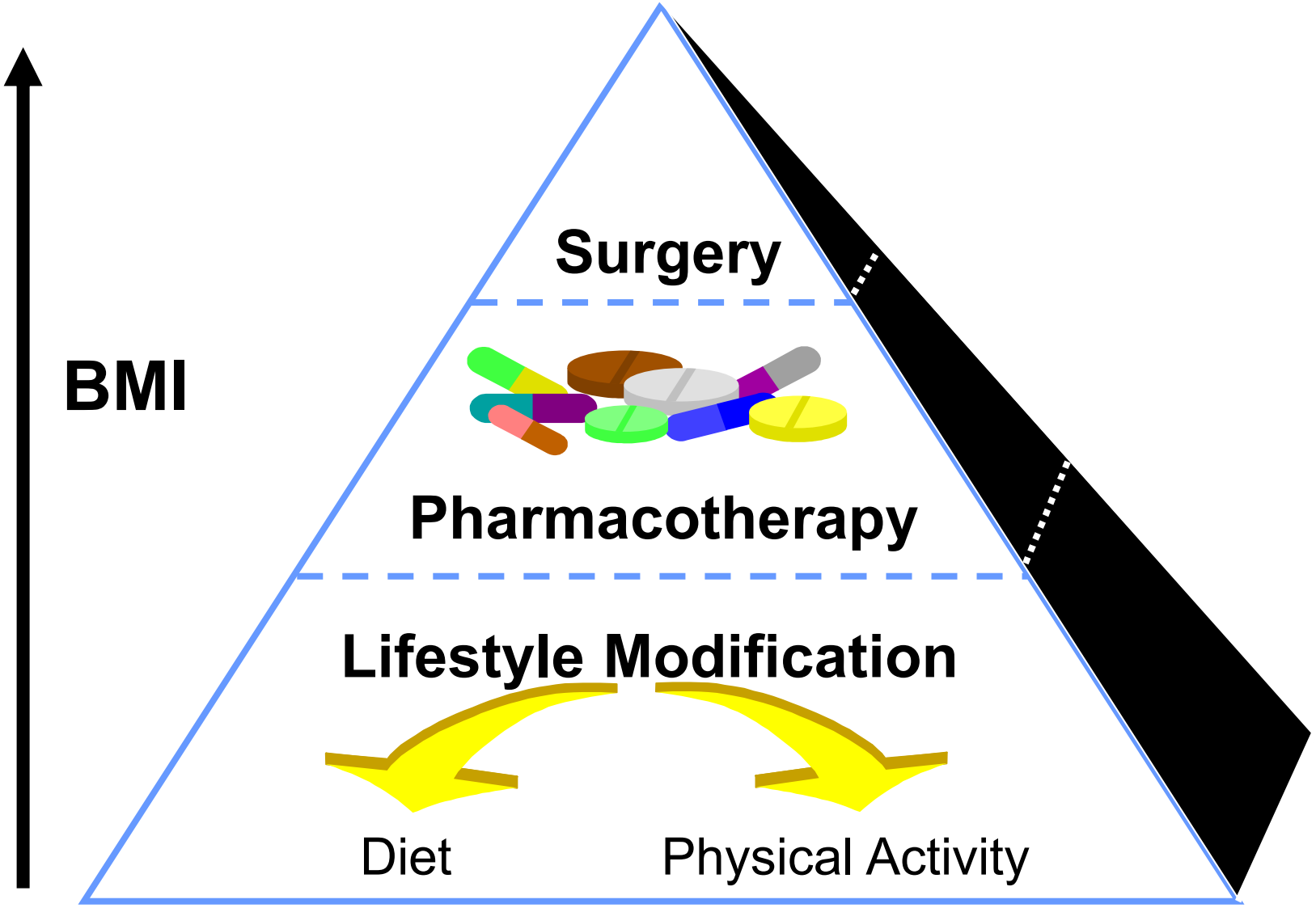
Anti-Obesity Drugs
- Current Status & Application in Diabetic Patients -

순천향의대 부천병원
내분비내과
김 철희

Obesity Treatment Pyramid



Selecting Treatment for Obesity

Treatment	BMI Category					
	< 24.9	25-26.9	27-29.9	30-35	35-39.9	>40
Diet, exercise, behavior therapy	With co-morbidities	With co-morbidities	+	+	+	
Pharmacotherapy			With co-morbidities	+	+	+
Surgery					With co-morbidities	+

Source: The Practical Guide to the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.

History of Anti-obesity Drugs

- Late 1880s: Thyroid extract
- 1920's: Laxatives
- 1930's: Dinitrophenol
- 1940's: Amphetamines
- 1960's: Rainbow pills (digitalis/diuretics)
- 1970's: Aminorex
- 1990's: Fenfluramine + Phentermine (Fen-Phen)
- 1998: Sibutramine
- 1999: Orlistat
- 2012: Lorcaserine (Belviq)

  Phentermine + Topiramate (Qsymia)

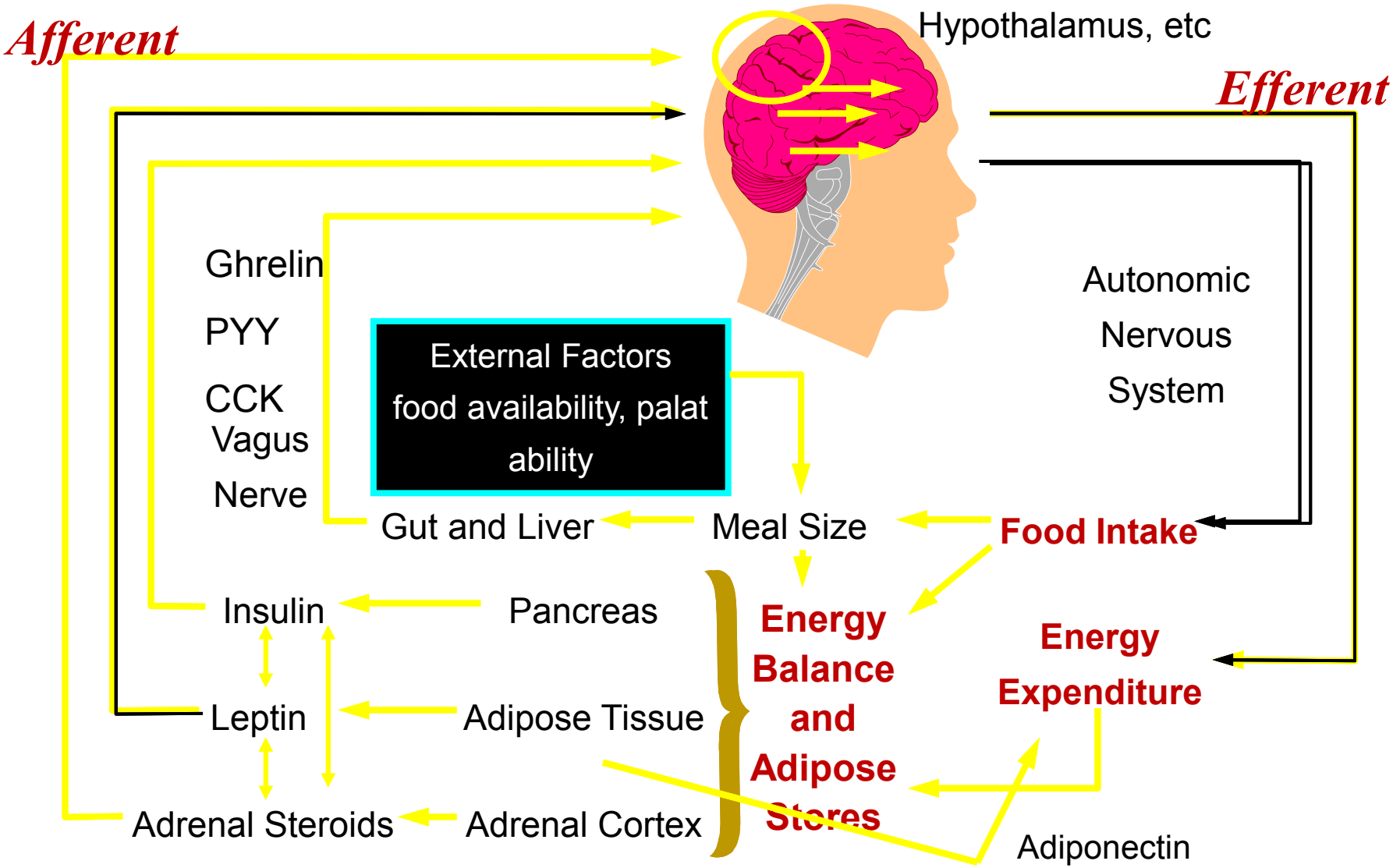
Unintended Consequences of Drug Treatment for Obesity

Year	Drug	Consequence
1892	Thyroid	Hyperthyroidism
1932	Dintrophenol	Cataracts/Neuropathy
1937	Amphetamine	Addiction
1968	Aminorex	Pulmonary Hypertension
1997	Phen/Fenfluramine	Valvulopathy
1998	Phenylpropanolamine	Strokes
2003	Ma Huang (ephedra)	Heart attacks/stroke
2007	Ecopipam (Dopamine)	Depression/Suicide
2008	Rimonabant (CB-1)	Depression
2010	Sibutramine	CVD Risk

Bray GA Battle of the Bulge, Dorrance Publishing 2007 p. 59

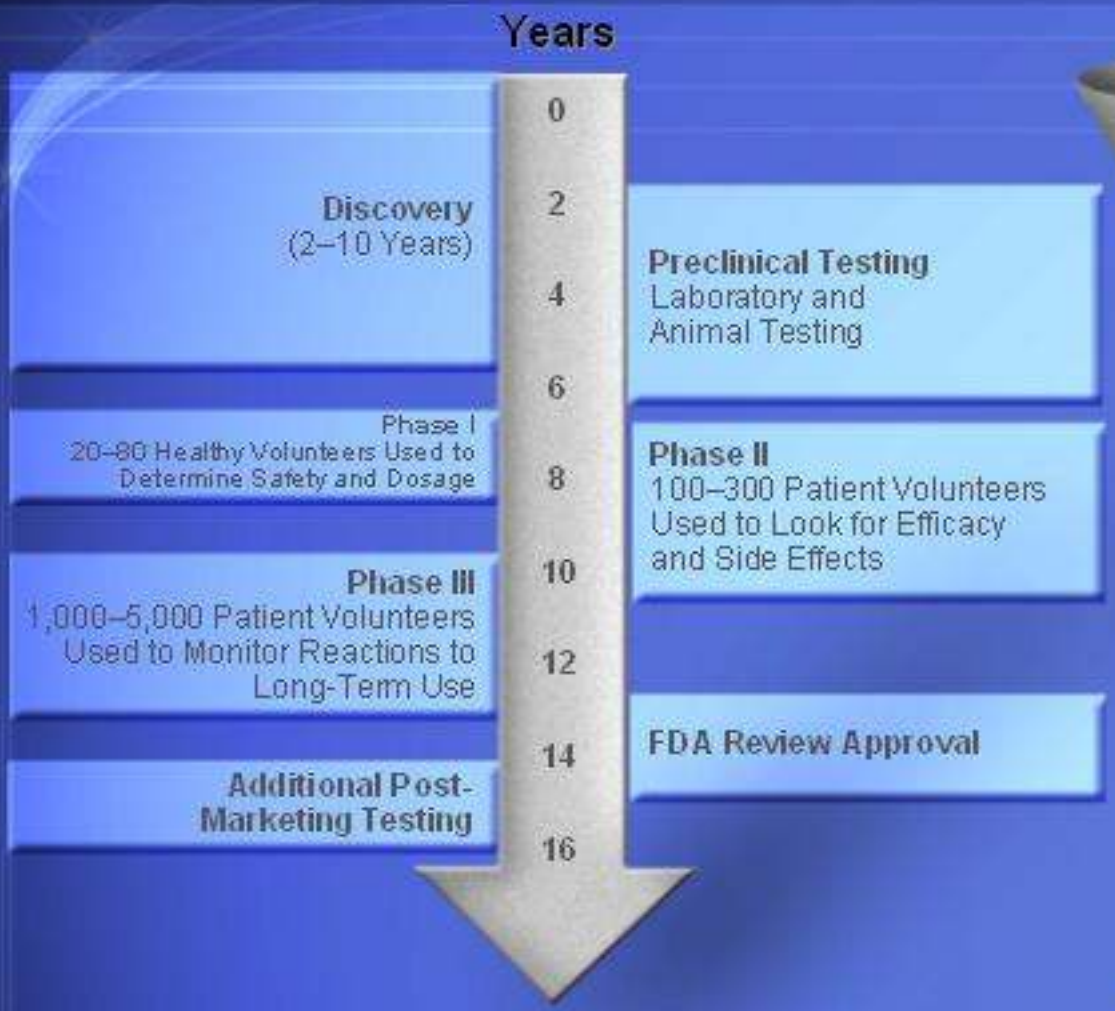
Why is it so hard to lose weight?

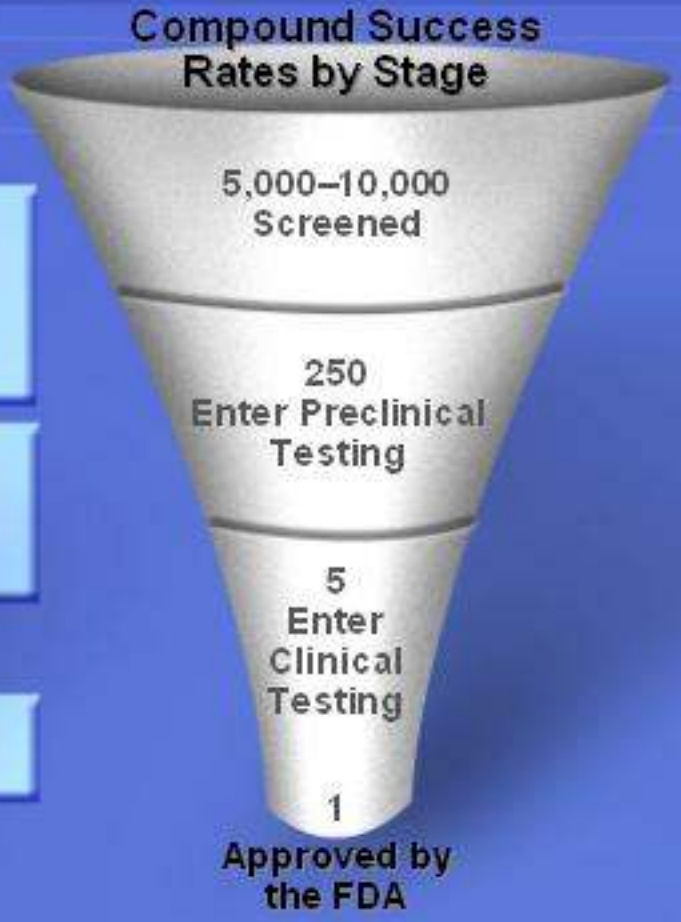
Weight is controlled by a feedback system.



Aronne LJ. Adapted from Campfield LA, et al. *Science.* 1998;280:1383-1387; and Porte D, et al. *Diabetologia.* 1998;41:863-881.

