Endoscopic and Minimally Invasive Bariatrics: Medical Management of Obesity

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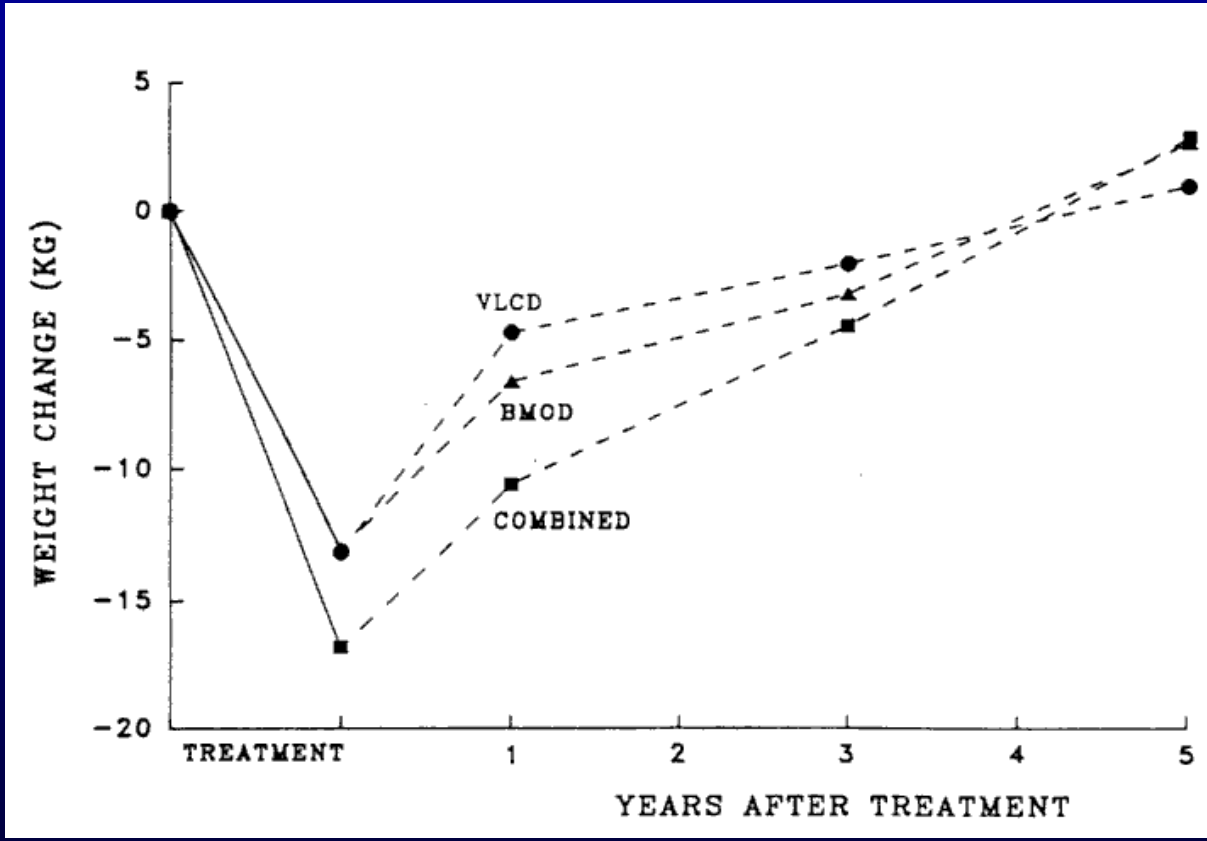
Judith Korner, MD, PhD
Professor, Department of Medicine
Division of Endocrinology
Director, Weight Control Center
Columbia University Medical Center

Cornerstone of Weight Loss Treatment

- **Behavior Therapy, Diet, Exercise**

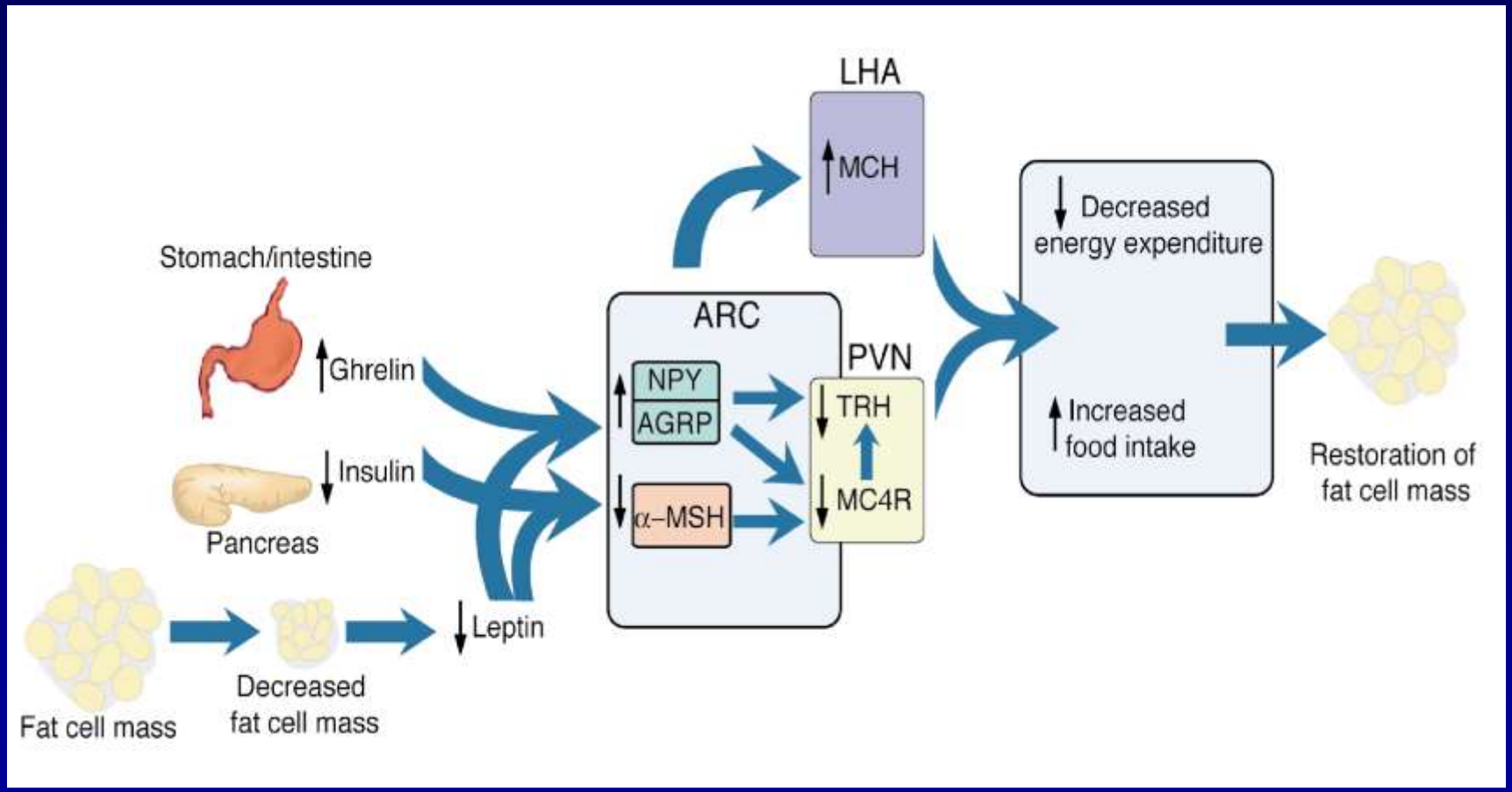
Long-Term Weight Loss with Non-Pharmacologic Treatment



VLCD: ≤800 kcal/day BMOD: behavior + 1200kcal/day Combined: VLCD + behavior

Wadden Annals of Int Med 119:688 1993

Neurohormonal Changes Associated with Weight Loss



Korner & Aronne, J Clin Invest 111:565-570 (2003)

A Guide to Selecting Treatment: National Institutes of Health (NIH) Guidelines*

Treatment	Body Mass Index (BMI) (kg/m^2)				
	25–26.9	27–29.9	30–34.9	35–39.9	≥40
Diet, physical activity, behavior therapy	Yes with comorbidities	Yes with comorbidities	Yes	Yes	Yes
Pharmaco-therapy		Yes with comorbidities	Yes	Yes	Yes
Weight-loss surgery			***	Yes with comorbidities	Yes

*_Yes_ alone indicates that the treatment is indicated regardless of the presence or absence of comorbidities. The solid arrow signifies the point at which therapy is initiated.

