

American Association of Clinical Endocrinologists
Hynes Convention Center
Boston, Massachusetts
May 16, 2018

Detours in the Discovery of Drugs to Treat Obesity

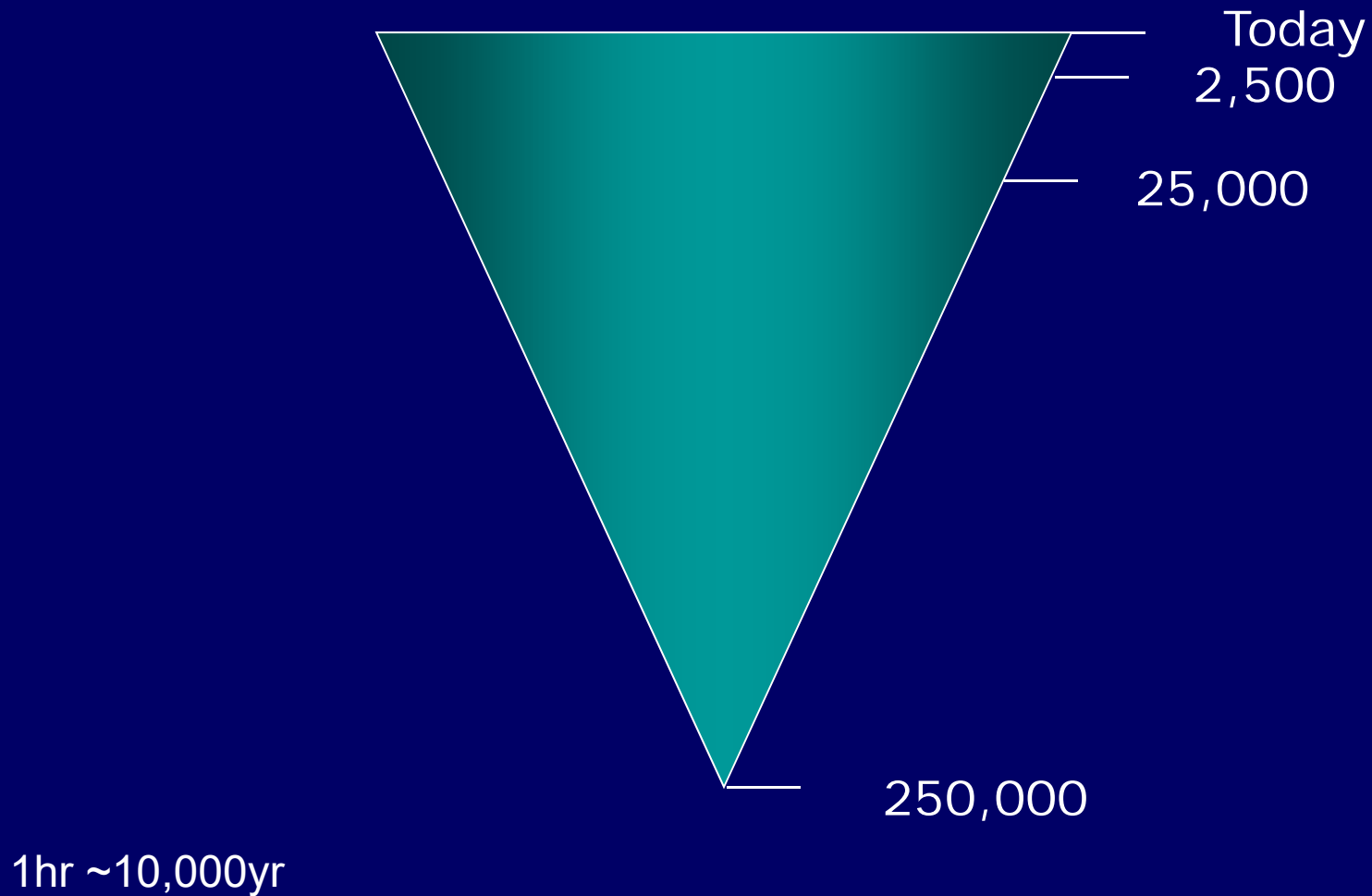


George A. Bray, MD, MACP
Boyd Professor Emeritus
Pennington Center/LSU
Baton Rouge, Louisiana

Objectives

- Describe the expansion of knowledge about treating obesity
- Identify unintended consequences of drug therapy for obesity
 - Rainbow Pills
 - Amphetamine and its congeners
 - Anti-depressants & other neural drugs
 - Peptides

Knowledge Has Expanded Nearly Logarithmically



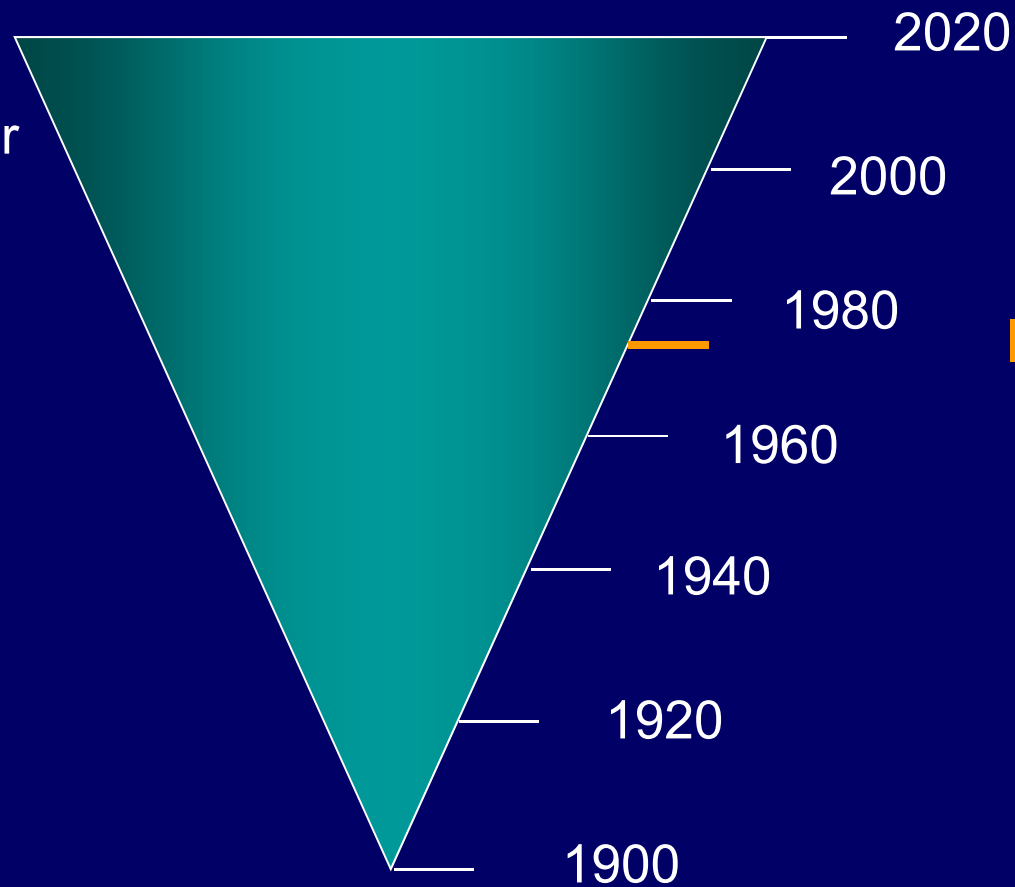
The Last 30+ Seconds

Historical Events

Leptin
Doubly-labeled Water
Obesity Epidemic
Lifestyle therapy
Gastric Bypass
Metabolic chambers
Central Adiposity
World War II