New Product Development – A Risky and Expensive Proposition

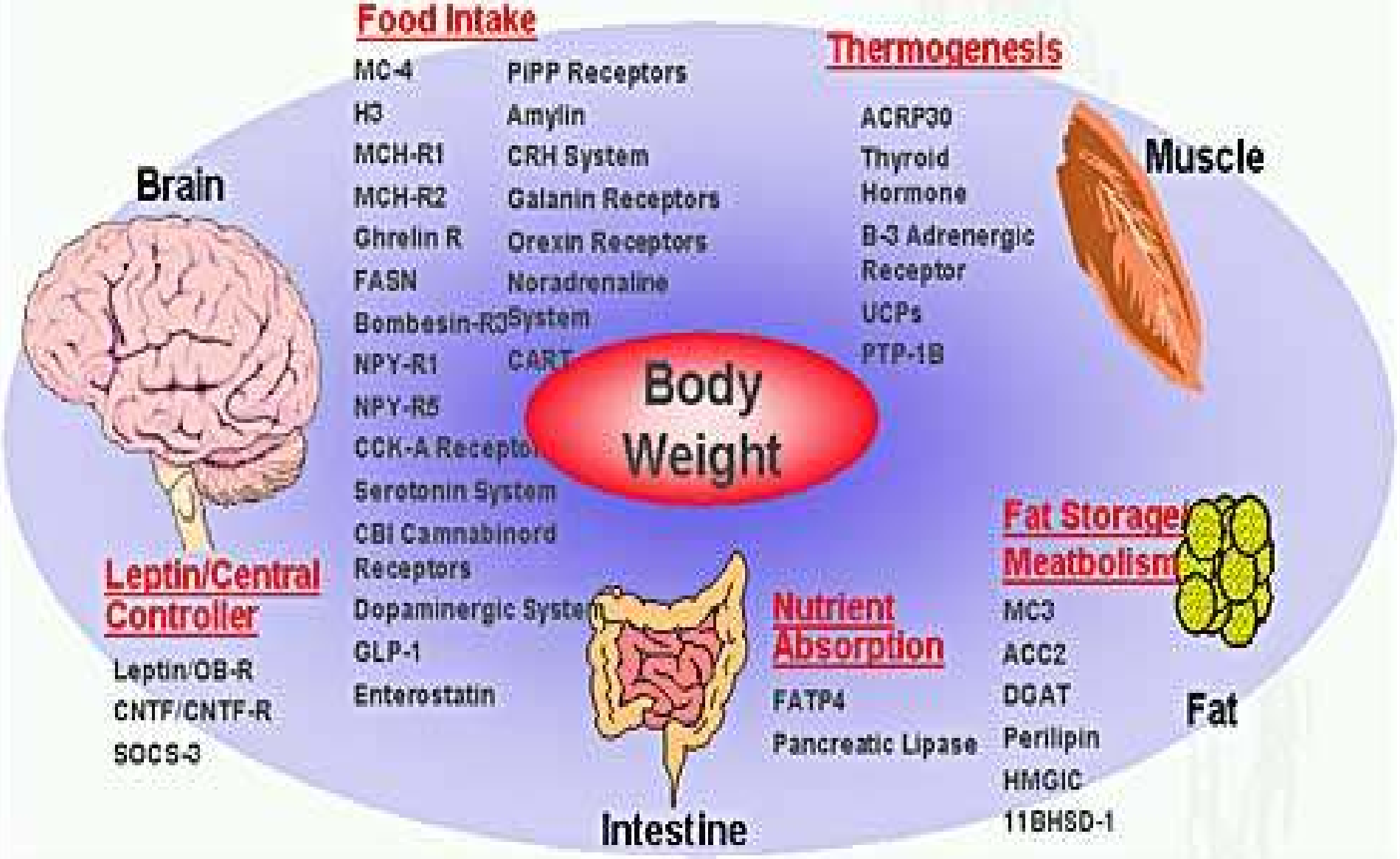




Net Cost: $802 Million Invested Over 15 Years

Source: Tufts Center for the Study of Drug Development

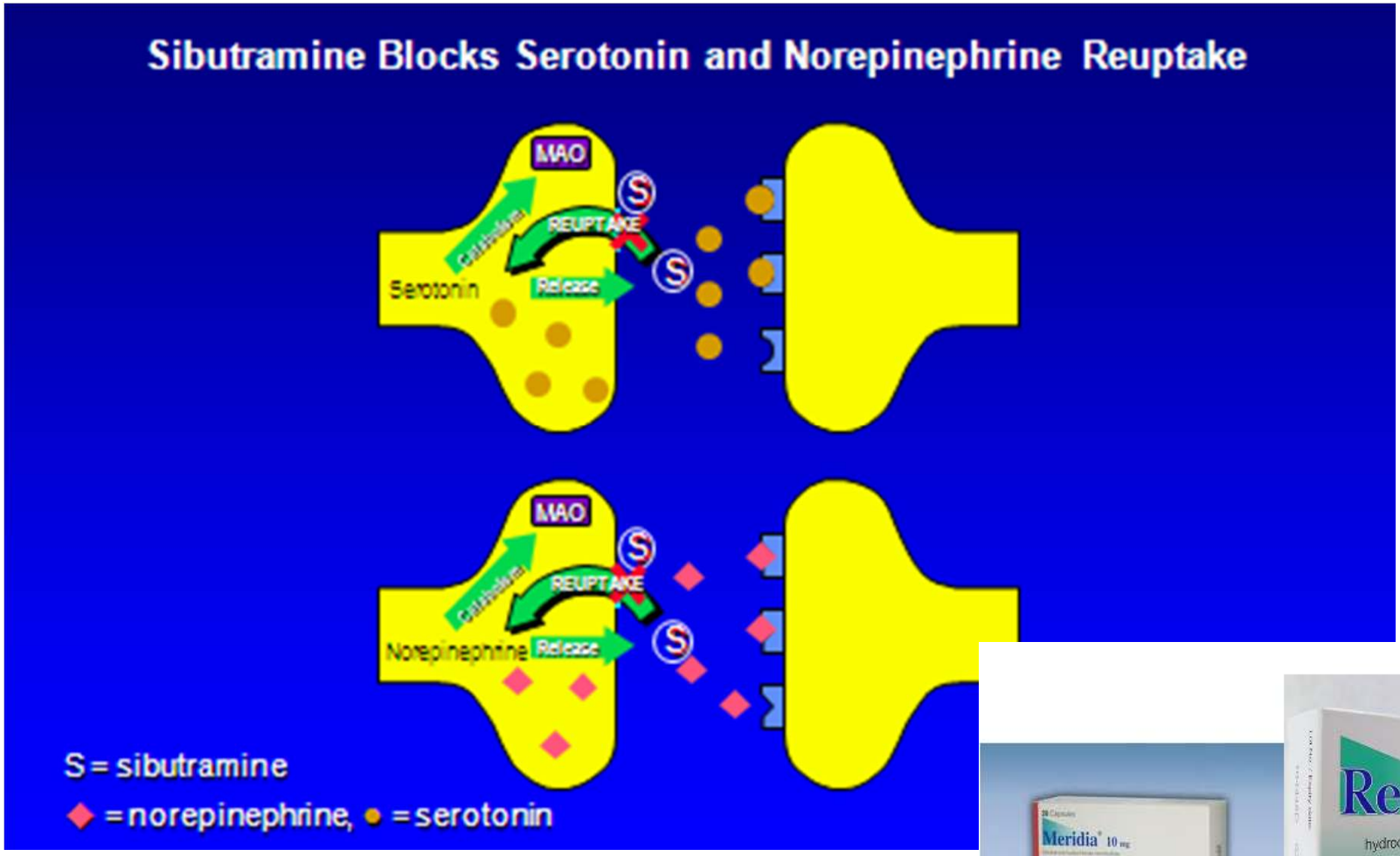
Pathways and Targets for Obesity



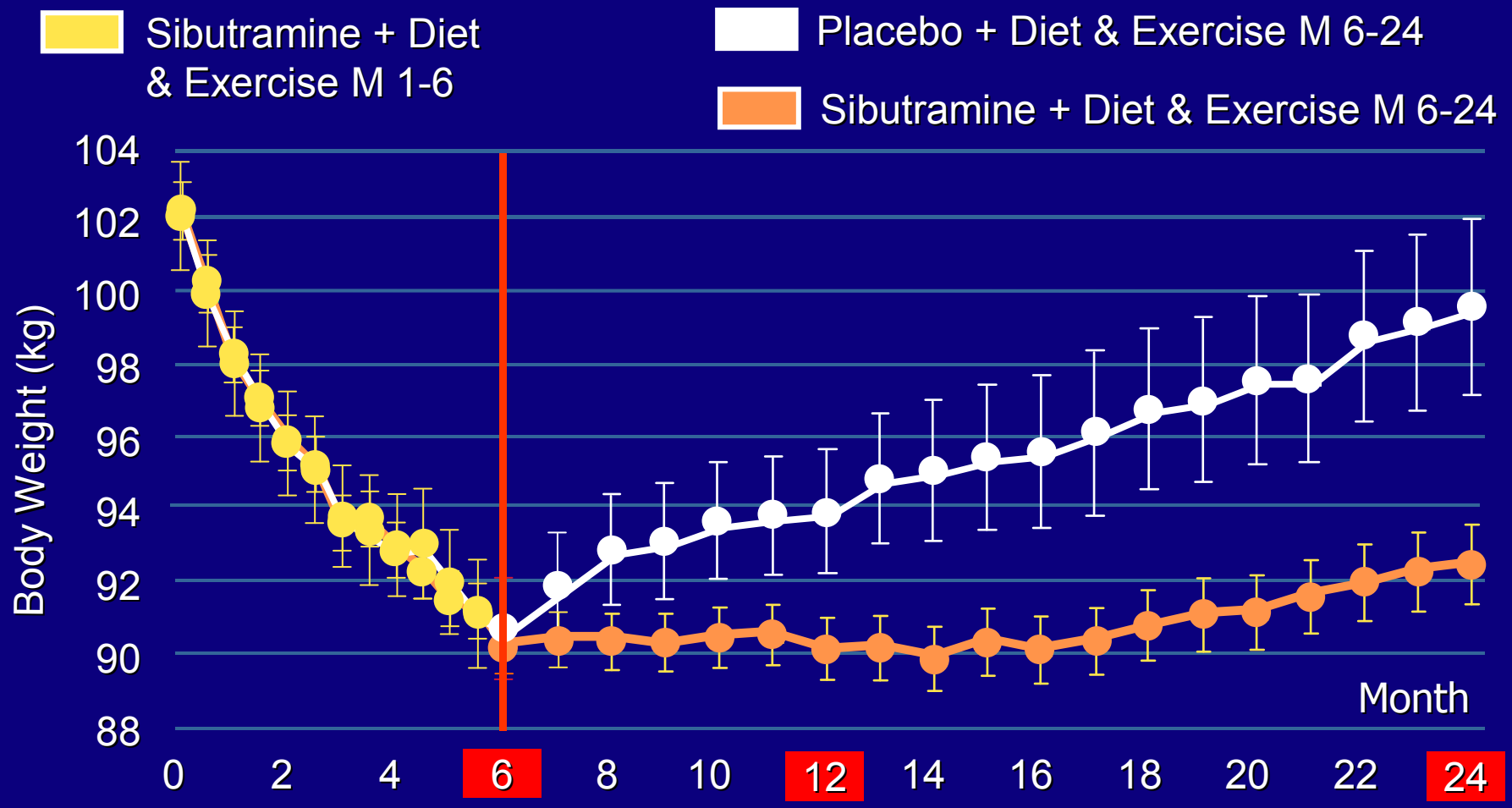
Classes of Anti-Obesity Drugs

- **Appetite suppressants**
  - **Noradrenergic (Schedule IV)**
    - Phentermine (Adipex, Fastin)
    - Diethylpropion (Tenuate)
  - **Noradrenergic (Schedule III)**
    - Benzphetamine (Didrex)
    - Phendimetrazine (Bontril)
  - **Serotonergic**
    - Fenfluramine, dexfenfluramine
  - **Mixed Noradrenergic & Serotonergic**
    - Sibutramine (Meridia)
- **Nutrient absorption reducers**
  - **Lipase inhibitor**
    - Orlistat (Xenical)

Sibutramine

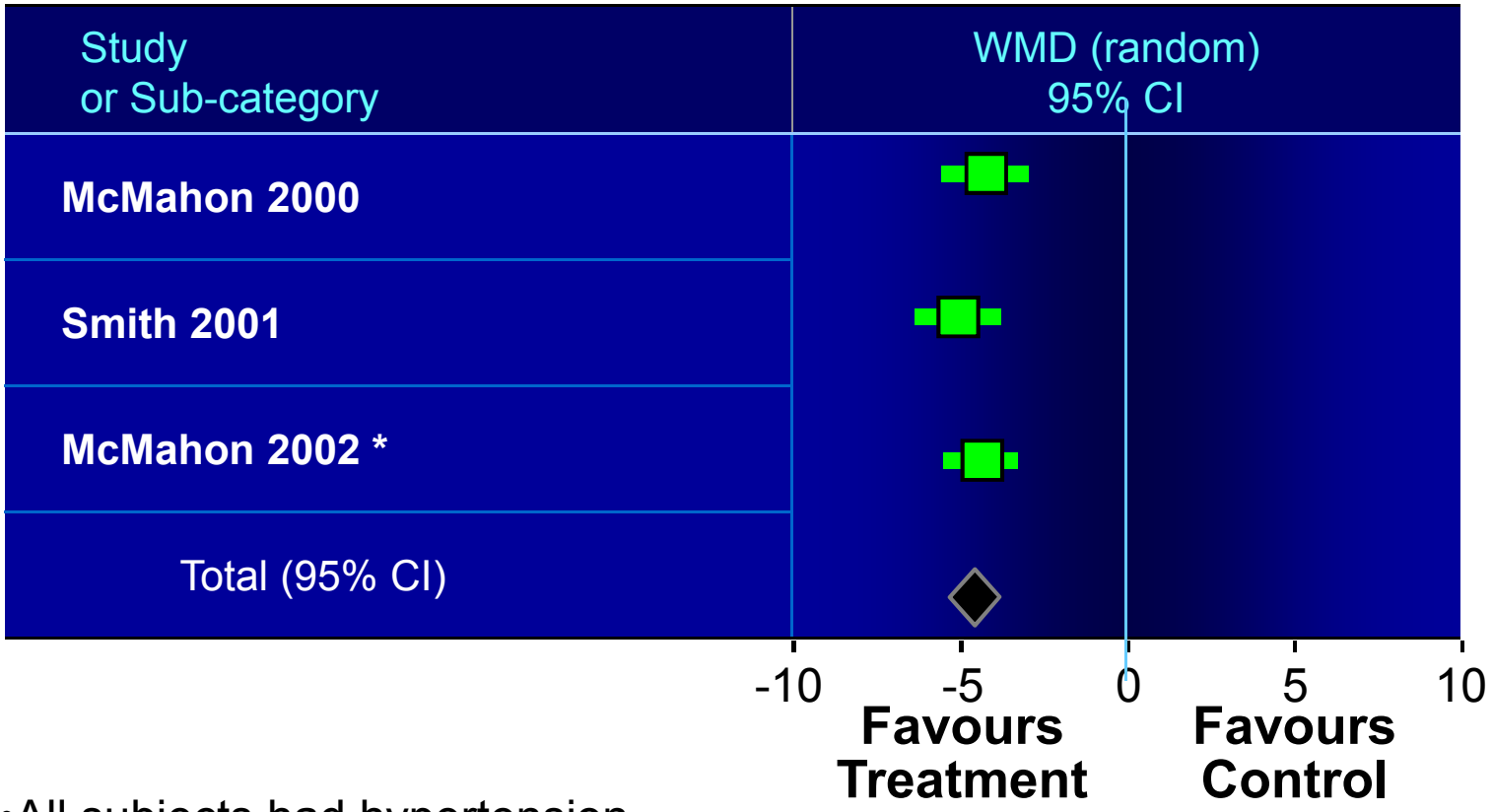


Sibutramine: 2-Year Efficacy
Weight Loss and Weight Maintenance



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

Meta-analysis of RCTs Evaluating Effect of Sibutramine Therapy on Weight Loss at 1-Year



•All subjects had hypertension
WMD=weighted mean difference

Padwal et al. Int J Obes 2003;27:1437

Sibutramine – Side Effects

- Increased blood pressure, tachycardia
- Arrhythmia
- Dry mouth, constipation, headache, insomnia
- Somnolence and fatigue
- Mood effects - depression and rebound depression ?
- GI effects: unsettled stomach, stomach pains, bowel habit alterations

Sibutramine Contraindications

- Taking concomitant monoamine oxidase inhibitor (MAOI) therapy
- With anorexia nervosa
- Using any other centrally-acting appetite suppressant
- **Uncontrolled hypertension**
- **Coronary heart disease**
- **Congestive heart failure**
- **Arrhythmias**
- **Stroke**
- Severe renal or liver dysfunction
- Narrow-angle glaucoma

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

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ABSTRACT

BACKGROUND

The long-term effects of sibutramine treatment on the rates of cardiovascular events and cardiovascular death among subjects at high cardiovascular risk have not been established.

METHODS

We enrolled in our study 10,744 overweight or obese subjects, 55 years of age or older, with preexisting cardiovascular disease, type 2 diabetes mellitus, or both to assess the cardiovascular consequences of weight management with and without sibutramine in subjects at high risk for cardiovascular events. All the subjects received sibutramine in addition to participating in a weight-management program during a 6-week, single-blind, lead-in period, after which 9804 subjects underwent random assignment in a double-blind fashion to sibutramine (4906 subjects) or placebo (4898 subjects). The primary end point was the time from randomization to the first occurrence of a primary outcome event (nonfatal myocardial infarction, nonfatal stroke, resuscitation after cardiac arrest, or cardiovascular death).

RESULTS

The mean duration of treatment was 3.4 years. The mean weight loss during the lead-in period was 2.6 kg; after randomization, the subjects in the sibutramine group achieved and maintained further weight reduction (mean, 1.7 kg). The mean blood pressure decreased in both groups, with greater reductions in the placebo group than in the sibutramine group (mean difference, 1.2/1.4 mm Hg). The risk of a primary outcome event was 11.4% in the sibutramine group as compared with 10.0% in the placebo group (hazard ratio, 1.16; 95% confidence interval [CI], 1.03 to 1.31; P=0.02). The rates of nonfatal myocardial infarction and nonfatal stroke were 4.1% and 2.6% in the sibutramine group and 3.2% and 1.9% in the placebo group, respectively (hazard ratio for nonfatal myocardial infarction, 1.28; 95% CI, 1.04 to 1.57; P=0.02; hazard ratio for nonfatal stroke, 1.36; 95% CI, 1.04 to 1.77; P=0.03). The rates of cardiovascular death and death from any cause were not increased.

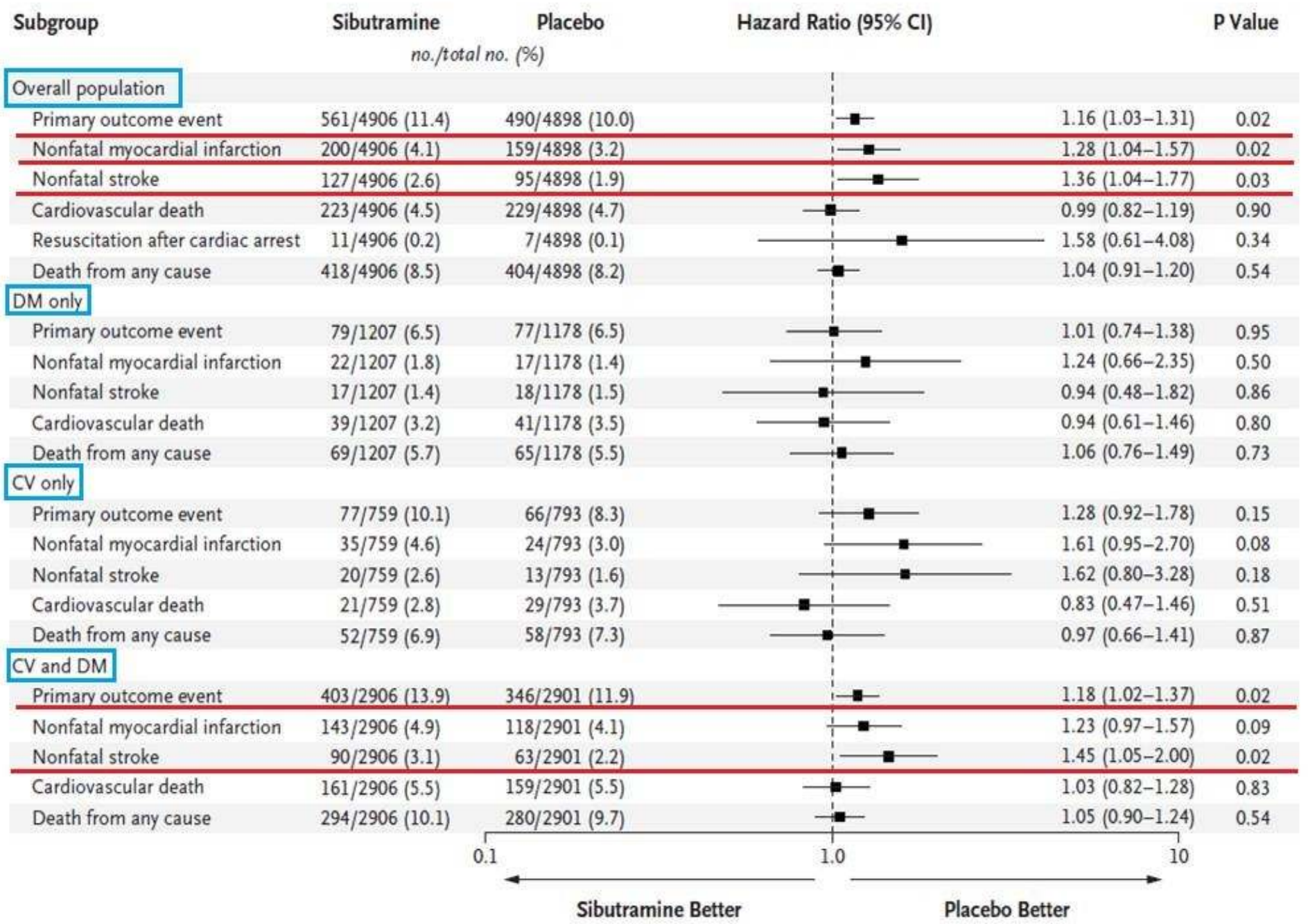
CONCLUSIONS

Subjects with preexisting cardiovascular conditions who were receiving long-term sibutramine treatment had an increased risk of nonfatal myocardial infarction and nonfatal stroke but not of cardiovascular death or death from any cause. (Funded by

From the London School of Hygiene and Tropical Medicine (W.P.T.J.) and University College London Vascular Physiology Unit (N.F.) — both in London; the Boden Institute of Obesity, Nutrition, and Exercise, University of Sydney, Sydney (I.D.C.); Catholic University of Rio de Janeiro, Rio de Janeiro (W.C.); Antwerp University Hospital, Antwerp, Belgium (L.F.V.G.); Associazione Nazionale Medici Cardiologi Ospedalieri Research Center, Florence, Italy (A.P.M.); the Department of Cardiology, Gentofte University Hospital, Hellerup, Denmark (C.T.-P.); the University of Alberta, Royal Alexandra Hospital, Edmonton, Canada (A.M.S.); and Abbott Laboratories, Abbott Park, IL (G.M.S., R.A.R., C.L.R.). Address reprint requests to Dr. James at IASO, 28 Portland Pl., London W1B 1LY England, or at jeanhjames@aol.com.

*Investigators participating in the Sibutramine Cardiovascular Outcomes (SCOUT) trial are listed in the Appendix.

N Engl J Med 2010;363:905-17.


Subgroup
Sibutramine
Placebo
no./total no. (%)
Hazard Ratio (95% CI)
P Value
Overall population
Primary outcome event 561/4906 (11.4) 490/4898 (10.0) 1.16 (1.03–1.31) 0.02
Nonfatal myocardial infarction 200/4906 (4.1) 159/4898 (3.2) 1.28 (1.04–1.57) 0.02
Nonfatal stroke 127/4906 (2.6) 95/4898 (1.9) 1.36 (1.04–1.77) 0.03
Cardiovascular death 223/4906 (4.5) 229/4898 (4.7) 0.99 (0.82–1.19) 0.90
Resuscitation after cardiac arrest 11/4906 (0.2) 7/4898 (0.1) 1.58 (0.61–4.08) 0.34
Death from any cause 418/4906 (8.5) 404/4898 (8.2) 1.04 (0.91–1.20) 0.54
DM only
Primary outcome event 79/1207 (6.5) 77/1178 (6.5) 1.01 (0.74–1.38) 0.95
Nonfatal myocardial infarction 22/1207 (1.8) 17/1178 (1.4) 1.24 (0.66–2.35) 0.50
Nonfatal stroke 17/1207 (1.4) 18/1178 (1.5) 0.94 (0.48–1.82) 0.86
Cardiovascular death 39/1207 (3.2) 41/1178 (3.5) 0.94 (0.61–1.46) 0.80
Death from any cause 69/1207 (5.7) 65/1178 (5.5) 1.06 (0.76–1.49) 0.73
CV only
Primary outcome event 77/759 (10.1) 66/793 (8.3) 1.28 (0.92–1.78) 0.15
Nonfatal myocardial infarction 35/759 (4.6) 24/793 (3.0) 1.61 (0.95–2.70) 0.08
Nonfatal stroke 20/759 (2.6) 13/793 (1.6) 1.62 (0.80–3.28) 0.18
Cardiovascular death 21/759 (2.8) 29/793 (3.7) 0.83 (0.47–1.46) 0.51
Death from any cause 52/759 (6.9) 58/793 (7.3) 0.97 (0.66–1.41) 0.87
CV and DM
Primary outcome event 403/2906 (13.9) 346/2901 (11.9) 1.18 (1.02–1.37) 0.02
Nonfatal myocardial infarction 143/2906 (4.9) 118/2901 (4.1) 1.23 (0.97–1.57) 0.09
Nonfatal stroke 90/2906 (3.1) 63/2901 (2.2) 1.45 (1.05–2.00) 0.02
Cardiovascular death 161/2906 (5.5) 159/2901 (5.5) 1.03 (0.82–1.28) 0.83
Death from any cause 294/2906 (10.1) 280/2901 (9.7) 1.05 (0.90–1.24) 0.54
0.1
1.0
10
Sibutramine Better
Placebo Better

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Sibutramine — Another Flawed Diet Pill

Gregory D. Curfman, M.D., Stephen Morrissey, Ph.D., and Jeffre[illegible] Drazen, M.D.