*** ***The FDA has approved use of LAGB for patients with BMI ≥ 30 who also have at least one condition linked to obesity, such as heart disease or diabetes.***

NIH/NHLBI, NAASO. *The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.* Bethesda, Md: NIH; 2000.

History of Drugs for Weight Loss

- 1947: ~~Methamphetamine~~
  Phendimetrazine (Bontril)
- 1957: Phentermine (Adipex, Suprenza)
- 1982: Diethylpropion (Tenuate)
  ~~Phenolpropanolamine (Dexedrin, Acutrim)~~
- 1973: ~~Fenfluramine~~
- 1996: ~~Dexfenfluramine (Redux)~~
- 1997: ~~Meridia (sibutramine)~~
- 1999: Orlistat (Xenical/Alli)
- 2012: Lorcaserin (Belviq)
- 2012: Topiramate + Phentermine (Qsymia)
- 2014: Bupropion + Naltrexone (Contrave)
- 2014: Liraglutide (Saxenda)

Drugs That May Promote Weight Gain

- Psychiatric/neuro
  - Antipsychotics
  - Antidepressants
  - Lithium
  - Antiepileptics
- Steroid hormones
  - Hormonal contraceptives
  - Corticosteroids
  - Progestational steroids
- Diabetes treatments
  - Insulin
  - Sulfonylureas
  - Thiazolidinedione
- Antihistamines
- β-adrenergic blockers

Adapted from Aronne LJ, Segal KR. *J Clin Psychiatry*. 2003;64(Suppl 8):22-29.

Noradrenergic Agents

- Schedule IV drugs have a low potential for abuse
- **Phentermine** (Adipex-P, Fastin): 18.75-37.5 mg/day
- **Phentermine resin** (Ionamin): 15-30 mg/day
- **Diethylpropion** (Tenuate, Tenuate Dospan):

  25 mg 3x/day or sustained release 75 mg/day
- **Phenylpropanolamine** (Dexatrim, Acutrim): withdrawn from market due to association with hemorrhagic stroke

Yanovski NEJM 346:591 2002

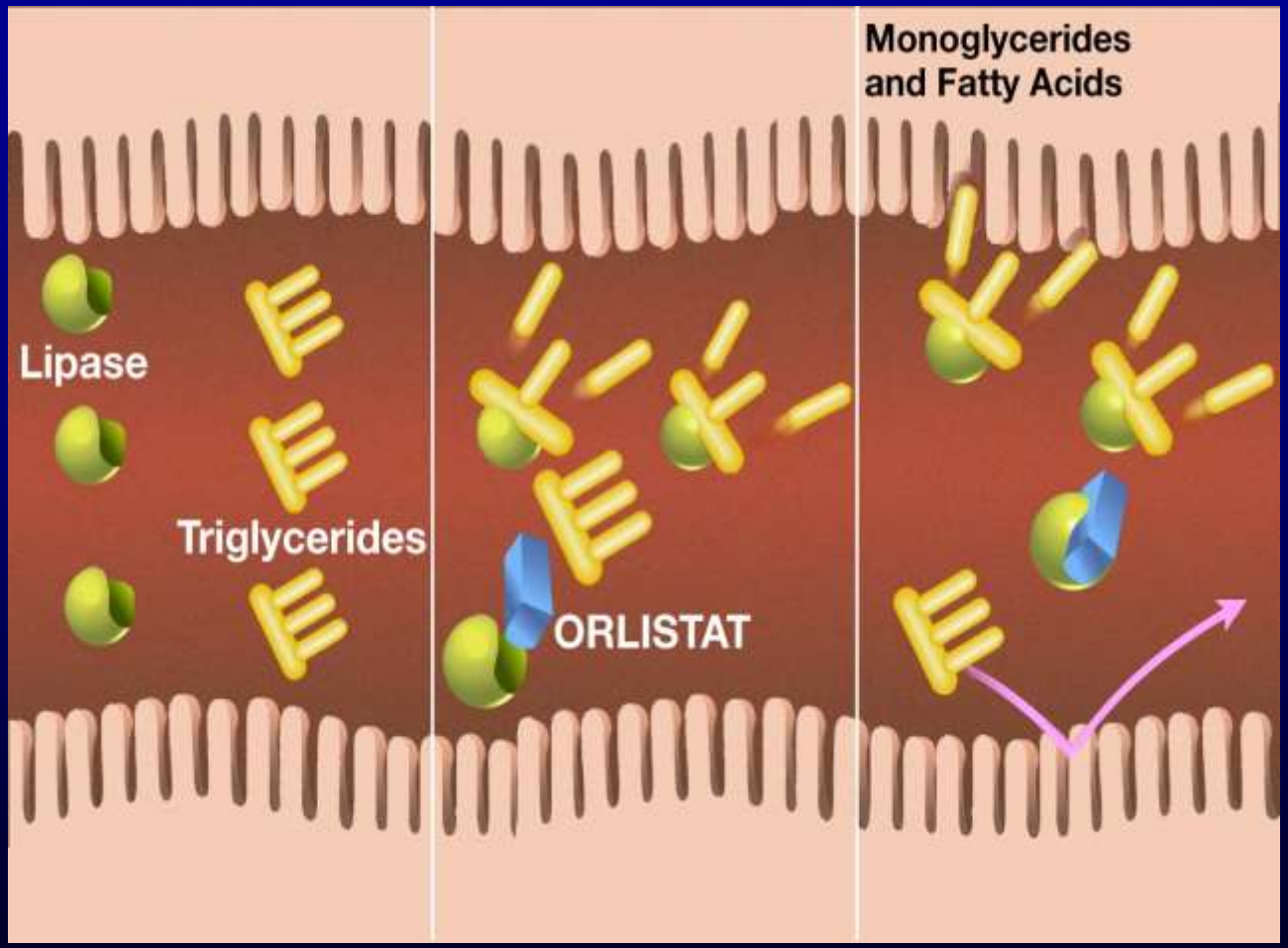
Noradrenergic Agents (cont' d)

- Approved by the FDA for short-term use:

  ~ 3 months

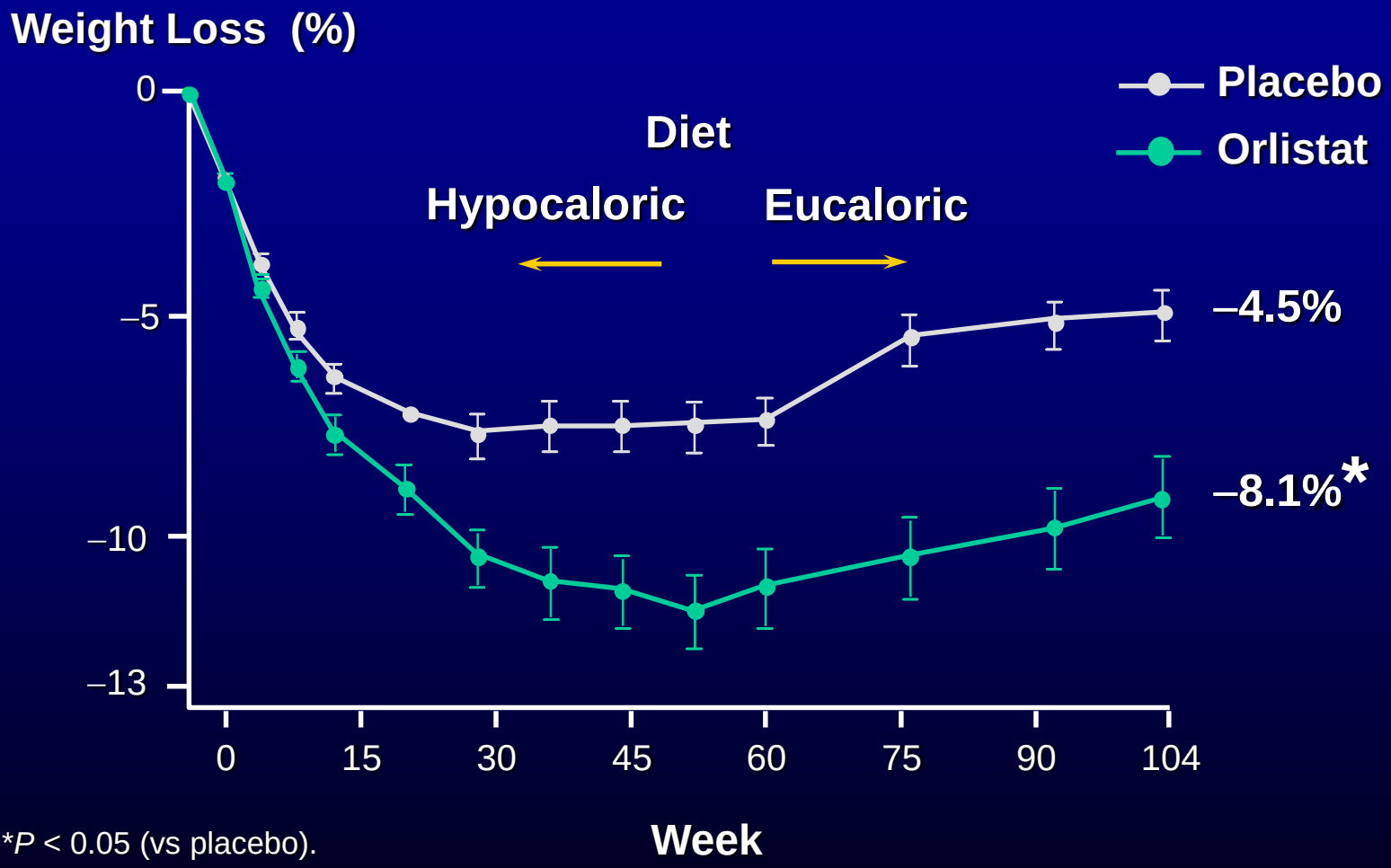
- Studies show between 2-10 kg weight loss over placebo
- Side effects: insomnia, dry mouth, constipation, euphoria, palpitations, hypertension

Orlistat: Mechanism of Action



30% of fat not absorbed

Weight Change Over 104 Weeks



*$P < 0.05$ (vs placebo).

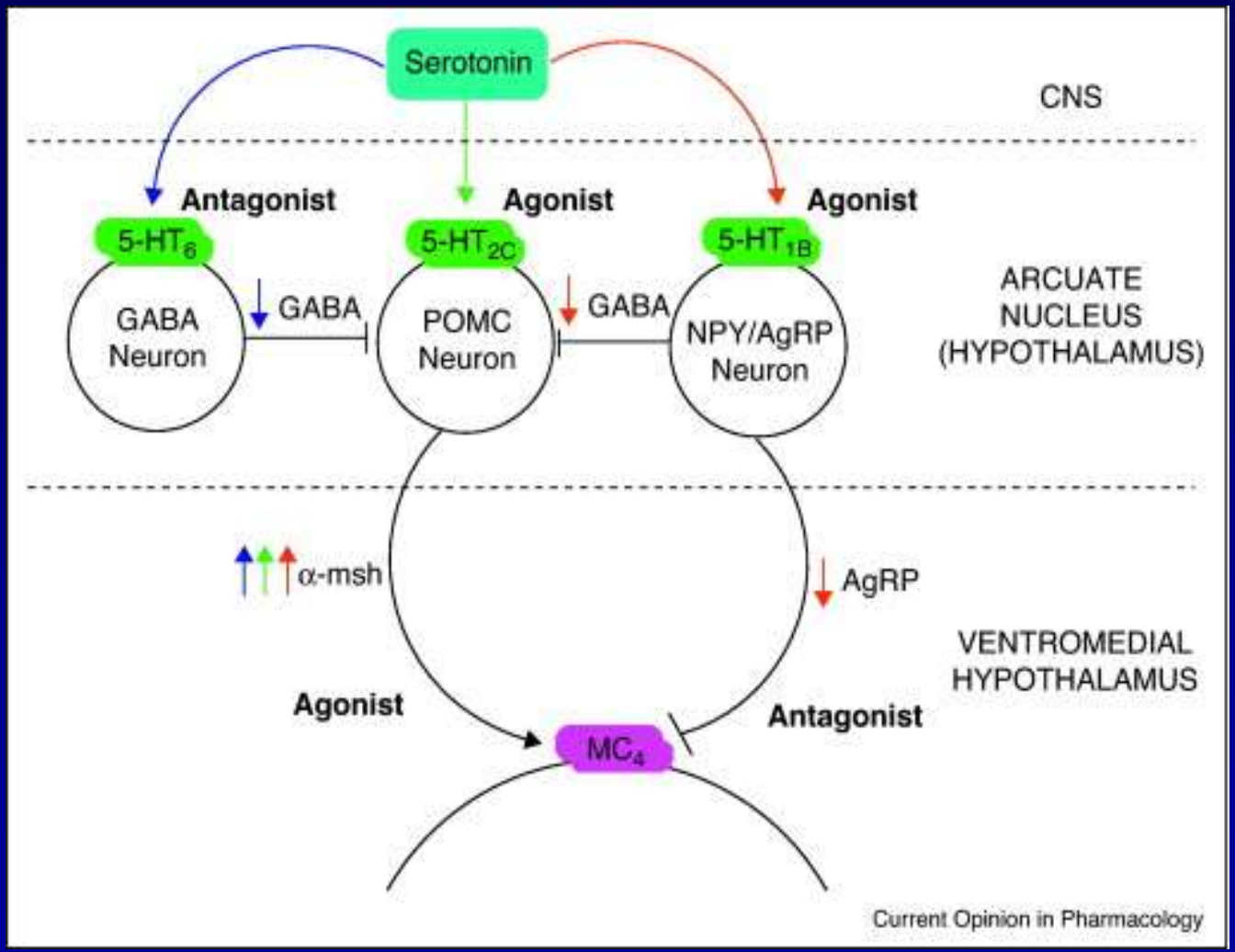
Sjöström L, et al. *Lancet*. 1998;352:167–172.