World War I

Cushing's Syndrome
Babinski-Frohlich



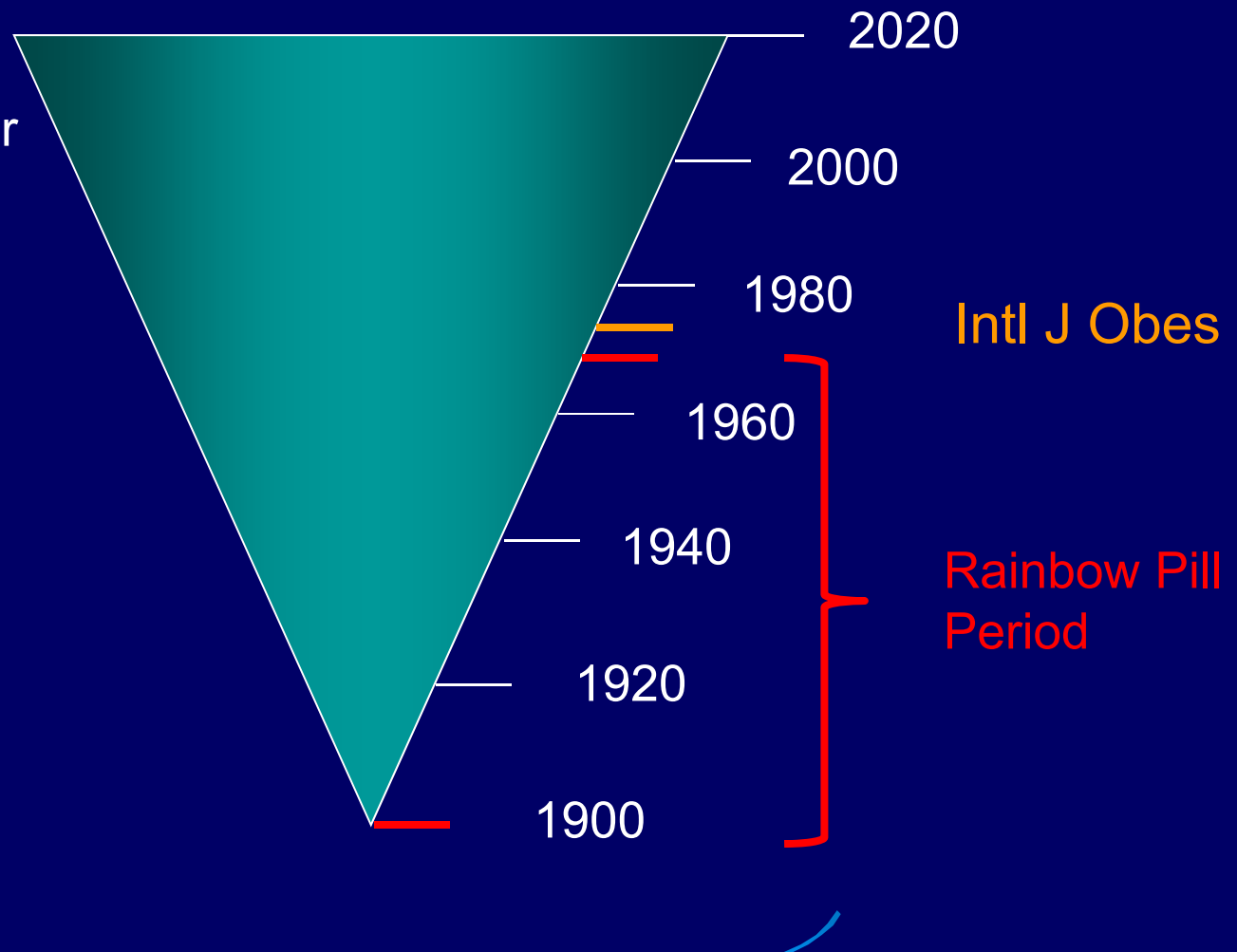
30 sec ~100yr

The Last 30+ Seconds

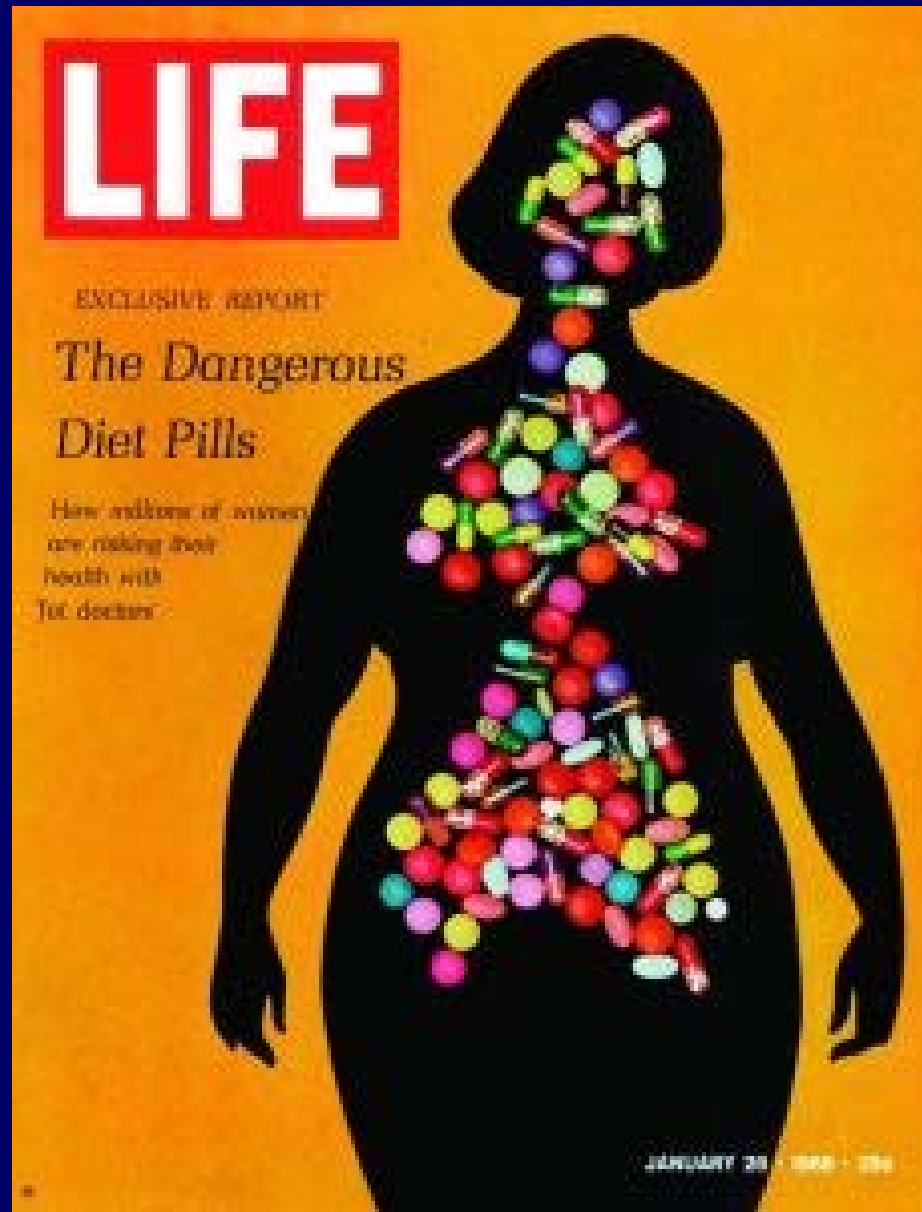
Historical Events

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Rainbow Pills – 1892-1967



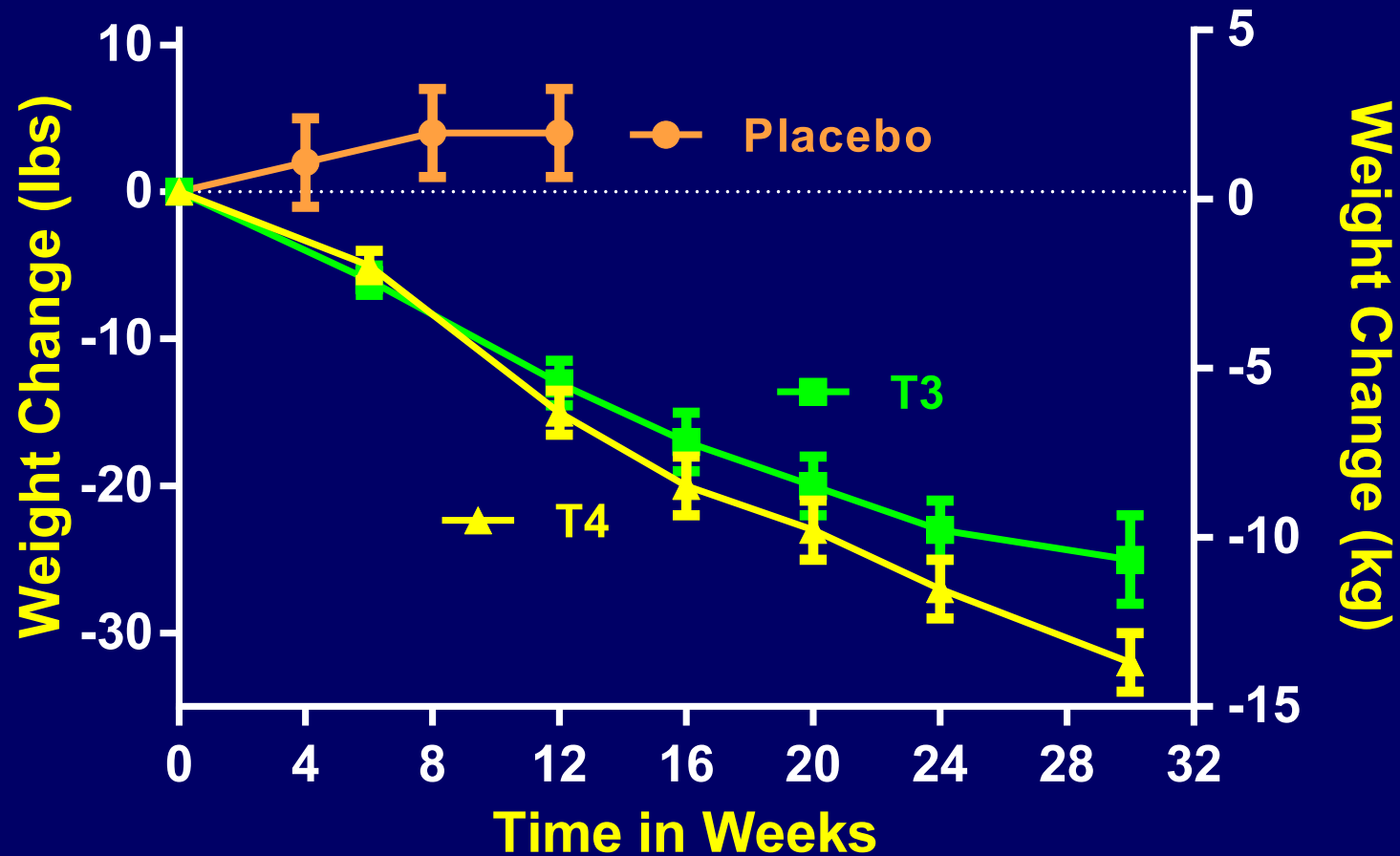
Rainbow Pill Period – 1892-1967

- Thyroid hormone
- Dinitrophenol
- Digitalis
- Diuretics
- Amphetamine

Thyroid Hormone

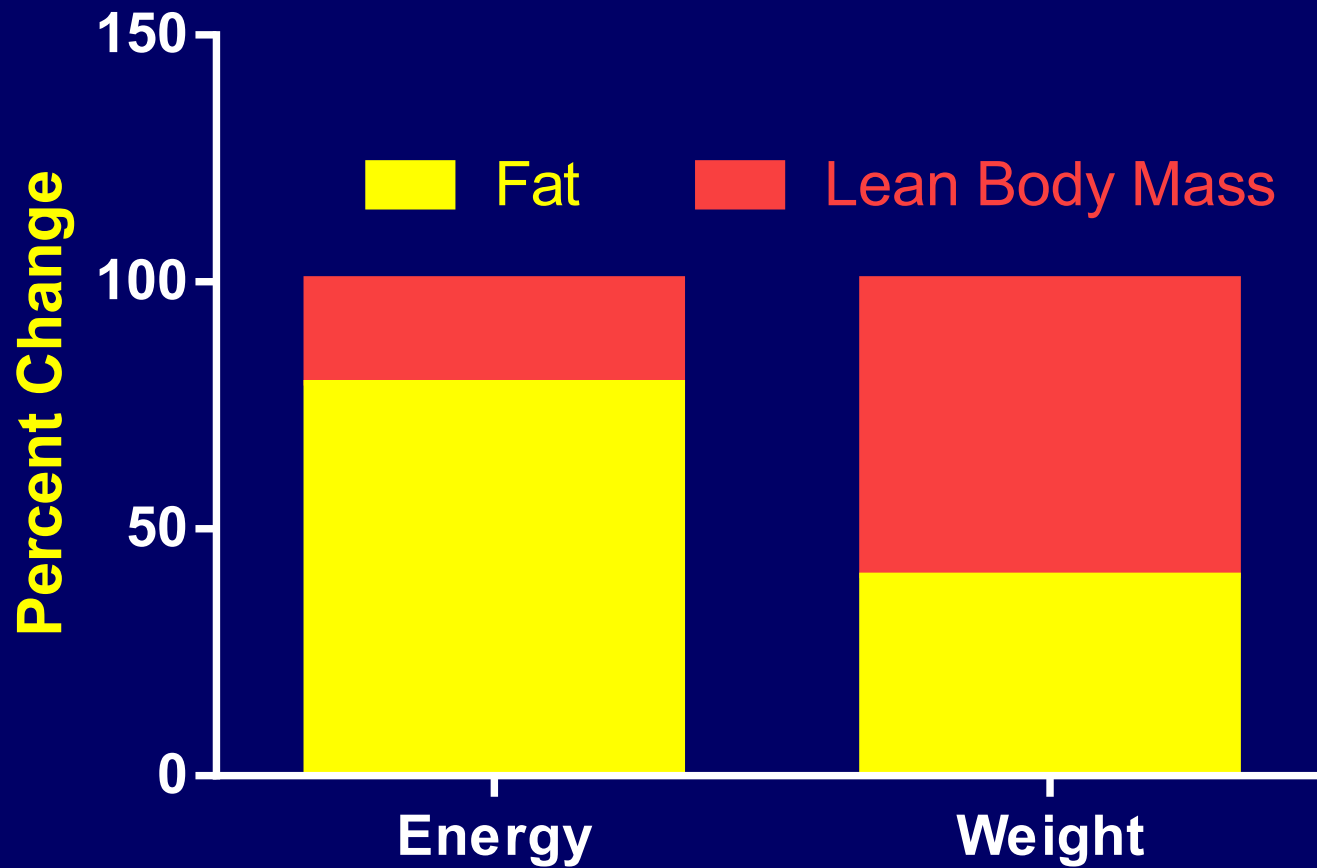
- First used in 1892 shortly after thyroid extract was isolated
- Thyroid extract, thyroxine and triiodothyronine cause weight loss by increasing metabolic rate
- The weight loss contains a more than desirable fraction of lean body mass.

Effect of Triiodothyroine and Thyroxine on Body Weight



Bray, GA. *Obesity in Perspective* 1975

Effect of Triiodothyronine on Weight and Fat Loss

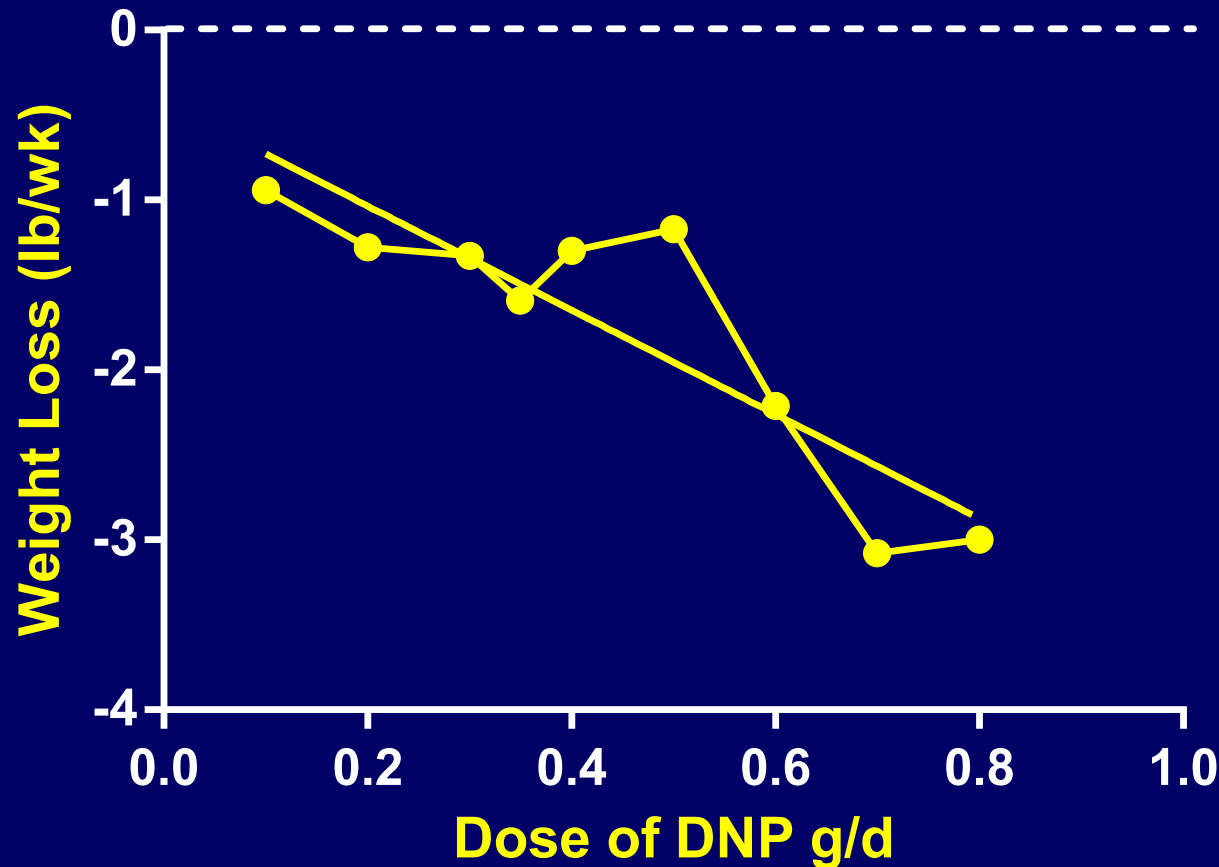


Bray, GA. *Obesity in Perspective* 1975

Dinitrophenol

- Dinitrophenol (DNP) is a product of the organic chemical industry.
- It entered clinical use following the observation that munition workers handling this compound lost weight
- DNP produces weight loss by uncoupling oxidative phosphorylation
- It also produces cataracts, neuropathy and death

Dinitrophenol Produces Dose-Related Weight Loss



Dinitrophenol raises metabolic rate but it also produces cataracts, causes neuroapthy and death

Digitalis and Diuretics

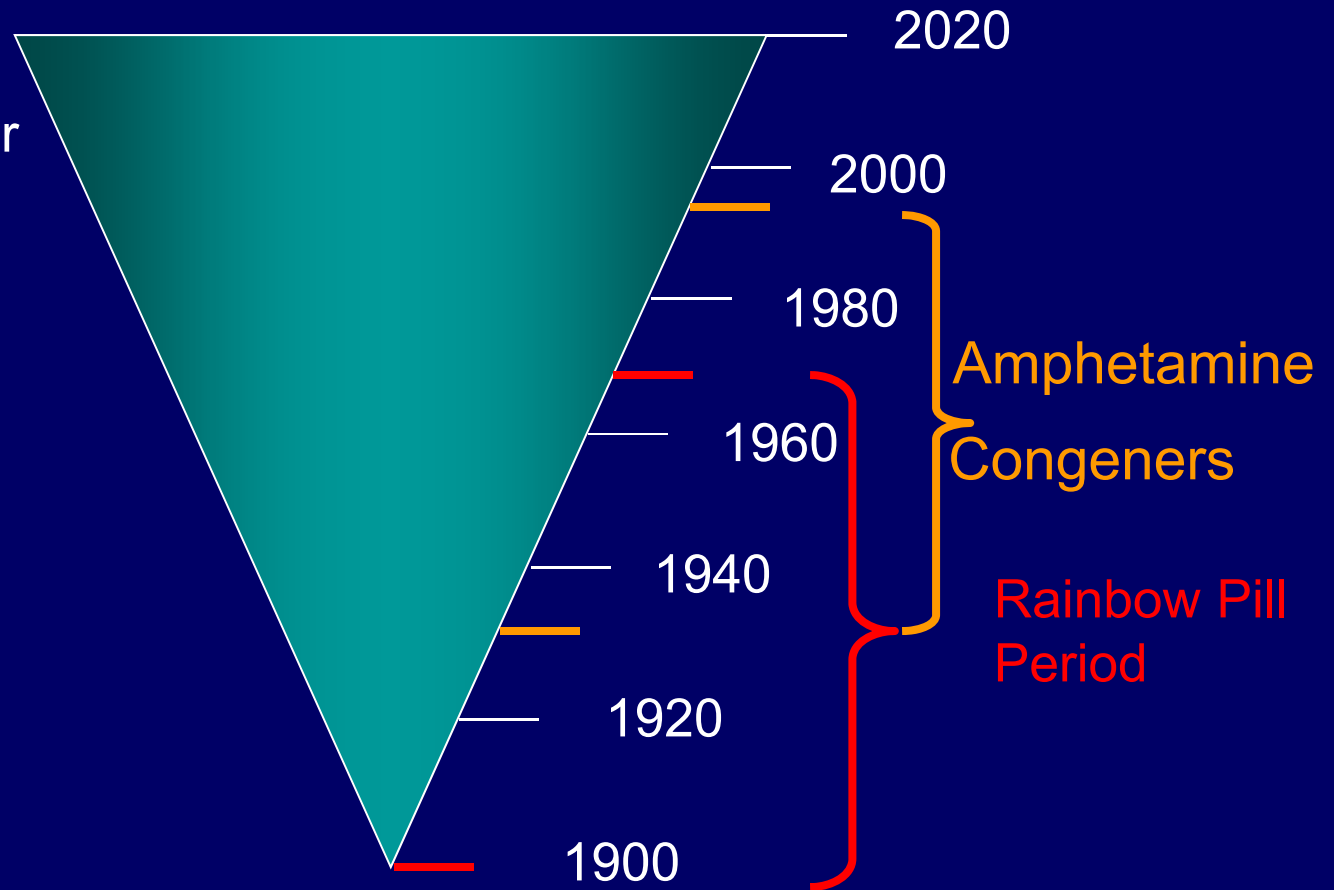
- Digitalis came into use as a treatment for the patient with obesity because “nausea” and weight loss are side effects of the drug which has a narrow window of tolerance.
- Diuretics increase fluid loss and thus weight loss, even though there is no loss of fat.

