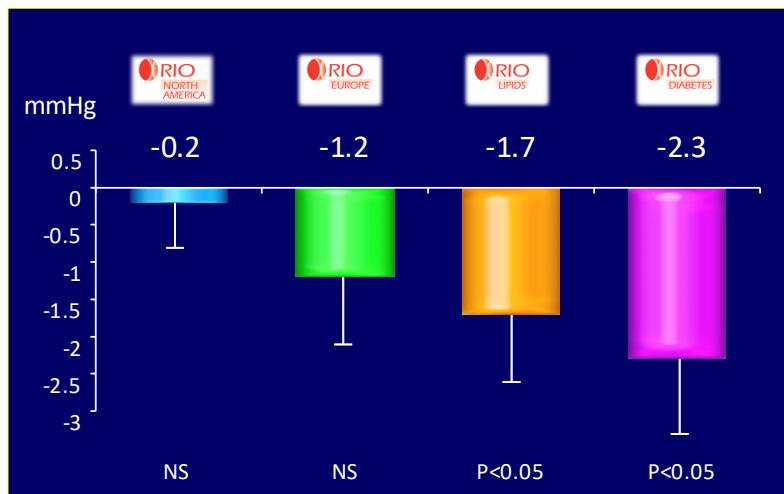
HDL-cholesterolo (%)



Trigliceridi (%)



Mean (+ SEM)



Rimonabant (ACOMPLIA)

RIO-Europe → Serious Adverse Events

| | Placebo (n=305) | Rimonabant 5 mg (n=603) | Rimonabant 20 mg (n=599) |
|--|-----------------|----------------------------|-----------------------------|
| Any serious adverse event | 23 (7.5%) | 45 (7.5%) | 52 (8.7%) |
| Respiratory disorders | 0 | 0 | 2 (0.3%) |
| Psychiatric disorders | 1 (0.3%) | 2 (0.3%) | 9 (1.5%) |
| Nervous system disorders | 3 (1.0%) | 7 (1.2%) | 3 (0.5%) |
| Ear disorders | 0 | 0 | 1 (0.2%) |
| Cardiac disorders | 0 | 2 (0.3%) | 2 (0.3%) |
| Vascular disorders | 0 | 2 (0.3%) | 3 (0.5%) |
| Gastrointestinal disorders | 3 (1.0%) | 3 (0.5%) | 2 (0.3%) |
| Hepatobiliary disorders | 3 (1.0%) | 5 (0.8%) | 1 (0.2%) |
| Musculoskeletal and connective disorders | 6 (2.0%) | 13 (2.2%) | 10 (1.7%) |
| Renal and urinary disorders | 0 | 2 (0.3%) | 2 (0.3%) |
| Reproductive system and breast disorders | 1 (0.3%) | 2 (0.3%) | 3 (0.5%) |
| Investigations | 1 (0.3%) | 0 | 1 (0.2%) |
| Injury, poisoning, and procedure complications | 4 (1.3%) | 5 (0.8%) | 4 (0.7%) |
| Neoplasms: benign, malignant, and unspecified | 2 (0.7%) | 5 (0.8%) | 7 (1.2%) |
| General disorders | 0 | 0 | 1 (0.2%) |