Orlistat: Safety

- GI events (flatulence, anal leakage) are related to increased fecal fat excretion and are a predictable consequence of the mode of action of orlistat
  - Events may help/hinder compliance as patients test their limits
- Reductions in fat-soluble vitamins levels and absorption of some medications have been demonstrated
- Vitamin supplementation is recommended
- Post-marketing reports of liver injury but no cause-effect relationship with orlistat has been established

Xenical [package insert]. Nutley, NJ: Roche Laboratories Inc; 2007 and FDA

Lorcaserin (Belviq)- Mechanism of Action



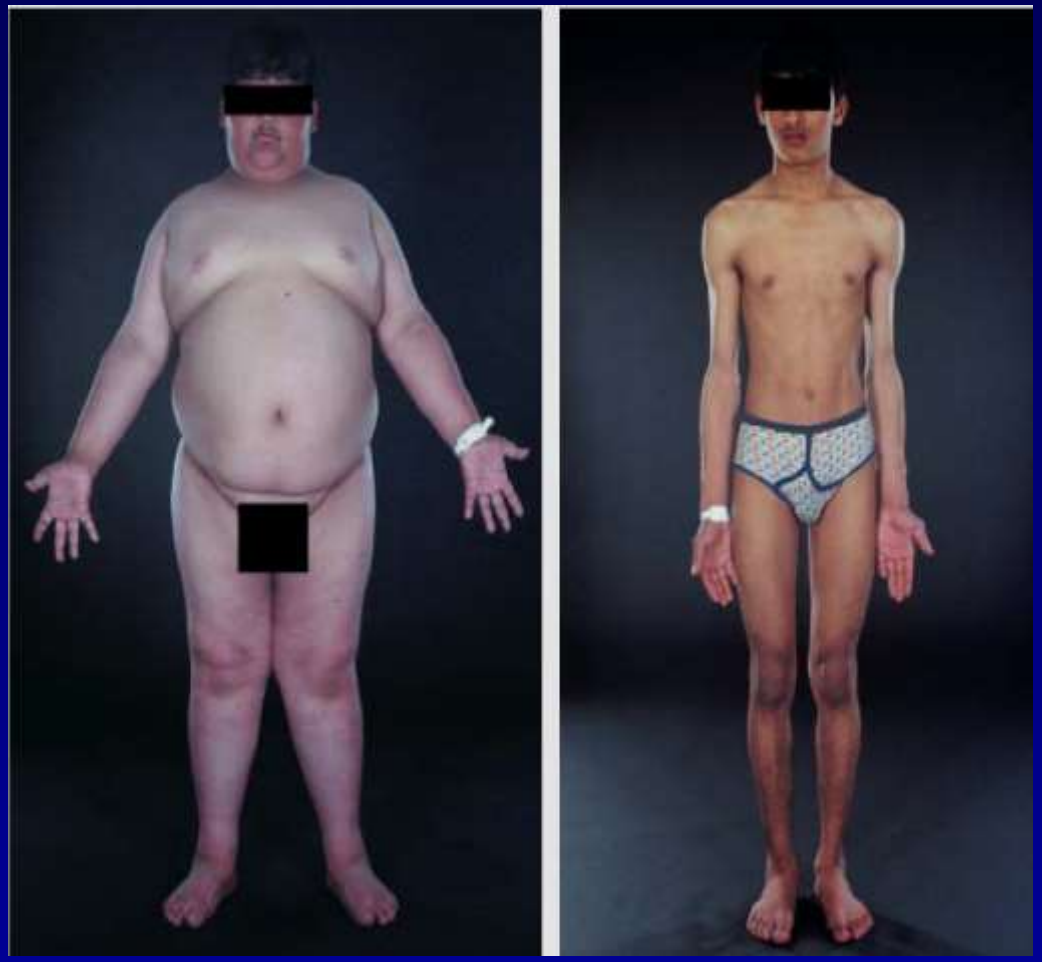
Sargent B and Henderson A. Current Opinion in Pharmacology. February 2011, 11(1): 52–58

5-HT 1B: pulmonary HTN; 5-HT 2B: pulmonary HTN and cardiac valvulopathy

MC4R Deficiency

9 yo boy

MC4R -/-



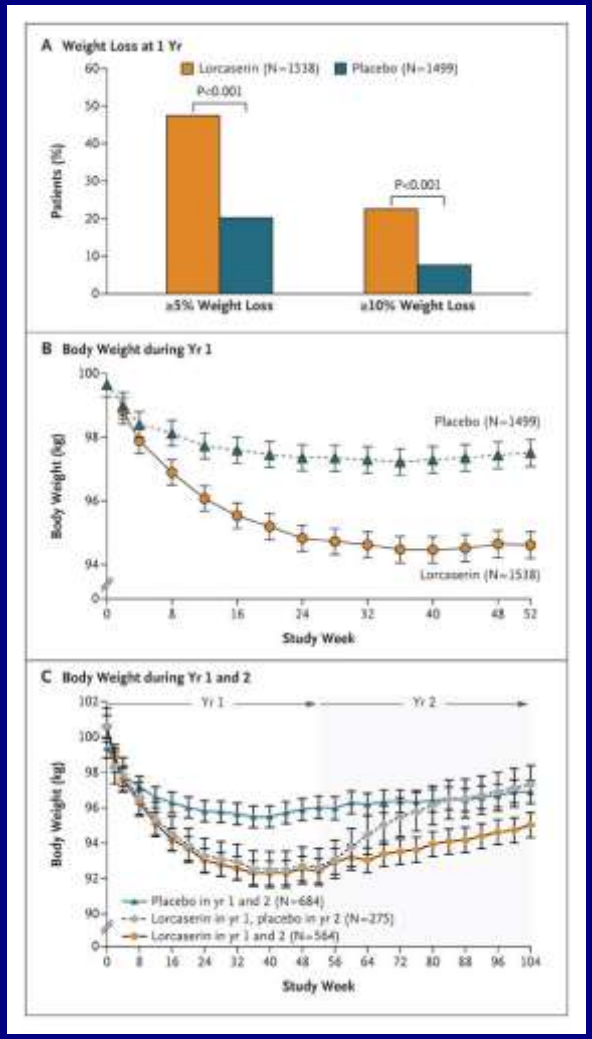
16 yo brother

MC4R +/+

Phenotype: hyperphagia, obesity, increased bone mineral density, incr linear growth, severe hyperinsulinemia

Farooqi S, O'Rahilly S. Endocrine Reviews. 27 (7):710-18. Farooqi et al. 2003 NEJM 348:1085-1095.

Lorcaserin: Serotonin receptor 5-HT2c Agonist (no valvulopathy)