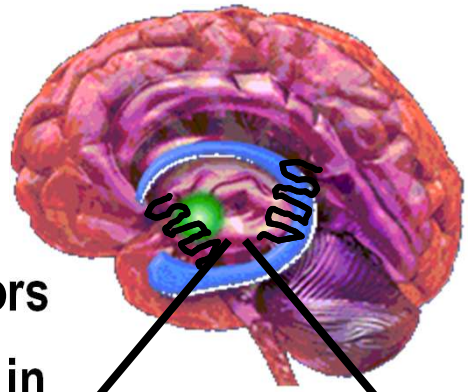
WITHDRAWN 2010

On September 15, 2010, an advisory committee of [illegible] completed. In the the Food and Drug Administration (FD[illegible] 0,000 patients who to determine the fa[illegible] d had preexisting suppressant dr[illegible] s mellitus, or both Meridia. This r[illegible] receive sibutramine FDA is based o[illegible] ion to participating in indi- Sibutramine C[illegible] diet and exercise programs, for an trial, the resul[illegible] ge of 3.4 years. As in many trials of weight- issue of the *Jo*[illegible] loss drugs, the dropout rate was high (>40%). tee will be ask[illegible] the drug The primary end point, incident cardiovascular should be sub[illegible] tory action. events, was observed significantly more frequent-

Sibutramin[illegible] that blocks the reuptake ly in the sibutramine group than in the placebo of serotonin and norepinephrine by presynaptic group (11.4% vs. 10.0%, P=0.02). The finding nerve terminals and thereby induces satiety, was was driven principally by a higher incidence of approved by the FDA in 1997. In that same year, nonfatal myocardial infarction and nonfatal two other appetite-suppressant drugs that func- stroke among sibutramine-treated subjects who tion by a similar mechanism of action, fenflura- had preexisting cardiovascular disease. The sub- mine and dexfenfluramine, were removed from group with diabetes but no evidence of preexist- the market because of serious, unexpected car- ing cardiovascular disease had no increase in diovascular adverse events, primary pulmonary the risk of cardiovascular events, though diabetic hypertension and valvular regurgitation, which re- subjects with cardiovascular disease did have an sulted in substantial morbidity and mortality.[2] increase in risk.

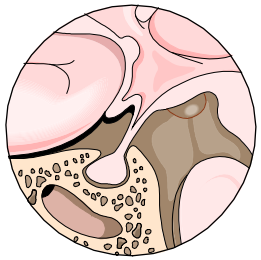
Endogenous Cannabinoid Blockers - Rimonabant

CENTRAL NERVOUS SYSTEM

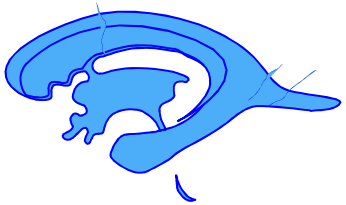


CB_1 receptors are present in the brain

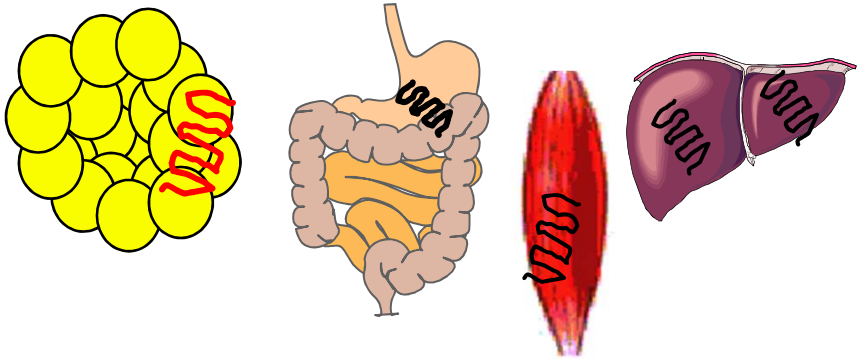
Hypothalamus



Limbic system



PERIPHERAL TISSUES

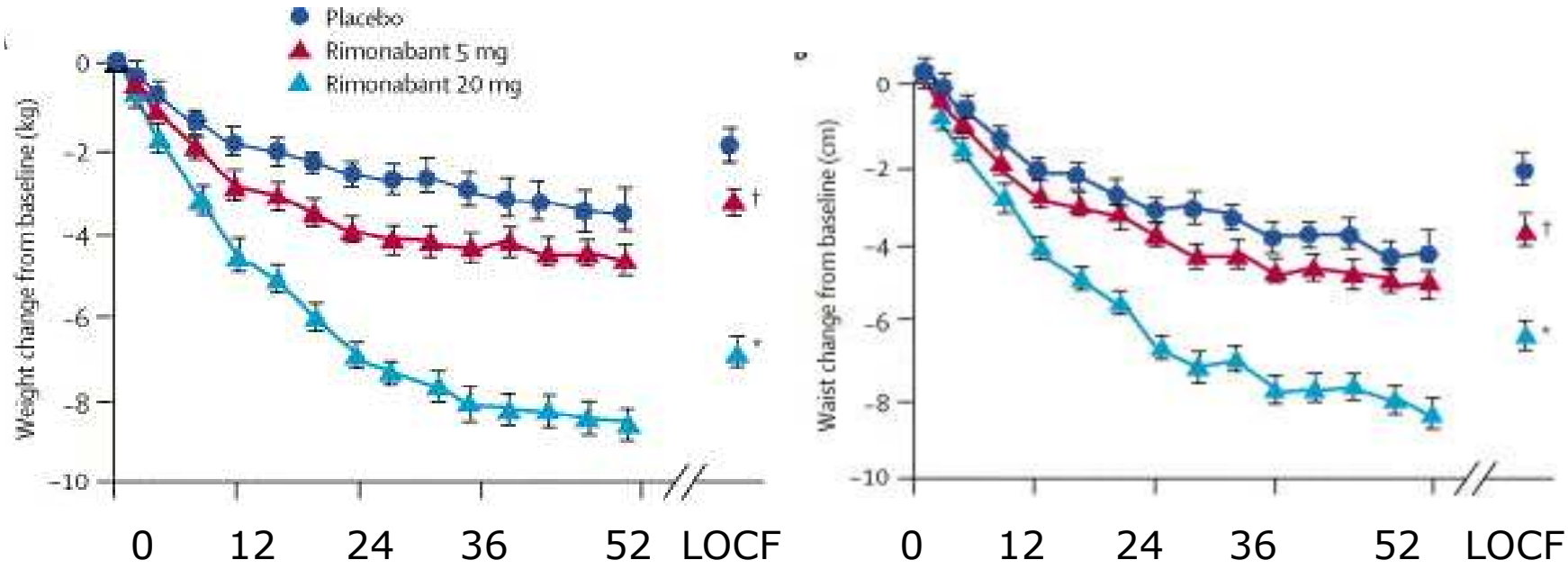


CB_1 are present in adipose tissue, the GI tract, liver and skeletal muscle

ECS effects occur through:

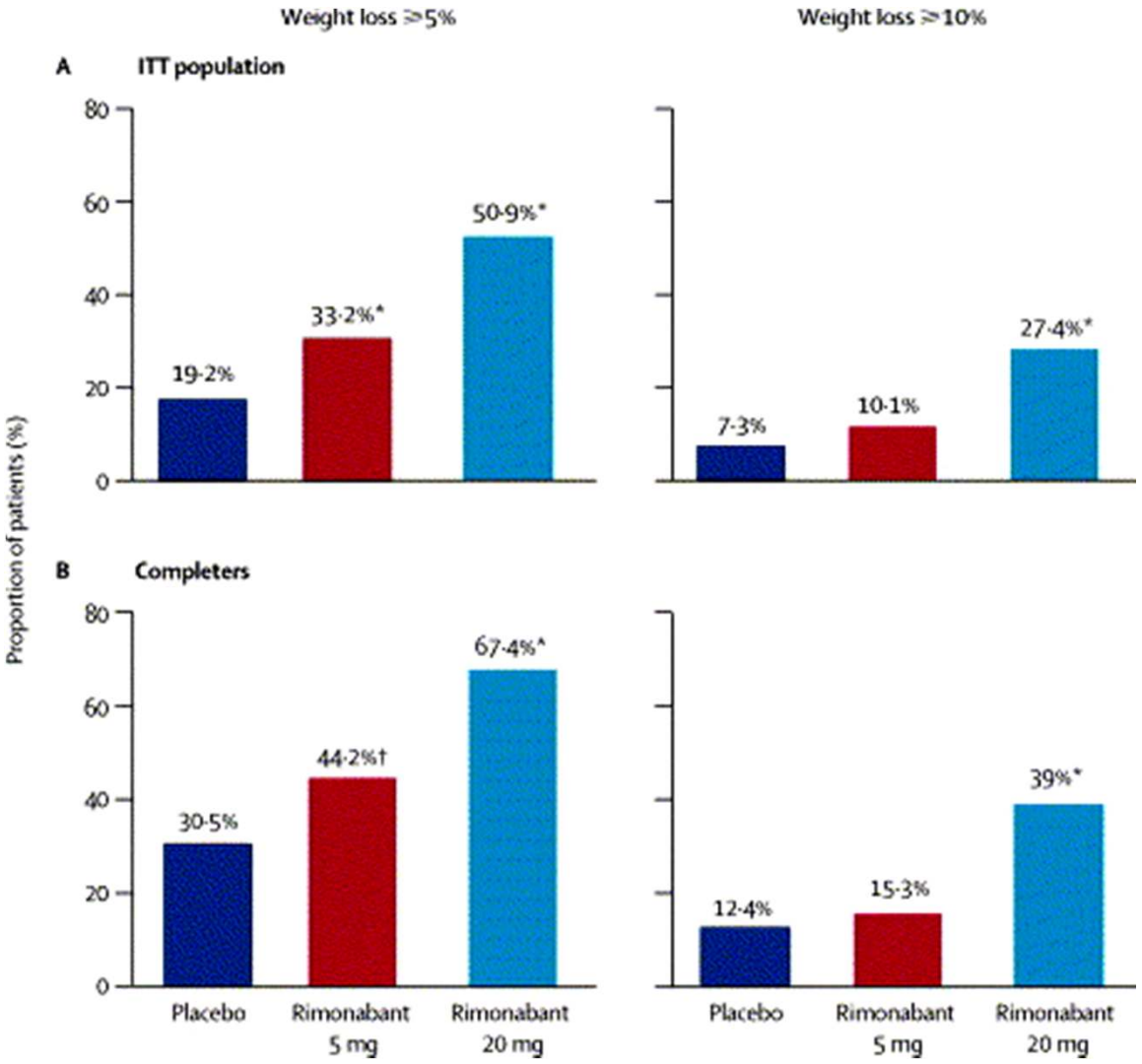
1) **interactions with hypothalamic and other brain circuits pathways regulating energy balance**
2) **Peripheral effects in adipose tissue, the gut, muscle and liver**

Change from Baseline in Body Weight and Waist Circumference: RIO-Europe Trial



Van Gaal LF et al. *Lancet* 2005;365:1389-1397.

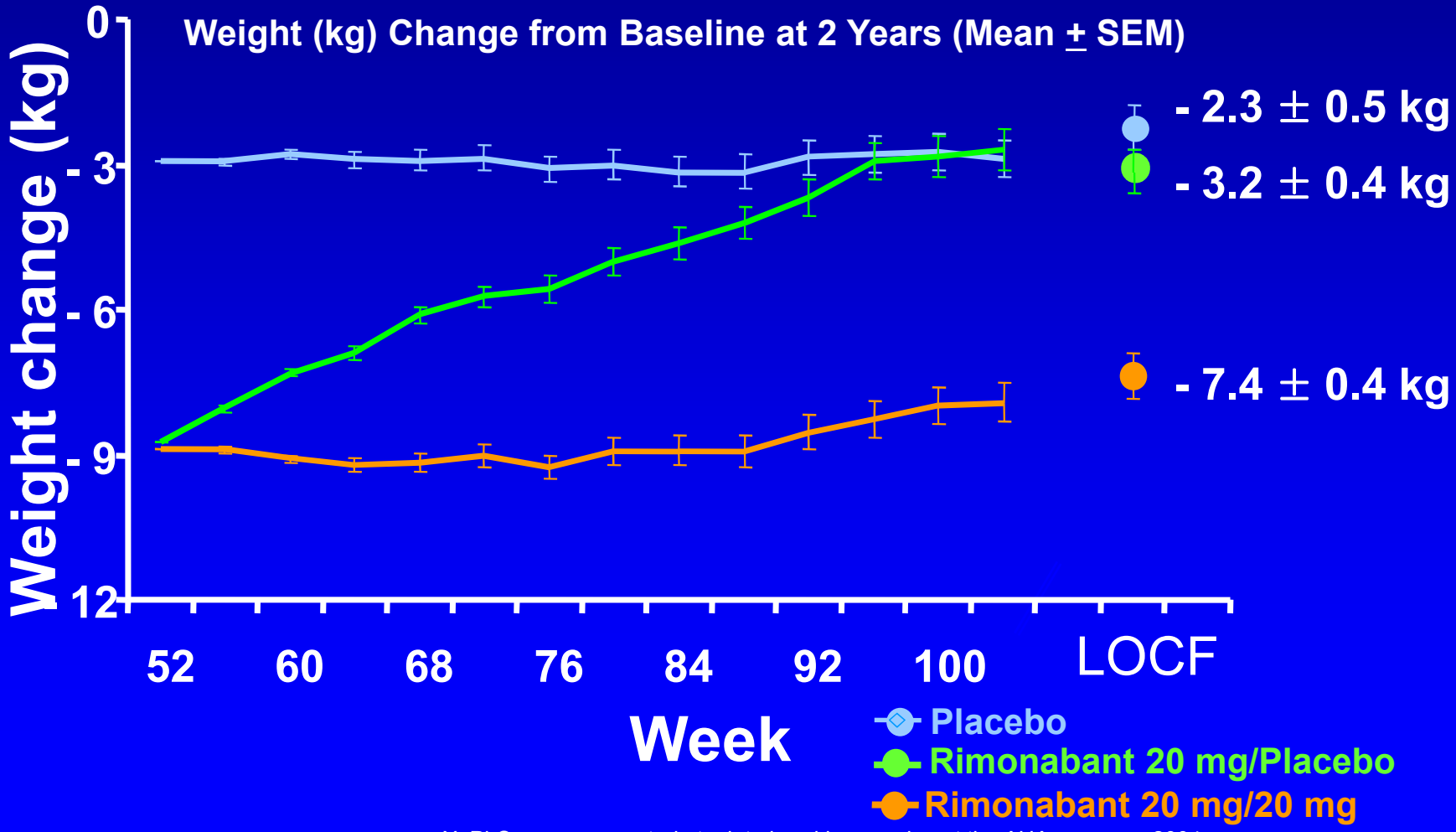
Proportion of Patients Who Lost ≥5% and ≥10% of Baseline Weight at 1 Year: RIO-Europe



Van Gaal LF et al. *Lancet* 2005;365:1389-1397.

Prevention of weight regain by chronic therapy: RIO-North America

ITT-LOCF

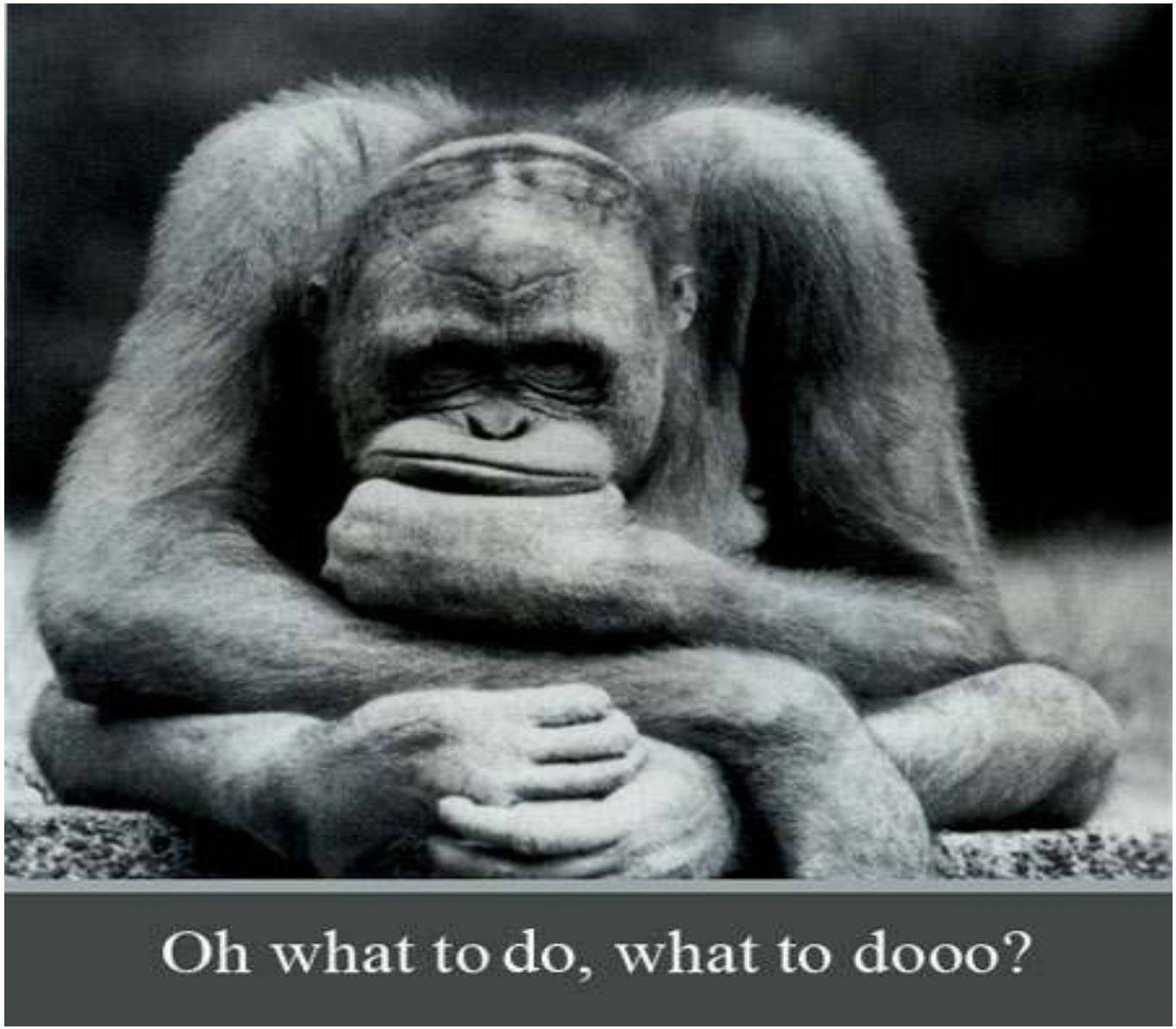


X. Pi-Sunyer, presented at a late breaking session at the AHA congress 2004

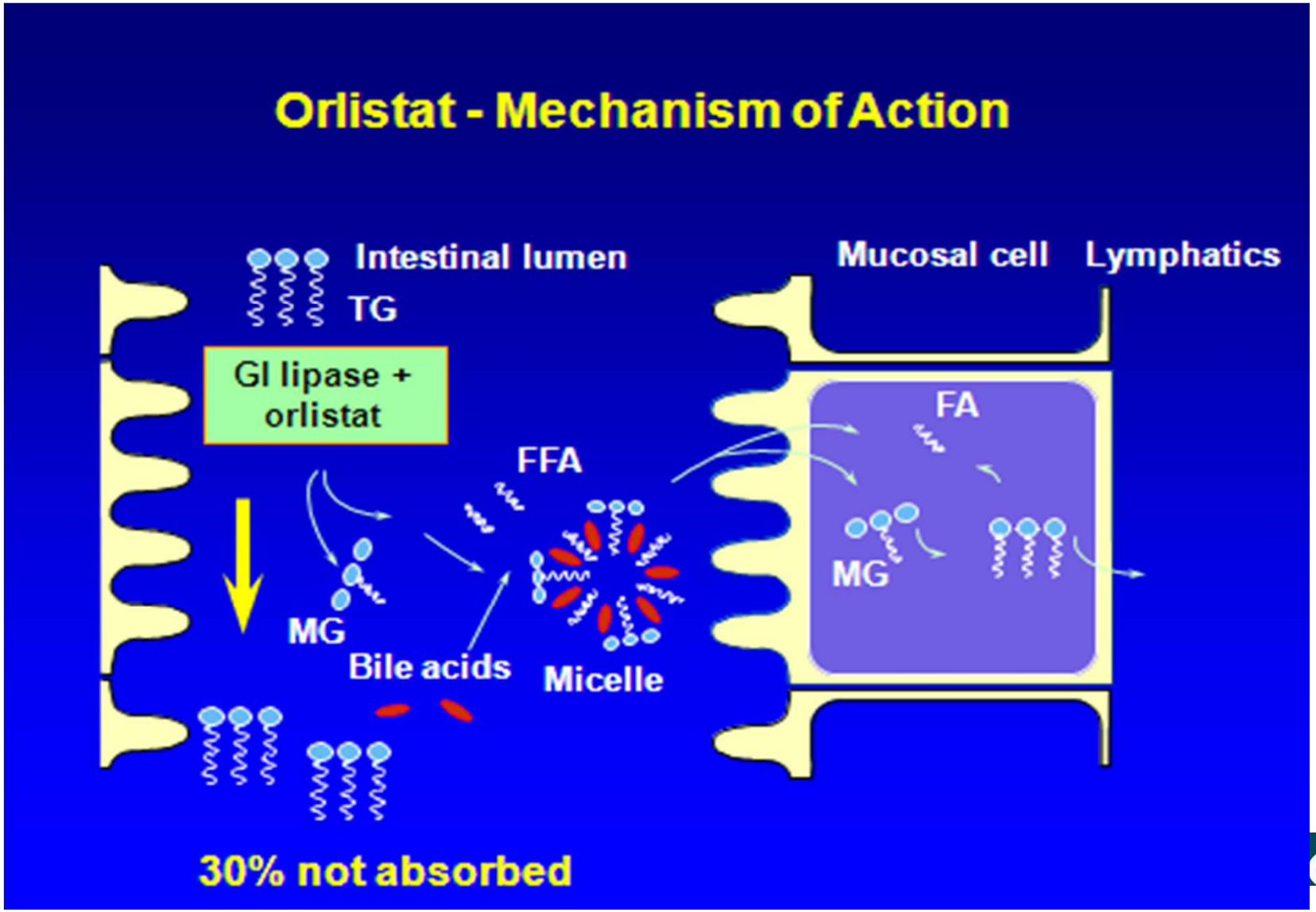
Rimonabant

- Consistently show significant weight reductions (mean difference 4.9kg) compared to placebo at 20 mg/day
- Improved cardiometabolic risk factors
- Improved A1c in diabetic patients
- Concern for significant rate of anxiety and depression
- Approved in Europe in June 2006
- Not approved in US because of increased depression and suicidal ideation (2007)
- Suspended in Europe in October 2008