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

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

Long-term Drug Treatment for Obesity

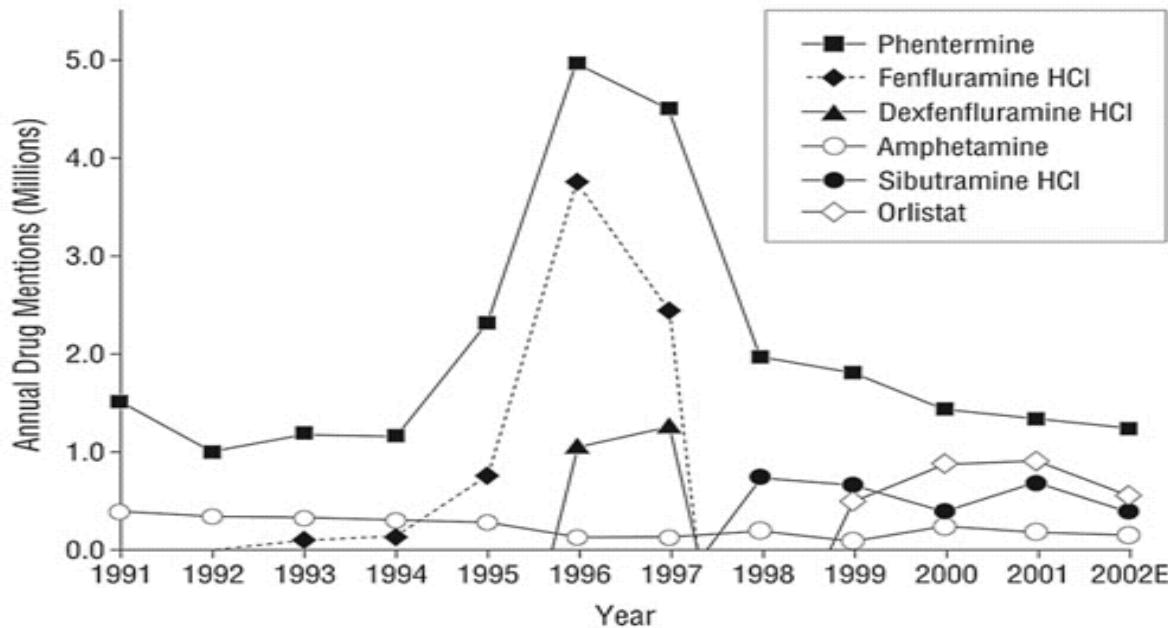
A Systematic and Clinical Review

| Generic Drug (Proprietary Name[s]) Dose Frequency/d) | Mechanism of Action | Wholesale Price/mo, \$ ^a | 1-y Weight Change Relative to Placebo, Mean (95% CI), kg ^b | Common Adverse Effects |
|--|--|--|---|---|
| Short-term approval^c | | | | |
| Phentermine 15-37.5 mg (Adipex-P, Fastin, Oby-Cap, Ionamin, Others; 1×) ^d | Noradrenergic causing appetite suppression | 6-45 | Not included | Insomnia, elevation in heart rate, dry mouth, taste alterations, dizziness, tremors, headache, diarrhea, constipation, vomiting, gastrointestinal distress, anxiety, and restlessness ^e |
| Diethylpropion 25 mg or 75 mg, SR (Tenuate, Tenuate Dospan, Tepanil; low dose, 3×; SR dose, 1×) ^d | Noradrenergic causing appetite suppression | 47-120 | Not included | Same as phentermine ^e |
| Phendimetrazine 17.5-70 mg or 105 mg, SR (Bontril; lower doses, 2-3×; SR dose, 1×) ^f | Noradrenergic causing appetite suppression | 6-20 | Not included | Same as phentermine ^e |
| Benzphetamine 25-50 mg (Didrex, 1-3×) ^f | Noradrenergic causing appetite suppression | 20-50 | Not included | Same as phentermine ^e |
| Long-term approval^c | | | | |
| Orlistat 60 mg (Alli) or 120 mg (Xenical; 3× within 1 h of a fat- containing meal) ^g | Lipase inhibitor caus- ing excretion of ap- proximately 30% of ingested triglycerides in stool | 60 mg, 45 120 mg, 207 | 60 mg, -2.5 kg (-1.5 to -3.5) 120 mg, -3.4 kg (-3.2 to -3.6) | Oily spotting, flatus with dis- charge, fecal urgency, fatty oily stool, increased defecation, fecal incontinence ^h |
| Lorcaserin 10 mg (Belviq; 2×) ^d | Highly selective sero- tonergic 5-HT2C re- ceptor agonist causing appetite suppression | 240 | -3.2 kg (-2.7 to -3.8) | Headache, dizziness, fatigue, nau- sea, dry mouth, cough, and constipation; and in patients with type 2 diabetes, back pain, cough, and hypoglycemia ^h |
| Phentermine plus topira- mate-ER (Qsymia; 3.75 mg/23 mg for 2 weeks, increased to 7.5 mg/46 mg, escalating to a max of 15 mg/92 mg; 1×) ^d | Noradrener- gic + GABA-receptor activator, kainite /AMPA glutamate re- ceptor inhibitor caus- ing appetite suppression | 140-195 | 7.5 mg/46 mg, -6.7 kg (-5.9 to -7.5) 15 mg/92 mg, -8.9 kg (-8.3 to -9.4) | Paresthesias, dizziness, taste alter- ations, insomnia, constipation, dry mouth, elevation in heart rate, memory or cognitive changes ^h |

SHORT TERM APPROVAL

| Generic Drug (Proprietary Name[s]) Dose Frequency/d) | Mechanism of Action | Wholesale Price/mo, \$ ^a | 1-y Weight Change Relative to Placebo, Mean (95% CI), kg ^b | Common Adverse Effects |
|---|---|--|--|---|
| Short-term approval ^c | | | | |
| Phentermine 15-37.5 mg (Adipex-P, Fastin, Oby-Cap, Ionamin, Others; 1×) ^d | Noradrenergic causing appetite suppression | 6-45 | Not included | Insomnia, elevation in heart rate, dry mouth, taste alterations, dizziness, tremors, headache, diarrhea, constipation, vomiting, gastrointestinal distress, anxiety, and restlessness ^e |
| Diethylpropion 25 mg or 75 mg, SR (Tenuate, Tenuate Dospan, Tepanil; low dose, 3×; SR dose, 1×) ^d | Noradrenergic causing appetite suppression | 47-120 | Not included | Same as phentermine ^g |
| Phendimetrazine 17.5-70 mg or 105 mg, SR (Bontril; lower doses, 2-3×; SR dose, 1×) ^f | Noradrenergic causing appetite suppression | 6-20 | Not included | Same as phentermine ^g |
| Benzphetamine 25-50 mg (Didrex; 1-3×) ^f | Noradrenergic causing appetite suppression | 20-50 | Not included | Same as phentermine ^g |

Drug use data: 1991-2002



Annual volume of antiobesity medications reported in the United States, 1991–2002, IMS HEALTH National Disease and Therapeutic Index. Data for 2002 are an estimate (E) based on January to March 2002 figures. HCl indicates hydrochloride.

From: Stafford: Arch Intern Med, Volume 163(9).May 12, 2003.1046–1050

LONG TERM APPROVAL

| | | | | |
|--|--|--------------------------|---|---|
| Orlistat 60 mg (Alli) or 120 mg (Xenical; 3× within 1 h of a fat-containing meal) ^g | Lipase inhibitor causing excretion of approximately 30% of ingested triglycerides in stool | 60 mg, 45 120 mg, 207 | 60 mg, -2.5 kg (-1.5 to -3.5) 120 mg, -3.4 kg (-3.2 to -3.6) | Oily spotting, flatus with discharge, fecal urgency, fatty oily stool, increased defecation, fecal incontinence ^h |
| Lorcaserin 10 mg (Belviq; 2×) ^d | Highly selective serotonergic 5-HT2C receptor agonist causing appetite suppression | 240 | -3.2 kg (-2.7 to -3.8) | Headache, dizziness, fatigue, nausea, dry mouth, cough, and constipation; and in patients with type 2 diabetes, back pain, cough, and hypoglycemia ^h |
| Phentermine plus topiramate-ER (Qsymia; 3.75 mg/23 mg for 2 weeks, increased to 7.5 mg/46 mg, escalating to a max of 15 mg/92 mg; 1×) ^d | Noradrenergic + GABA-receptor activator, kainite /AMPA glutamate receptor inhibitor causing appetite suppression | 140-195 | 7.5 mg/46 mg, -6.7 kg (-5.9 to -7.5) 15 mg/92 mg, -8.9 kg (-8.3 to -9.4) | Paresthesias, dizziness, taste alterations, insomnia, constipation, dry mouth, elevation in heart rate, memory or cognitive changes ^h |