Smith SR et al. N Engl J Med 2010;363:245-256

The NEW ENGLAND JOURNAL of MEDICINE

Lorcaserin (Belviq): Adverse Effects/warnings/precautions

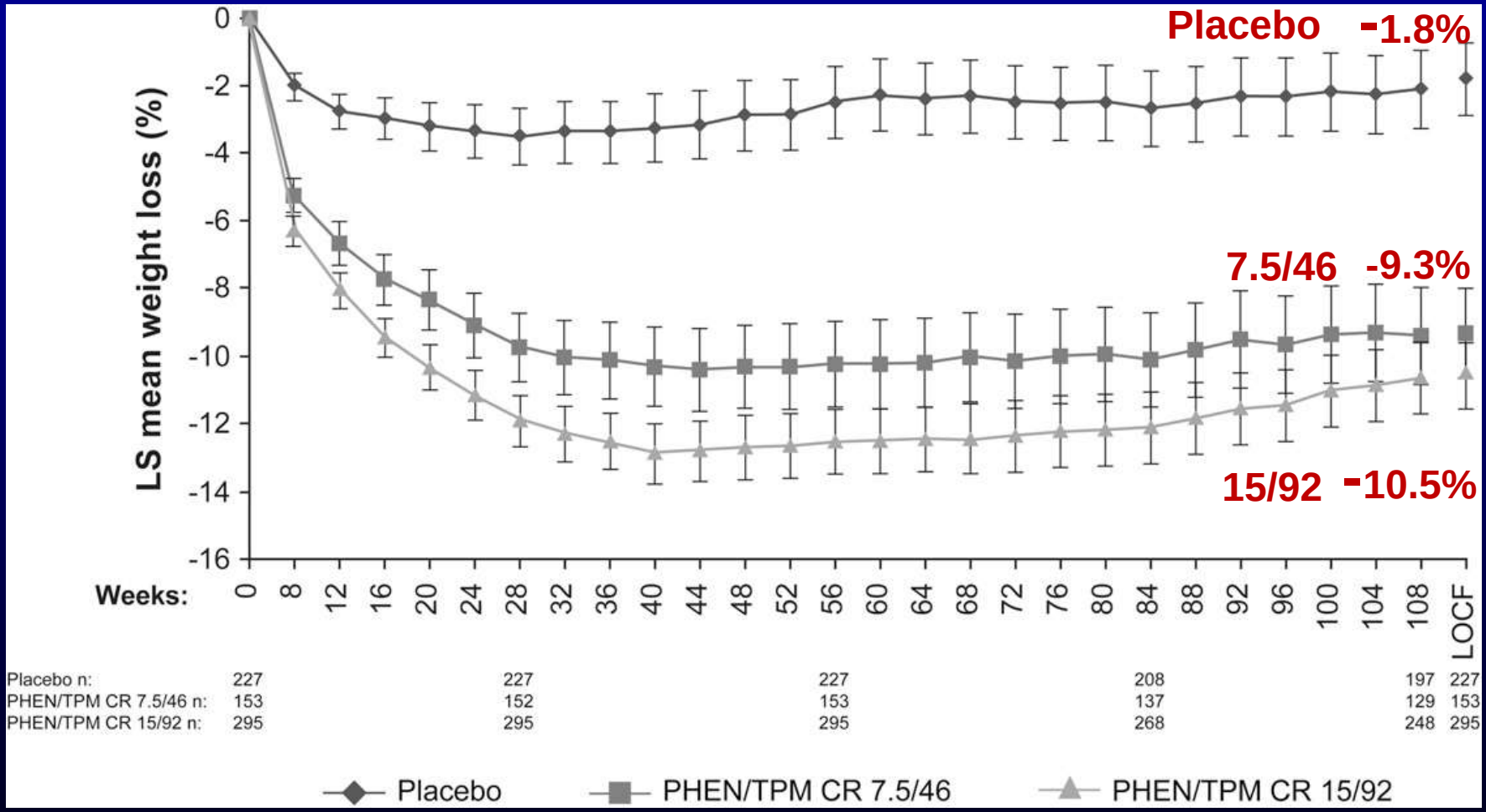
- Most common adverse effects: headache (17%), dizziness, fatigue, nausea, dry mouth, constipation, hypoglycemia (in pts with DM)
- Serotonin syndrome or Neuroleptic malignant syndrome: esp in conjunction with SSRIs, TCAs, triptans, MAOIs, antipsychotics, bupropion, dextromethorphan, St. John's Wort
- Bradycardia: 5-10 bpm decr in HR
- Lab changes: incr PRL or decr WBC count
- Should not take with drugs associated with valvular heart disease (ie. cabergoline)

Phentermine-Topiramate (Qsymia)

- Phentermine
  - Increase in NE -> incr metabolism -> incr locomotor activity
  - Increase in DA -> decr appetite
- Topiramate
  - Decr appetite via unknown mechanism (GABA)

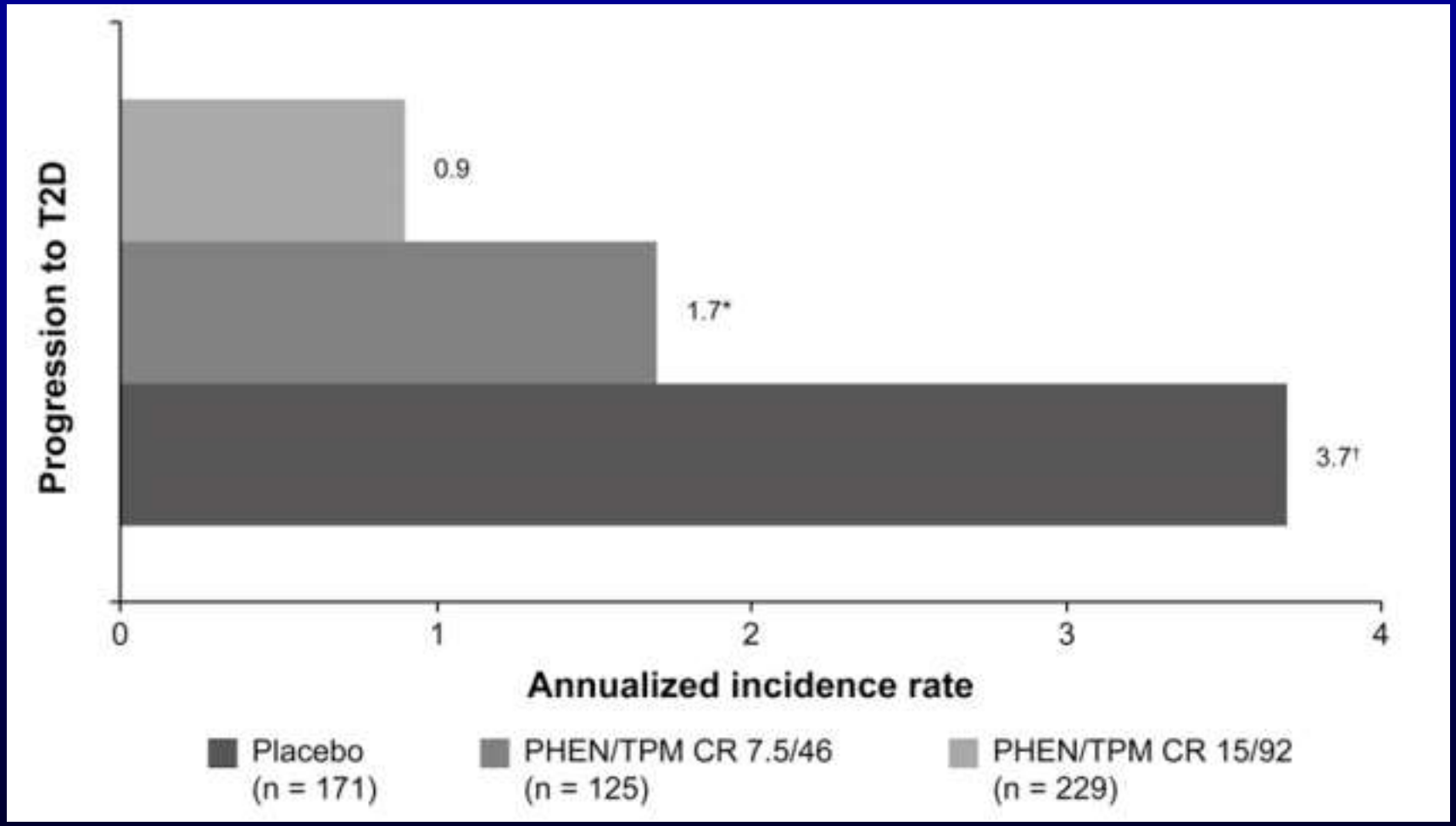
Smith, et al, Annals of Pharmacotherapy March 2013, 47:340-349

Effect of Phentermine/Topiramate ER (Qsymia) on Weight Loss in Obese Adults Over 2 Years



Garvey WT, et al. *Am J Clin Nutr*. 2012;95:297-308.