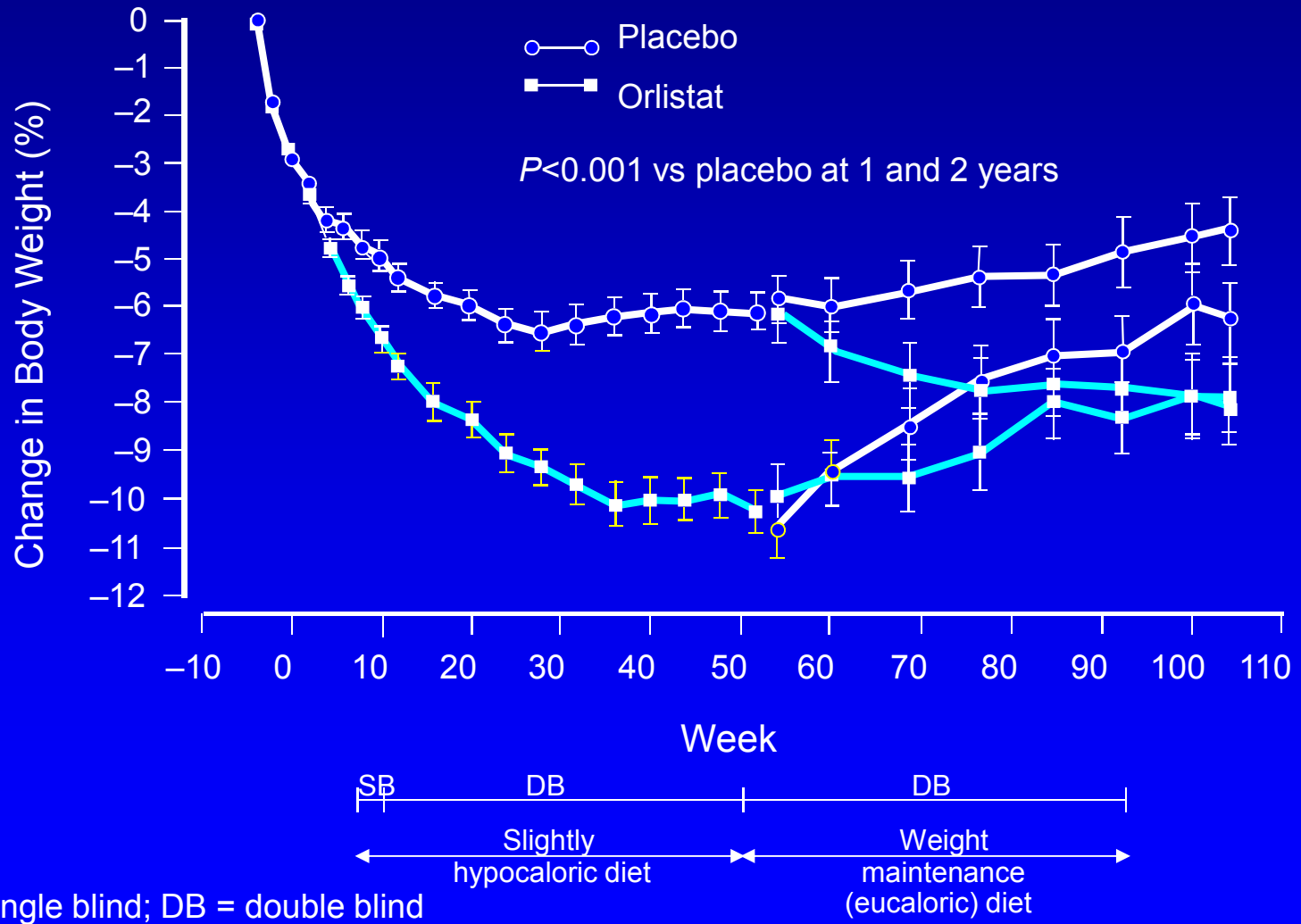
WITHDRAWN


Oh what to do, what to dooo?

Orlistat (Xenical)



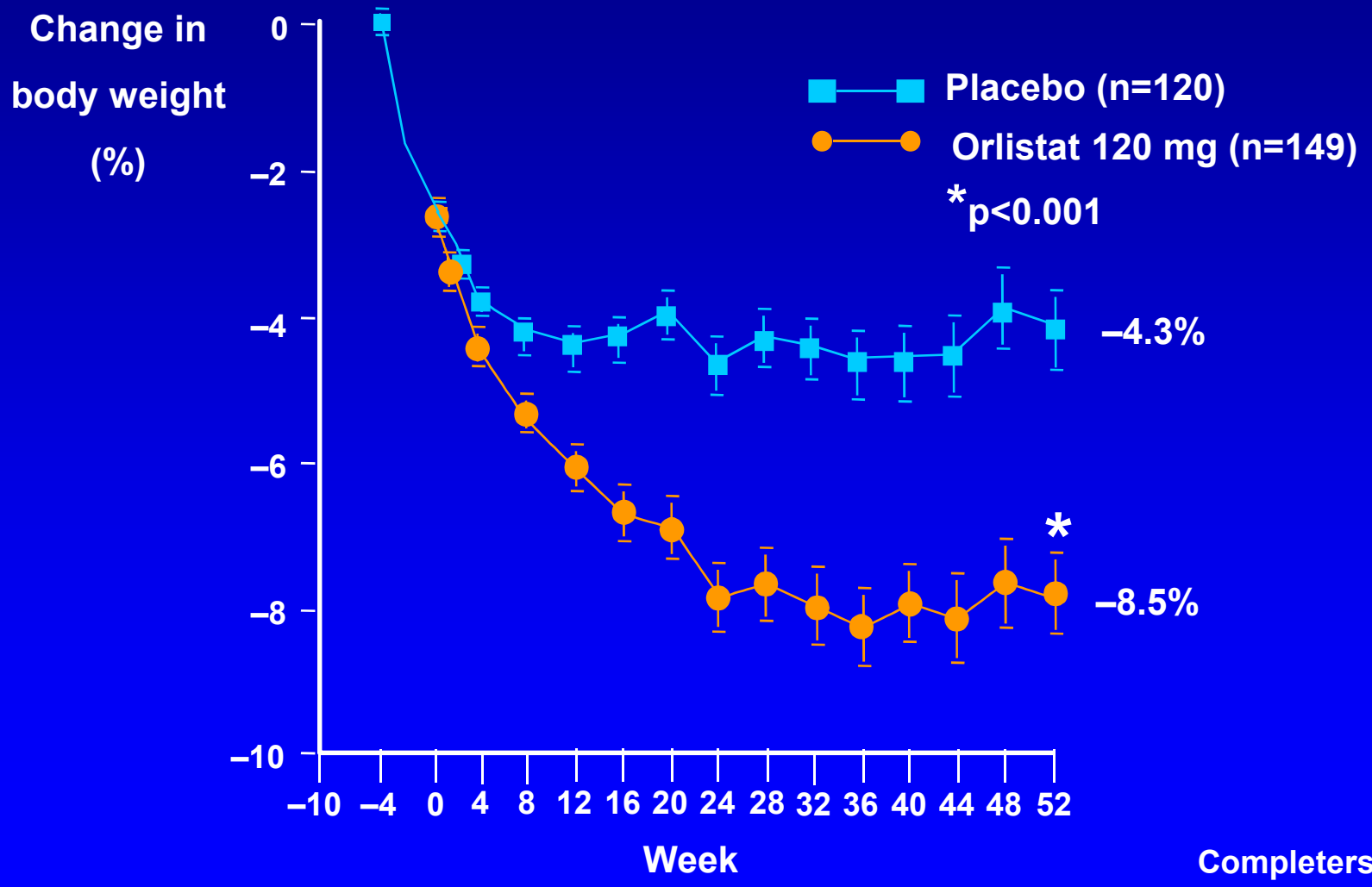
Orlistat: Weight Loss and Maintenance Over 2 Years



SB = single blind; DB = double blind

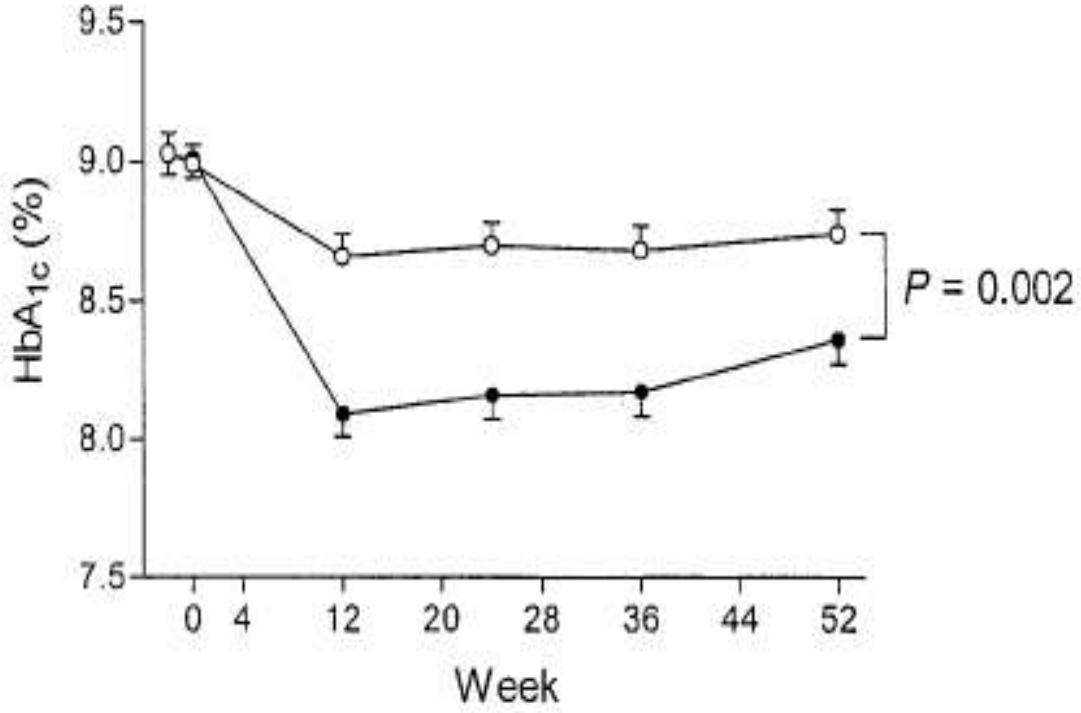
Adapted with permission from Sjöström L et al. *Lancet*. 1998;352:167.

Orlistat in primary care



Completers: BM14161

Orlistat - Effect on HbA1c in T2DM



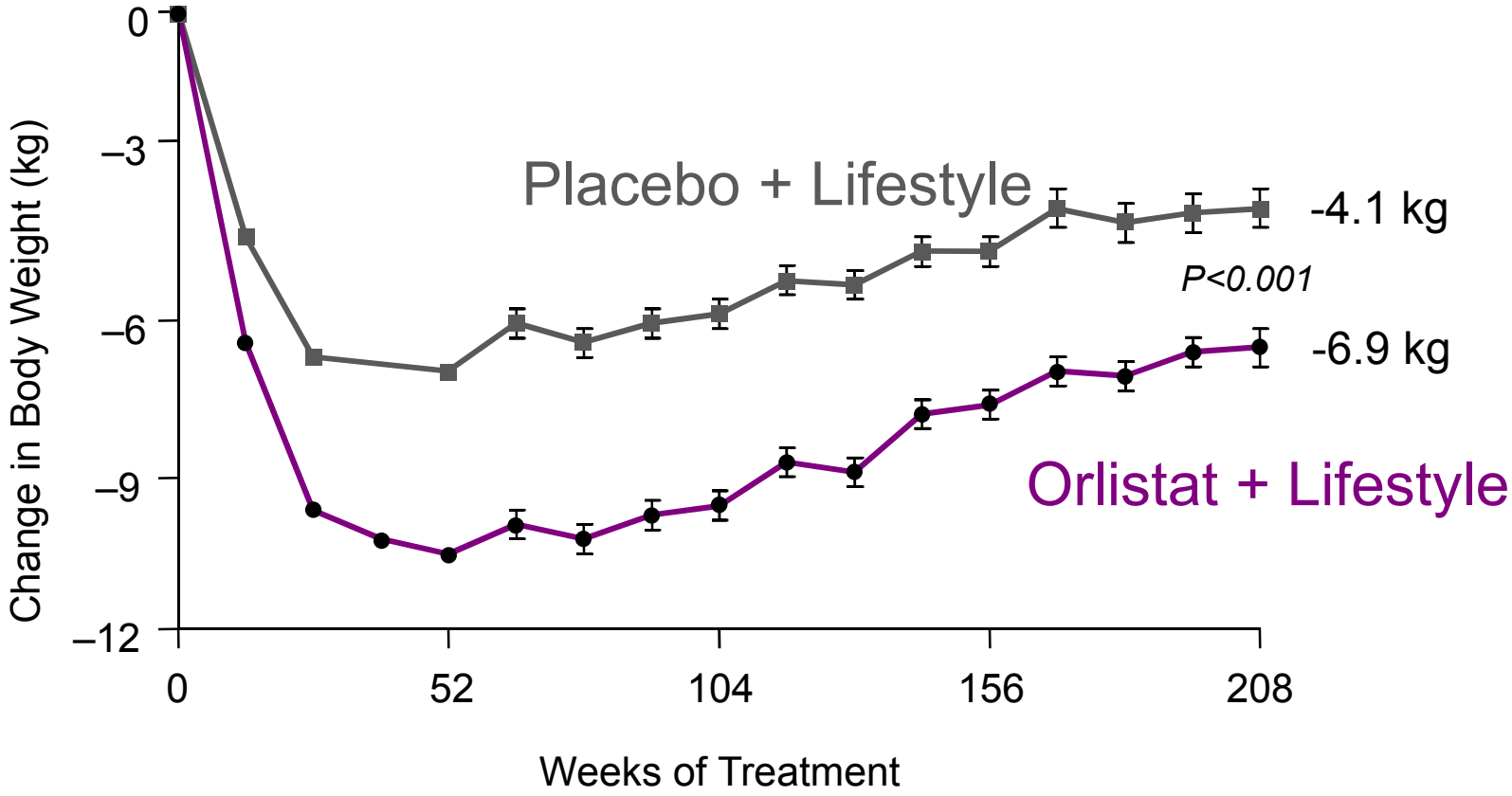
The improvement in HbA1c by 0.62%

Figure 4—*HbA1c over 1 year of double-blind treatment with placebo* (E) *or 120 mg orlistat* (F)*.*

P=*0.002, least-squares mean difference from placebo in the change from baseline over 52 weeks.*

DIABETES CARE, VOLUME 25, NUMBER 6, JUNE 2002

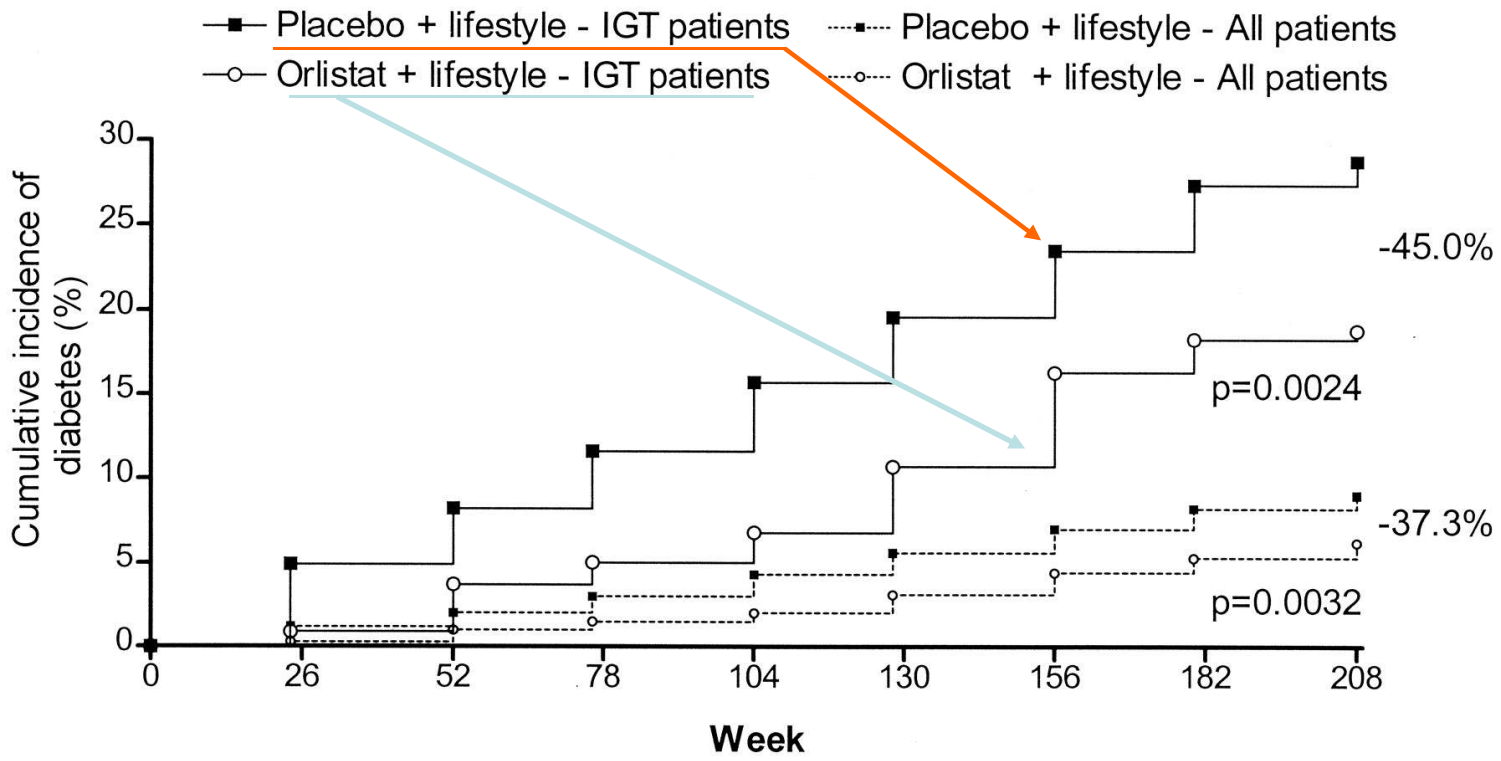
Effect of Long-term Treatment With Orlistat (The XENDOS Study)



Torgerson JS et al. *Diabetes Care.* 2004;27(1):155–161.