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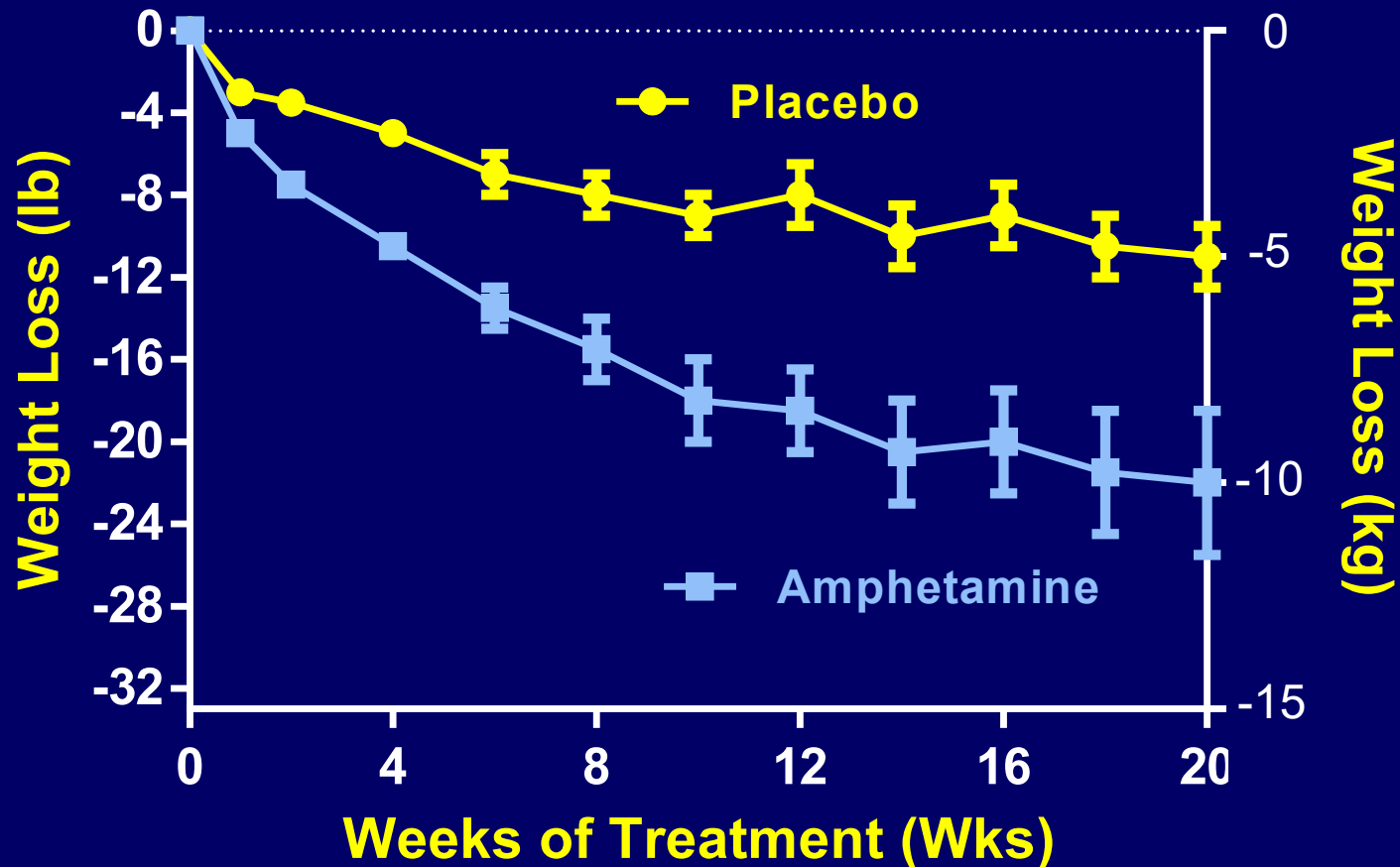
World War I
Cushing's Syndrome
Babinski-Frohlich



Amphetamine and Its Congeners

- Amphetamine, a beta-phenethylamine, was synthesized in 1887.
- It was used to combat narcosis in the 1930s because it kept people awake. Weight loss was noted in these trials
- In 1937 Leskes and Meyerson did a “clinical trial” on amphetamine and published it in the NEJM.
- Addiction noted, particularly with methamphetamine.
- Many other beta-phenethylamines synthesized including phentermine and fenfluramine

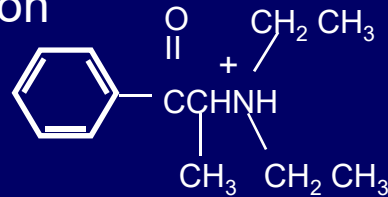
Weight Loss with Amphetamine vs Placebo



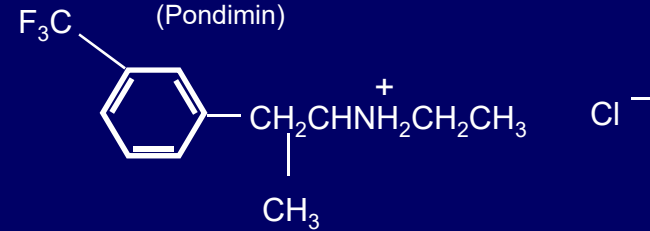
Bray, GA. *The Obese Patient* Philadelphia, W.B. Saunders, 1976

Some Amphetamine Congeners

Diethylpropion
(Tenuate, Tepanil)



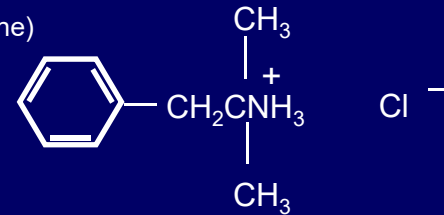
Fenfluramine
(Pondimin)



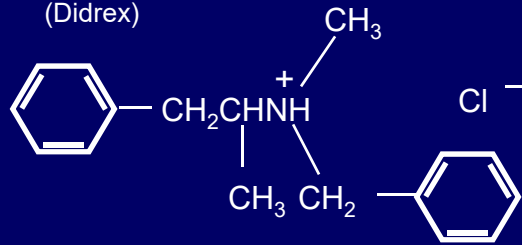
Mazindol
(Mazanor, Sanorex)



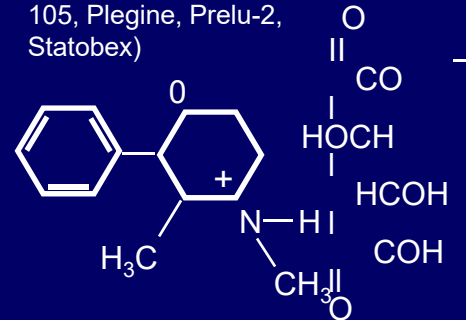
Phentermine
(Adipex-P, Fastin, Obermine)



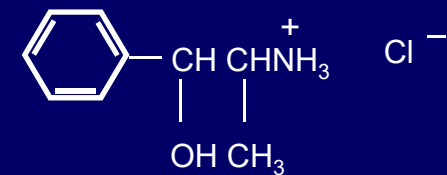
Benzphetamine
(Didrex)



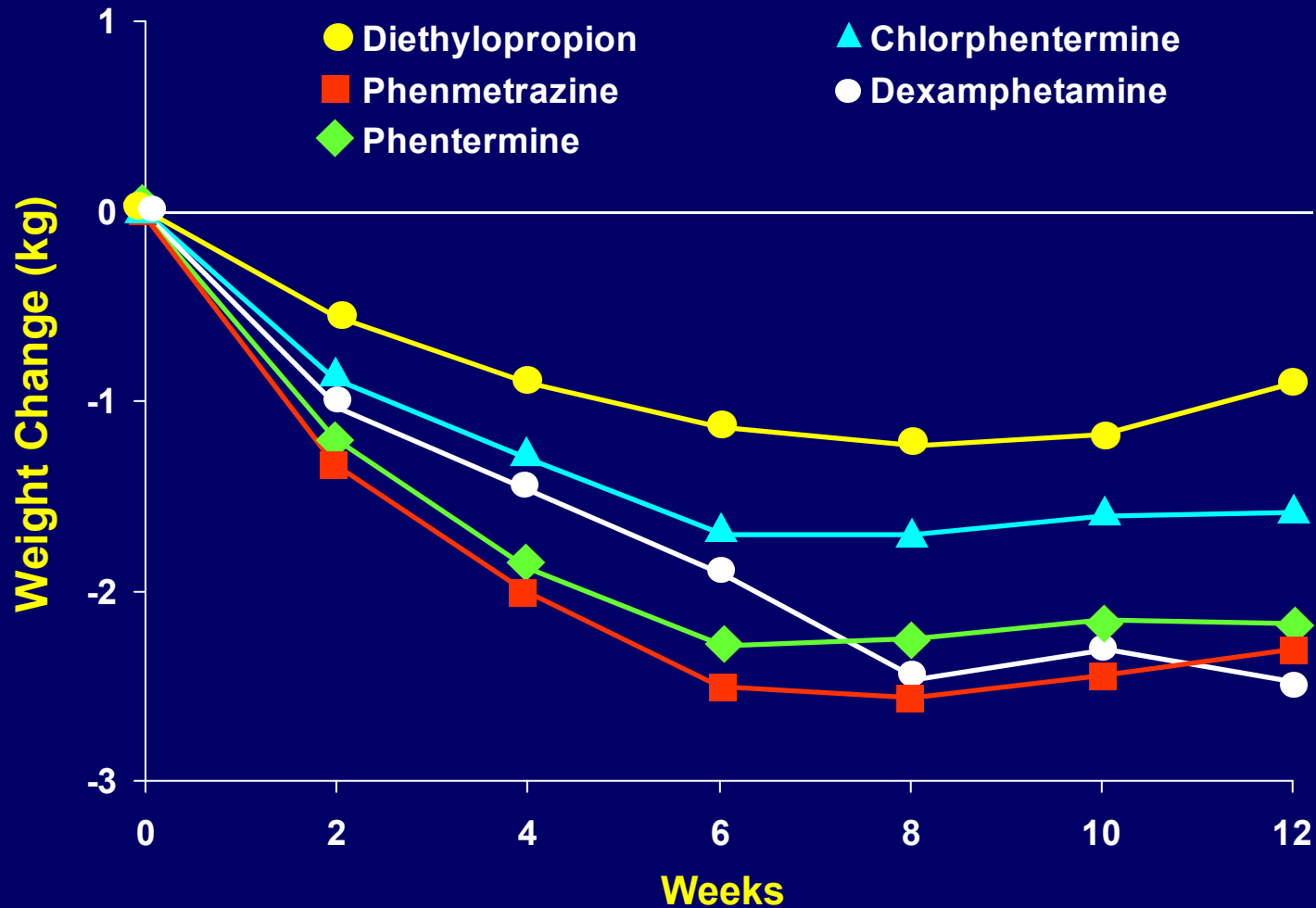
Phendimetrazine
(Adipost, Bontril PDM, Melfiat-105, Plegine, Prelu-2, Statobex)



Phenylpropanolamine
(Acutrim, Dexatrim)

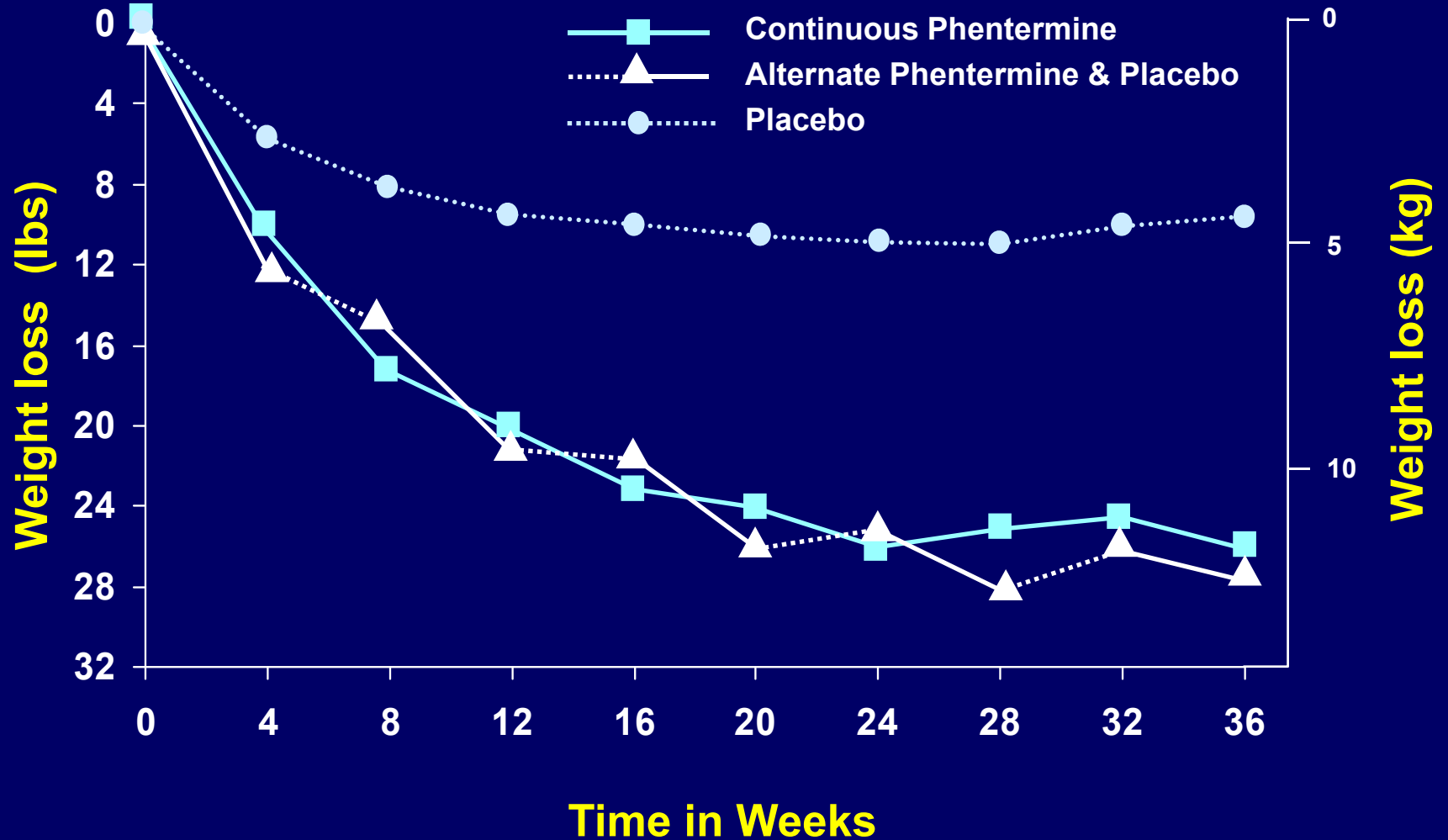


Weight Loss with Various Amphetamine Congeners



Munro J.F. *The Treatment of Obesity*, Lancaster, England: MTP Press, Ltd, 1979

Phentermine: A Noradrenergic Drug

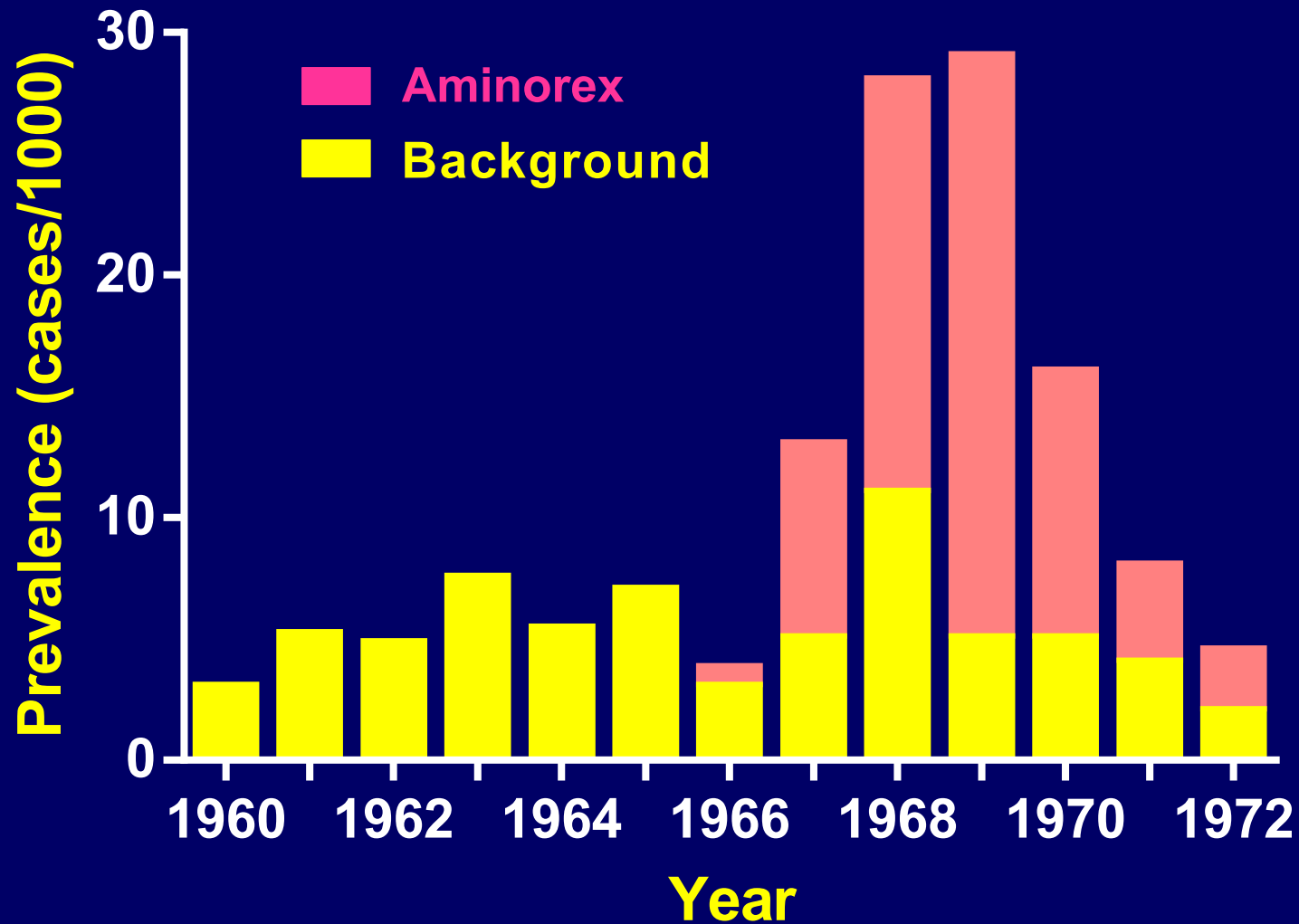


Munro JF Br Med J. 1968 Feb 10;1(5588):352-4.