Decrease Progression to T2D



Adverse events:

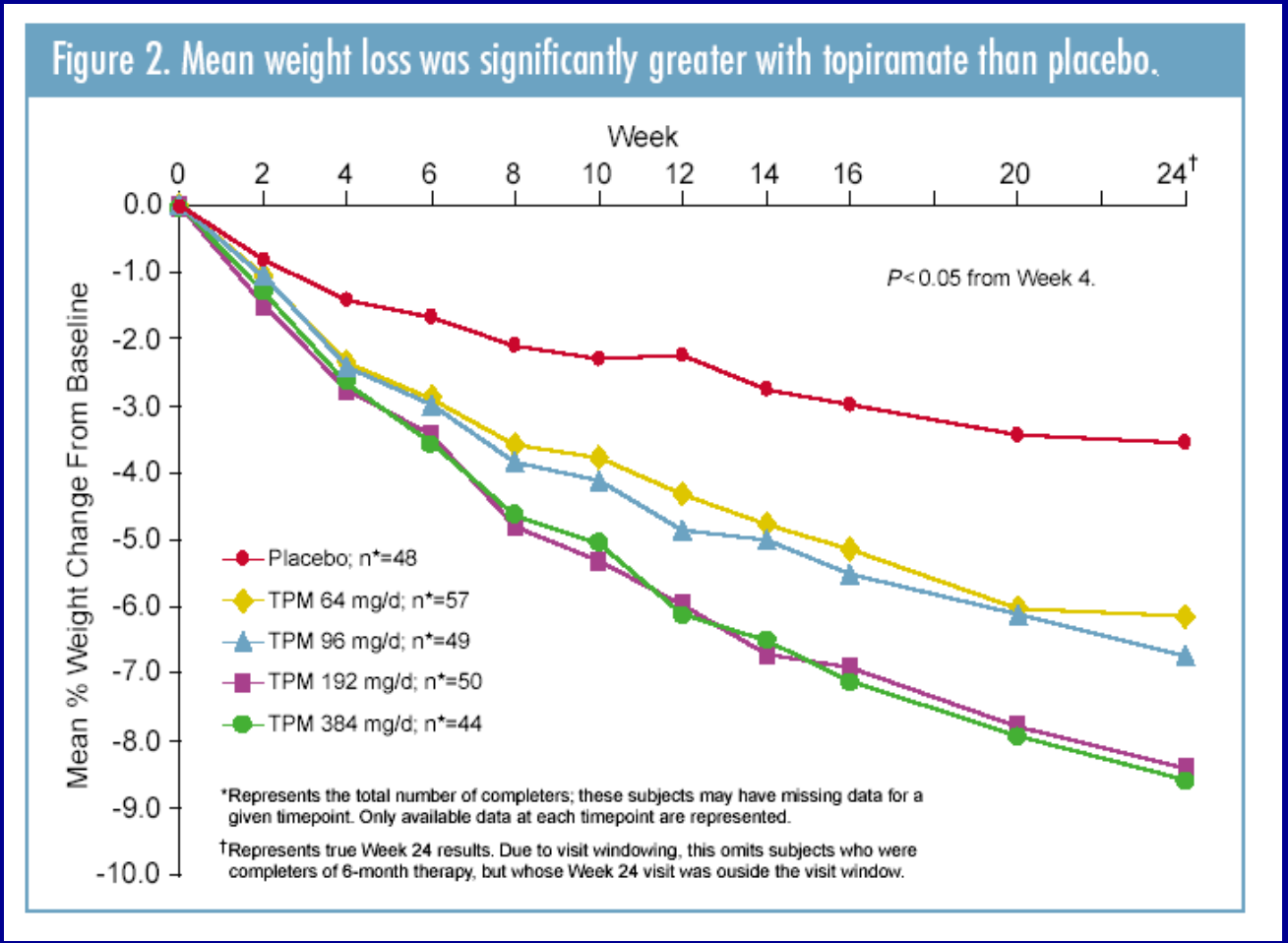
Most common: paraesthesia, dizziness, dysqueusia, insomnia, constipation, dry mouth

Other: increase HR, depression, anxiety , irritability, impairment of concentration, **difficulty with memory and word finding**, acute angle closure glaucoma, nephrolithiasis, hyperchloremic non-anion gap metabolic acidosis, hypokalemia

CLEFT PALATE

Topiramate

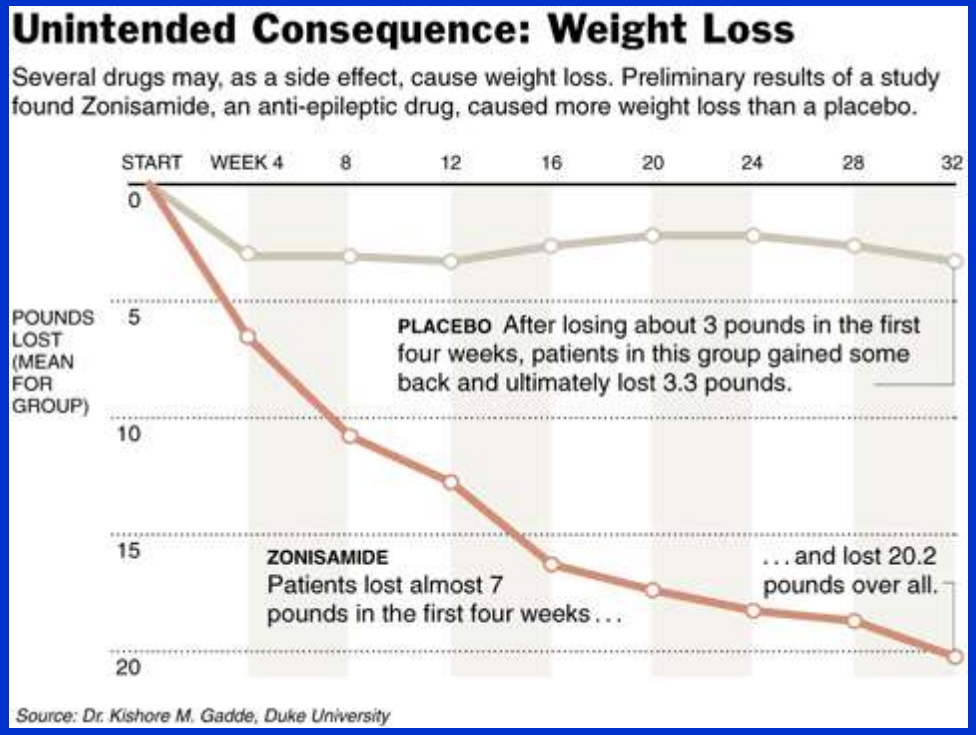
Randomized double-blind placebo-controlled trial in obese adults



Bray et al, Obesity Research, (2003) 11:722

Zonisamide

- Zonisamide, an antiepileptic with dopaminergic, serotonergic activity and Na & Ca channel blocker
- 16 week RCT with 16 week single blind extension
- Dose 400 – 600mg/day
- 60 subjects randomized, 51 completed
- Most common side effect: fatigue