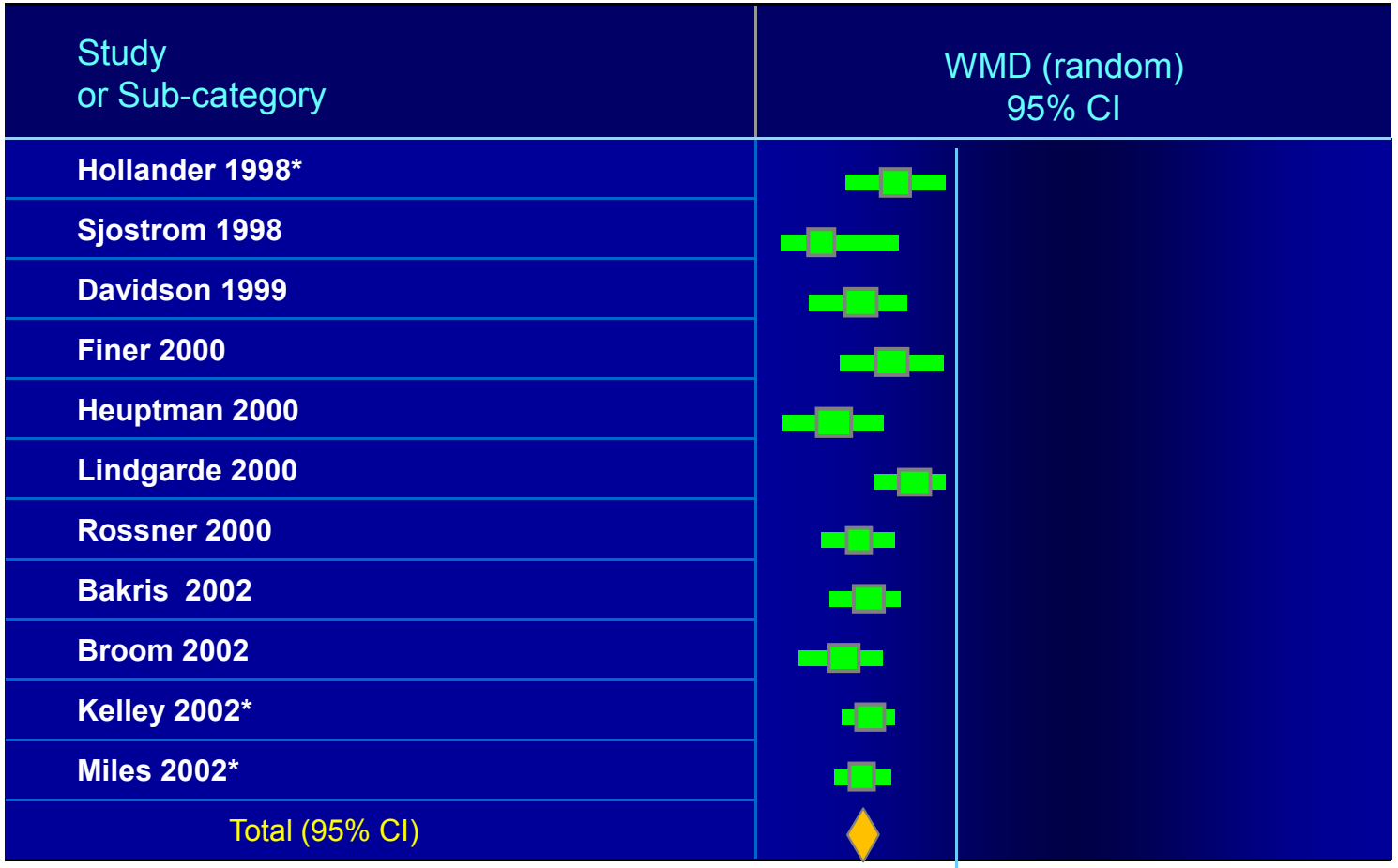
4-year long RCT of orlistat as an adjunct to lifestyle for the prevention of type 2 diabetes

Weight loss with orlistat + lifestyle reduced the risk of type 2 diabetes more than lifestyle alone



Diabetes Care. 2004 Jan;27(1):155-61

Meta-analysis of RCTs Evaluating Effect of Orlistat Therapy on Weight Loss at 1-Year



*All subjects had type 2 diabetes
WMD=weighted mean difference

Padwal et al. Int J Obes 2003;27:1437

Side Effects of Orlistat

- GI side effects due to inhibition of fat absorption:

  bloating, pain, fecal urgency, Incontinence, liquid stools, flatulence with discharge, oily spotting

  - severity generally related to amount of fat eaten

- Mild malabsorption of fat soluble vitamins (like A, E)
  - which can be overcome by oral supplementation

Diet Pill for Dogs…

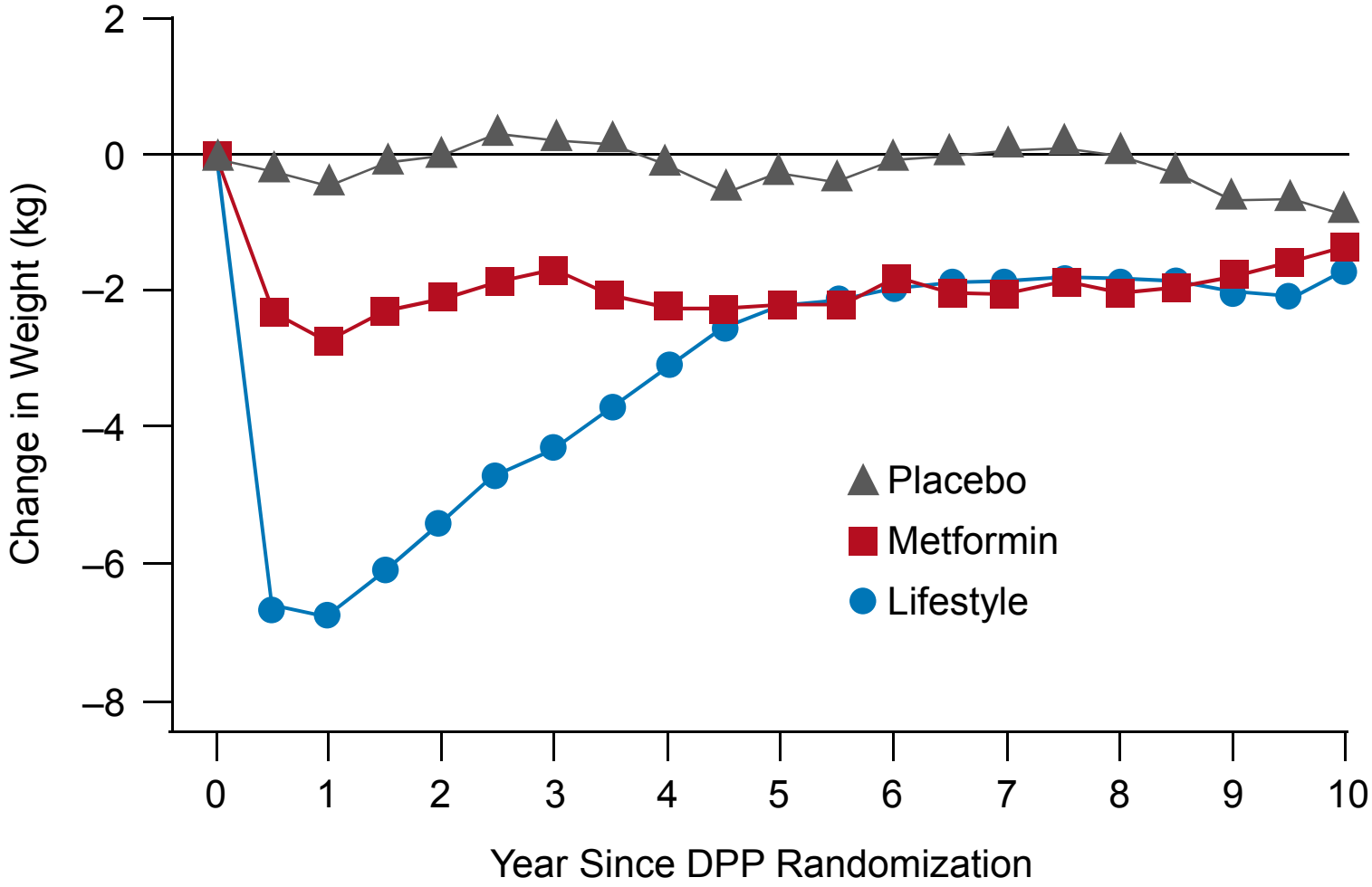
- Substitute for exercise and food reduction
- Slentrol is the first FDA-approved diet pill for dogs

TREATMENT OF COMBINED OBESITY AND DIABETES

Anti-diabetic Agents Associated with Weight Loss

- Metformin
- GLP-1 agonists
- Amylin

DPP: Metformin and Lifestyle Over Time



DPP Research Group. *Lancet.* 2009;374(9702):1677–1686.

Metformin Compared to Others

- 150 women with BMI >30 randomized to the following
  - Sibutramine 10 mg po BID (Higher than normal dose)
  - Orlistat 120 mg po TID
  - Metformin 850 mg po BID
- All groups also with lifestyle interventions/ nutrition counseling
- No placebo group
- 6 months follow up

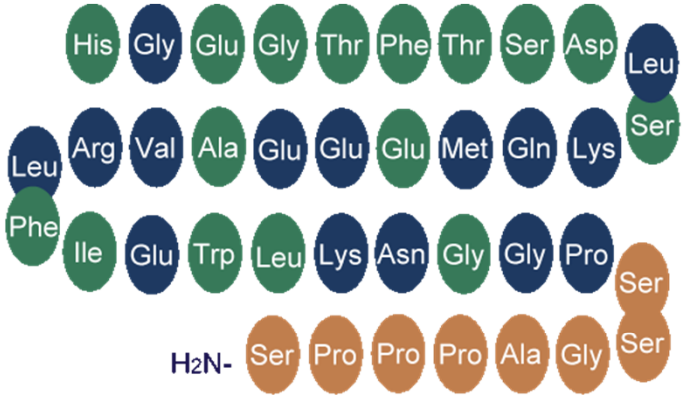
	% decrease BMI	% decrease waist circumference
Sibutramine	13.57	10.43
Orlistat	9.09	6.64
Metformin	9.90	8.10

Gokcel A, et al. Diab Obes Metab 2002.

Glucagon-Like Peptide 1

- GLP-1 is the 7-36 amino acid sequence of glucagon
- It is an incretin that is released from the L-cells of the intestine and enhances insulin release in the presence of glucose
- It reduces glucagon release from the α-cells
- It slows gastric emptying
- It reduces food intake

Exenatide



- From saliva of the Gila Monster
- 53% homologous with GLP-1
- Insensitive to DPP-4
- Full agonist at the GLP-1 receptor
- Metabolically stable
- t½ 4-5 hr after sc injection

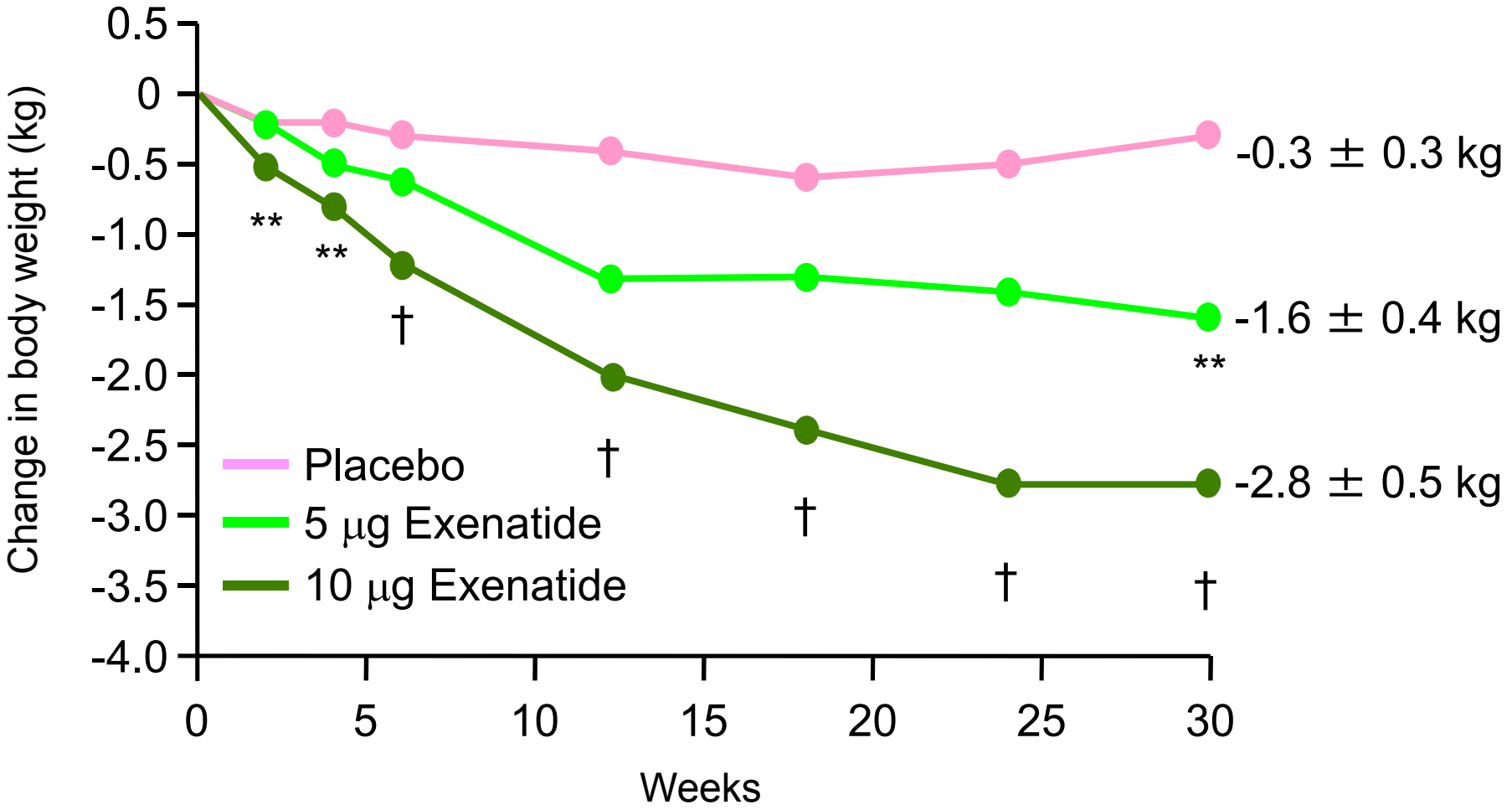
Liraglutide

- Based on human GLP-1 (7-37)
- 97% homologous with GLP-1
- Resistant to DPP-4
- Full agonist at the GLP-1 receptor
- Noncovalent binding to albumin, self-association, slow release from injection site gives prolonged survival time
- t½ 12 hr after sc injection

Conserved Substituted Additional (relative to human GLP-1 7-37)

Chen YE, et al. J Biol Chem.1997;272:4108-4115; Knudsen LB, et al. J Med Chem. 2000;43:1664-1669.

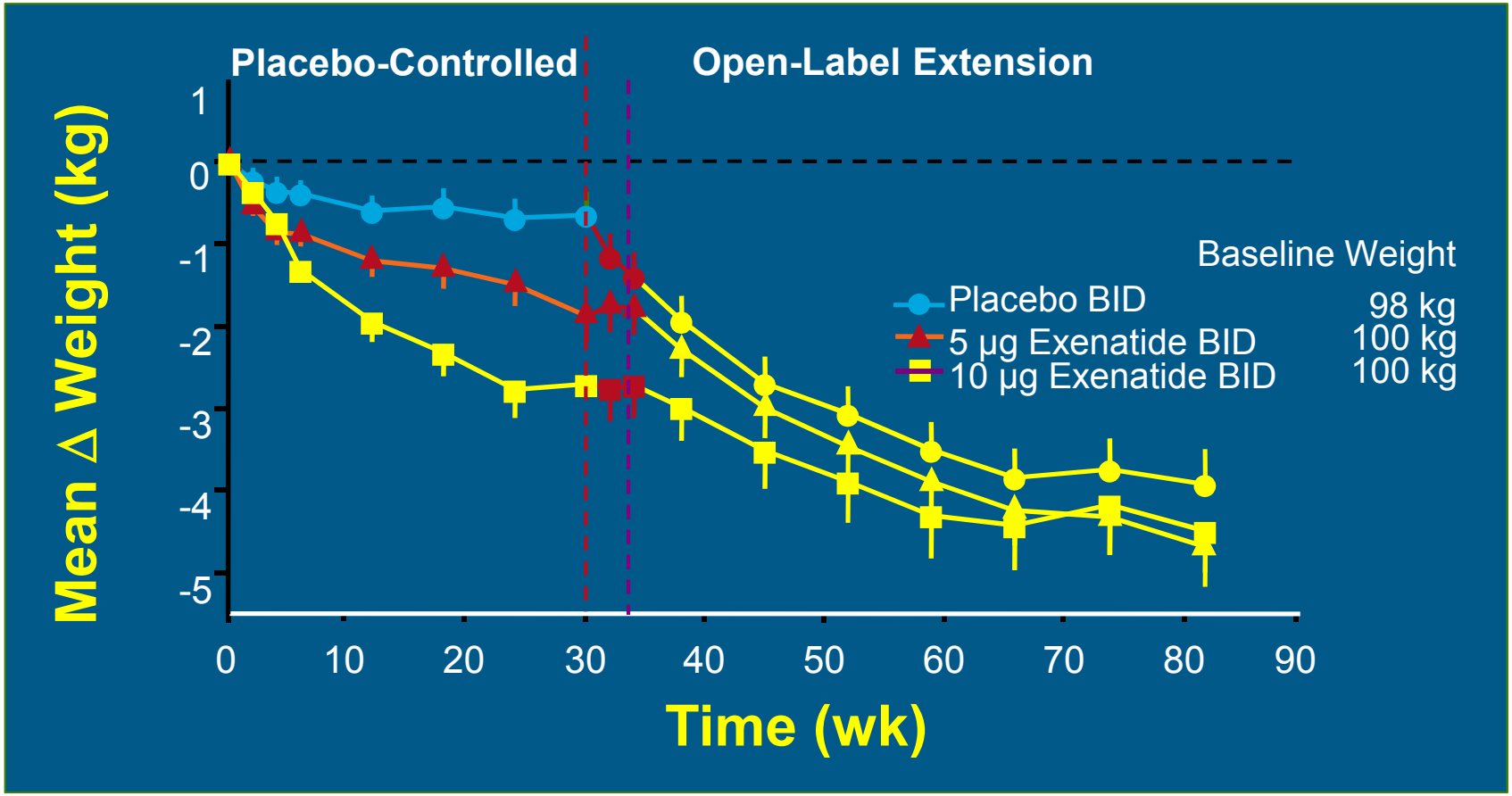
Exenatide: An Anti-diabetic Drug That Produces Weight Loss



**$P \leq .05$ vs placebo; †$P \leq .001$ vs placebo.

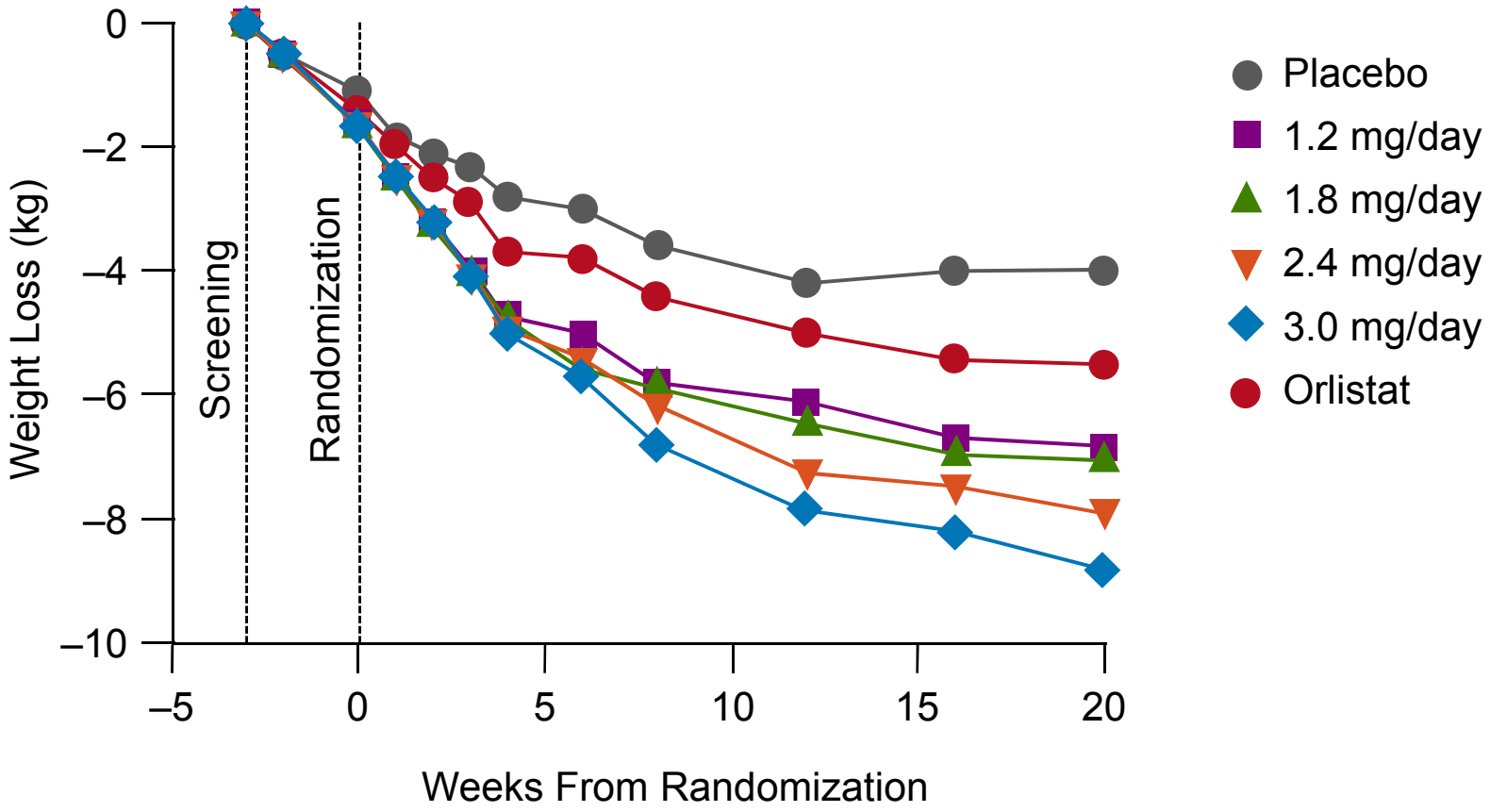
Defronzo RA, et al. *Diabetes Care.* 2005;28:1092-1100.