Orlistat- XENDOS TRIAL

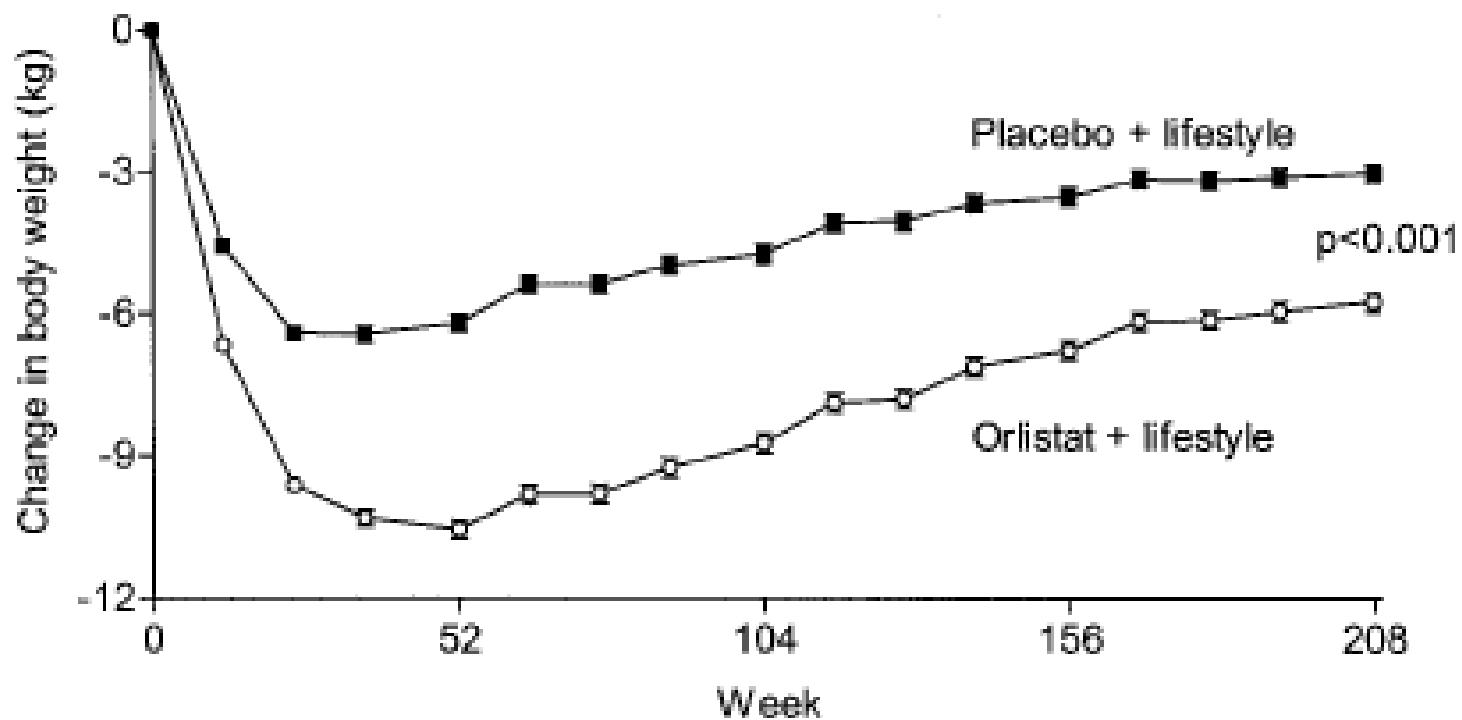
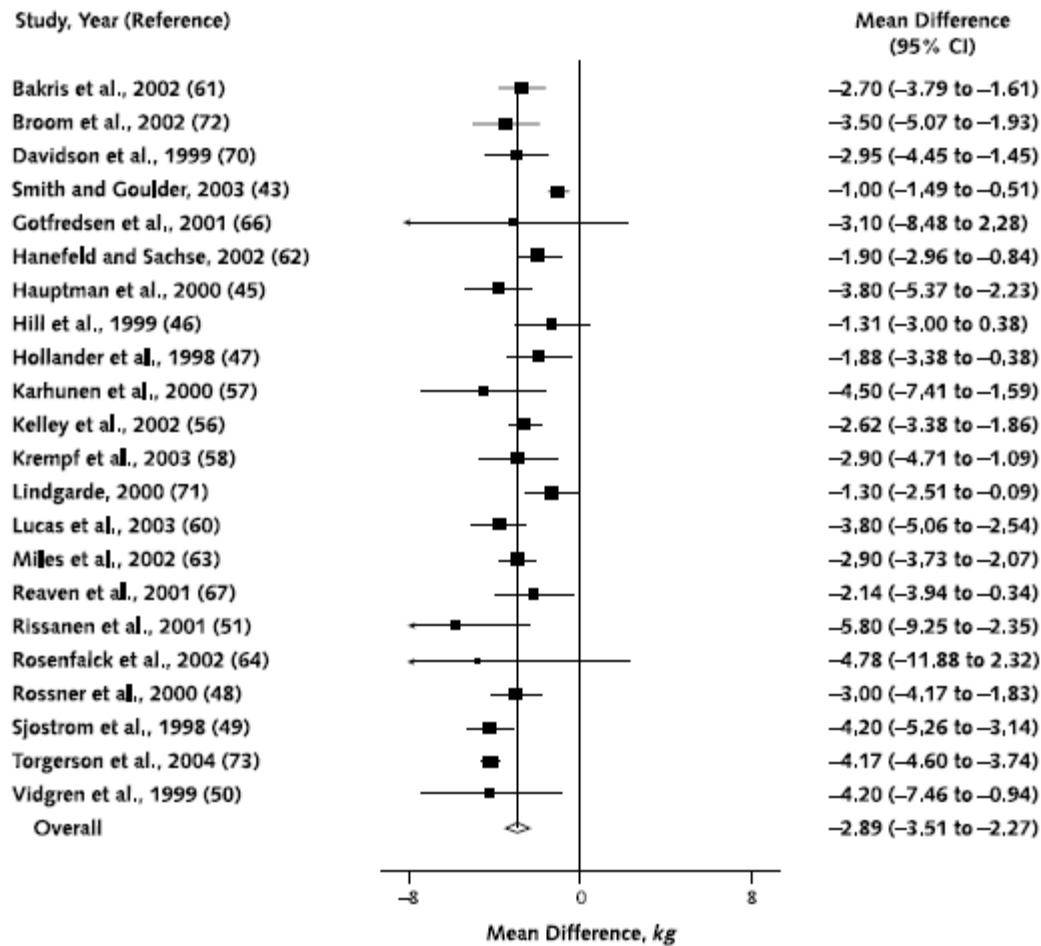


Figure 2—Weight loss (means \pm SEM) during 4 years of treatment with orlistat plus lifestyle changes or placebo plus lifestyle changes in obese patients (LOCF data).