Placebo
1.8% weight loss

Zonisamide
9.4 % weight loss
in 32 weeks

Gadde KM, JAMA 2003 289:1820-1825

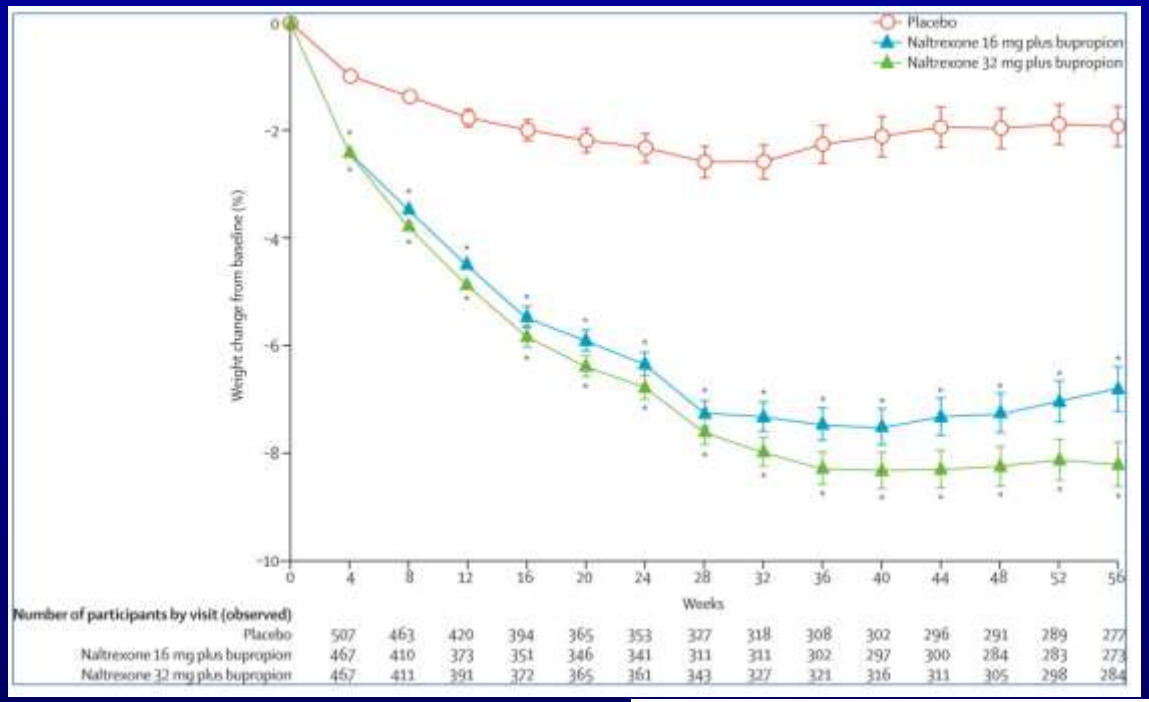
Graph, NY Times, 4/15/03

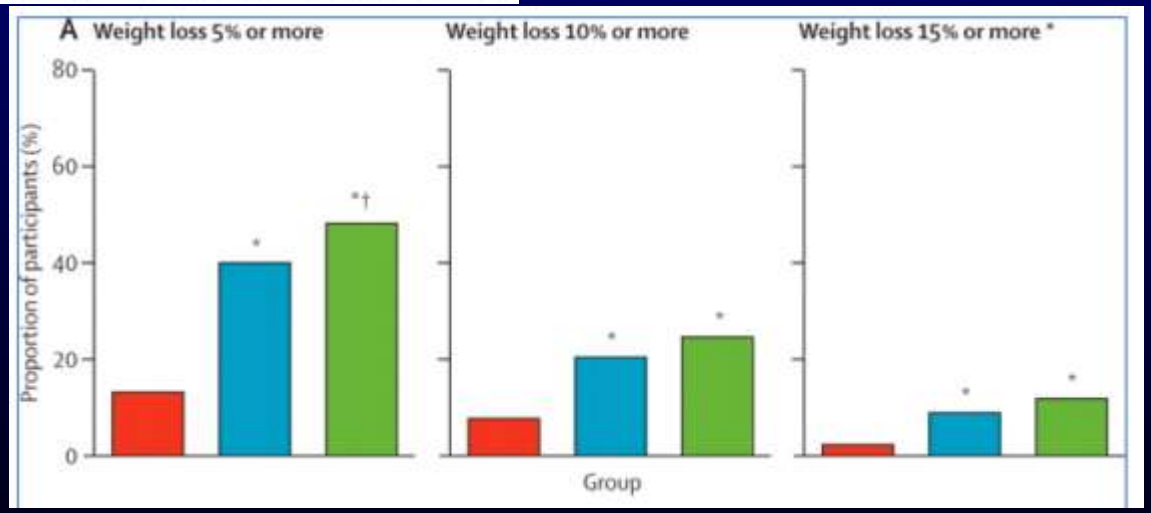
Naltrexone + Bupropion (Contrave)

Unclear mechanism of action:

- Bupropion stimulates POMC neurons; activates mesolimbic reward centers
- Naltrexone prevents inhibition of POMC neurons by beta-endorphin

Naltrexone + Bupropion (Contrave)





Greenway et al, Lancet 376:595-605, 2010

Naltrexone/Bupropion

Side Effects:

- Nausea, headache, constipation, dizziness, vomiting, and dry mouth were also more frequent in the naltrexone plus bupropion groups vs. placebo
- Transient increase of ~1 mm Hg in mean systolic and diastolic blood pressure and 2 bpm HR
- Combination treatment was not associated with increased depression or suicides vs. placebo BUT possible activation of mania, depression, suicide

Contraindications:

- Pregnancy, uncontrolled HTN, seizure disorders, anorexia or bulimia, use of other bupropion-containing products, MAOIs, CHRONIC OPIOD USE, ABRUPT DISCONTINUATION OF ALCOHOL
- May trigger an angle-closure attack

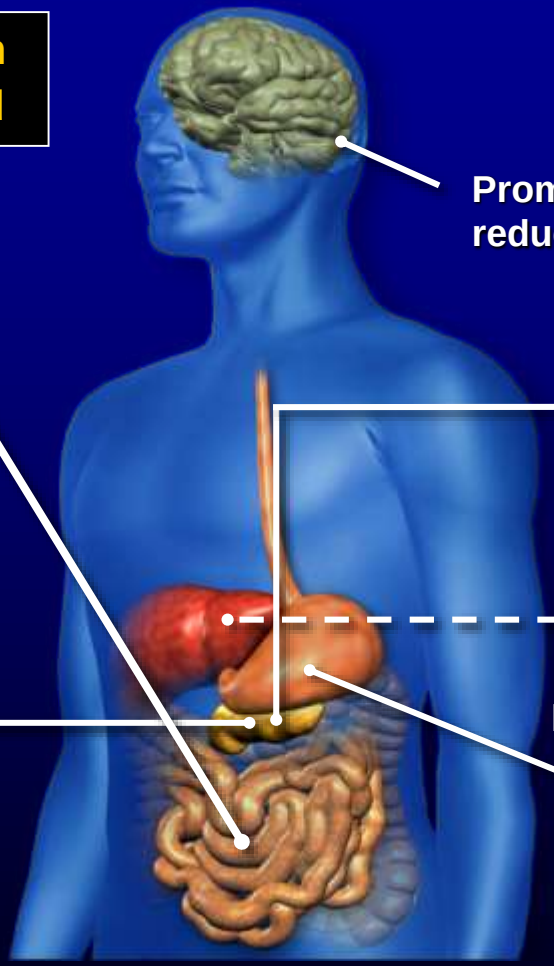
Other drug interactions:

- Antidepressants, antipsychotics, beta-blockers, Type 1D antiarrhythmics, ticlopidine, clopidogrel

Greenway FL, et al. Lancet. 2010 Aug 21;376(9741):595-605; Prescribing Information