Aminorex a Noradrenergic Drug & Primary Pulmonary Hypertension

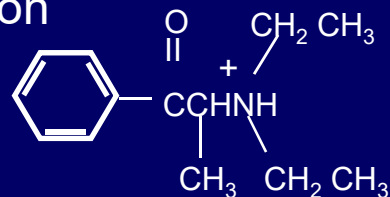
- An outbreak of primary pulmonary hypertension in Austria and Switzerland was noted shortly after the introduction of a new amphetamine congener in 1968 called aminorex
- A retrospective analysis showed that this drug was responsible for most of the cases of primary pulmonary hypertension in the years 1968-1972
- Fenfluramine and other sympathomimetics also increase the risk of primary pulmonary hypertension, but to a much smaller degree

Aminorex Epidemic of Iatrogenic Primary Pulmonary Hypertension

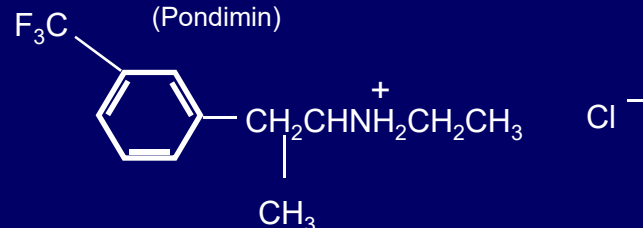


Some Amphetamine Congeners

Diethylpropion
(Tenuate, Tepanil)



Fenfluramine
(Pondimin)

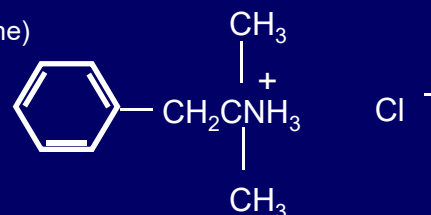


Mazindol
(Mazanor, Sanorex)



Phentermine

(Adipex-P, Fastin, Obermine)



Benzphetamine
(Didrex)



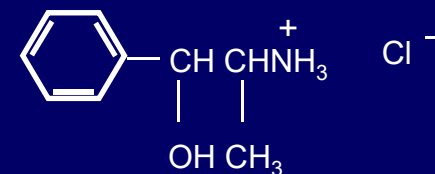
Phendimetrazine

(Adipost, Bontril PDM, Melfiat-105, Plegine, Prelu-2, Statobex)

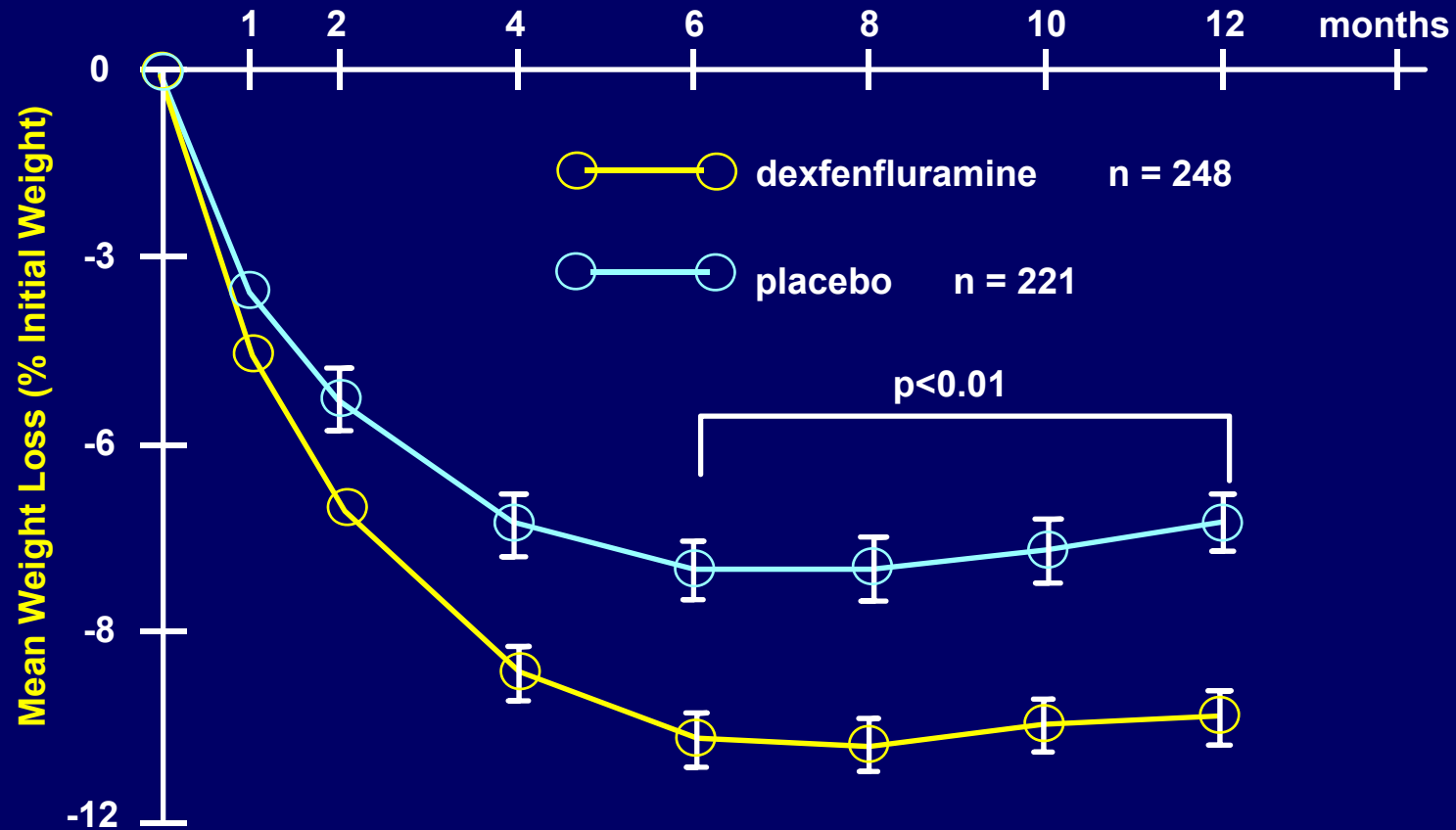


Phenylpropanolamine

(Acutrim, Dexatrim)

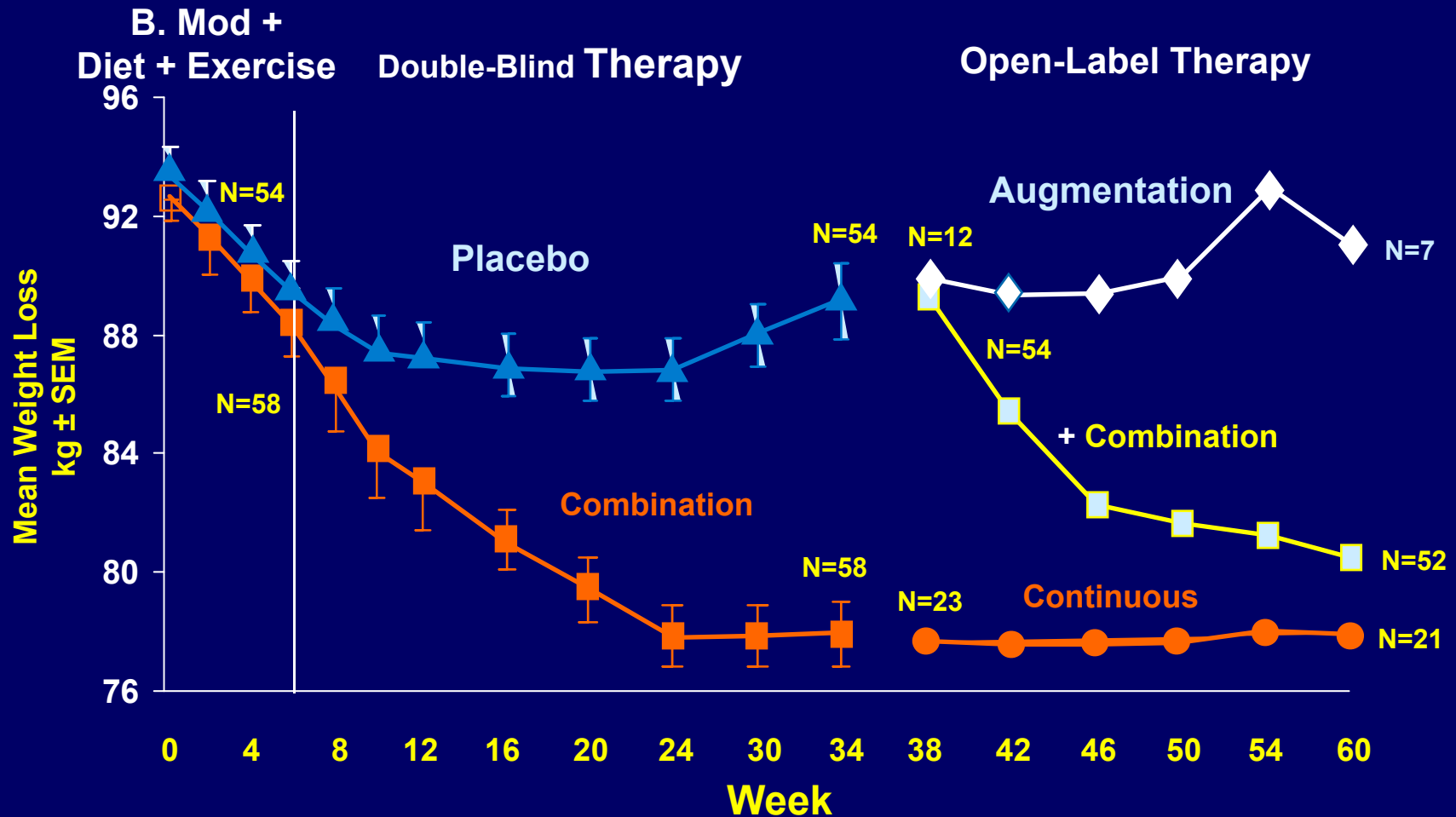


INDEX Study Completers



Treatment X Time Interaction To T12 $p < 0.001$ / T6 T12 $p < 0.01$

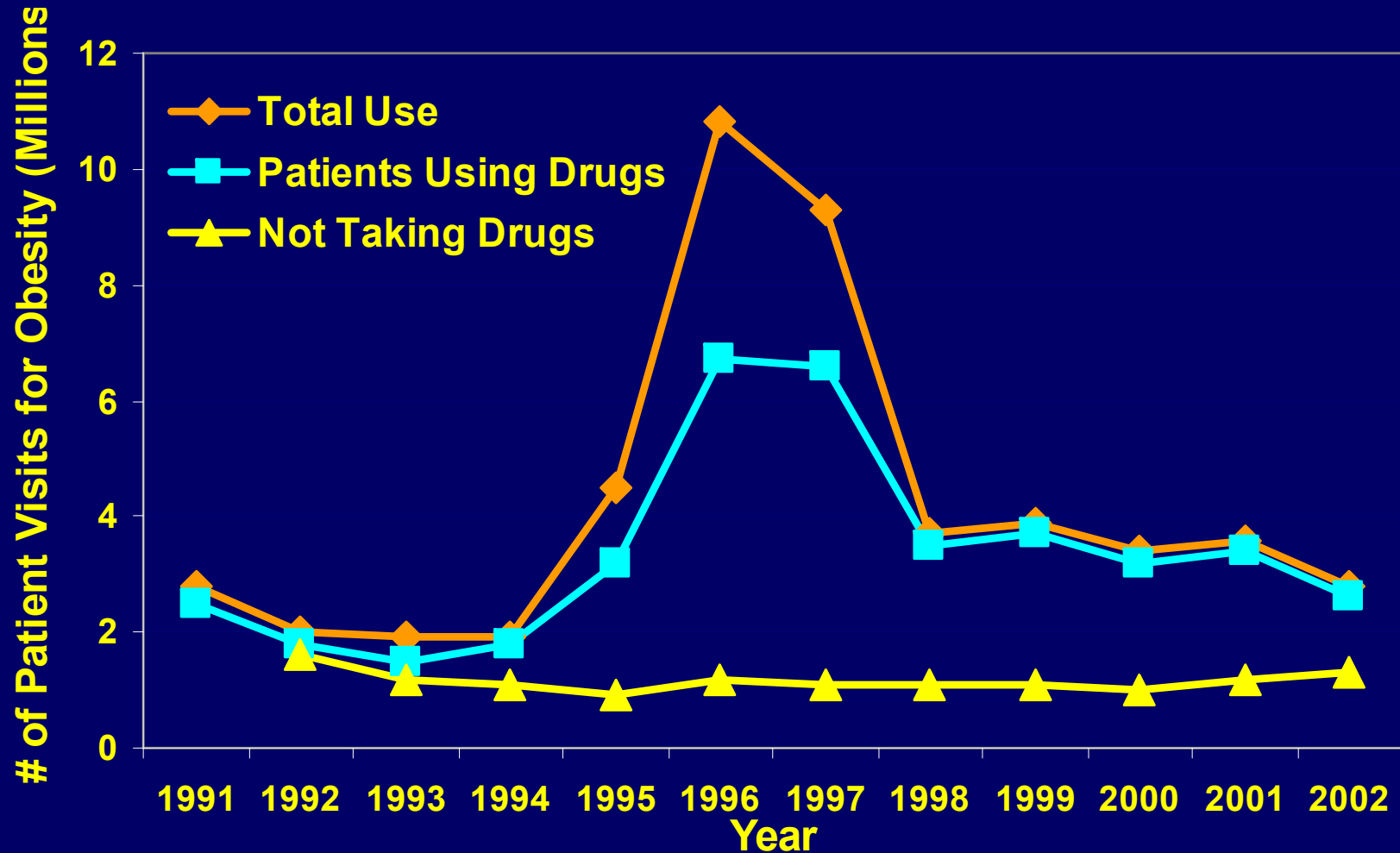
Combination of Fenfluramine and Phentermine Enhance Weight Loss