Orlistat- XENDOS

- After 4 years' treatment, the cumulative incidence of diabetes was:
 - 9.0% with placebo
 - 6.2% with orlistat
- This corresponds to a risk reduction of 37.3% in all patients ($P 0.0032$).
- Risk reduction in patients with IGT was 45.0%

METANALYSIS ORLISTAT

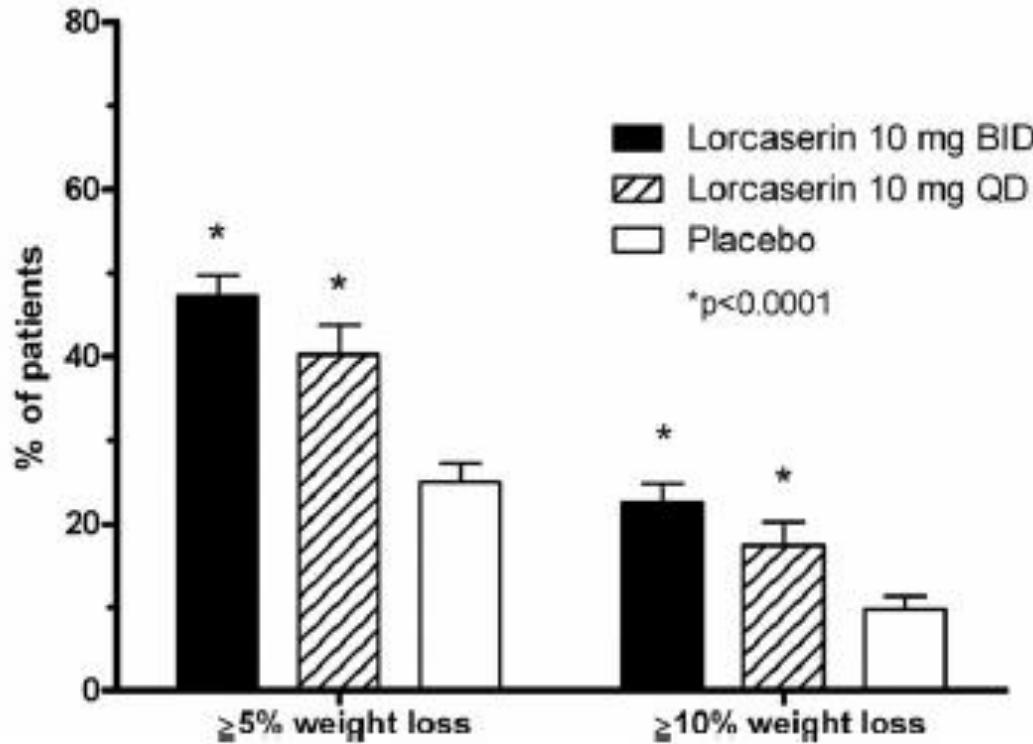


Orlistat – Side effects

- Because it blocks intestinal absorption of fat it can result in diarrhea and steatorrhea
- This is minimized by maintaining a strict low fat diet (<30% of diet)
- Another concern is the loss of fat soluble vitamins with a potential for malnutrition.
- To prevent this, recommend a daily multivitamin for all patients on this therapy

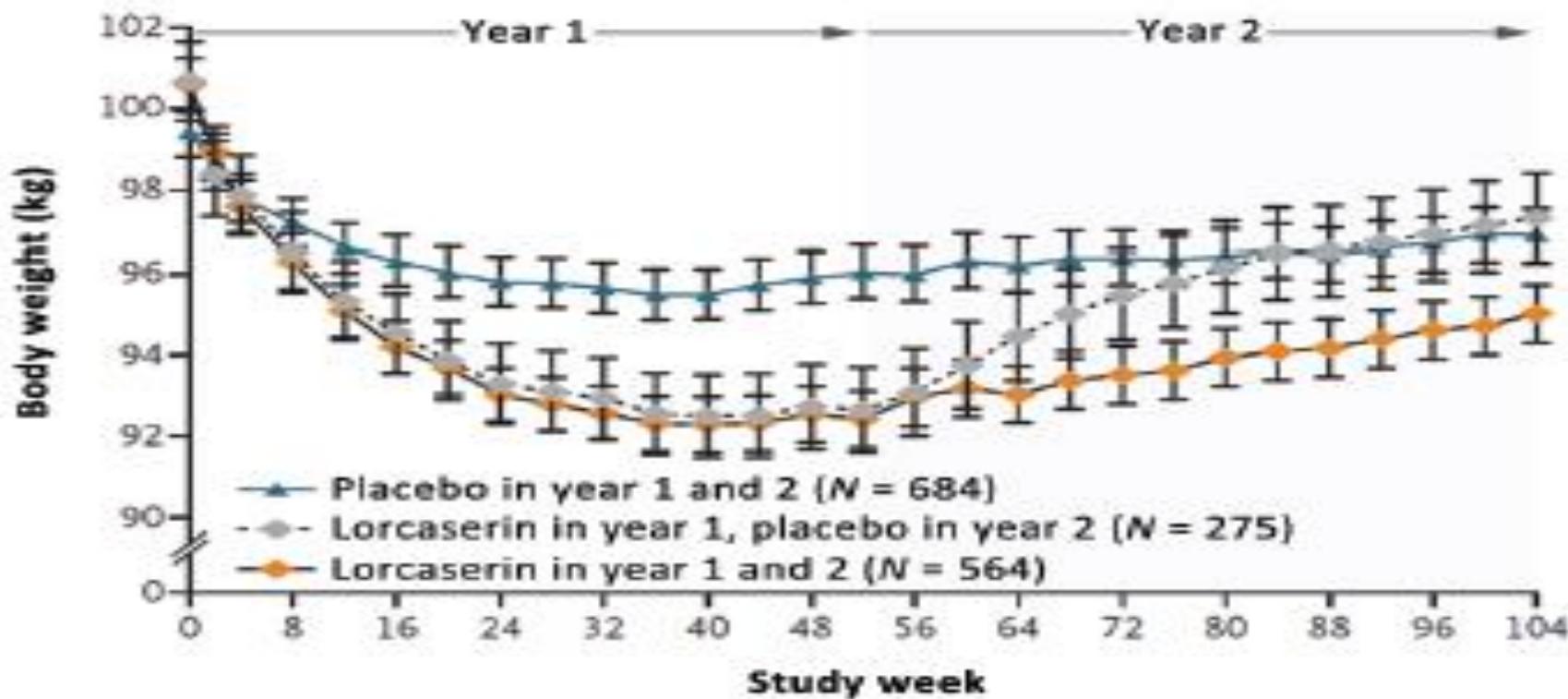
LOCARSERIN (FDA)