Exenatide Reduces Body Weight in Placebo Controlled & Open-Label Trial



82-wk completers; N = 393; Mean ± SE; Weight was a secondary endpoint
Data on file, Amylin Pharmaceuticals, Inc.

Liraglutide vs. Orlistat

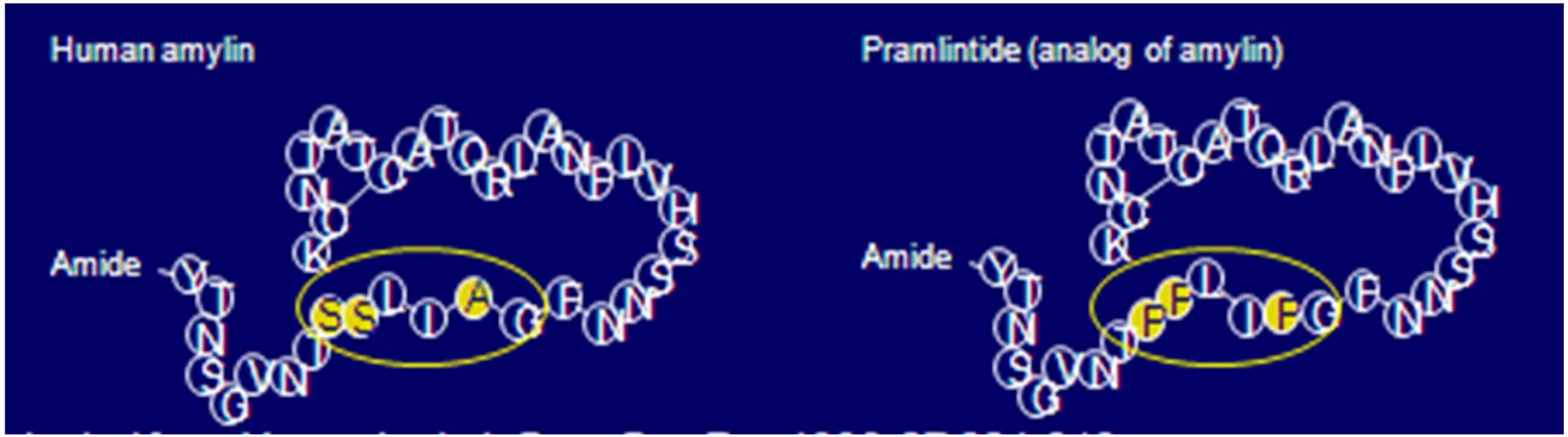


*Not approved for treatment of obesity.

Astrup A et al. *Lancet.* 2009;374(9701):1606–1616.

Pramlintide: An Amylin Analog

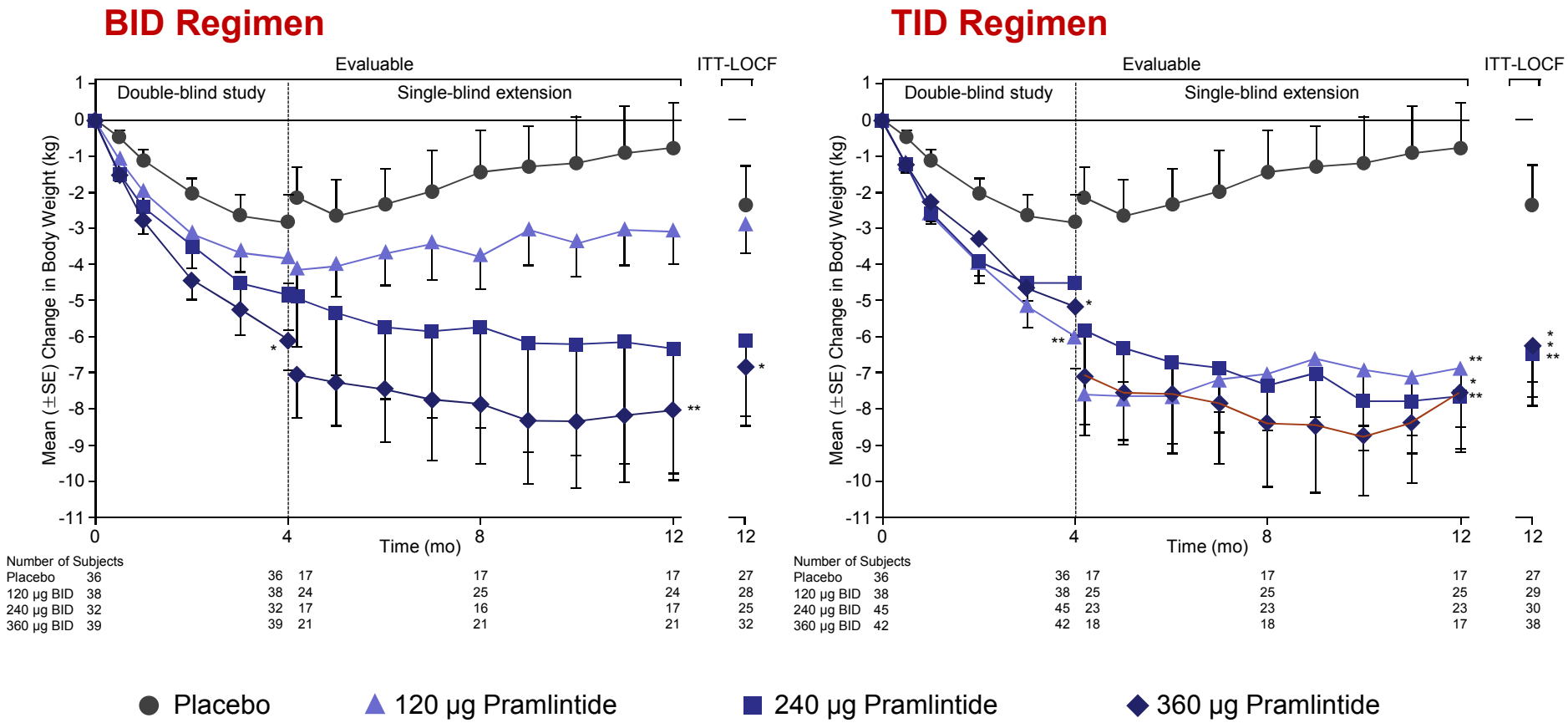
- An analog of amylin that overcomes the tendency of human amylin to:
  - Aggregate, form insoluble particles
  - Adhere to surfaces
- Pharmacokinetic and pharmacodynamic properties similar to human amylin



Adapted from Young A, et al. *Drug Dev Res* 1996; 37:231-248

Adapted from Westermark P, et al. *Proc Natl Acad Sci* 1990; 87: 5036-5040

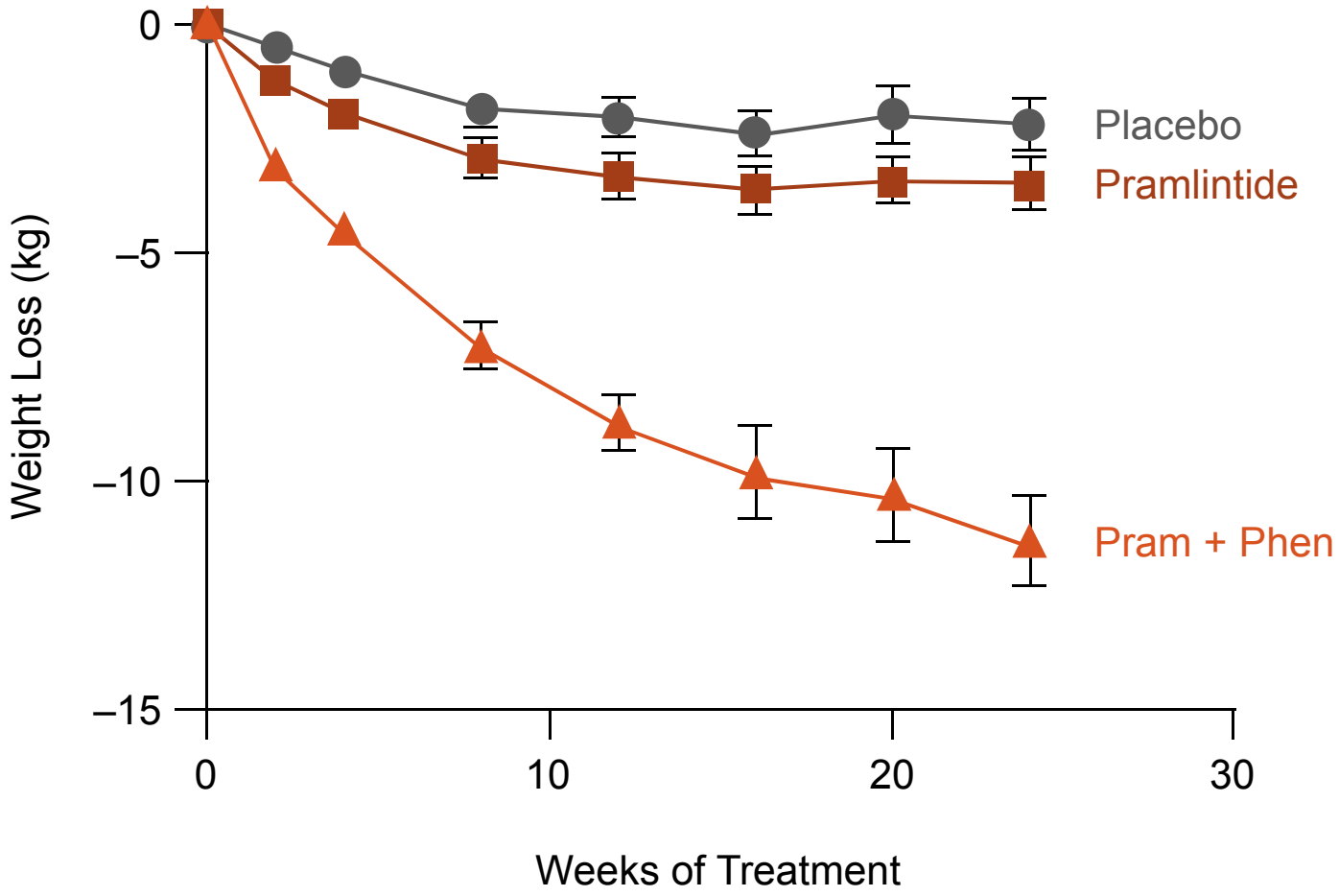
Pramlintide Produced Weight Loss



*P < 0.05 and **P < 0.01 for each pramlintide treatment group versus placebo.

Smith SR et al. *Diabetes Care.* 2008;31(9):1816–1823.

Combination of Pramlintide and Phentermine on Body Weight



Aronne L et al. *Obesity* (Silver Spring). 2010;18(9):1739–1746.

Emerging Anti-obesity Drugs & Drug Combinations

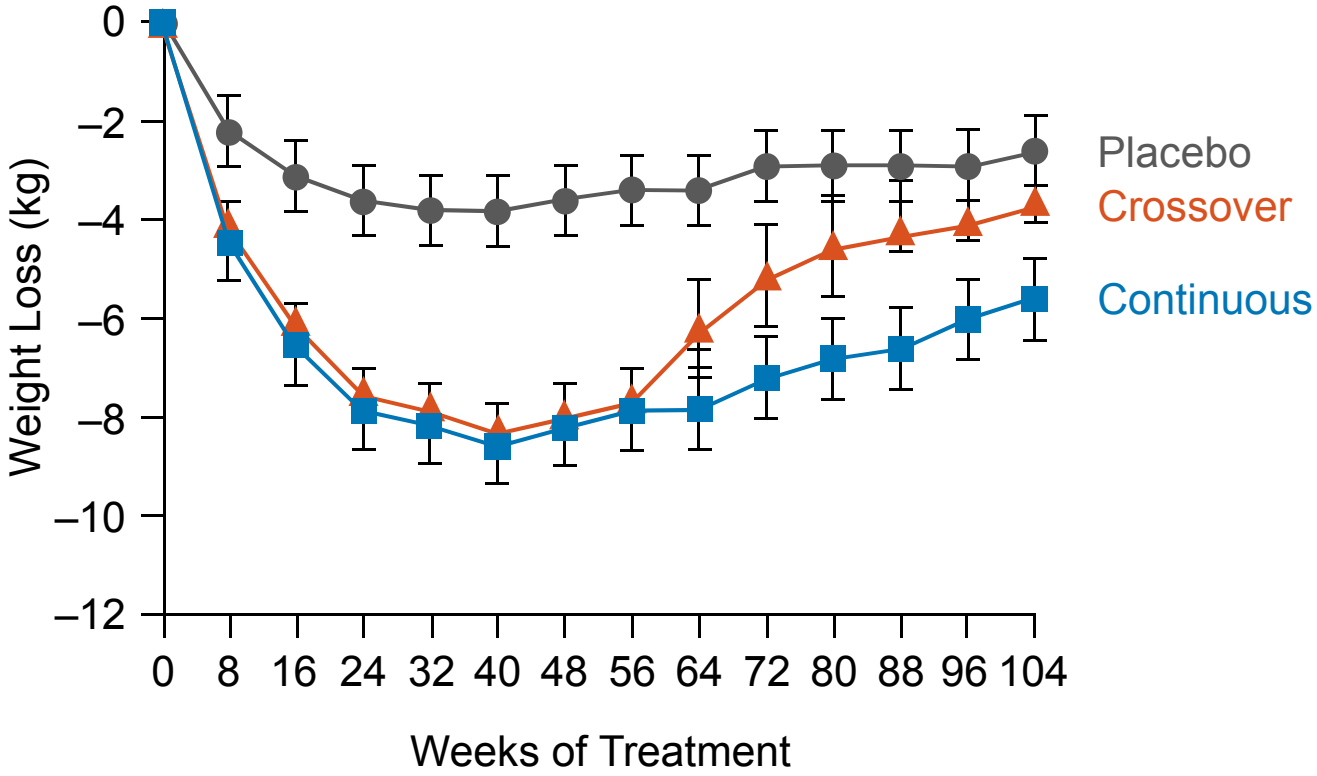
- **Lorcaserin**
  (selective 5-HT_{2C} receptor agonist)
- **Phentermine + Topiramate**
- **Naltrexone + Bupropion**

Lorcaserin (Belviq)
– Selective 5-HT_{2C} Receptor Agonist

- 5-HT_{2C} receptor activation of proopiomelanocortin (POMC) neurons results in α-MSH activation of melanocortin-4 receptors
- 5-HT_{2B} receptors are associated with valvulopathy
- Lorcaserin selectively targets the 5-HT_{2C} receptor
  - ~100-fold selectivity over 5-HT_{2B} receptor
  - ~15-fold selectivity over 5-HT_{2A} receptor
- Lorcaserin has not been found to be associated with valvulopathy

Smith SR, et al. NEJM. 2010;363:245-256.

Lorcaserin Produces Weight Loss
(Completers)



Placebo N = 684
Crossover N = 275
Continuous N = 564

Smith SR et al. *N Engl J Med.* 2010; 363(3):245–256.

Lorcaserin Did Not Increase the Rate of FDA Valvulopathy

Treatment	N	n (%)	*P*
Week 52			
Lorcaserin 10 mg BID	1278	**34 (2.66%)**	**.70[a]**
Placebo	1194	**28 (2.35%)**	
Week 104			
Lorcaserin/lorcaserin	500	13 (2.6%)	**.99[a]**
Lorcaserin/placebo	258	5 (**1.9%**)	
Placebo/placebo	627	17 (2.7%)	

N = number of evaluable echo pairs; n = number (%) with FDA valvulopathy

[a]Vs placebo with Fisher's exact test

Smith SR, et al. ADA 2009. Late-Breaking Abstract 96.

Lorcaserin: Adverse Events Reported by 5% or More

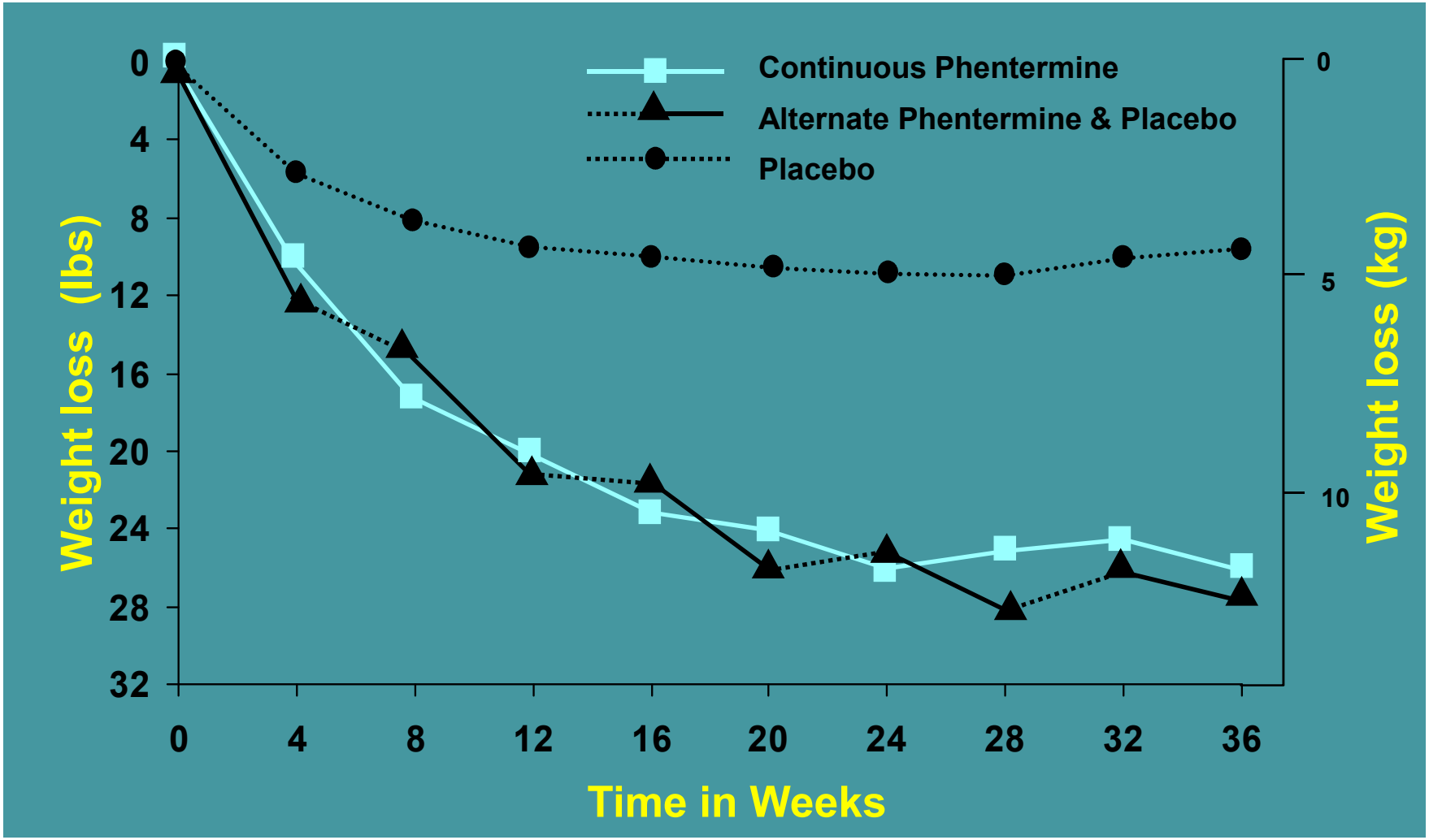
N (%)	Lorcaserin (N = 1593)	Placebo (N = 1584)
Headache	287 (18.0)	175 (11.0)
Dizziness	130 (8.2)	60 (3.8)
Nausea	119 (7.5)	85 (5.4)
Constipation	106 (6.7)	64 (4.0)
Fatigue	95 (6.0)	48 (3.0)
Dry mouth	83 (5.2)	37 (2.3)

Smith SR, et al. ADA 2009. Late-Breaking Abstract 96.