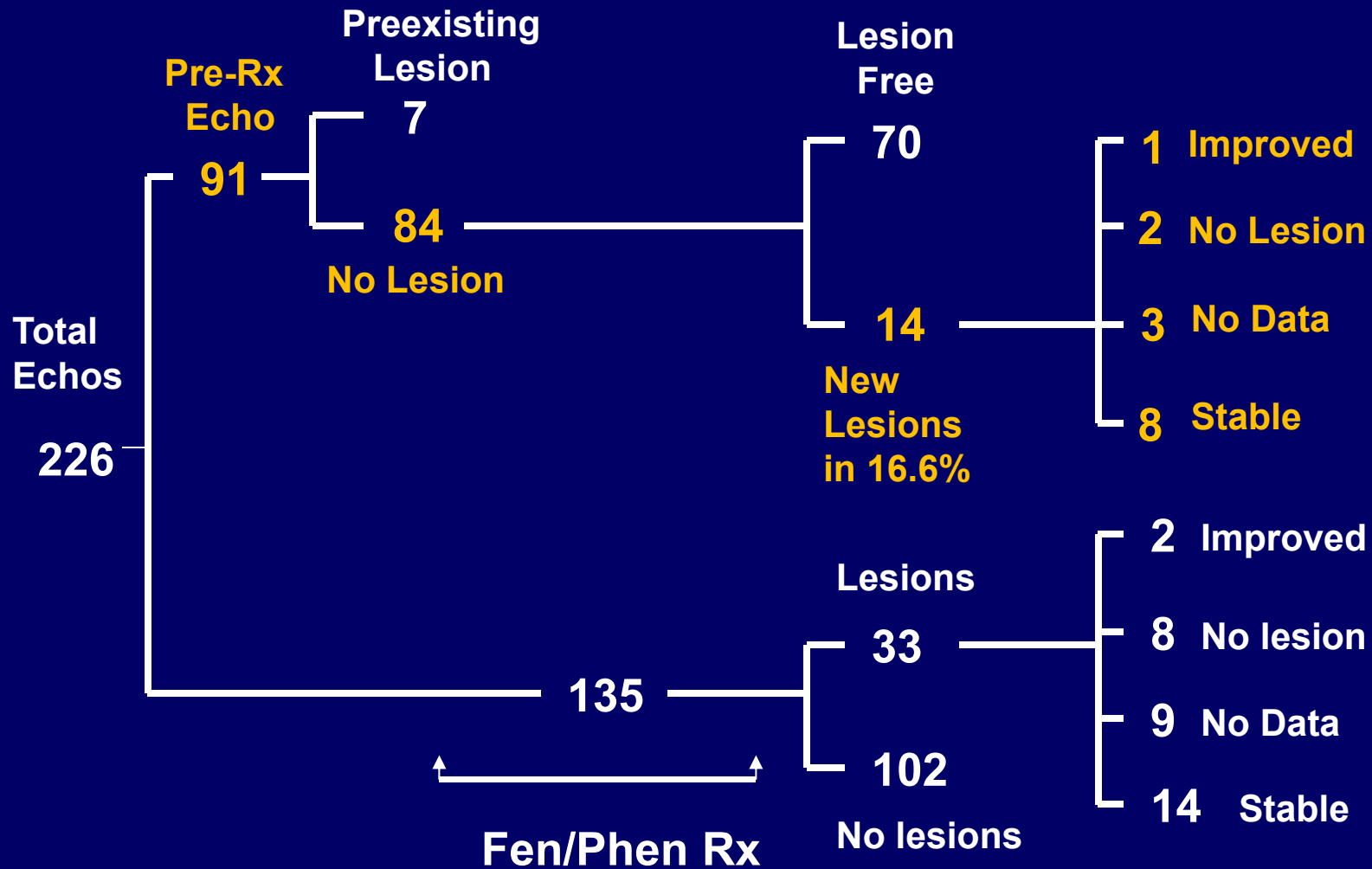
NOTE: 130 run-in patients; 121 randomized; 112 34-week completers.

Weintraub et al, Clin Pharmacol Ther. 1992;51:586-94; 1992;51:595-601

Use of Drugs to Treat Obesity Peaked with Fen/Phen



Ventricular Regurgitation Stopped Fenfluramine & Dexfenfluramine



Premises Underlying Treatment for Obesity

- First – Do no harm and make sure the benefits outweigh the risks of treatment
- Second – Treatment doesn't work when not used and benefits of weight loss don't happen if you don't lose weight

What Action Would You Take?

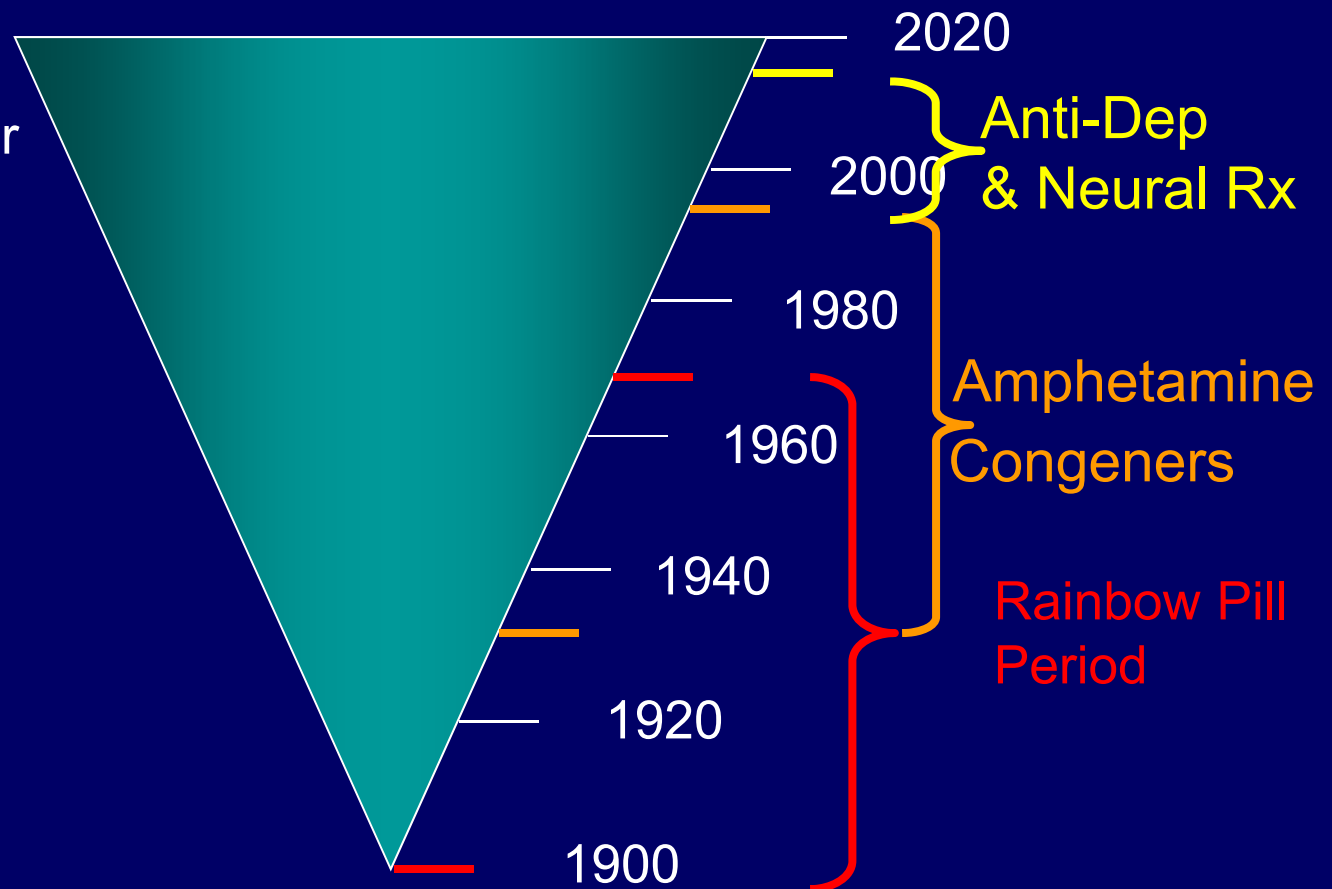
1. Continue Marketing of Fenfluramine Because it has been on the market since 1972?
2. Limit its use to people already taking it?
3. Limit its use to people at “high risk”
4. Remove it from the market?

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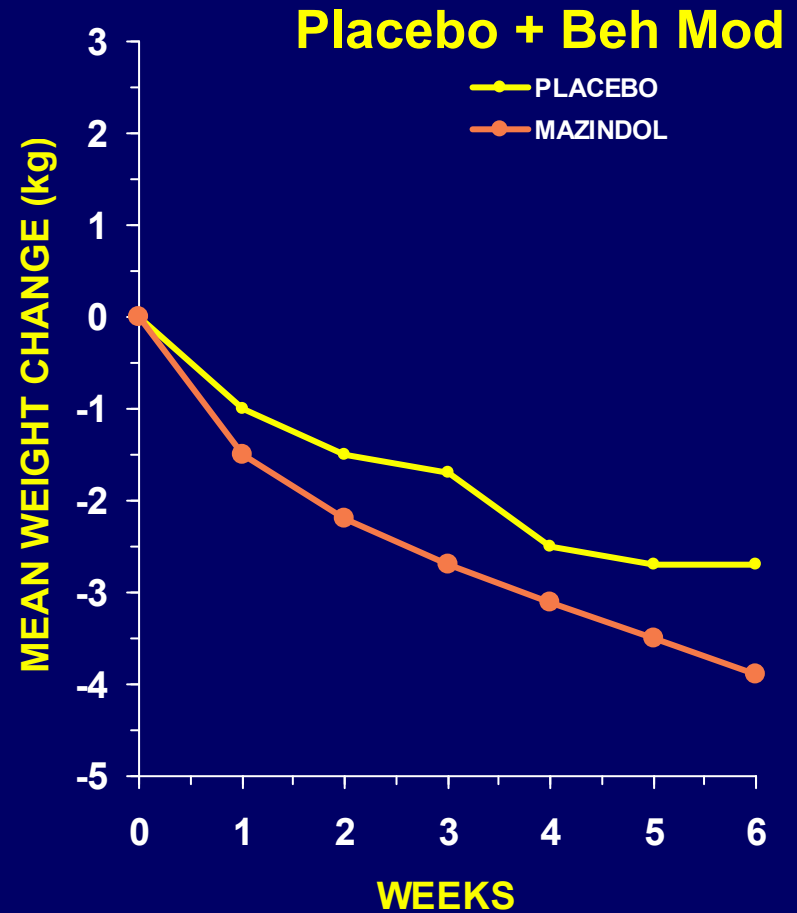
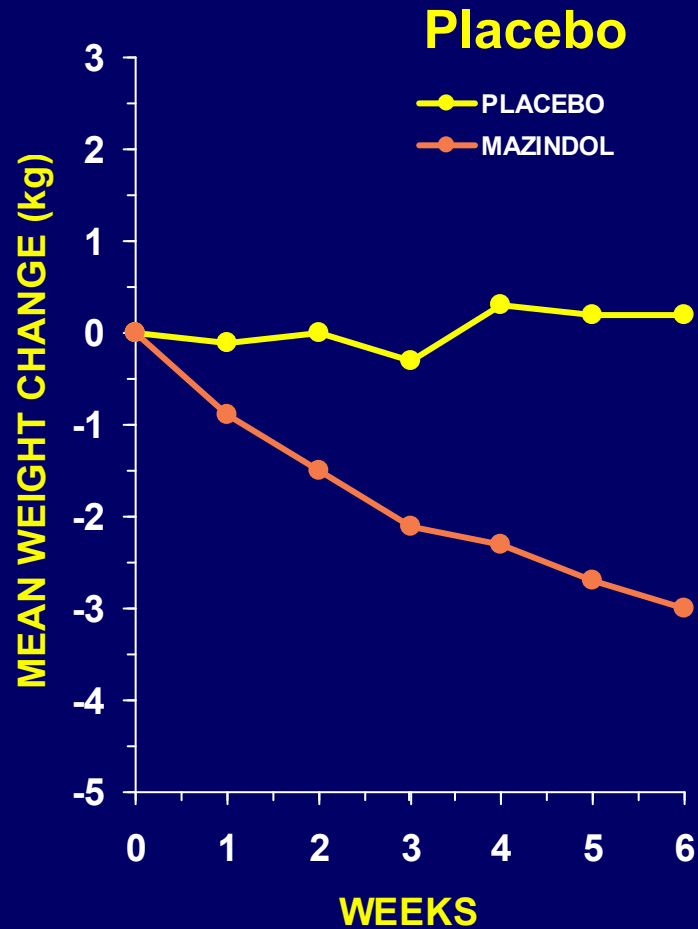
Anti-Depressants and Neural Drugs as Weight Loss Drugs

- Mazindol
- Fluoxetine
- Sibutramine
- Rimonabant

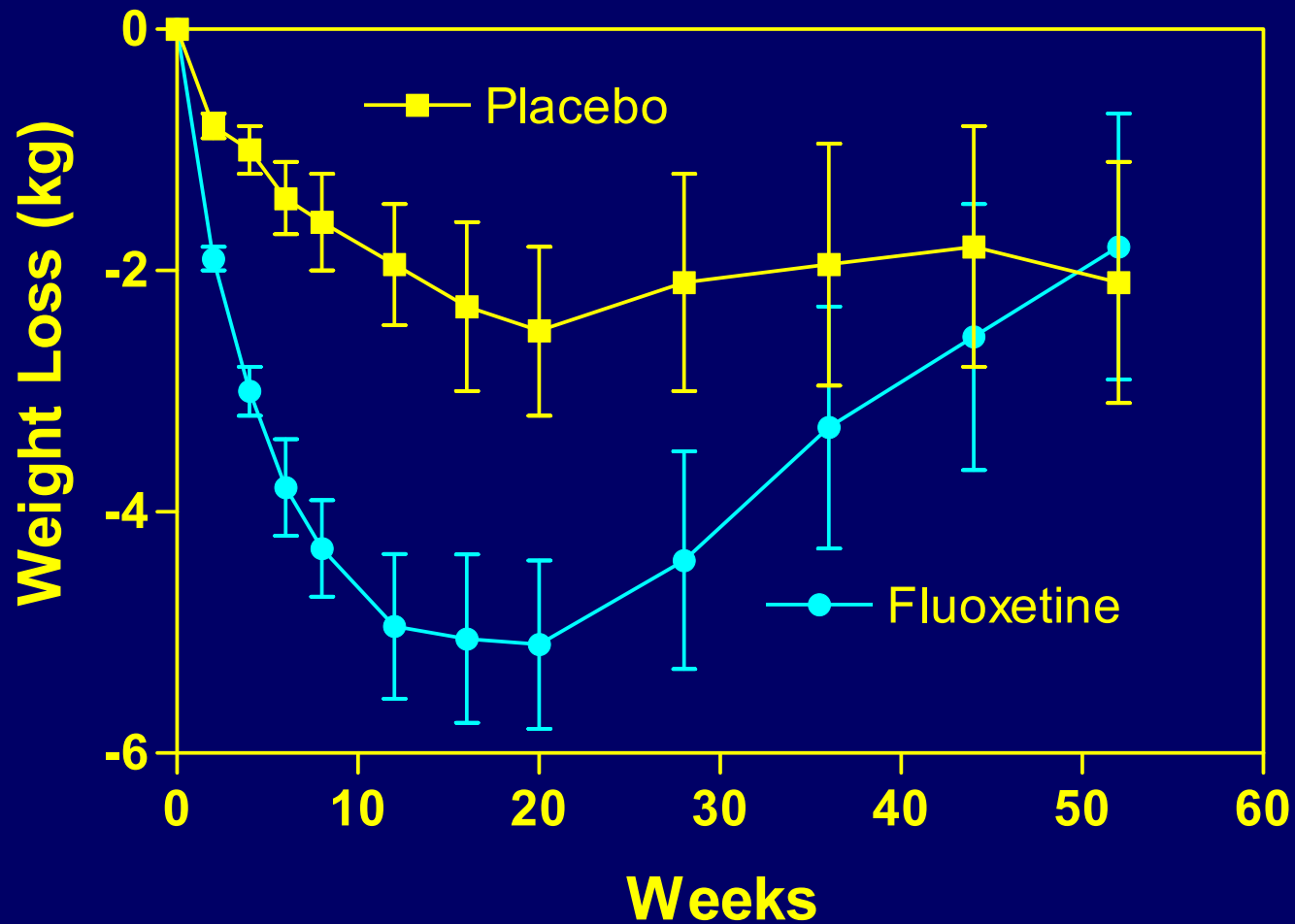
Anti-Depressants and Neural Drugs as Weight Loss Drugs

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Mazindol – A Tricyclic Weight Loss Drug