A One-Year Randomized Trial of Lorcaserin for Weight Loss in Obese and Overweight Adults: The BLOSSOM Trial



(J Clin Endocrinol Metab 96: 3067–3077, 2011)

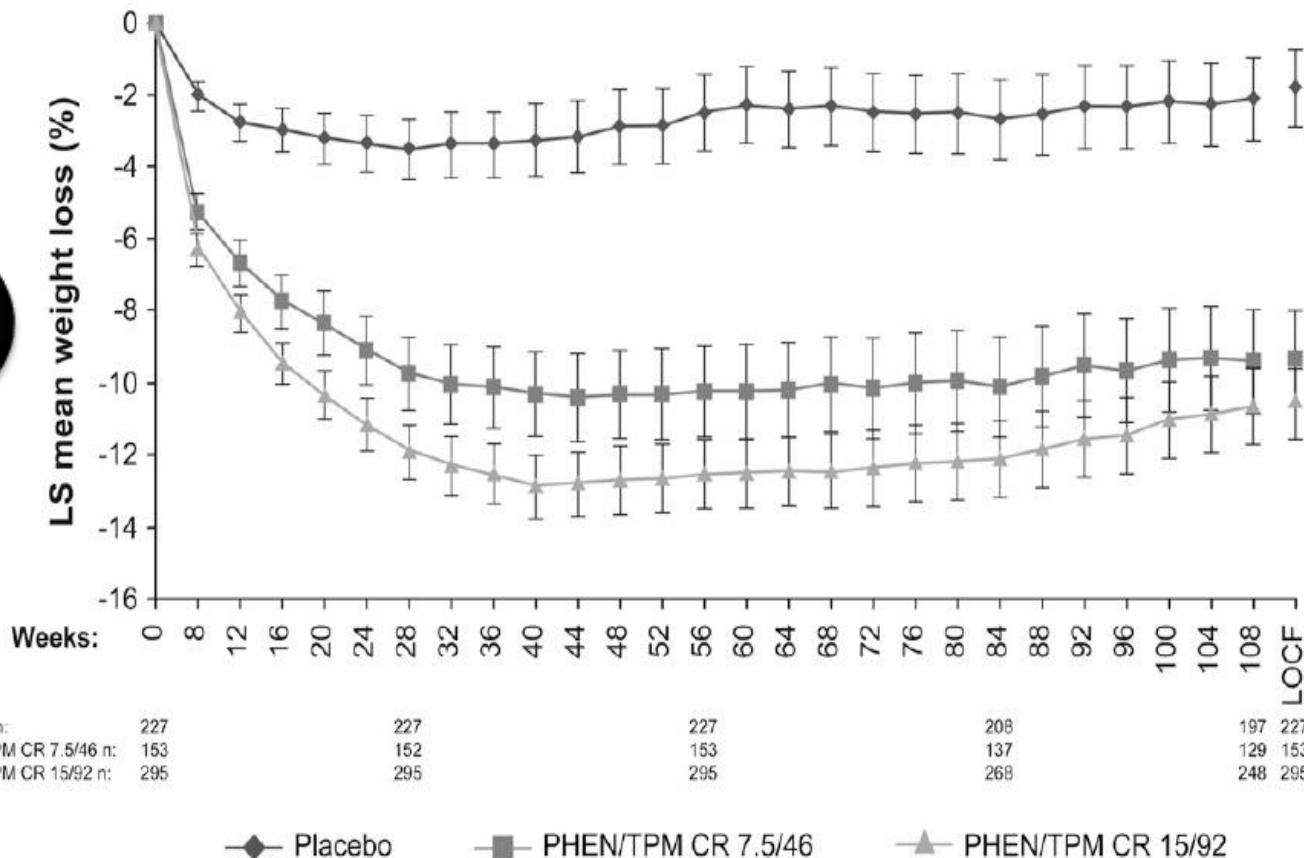
LORCASERIN TRIALS



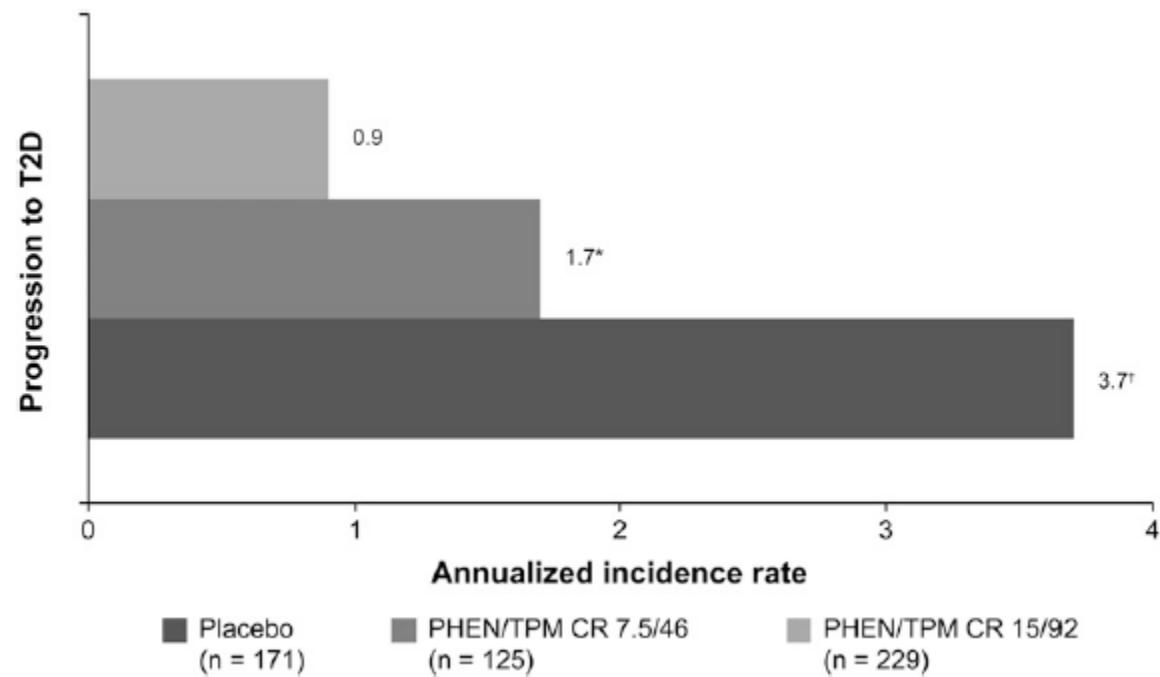


Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study^{1–3} (FDA)

-14%



Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study¹⁻³



SAFETY

- Dry mouth, constipation, insomnia (phentermine effects)
- Dizziness, paresthesia, metabolic acidosis, alopecia, hypokalaemia (topiramate effects)

Potential effects

Teratogenicity, elevation in resting heart rate
depression

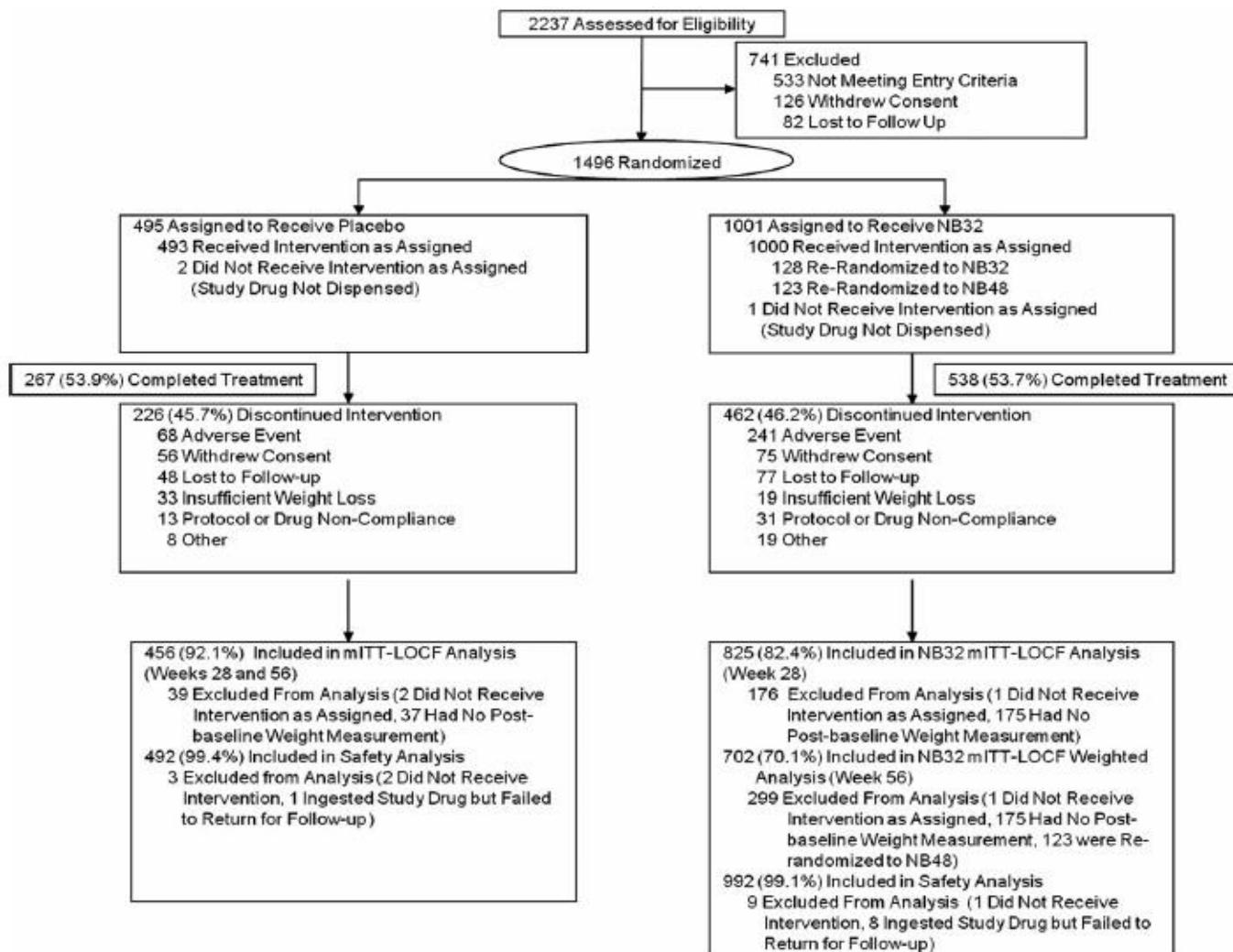
Case report: miopia, secondary angle closure
glaucoma