GLP-1 Modulates Numerous Functions in Humans

GLP-1: Secreted upon the ingestion of food



Promotes satiety and reduces appetite

Alpha cells:
↓ Postprandial glucagon secretion

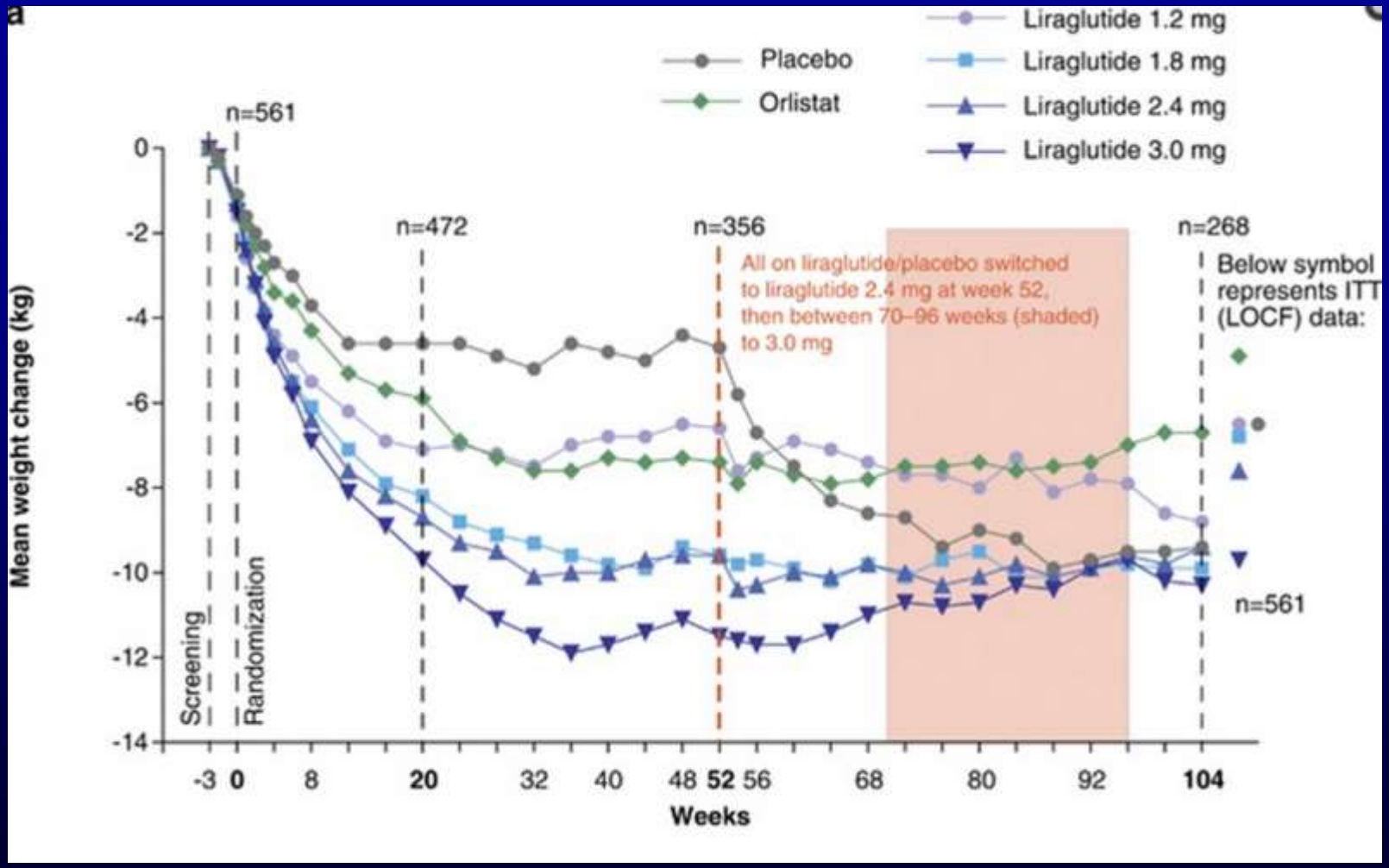
Liver:
↓ Glucagon reduces hepatic glucose output

Beta cells:
Enhances glucose-dependent insulin secretion

Stomach:
Helps regulate gastric emptying

Data from Flint A, et al. *J Clin Invest*. 1998;101:515-520; Data from Larsson H, et al. *Acta Physiol Scand.* 1997;160:413-422
Data from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553; Data from Drucker DJ. *Diabetes*. 1998;47:159-169

Effects of Liraglutide (GLP1R agonist) on Body Weight in Nondiabetic Obese Adults



10.3 kg weight loss

Astrup A, et al. *Int J Obes* 2012; 36: 843–854.

Data are mean (95% CI) for the ITT population

Liraglutide

Side Effects:

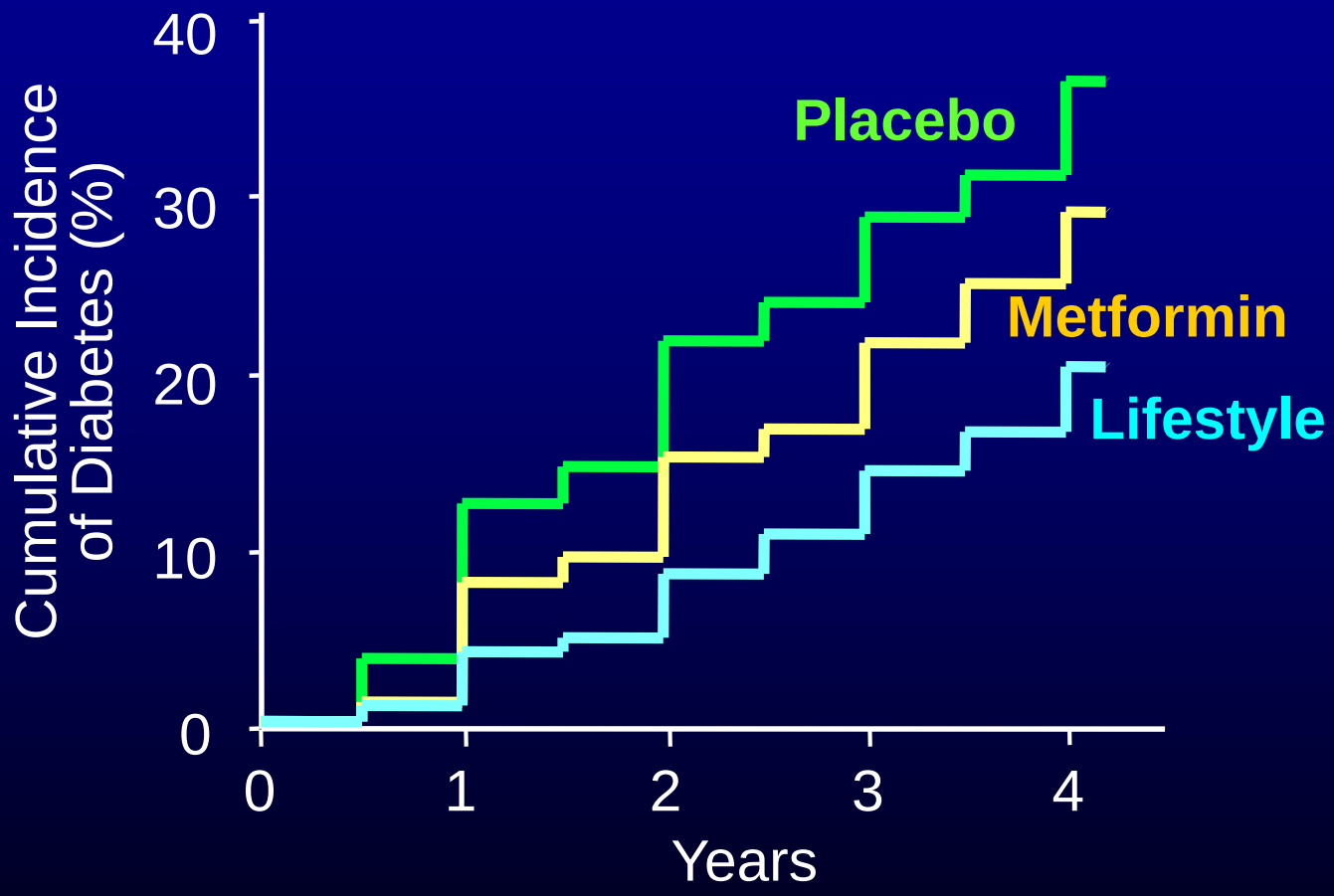
- Nausea, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase
- At year 1, nausea and/or vomiting was associated with greater weight loss with liraglutide 3.0 mg, but even those who did not experience these events lost more weight than those on placebo or orlistat

Warnings and Precautions:

- Acute pancreatitis, cholelithiasis, hypoglycemia, increase heart rate, renal impairment, hypersensitivity
- Thyroid C-cell tumors in rodents: contraindicated in patients with personal or family history of medullary thyroid carcinoma or MEN 2

Astrup A, et al. *Int J Obes (Lond).* Jun 2012; 36(6): 843–854 and Prescribing Information.

Diabetes Prevention Program – Modest Weight-Loss Reduces the Incidence of New-Onset Diabetes in an At-Risk Population



Weight loss	Decrease in risk*
0.1 kg	
2.1 kg	31%
5.6 kg	58%

P<0.001 for each comparison.

*Decrease in risk of developing diabetes, compared to placebo group.

Diabetes Prevention Program Research Group. *N Engl J Med.* 2002;346:393-403.

$$$$

- Not covered by Medicare/Medicaid and many commercial insurance
- Older generics (phentermine)
- Off-label use: i.e. metformin; topiramate +/- phentermine
- Discount programs/ Co-Pay
- Free lifestyle programs