Topiramate + Phentermine (Qsymia)

- Phentermine stimulates NE (norepinephrine) release from hypothalamic neurons
- It is approved for obesity but only short term
- Topiramate approved for epilepsy and migraine
- It also produces weight loss
- Once-a-day, oral formulation of phentermine and controlled-release topiramate developed to reduce adverse side effects

Weight Loss with Continuous and Intermittent Phentermine

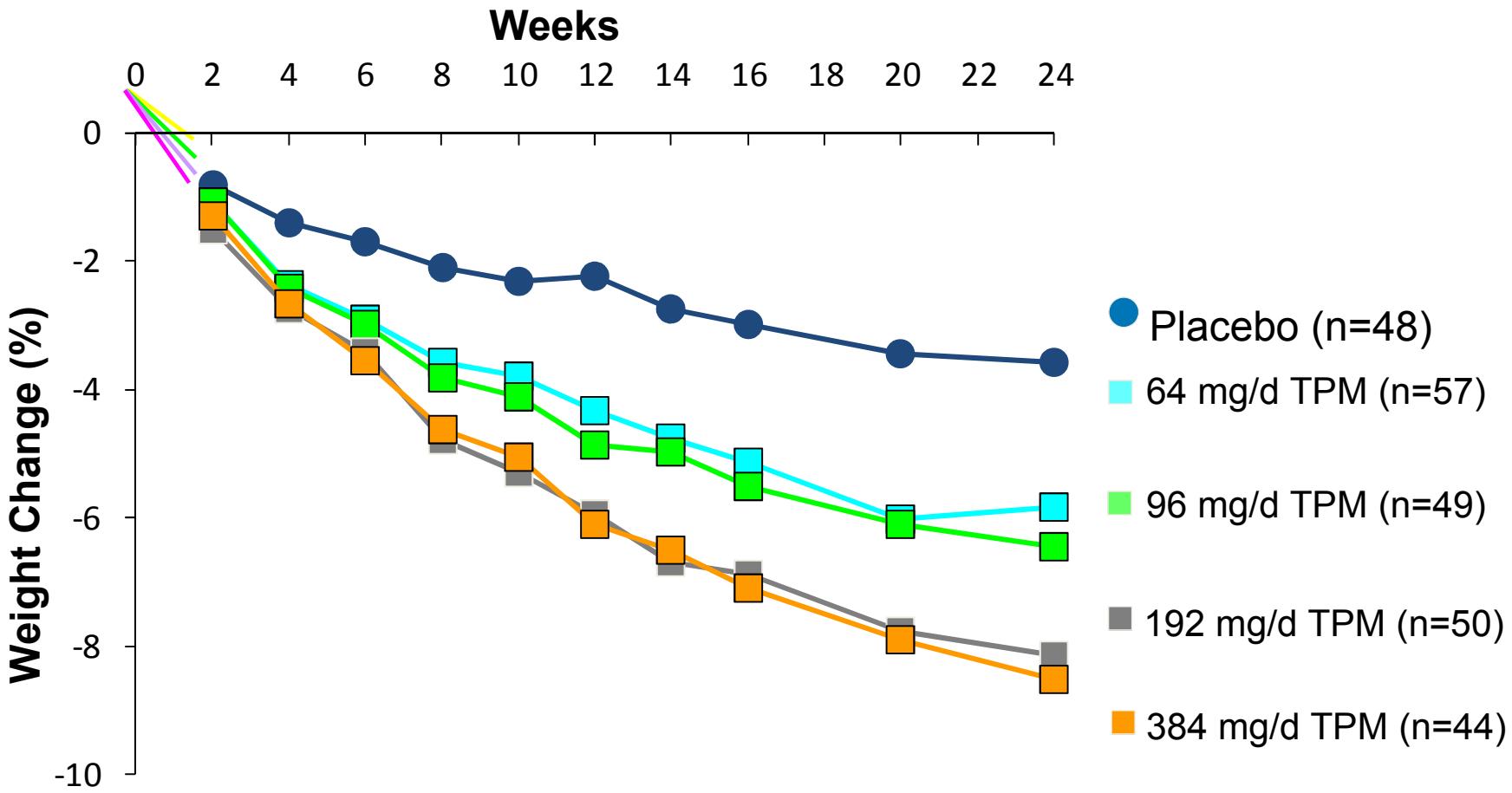


Munro JF et al BMJ 1968;1:352-4

Topiramate

- Antiepileptic and antimigraine
- Mechanism of action:
  - blockage of voltage-dependent sodium channels
  - augmentation of gamma-aminobutyrate acid activity at some subtypes of the GABA- A receptors
  - antagonism of AMPA/kainate subtype of the glutamate receptor
  - inhibition of the carbonic anhydrase enzyme, particularly isozymes II and IV .
- Side effects: Frequent CNS, paresthesias, change in taste

Topiramate : Percentage of Body Weight Change From Baseline to Week 24



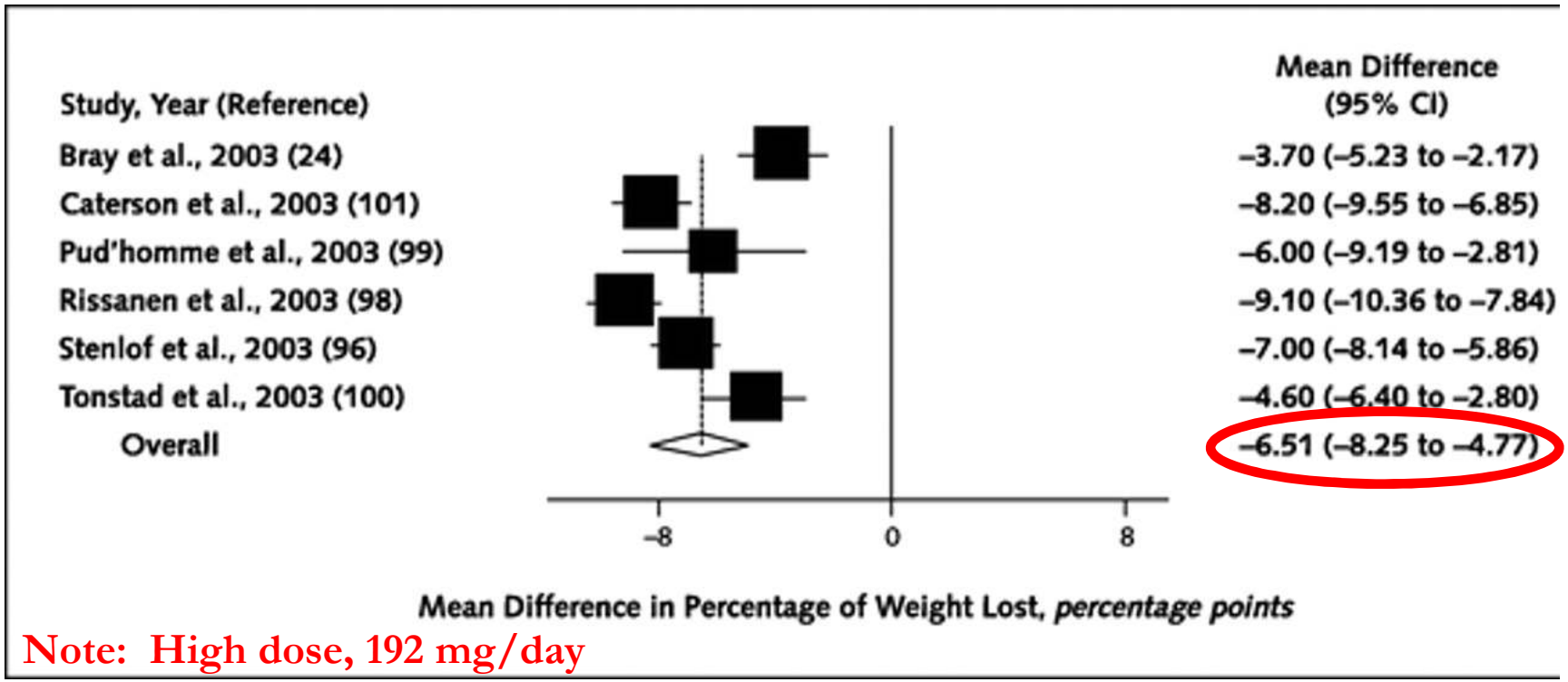
***P* < .05 from week 4**

TPM = topiramate

Bray G, et al. *Obes Res.* 2003;11:722-733.

Topiramate: Efficacy

Weight loss with topiramate versus placebo at 6 months

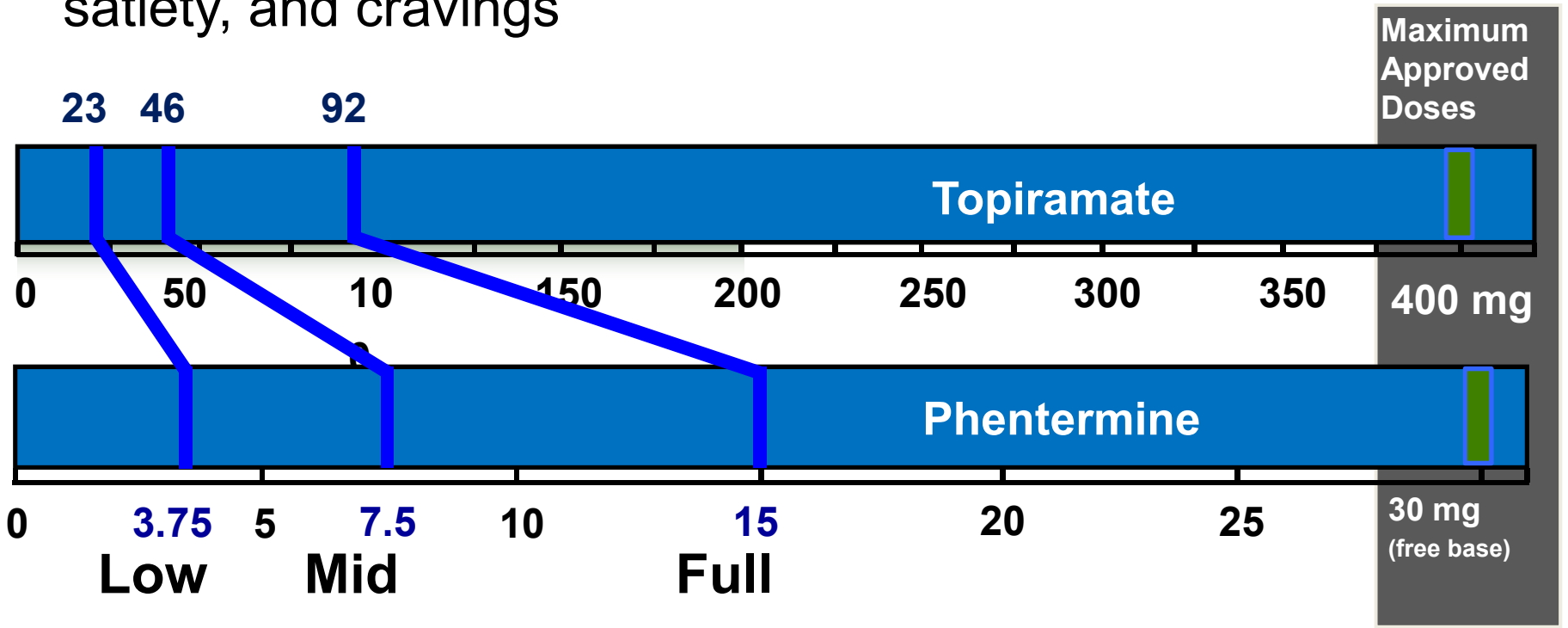


Note: High dose, 192 mg/day

Li, Z. et. al. Ann Intern Med 2005;142:532-546

Combination of Topiramate + Phentermine

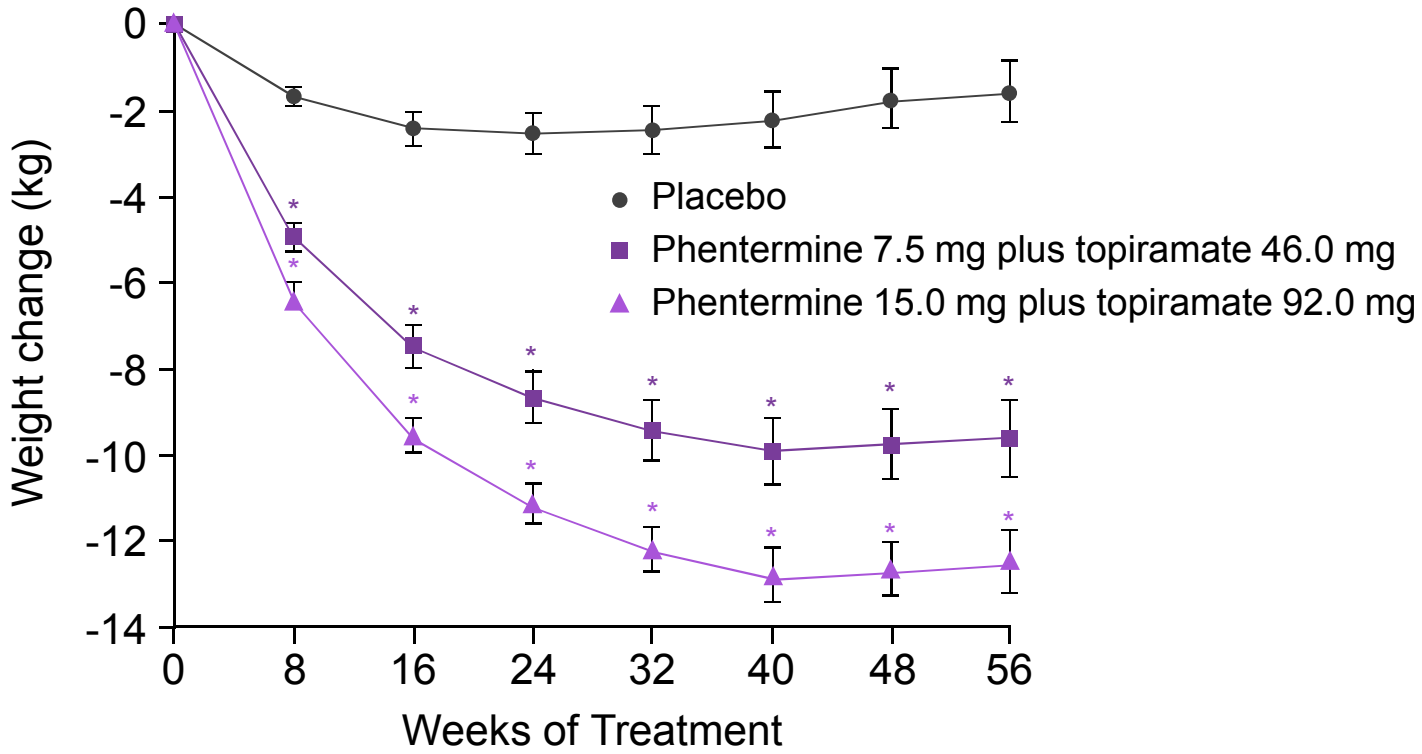
- Once-daily, oral, controlled-release formulation of low-dose phentermine and topiramate
- Specifically designed to affect normal eating patterns over 24 hours -- simultaneously addressing appetite, satiety, and cravings



Press release. Sept 9, 2009. Available at: http://ir.vivus.com/releasedetail.cfm?ReleaseID=407933

Accessed April 27, 2010.

Topiramate/Phentermine Produces Weight Loss (Completers)



Study completers								
Placebo	979	851	744	670	623	589	573	557
Phentermine 7.5 mg plus topiramate 46.0 mg	488	437	403	387	369	356	350	338
Phentermine 15.0 mg plus topiramate 92.0 mg	981	843	775	747	712	686	660	625

Gadde KM et al. *Lancet.* 2011;377(9774):1341–1352.

Topiramate + Phentermine : TEAEs > 5%

	EQUIP (N = 1264)			CONQUER (N = 2485)		
% of Patients (N = 3749)	Placebo	Low	Full	Placebo	Mid	Full
Dry mouth	3.7	6.7	17.0	2.4	13.5	20.8
Tingling	1.9	4.2	18.8	2.0	13.7	20.5
Constipation	6.8	7.9	14.1	5.9	15.1	17.4
Altered taste	1.0	1.3	8.4	1.1	7.4	10.4
Insomnia	4.9	5.0	7.8	4.7	5.8	10.3
Dizziness	4.1	2.9	5.7	3.1	7.2	10.0
Nausea	4.7	5.8	7.2	4.2	3.6	6.8
Blurred vision	3.1	6.3	4.5	3.6	4.0	6.0

Press release. Sept 9, 2009. Available at:
http://ir.vivus.com/releasedetail.cfm?ReleaseID=420114 Accessed April 27, 2010.

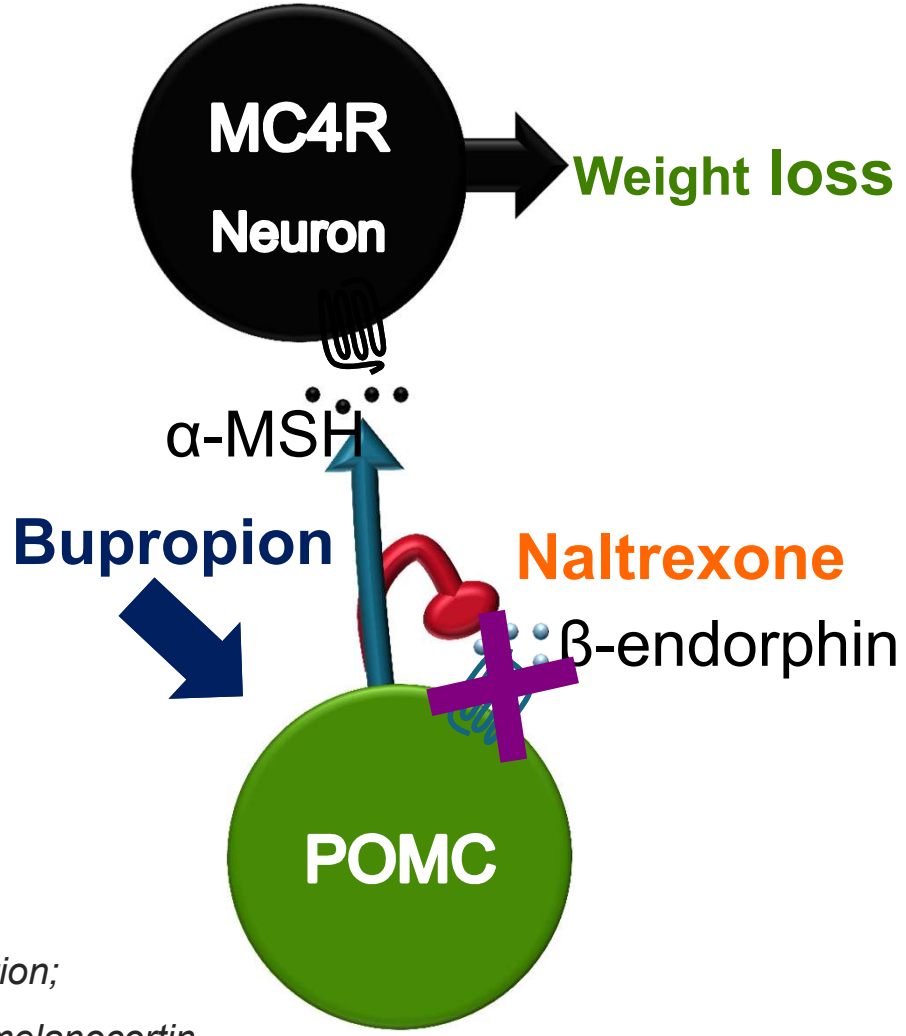
Bupropion and Naltrexone (Contrave)

- Bupropion is a norepinephrine reuptake inhibitor that is approved for smoking cessation and depression
- Naltrexone used to counteract opioid drugs
- 2011. 1. Failed to get US FDA approval due to concern about cardiovascular safety profile.

Naltrexone and Bupropion Rationally Designed Around MOA to Initiate and Sustain Weight Loss

Preclinical/clinical evidence for drug synergy

- Naltrexone/bupropion synergistic increase in POMC activity
- Synergistic decrease in food intake and body weight

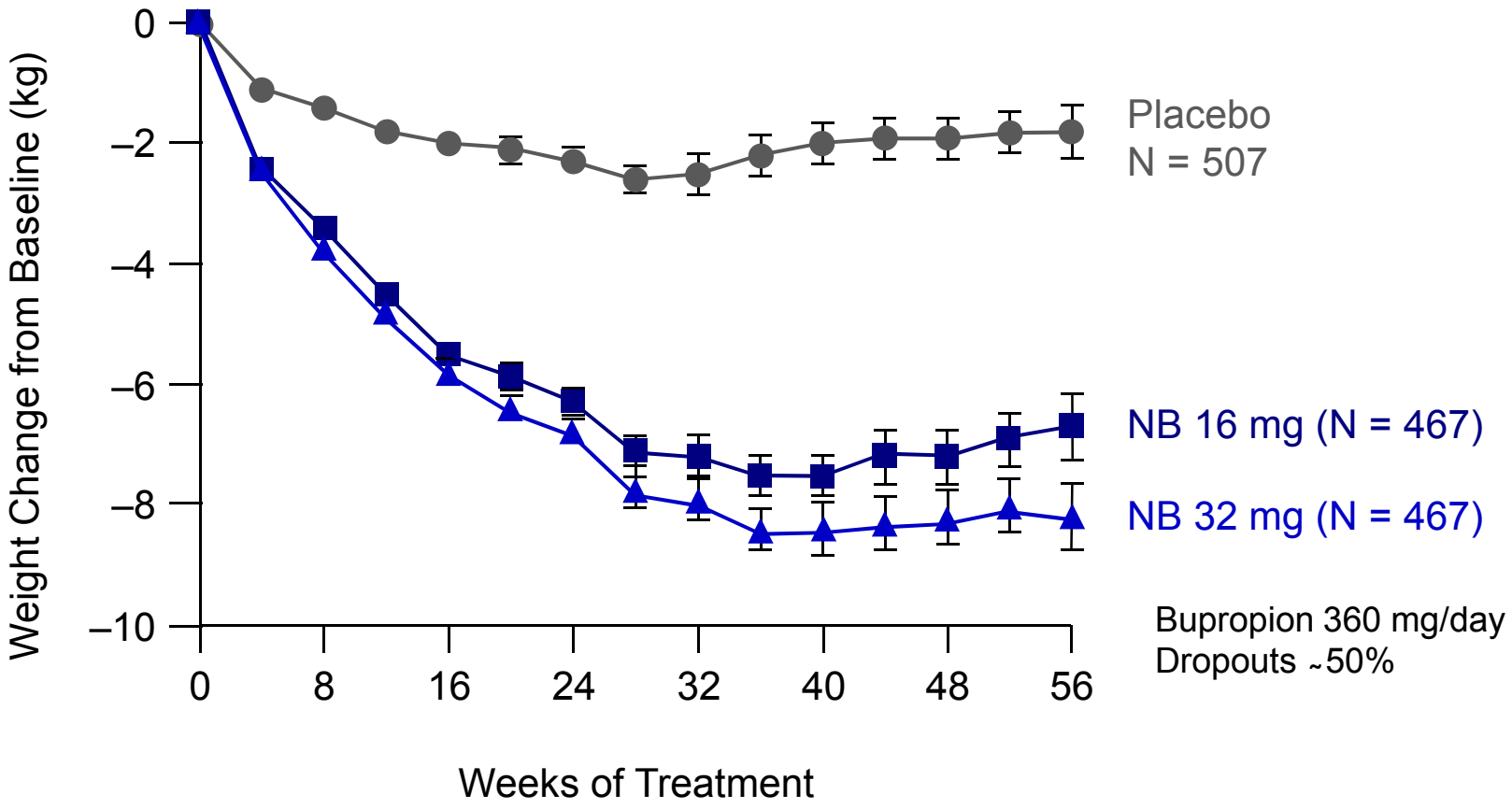


MC4R = melanocortin-4 receptor; MOA = mechanism of action;

MSH = melanocyte-stimulating hormone; POMC = proopiomelanocortin

Greenway FL, et al. *Obesity*. 2009;17:30-39.