Drugs in Late-Phase Clinical Trials for Obesity Treatment

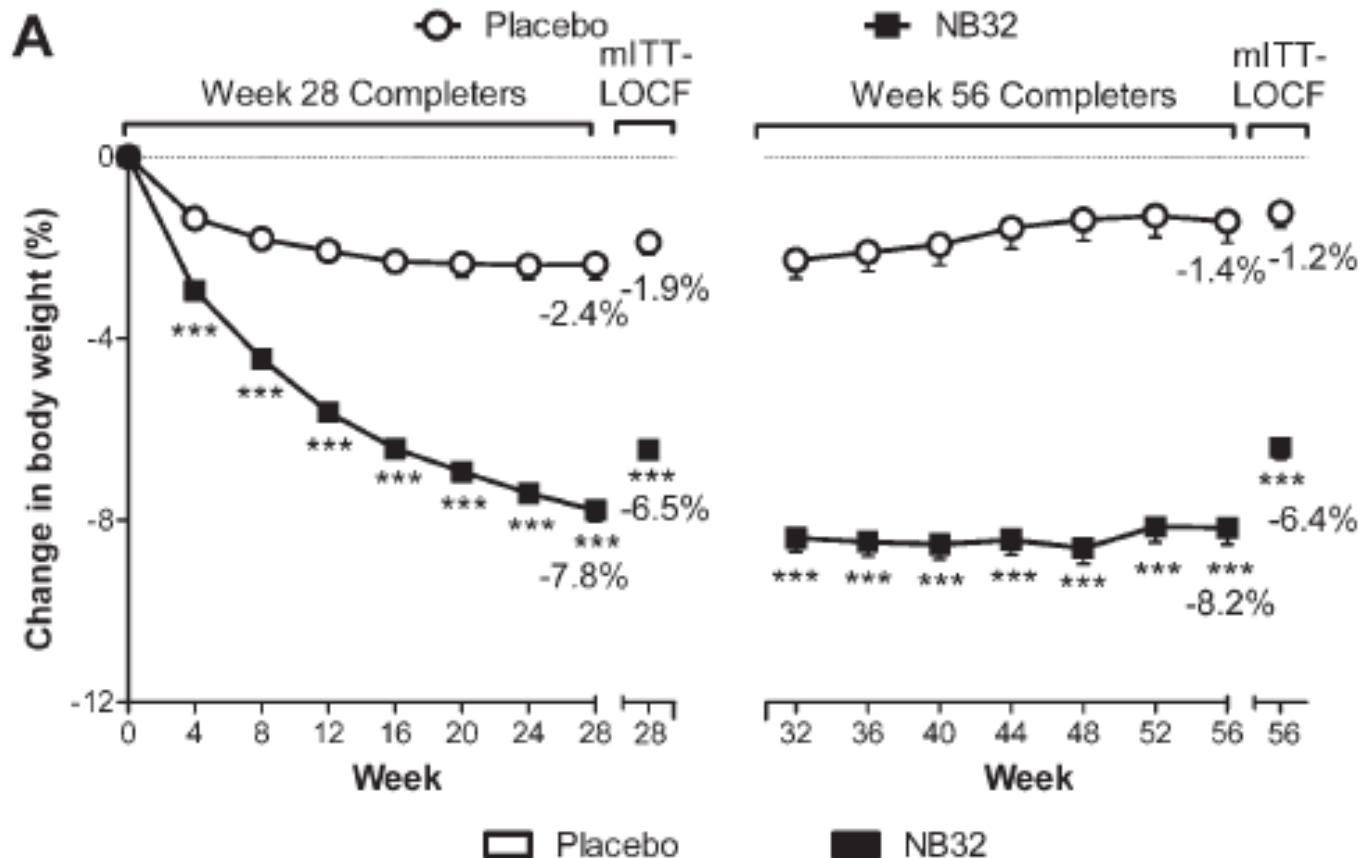
Naltrexone/Bupropion Trial

Glucagon-like peptide-1
receptor agonist

A Randomized, Phase 3 Trial of Naltrexone SR/Bupropion SR on Weight and Obesity-related Risk Factors (COR-II)



A Randomized, Phase 3 Trial of Naltrexone SR/Bupropion SR on Weight and Obesity-related Risk Factors (COR-II)



EMA/FDA

- MYSIMBA (NALTREXONE E BUPROPIONE) EMA
- CONTRAVE (NALTREXONE E BUPROPIONE) FDA

SOLO PAZIENTI OBESI O IN SOVRAPPESO CON PIU'
FATTORI DI RISCHIO
(ipertensione/ipercolesterolemia/diabete)

Se dopo 16 settimane il paziente non perde almeno
il 5% del peso iniziale, il farmaco non può essere
più prescritto

Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials

What is already known on this topic

Improved glycaemic control is associated with increased body weight

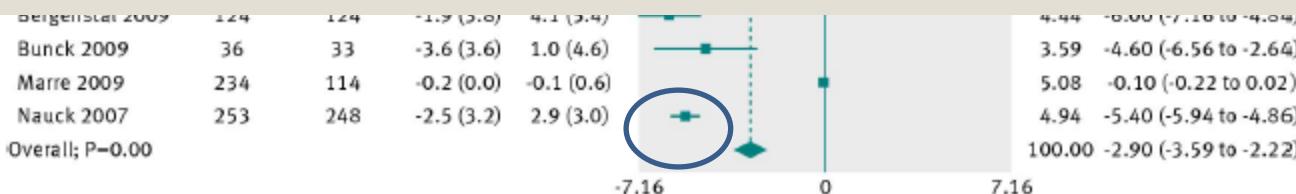
Agonists to the glucagon-like peptide-1 receptor (GLP-1R) enhance glucose homeostasis and suppress food intake and appetite

What this study adds

Treatment with clinically relevant doses of GLP-1R agonists for at least 20 weeks leads to weight loss in obese or overweight patients with or without type 2 diabetes mellitus in spite of an improved metabolic regulation

The effect of GLP-1R agonists could be more pronounced in patients without diabetes

GLP-1R agonists also reduce systolic and diastolic blood pressure and total cholesterol