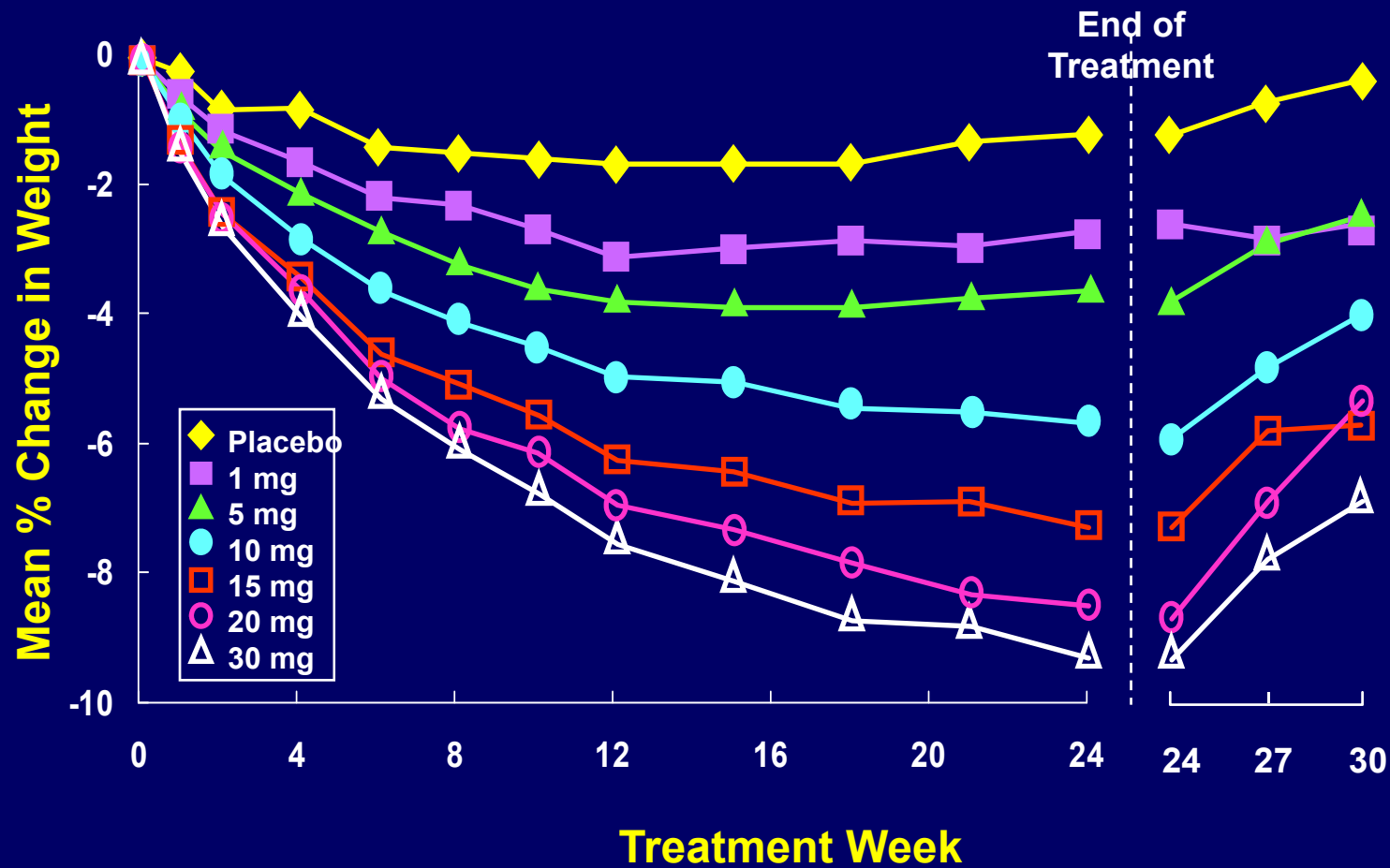


Effect of Fluoxetine on Body Weight



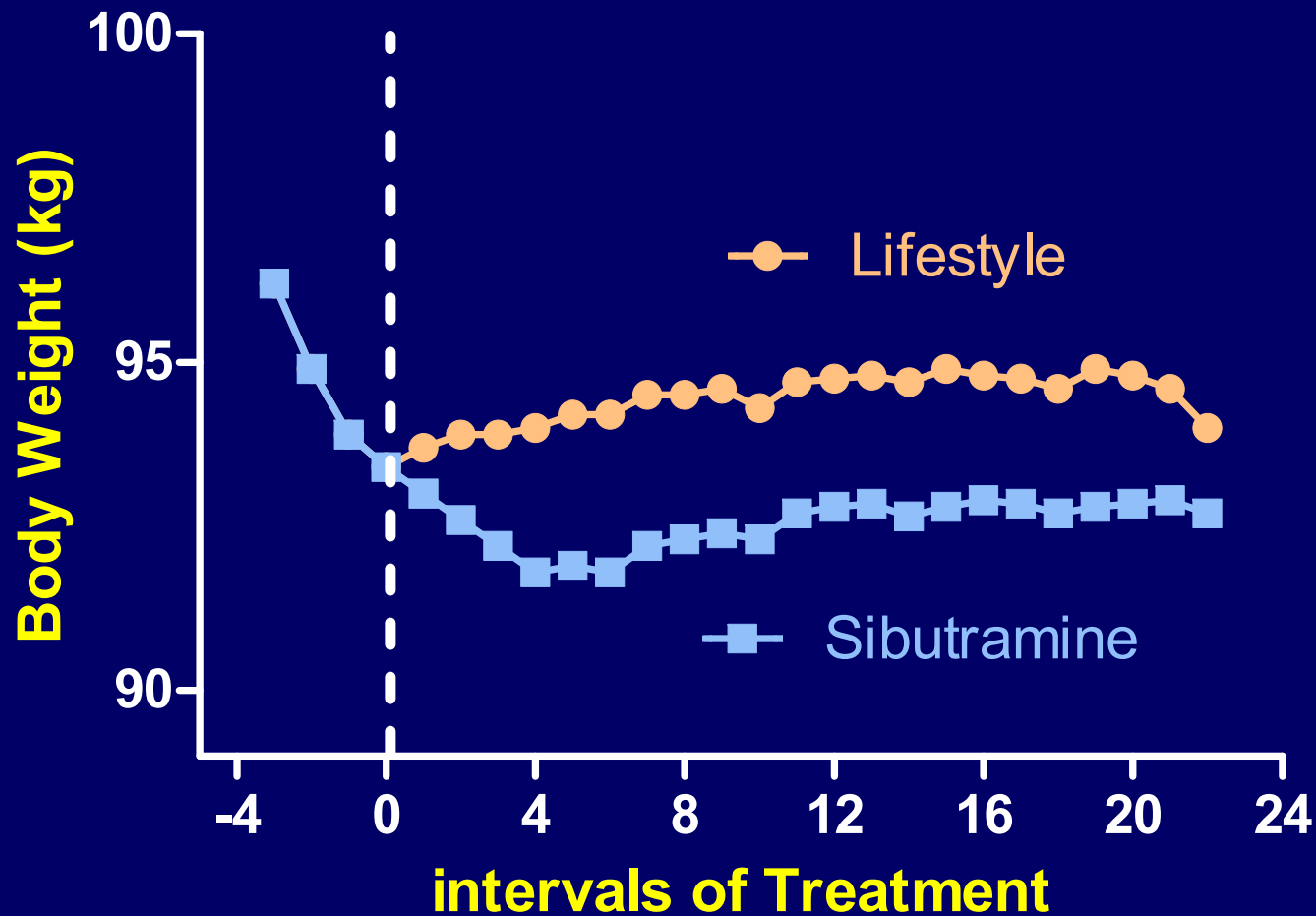
Goldstein et al IJO 1993;17:129-135

Sibutramine Produces Dose-Related Weight Loss



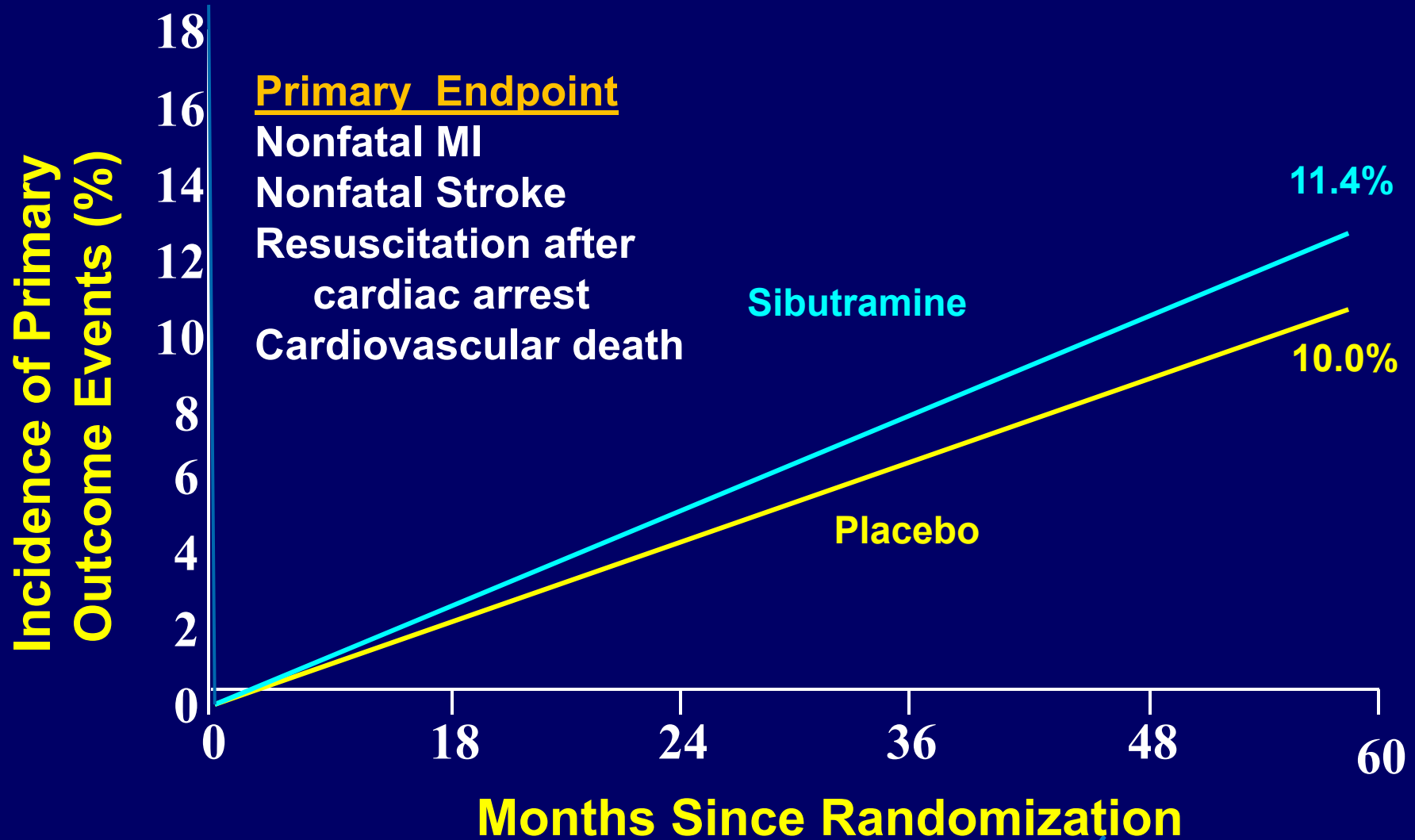
Sibutramine: 6 Month Dose-ranging study

Weight Loss during the SCOUT Study

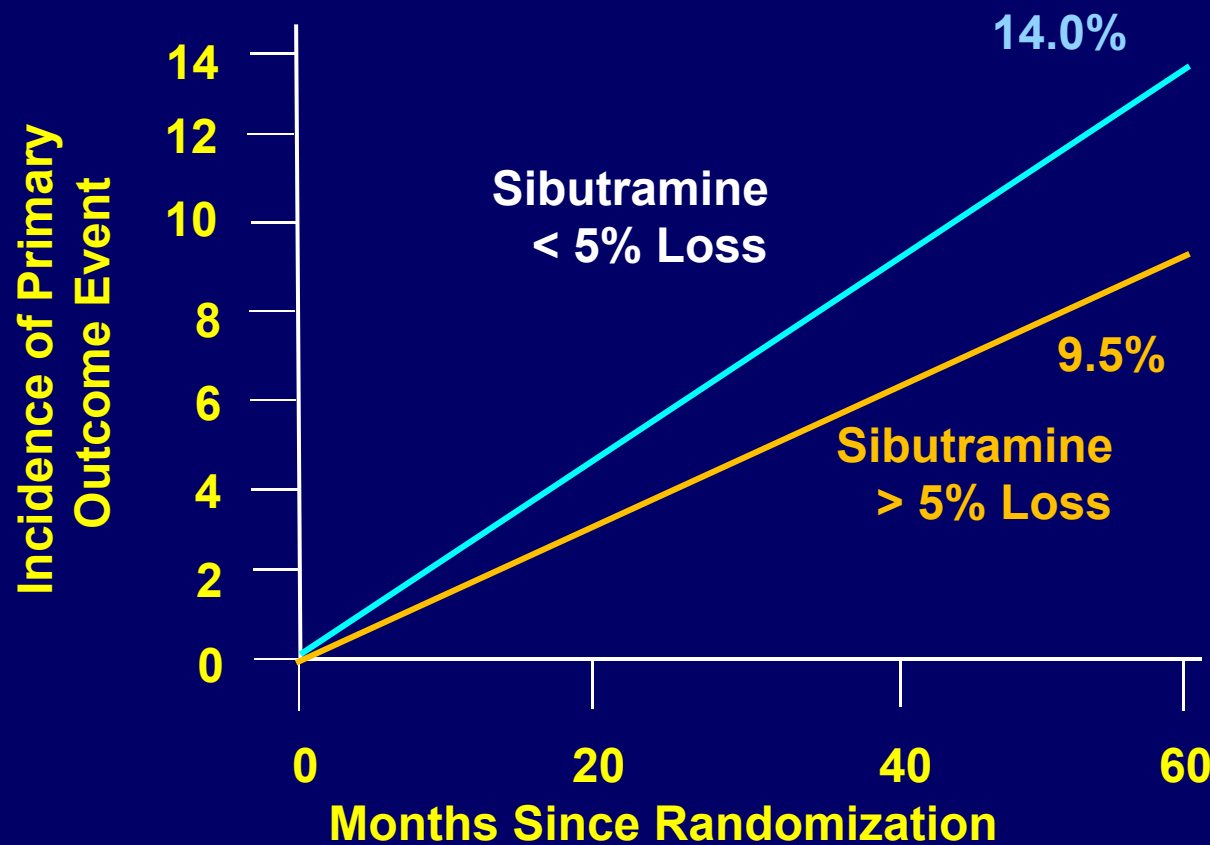


James PT et al NEJM 2010; FDA Briefing Document 15 Sept 2010

SCOUT Trial: Primary Outcome Worse with Sibutramine

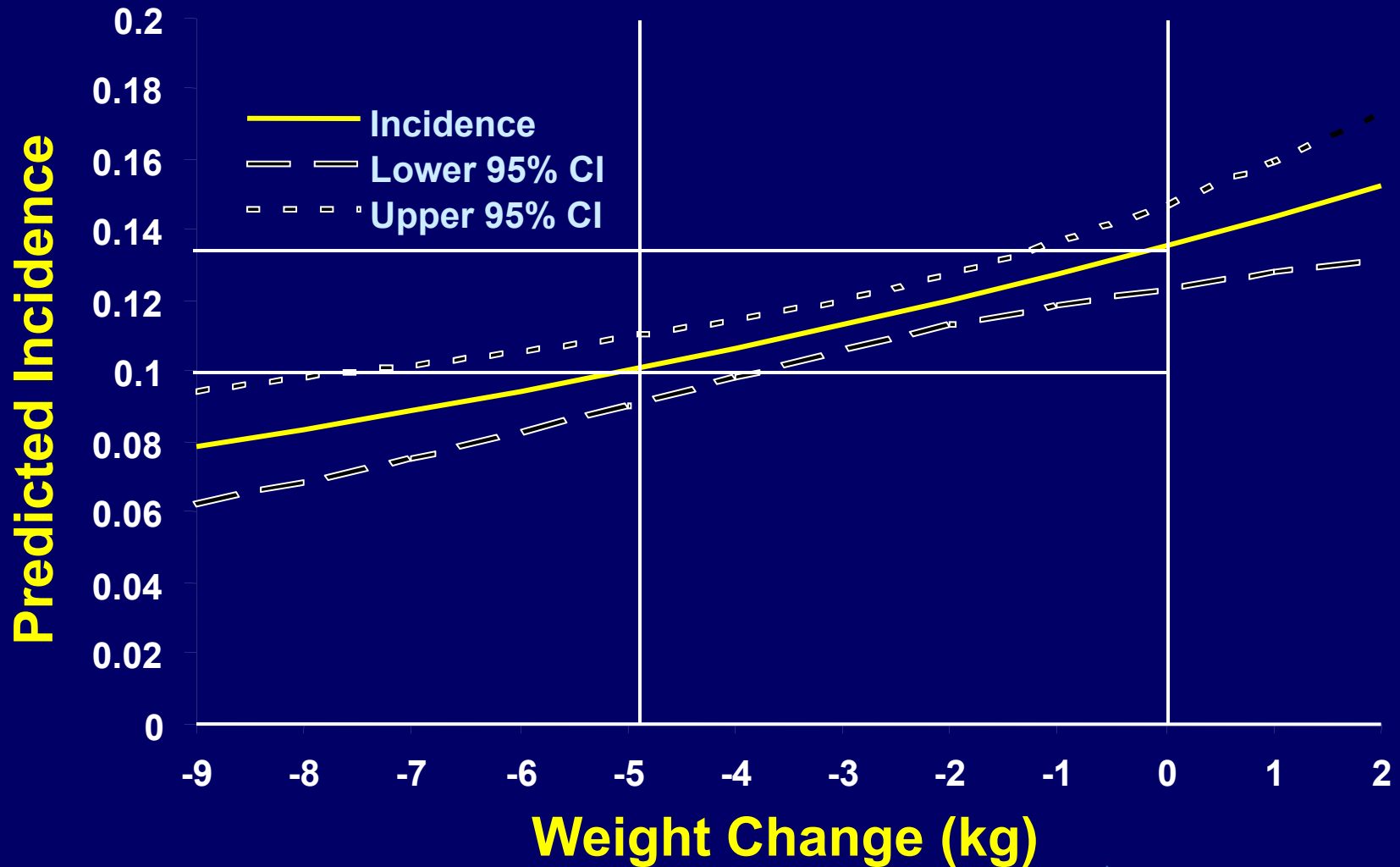


BUT Weight Loss Influences Primary Outcome Response to Sibutramine



SCOUT Study comparing the 30% of patients randomized to sibutramine who lost $\geq 5\%$ of their body weight against the 70% who lost $< 5\%$

Weight Change at Week 6 Predicts Primary Endpoint at Year 5 in SCOUT



What Action Would You Take?