Naltrexone-Bupropion Produces Weight Loss (Completers)

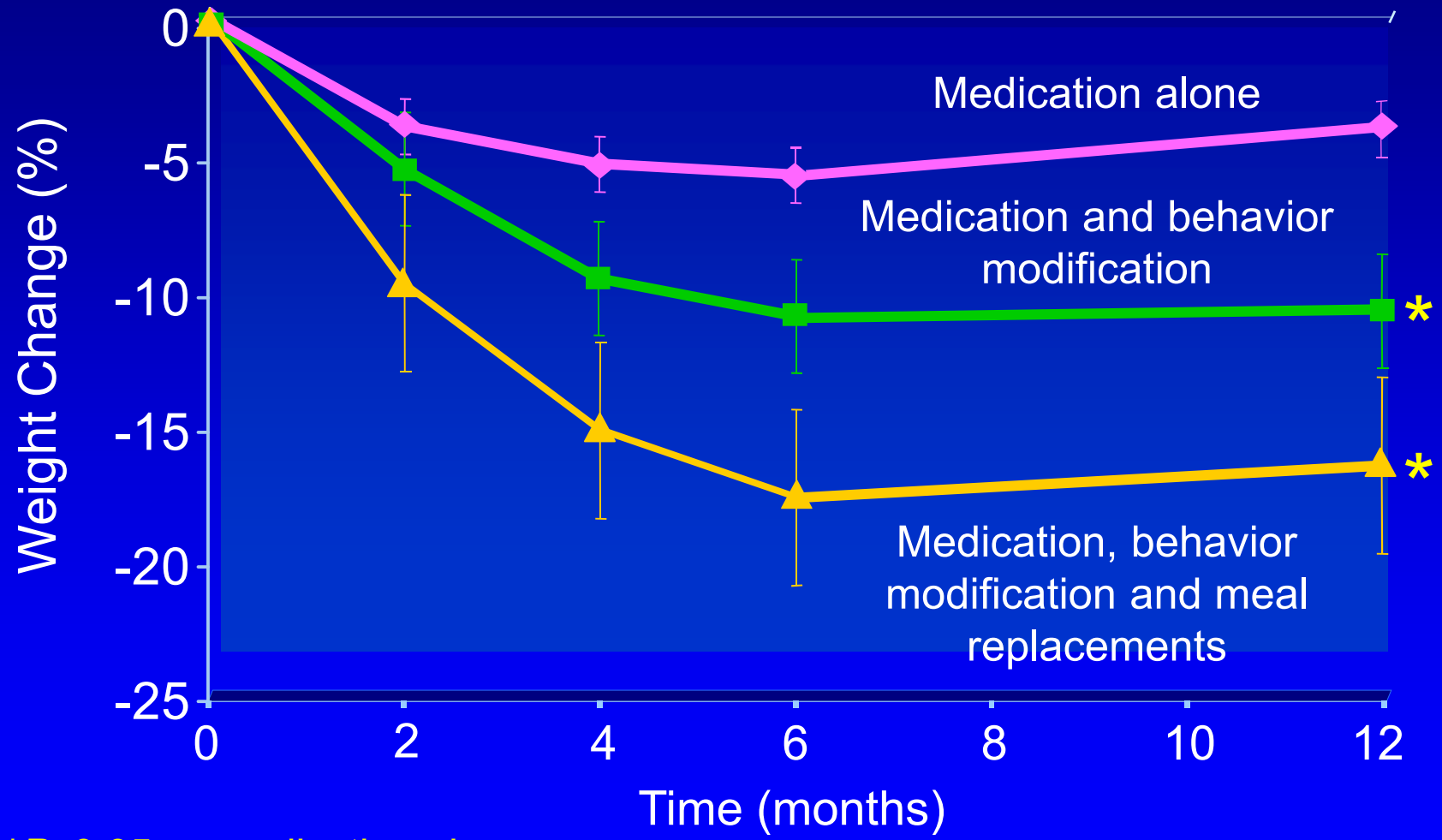


Greenway FL et al. *Lancet.* 2010;376(9741):595–605.

Naltrexone-Bupropion : Most Common Treatment-Emergent Adverse Events (TEAE)

	COR-I			COR-II	
	Placebo N=569	NB16 N=569	NB32 N=573	Placebo N=492	NB32/48 N=992
Nausea	5.3%	27.2%*	29.8%*	6.9%	29.2%*
Headache	9.3%	16.0%*	13.8%*	8.7%	17.5%*
Constipation	5.6%	15.8%*	15.7%*	7.1%	19.1%*
Dizziness	2.6%	7.7%*	9.4%*	3.7%	6.9%*
Vomiting	2.5%	6.3%*	9.8%*	2.0%	8.5%*
Dry mouth	1.9%	7.4%*	7.5%*	2.6%	9.1%*
Patients discontinuing due to a TEAE	**9.8%**	**21.4%***	**19.5%***	**13.8%**	**24.3%***
Nausea	0.4%	4.6%*	6.3%*	0.2%	6.0%*
Dizziness	0.5%	2.3%*	1.2%	0.2%	1.0%
Headache	0.7%	1.6%	0.9%	0.8%	2.6%*
Vomiting	0.2%	0.7%	0.9%	0%	0.8%
Insomnia	0.2%	0.7%	0.7%	1.0%	0.8%

Additive Effects of Behavior and Diet Therapy with Pharmacotherapy for Obesity



*$P<0.05$ vs medication alone.

Wadden et al. *Arch Intern Med* 2001;161:218.

The Washington Post

TUESDAY, MAY 7, 1996

HEALTH

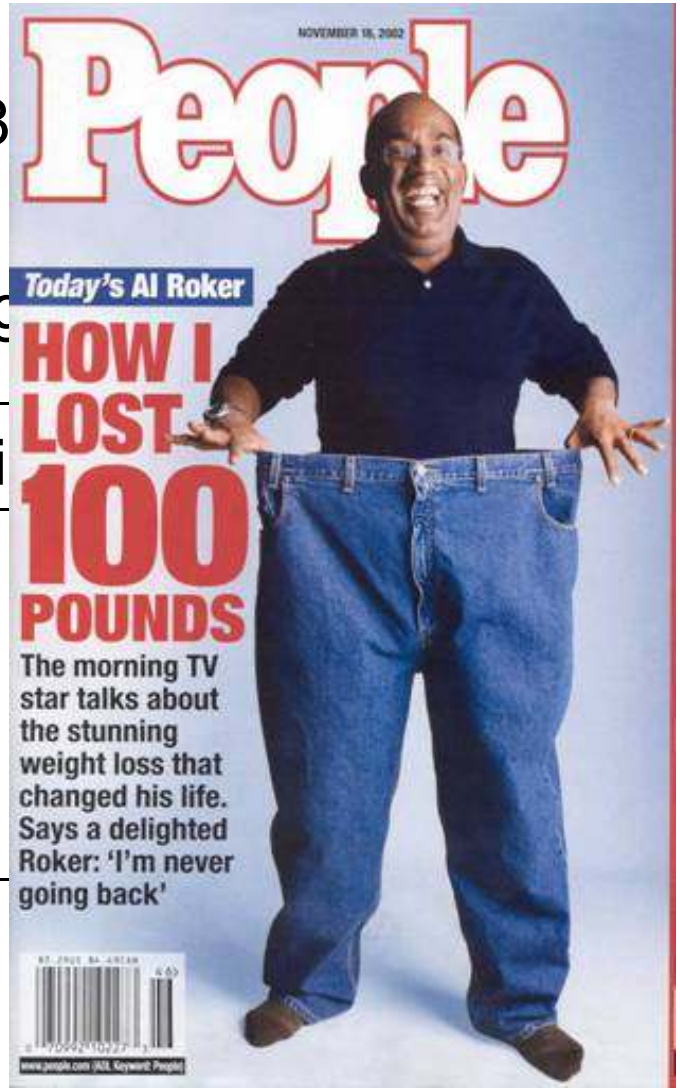
Sorry, Cathy, The New Diet Drug Won't Work All By Itself

(You Still Have to Exercise and Watch What You Eat)

What is the Desirable Weight Loss ?

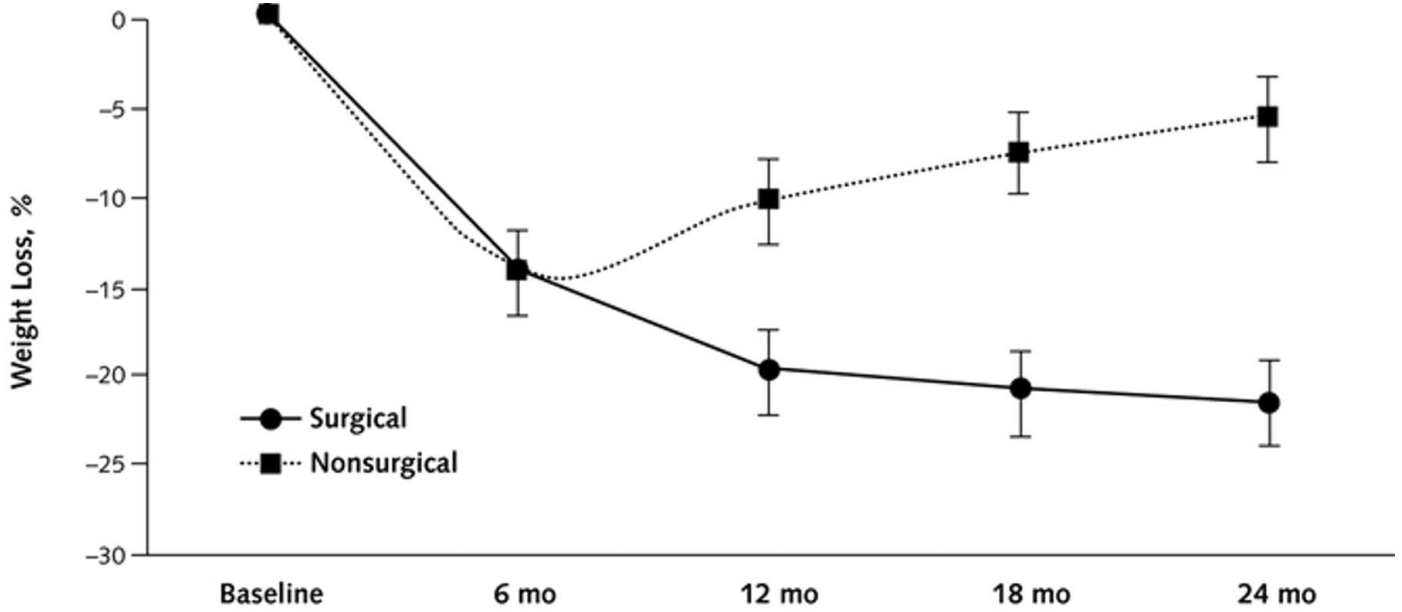
- Study design
  - 60 obese women, age 40 + 8
  - BMI 36.3 + 4.3 kg/m2
- Subjects questioned about their g

Defined Weights	% Reducti
Dream	38%
Happy	31%
Acceptable	25%
Disappointed	17%



Foster GD, et al. J Consult Clin Psychol 1997;65:79-85.

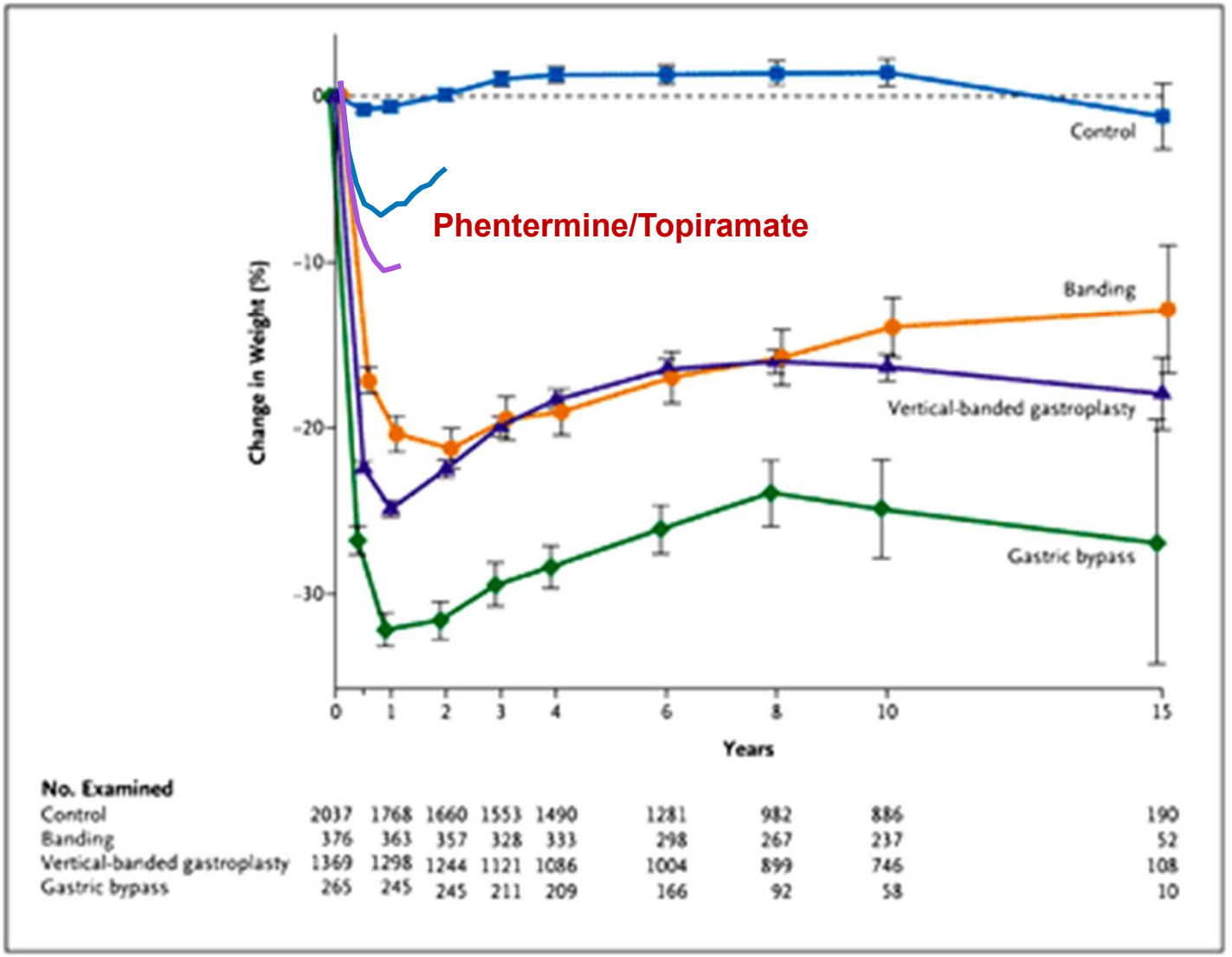
Mean % of Weight Loss in Patients with BMI 30-35



- Statistically significant improvement in metabolic syndrome in surgical group: 35% of pts in both groups initially, 24% of pts in non-surgical group and 3% of pts in surgical group at 2 yrs
- Surgical group adverse events: 1 port site infection, 4 prolapse of posterior gastric wall, 1 cholecystitis
- Non-surgical group adverse events: 1 diet intolerance, 8 orlistat intolerance, 4 cholecystitis

O'Brien, P. E. et. al. Ann Intern Med 2006;144:625-633

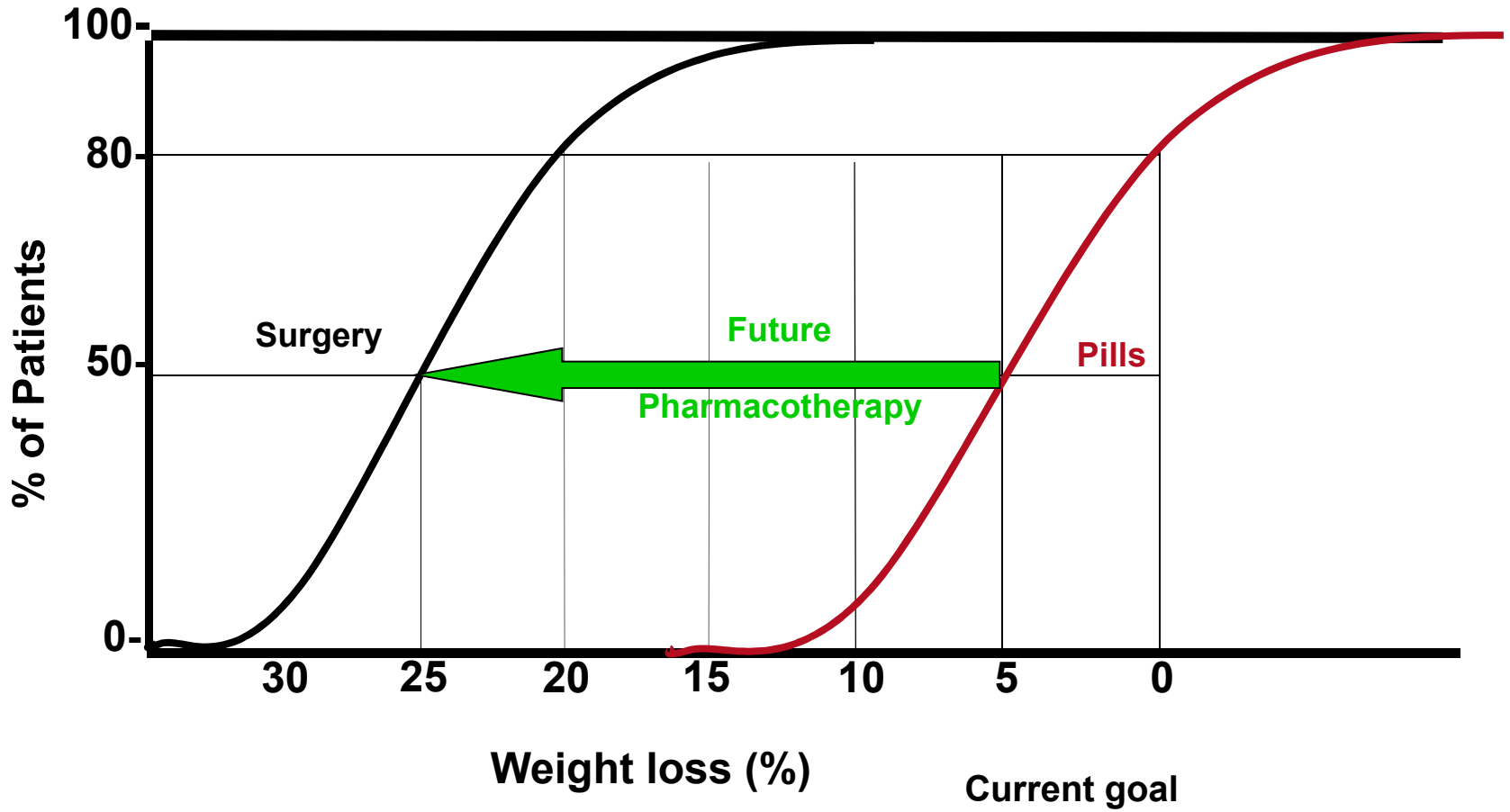
Percent Weight Loss in SOS



No. Examined									
Control	2037	1768	1660	1553	1490	1281	982	886	190
Banding	376	363	357	328	333	298	267	237	52
Vertical-banded gastroplasty	1369	1298	1244	1121	1086	1004	899	746	108
Gastric bypass	265	245	245	211	209	166	92	58	10

Sjostrom et al. NEJM 2007

Obesity: Unmet Medical Need in Metabolic Disease Space



Future Drug Targets