SAXENDA

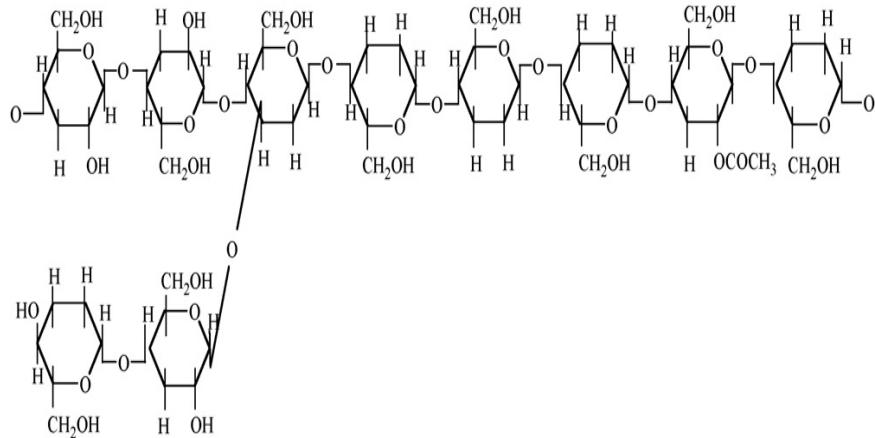
APPROVATO DA FDA 15-01-2015

- LIRAGLUTIDE
- SAXENDA E VICTOZA HANNO LO STESSO PRINCIPIO ATTIVO
- SONO DIVERSE LE DOSI: 3MG E 1.8 MG
- SAXENDA NON E' INDICATO PER IL TRATAMENTO DEL DIABETE MELLITO



GLUCOMANNANO

- Fibra con la **viscosità più elevata** (1g x 200 ml di acqua)
Raggiunge **100 volte il suo volume**
- Estratta dalla radice dell' **Amorphophallus konjac** con **numerosi effetti benefici** legati alla sua capacità di legare acqua e di essere fermentata dall'intestino



Catena polisaccaridica
ramificata
composta da unità di
D-mannosio e D-glucosio

GLUCOMANNANO



EFFETTO MECCANICO

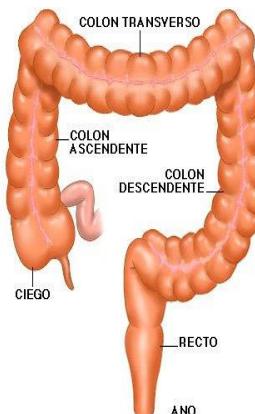
Forma una massa gelatinosa nello stomaco rallentando lo svuotamento gastrico (>>senso di sazietà)

EFFETTO METABOLICO

Rallenta l'assorbimento degli zuccheri
Riduzione insulino-resistenza

Riduce l'assorbimento dei grassi
Riduzione colesterolemia

Riduce riassorbimento e sintesi acidi biliari
Sintesi epatica di colesterolo ridotta



EFFETTO MICROBIOLOGICO E REGOLARITÀ INTESTINALE

- Viene fermentato dalla microflora (effetto salutistico)
- Aumento massa fecale
- Regolarizzazione del transito intestinale

CLAIM EFSA:

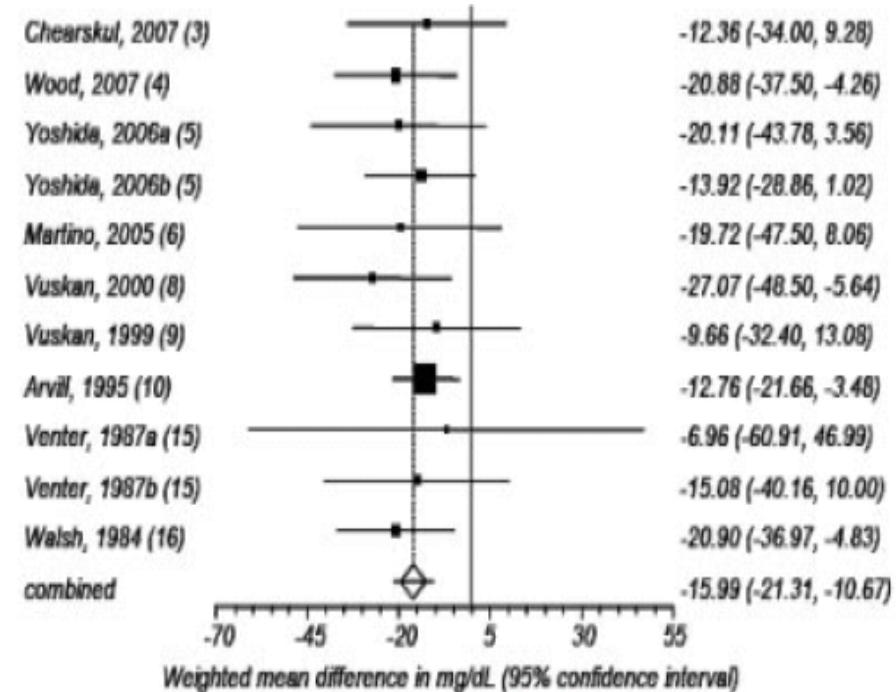
4 g/die di glucomannano

permettono il mantenimento di normali livelli di colesterolo

CLAIM EFSA:

3g/die glucomannano, suddiviso in 3 somministrazioni, insieme a 1-2 bicchieri di acqua, prima dei pasti e nell'ambito di una dieta ipocalorica, promuovono il calo ponderale

Meta-analisi del 2008



Un modesto calo ponderale riduce la mortalità e migliora lo stato di salute

Modesto calo ponderale, nel range del 5-10% del peso iniziale, è sufficiente a:

- Ridurre gli eventi cardiovascolari, la mortalità cardiovascolare, e la mortalità per ogni causa in pazienti con precedente MI (Singh BMJ, 1992)
- Ridurre la mortalità per diabete (> 30%) e la mortalità per ogni causa (> 20%) nei diabetici di tipo II (Williamson, Am J Epidemiol 1995)
- Ridurre (del 58%) il rischio di sviluppare diabete di Tipo II in pazienti sovrappeso (Tuomilehto, NEJM 2001, Diabetes Prevention Group, NEJM, 2002)
- Migliorare:
 - Ipertensione (Tuck, NEJM 1981)
 - Anormalità dell'assetto lipidico (Dattilo, Am J Clin Nutr 1992)
 - Controllo glicemico (Wing, Diabetes Care, 1993)

TAKE HOME MESSAGES

- Diet/lifestyle changes remain the mainstay of the treatment of obesity
- In patients not reaching goals, drugs might be an important tool
- Expect only modest weight loss at best with current drugs
- Be aware of their indications and contraindications
- Off label use of non-indicated products is not recommended
- Investigational agents may offer hope for treatment of obesity in the future

Thanks for your attempion

“But Doc, isn’t there a
pill I can take?”