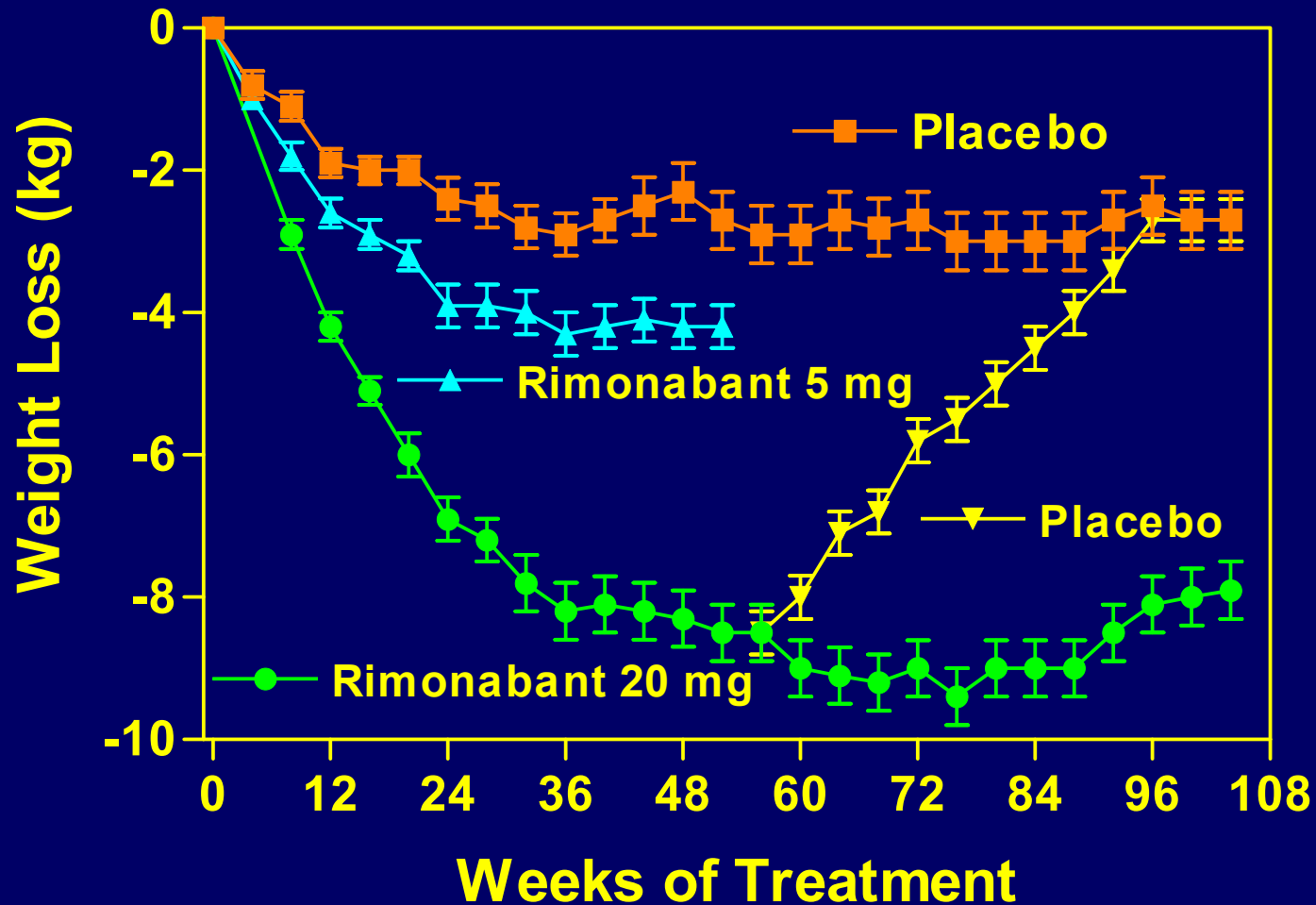
1. Continue Marketing of Sibutramine?
2. Limit its use to people already taking it?
3. Limit its use to people at “high risk”
4. Remove it from the market?

Cannabinoids and Weight Control

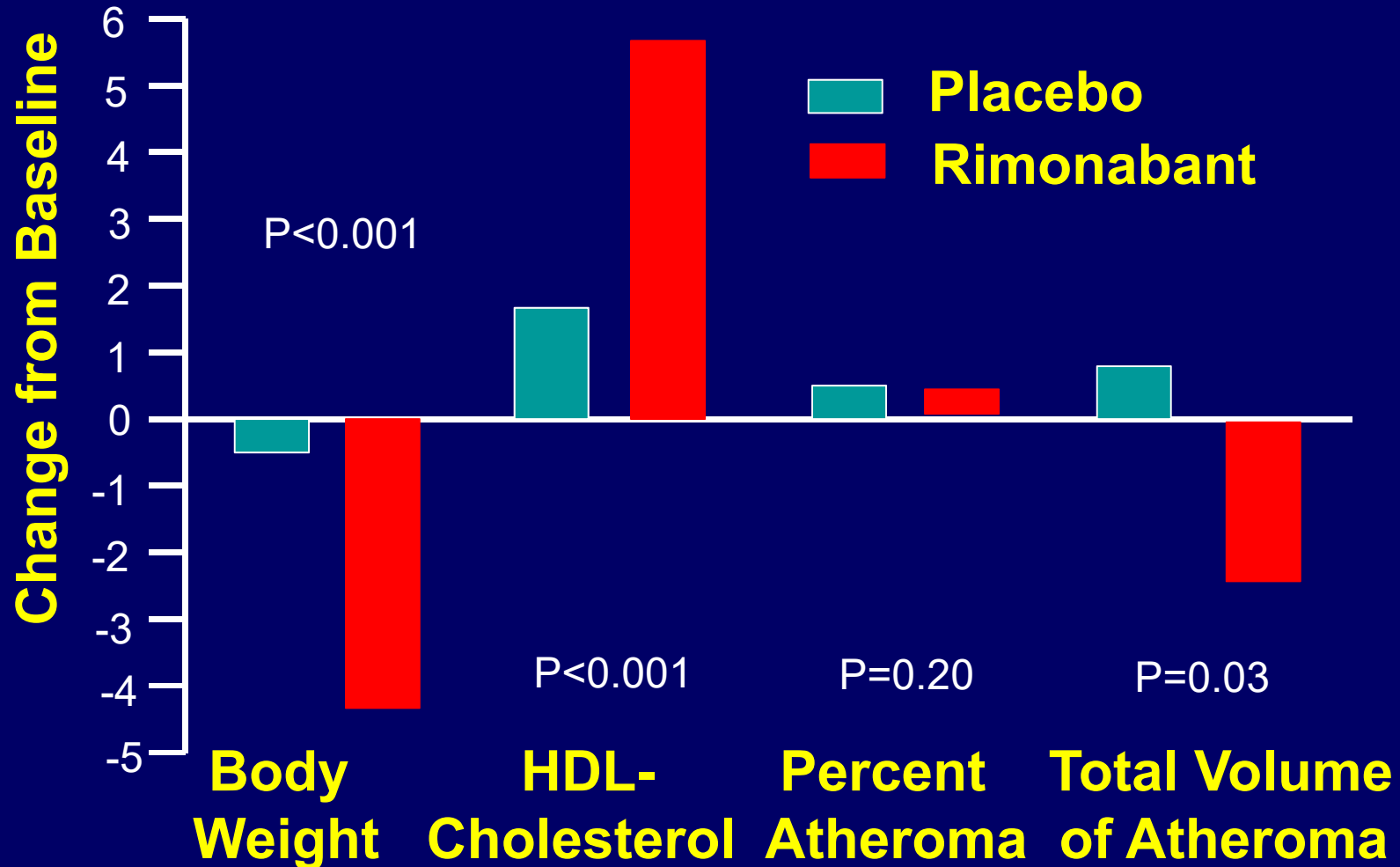
- Cannabis, the active ingredient in marijuana, stimulates food intake and pleasurable sensations.
- Blockade of the cannabinoid receptors reduces food intake, produces weight loss and produces behavioral problems.



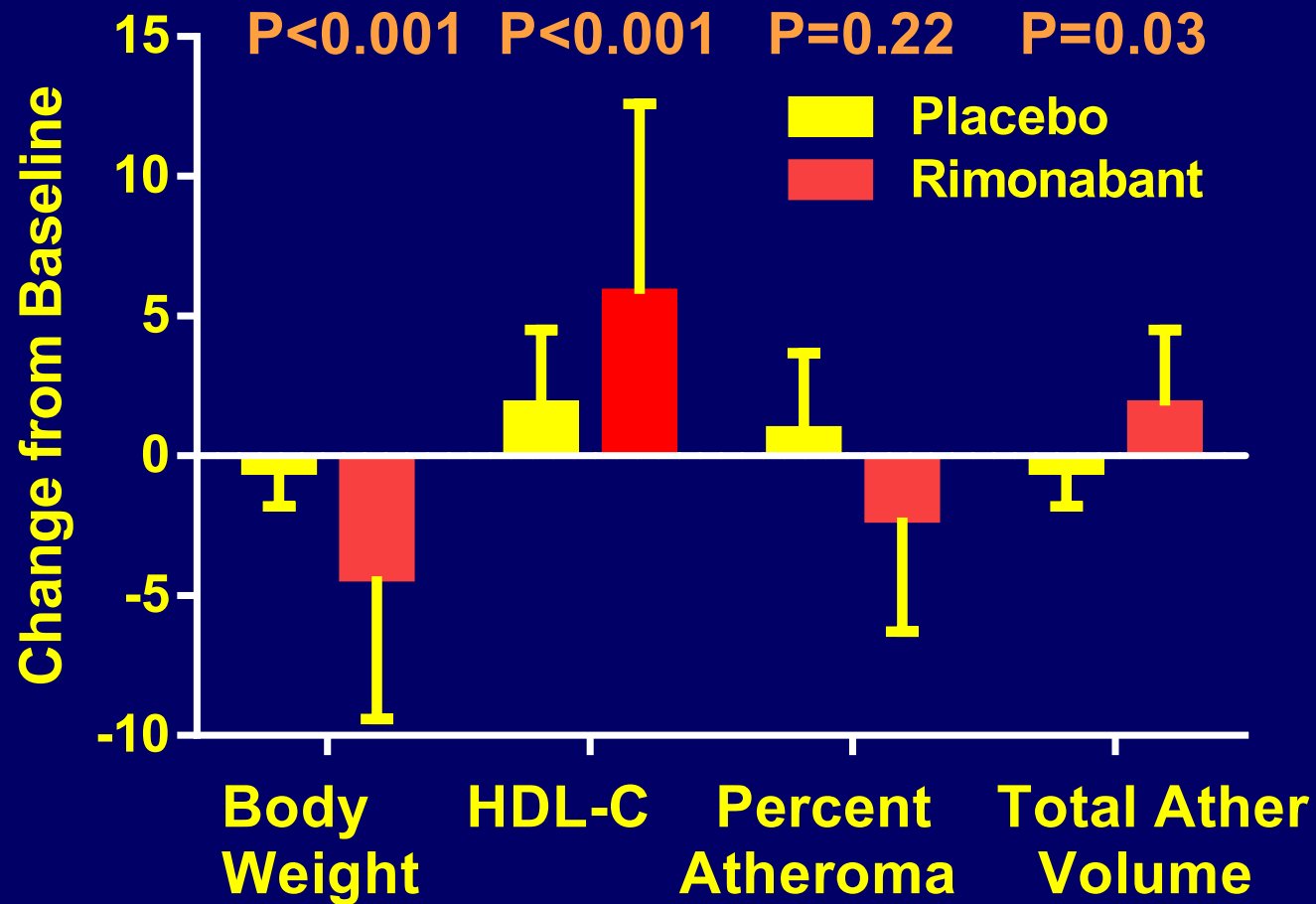
Rimonabant – Weight Loss and Regain After Cessation



Effects of Rimonabant on CV Risk and Body Weight: The Stradivarius Trial

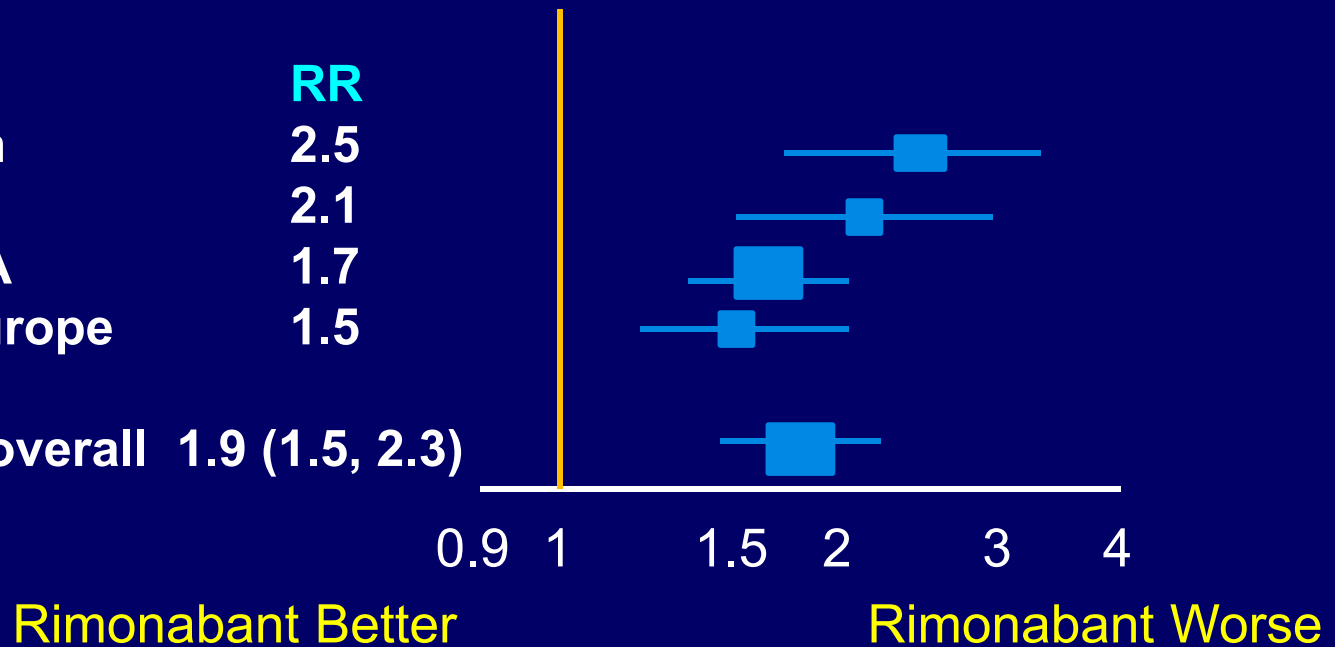


Effects of Rimonabant on CV Risk and Body Weight: The Stradivarius Trial



BUT: Rimonabant Increases the Risk of Suicidality

RIO Study	RR
Lipoprotein	2.5
Diabetes	2.1
Obese – NA	1.7
Obese – Europe	1.5
Psychiatric overall	1.9 (1.5, 2.3)



What Action Would You Take on Rimonabant?

1. Continue Marketing of Rimonabant?
2. Limit its use to people already taking it?
3. Limit its use to people at “high risk”
4. Remove it from the market?

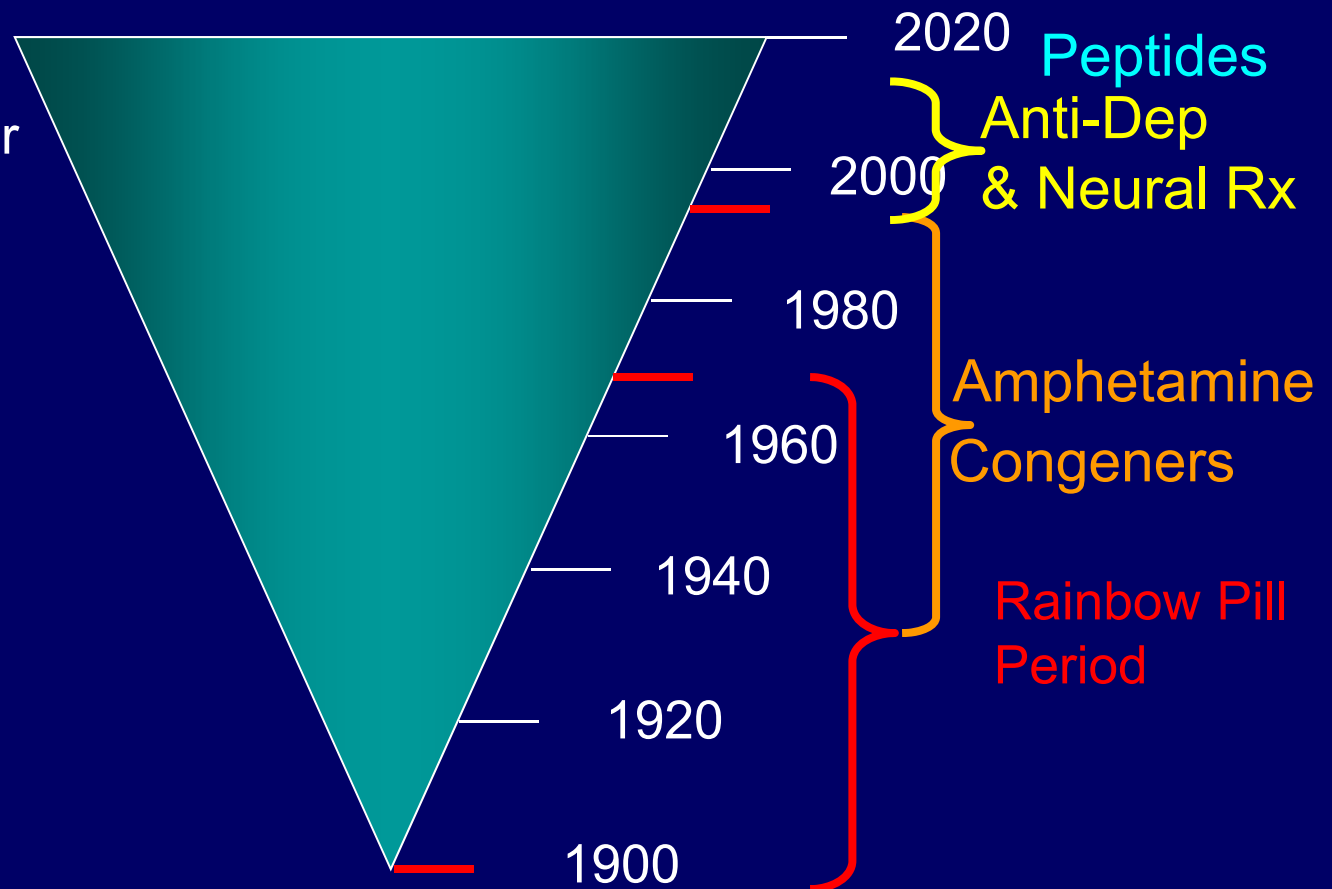
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The Peptide Period 1996 –

- Human Chorionic Gonadotrophin
- Cholecystokinin
- Leptin
- Axokine
- GI Peptides (GLP-1, GIP, Oxyntomodulin, Pancreatic polypeptide)

Human Chorionic Gonadotropin

- 1954 Simeon's published the book "*Pounds and Inches*" arguing that HCG which was used for testicular descent in people produced weight loss
- Multiple RCTs with HCG, including one by Greenway and Bray showed no effect
- In 2007 Dr. Mehmet Oz, the television physician published a diet book including human chorionic gonadotrophin.

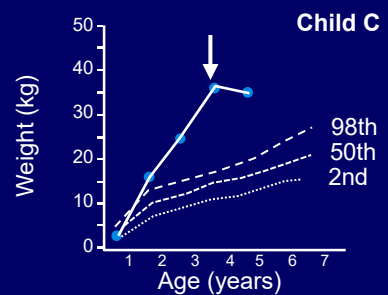
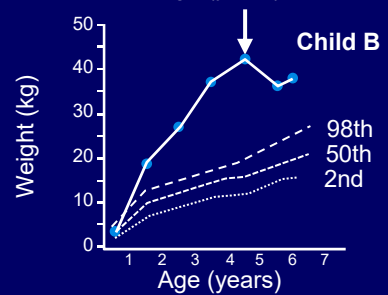
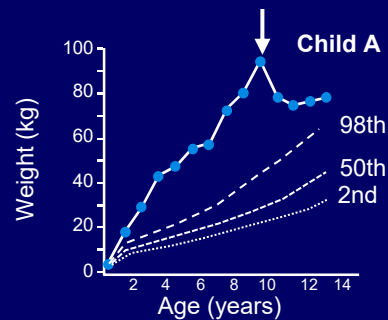
Cholecystokinin

- Cholecystokinin (CCK) produced by I cells in the gut stimulates gall bladder contraction.
- CCK acts through a seven-transmembrane GPCR which exists in 2 forms, CCK-A and CCK-B.
- Activation of pancreatic secretion and GI motility have reduced its potential use.

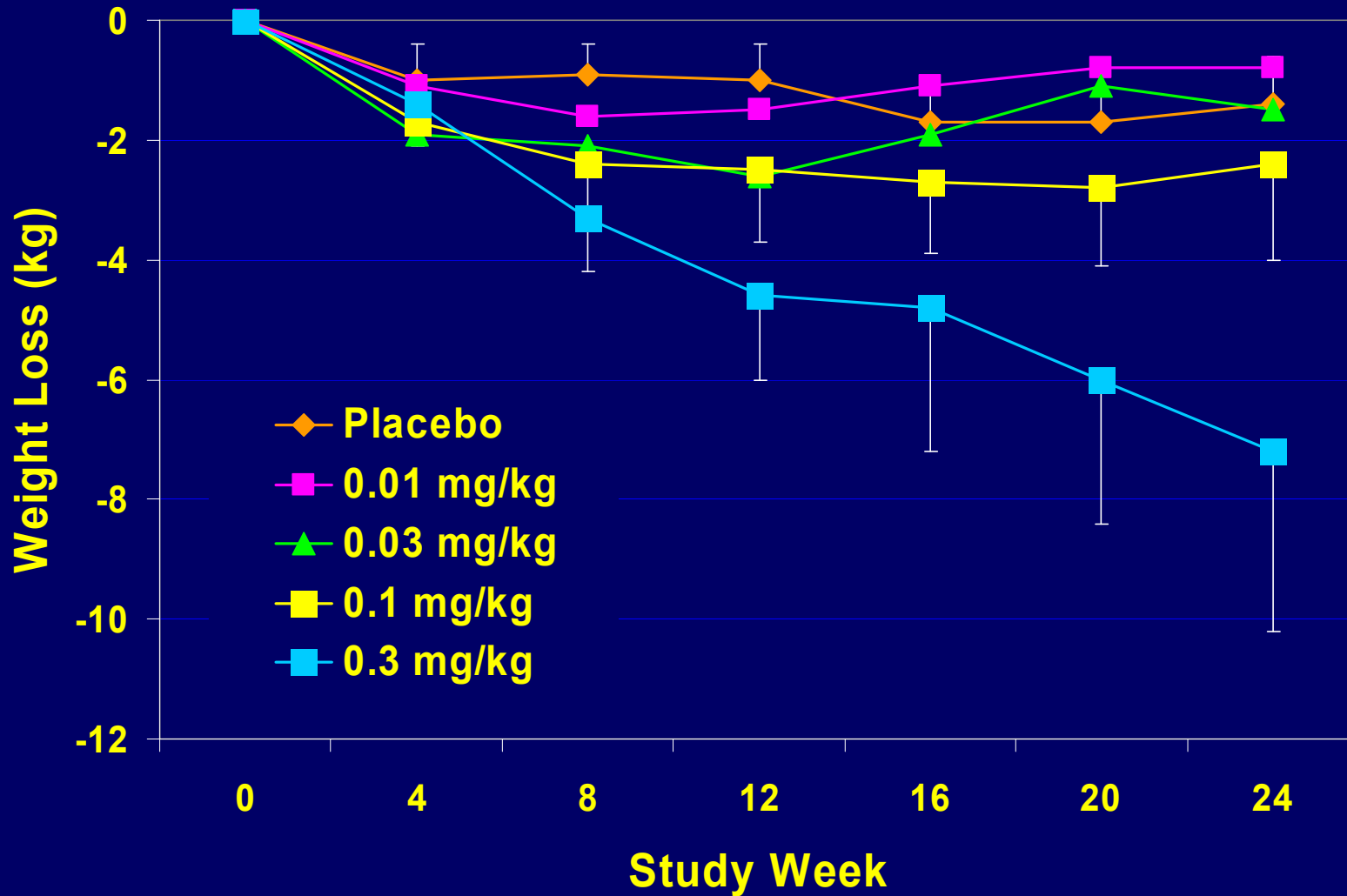
1994 Leptin Discovered

- Leptin produced primarily in adipose tissue acts on leptin receptors.
- There are 5 leptin receptors.
- In the brain leptin coordinately activates systems that inhibit food intake [proopiomelanocortin (POMC) makes α -melanocyte stimulating hormone (α -MSH) to reduce food intake] and represses systems that stimulate feeding [neuropeptide Y (NPY) and agouti related peptide Agrp)]

Leptin Deficiency and Treatment of Leptin

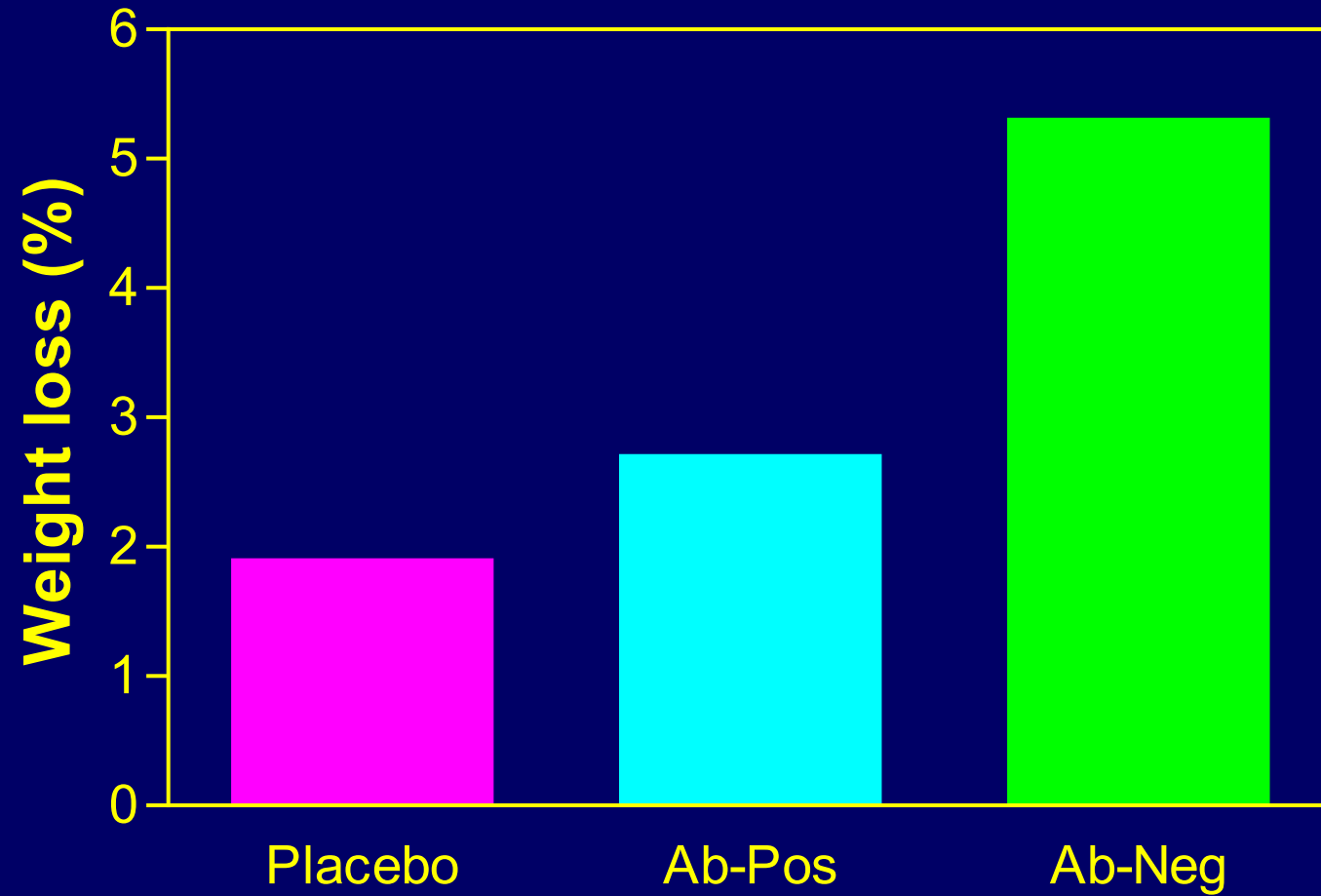


Leptin: Randomized Clinical Trial



Heymsfield et al JAMA 1999

Axokine and Weight Loss at One Year



Regeneron April 1, 2003

GI Peptides

- Several gut peptides reduce food intake.
- One of these has been approved, and others are under development

Unintended Consequences During Treatment of Obesity

Year	Drug	Consequence
1892	Thyroid	Hyperthyroidism
1932	Dintrophenol	Cataracts/Neuropathy
1937	Amphetamine	Addiction
1968	Rainbow Pills	Deaths-Arrhythmias
1971	Aminorex	Pulmonary Hypertension
1985	Gelatin-based VLCD	CV Deaths
1997	Phen/Fenfluramine	Valvulopathy
1998	Phenylpropanolamine	Strokes
2003	Ma Huang	Heart attacks/stroke
2007	Ecopipam	Depression
2010	Rimonabant	Depression
2011	Sibutramine	Increased mortality

Treatment for Obesity

The human body is composed
of head and limbs and torso
kept slim by gents at great expense
by ladies even more so.

Ogden Nash

Lesson For Today

- “When we say that science is essentially progressive this does not mean that in his quest for truth man follows always the shortest path. Far from it, he beats about the bush, does not find what he is looking for but finds something else, retraces his steps, loses himself in various detours, and finally after many wanderings touches the goal”. Sarton (p135)

That's All Folks!

