The Most Common Condition of all?

Jonathan Stoehr, MD PhD
Virginia Mason Medical Center

Disclosures

There is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Case Vignette (Part 1 of 4)

- **HPI:** 55 y/o woman presents for review of abnormal lab findings (fasting glucose 155). She denies polydipsia / polyuria, but is frustrated at her inability to lose weight despite increases in walking and water aerobics, and attention to diet.
- **PMH:** Hyperlipidemia, HTN, plantar fasciitis
- **MEDS**: Loestrin, Atenolol

Case Vignette (Part 2 of 4)

- **FH:** Type 2 diabetes in both parents
- **ROS:** Bilateral knee pain, fatigue (daytime sleepiness), heartburn
- **VITALS:** p85, bp 139/85, rr 18
  - Weight 211# (99kg), Ht 5'6", BMI 34

Case Vignette (Part 3 of 4)

- **EXAM:**
  - Central adiposity. No Cushingoid features.
  - Abd: limited by body habitus, liver edge palpated 4cm below costal margin
  - Skin: +skin tags. +Acanthosis nigricans.
  - Ext: non-pitting “lipedema”

Case Vignette (Part 4 of 4)

- **LABS:**
  - Fasting glucose 155, otherwise normal Chem7
  - ALT 65, AST 32, TBili 1.0, AlkPhos 52
  - A1c 6.9%

Questions

- **What is this patient's primary health problem?**
  A. Type 2 Diabetes
  B. Hyperlipidemia
  C. Hypertension
  D. Suspected Sleep Apnea
  E. Suspected Non-Alcoholic Fatty Liver
  F. GERD
  G. Obesity

- **How should our precious clinic time be budgeted to most effectively intervene?**

Objectives

- Briefly review the epidemiology and health impact of the obesity epidemic, and new relevant clinical practice guidelines.
- Review the clinical data on new medications approved for weight loss in obese patients.

Obesity: A threat to health, life expectancy & economy

- Obesity has passed cigarette smoking as the leading source of Quality-Adjusted Life Years lost in the USA.

  Am J Prev Med. 2010 Feb;38(2):138-44

- Obesity associated with $1,400 per year increase in direct medical costs per patient.
  Diabetes: $6,600 per year (per patient).

  CDC Data, Thomas Frieden

- Direct medical costs associated with overweight/obesity $113.9 billion in 2008.

  Obes Rev. 2011 Jan;12(1):50-61

Body Mass Index: Weight (kg) / Height (m^2)

	BMI
Underweight	< 18.5
Normal	18.5-24.9
Overweight	≥ 25
"Pre-Obese"	25-29.9
Obesity	≥ 30
Obesity Class I	30-34.9
Obesity Class II	35-39.9
Obesity Class III	≥ 40

Type 2 Diabetes
Hypertension
Hyperlipidemias
Cardiovascular Disease
NAFLD
Gallstone Disease
Obstructive Sleep Apnea
Degen. Joint Disease
Pulmonary Hypertension
Cancers: Breast, Kidney, Endometrium, Pancreas, Colon/Rectum, Thyroid, Gallbladder, Esophagus

Economic / Social Impact

Nearly 7 in 10 US Adults are Overweight and 35% are Obese

	Overweight	Obese	Obesity Class III
All	68.8%	35.7%	6.3%
All Females	63.7%	35.8%	8.1%
White, Non-Hispanic	59.5%	32.2%	7.1%
Black, Non-Hispanic	82.1%	58.5%	17.8%
Hispanic	75.7%	41.4%	6.0%
All Males	73.9%	35.5%	4.4%
White, Non-Hispanic	74.0%	36.2%	4.2%
Black, Non-Hispanic	69.9%	38.8%	7.4%
Hispanic	81.7%	37.0%	4.1%

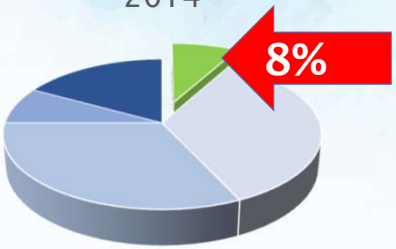
Obesity: Prevalent Among Patients Presenting with Common Complaints

Osteoarthritis

1448 unique patients, Q1 2014

Sleep Apnea

3218 unique patients, Q1 2014

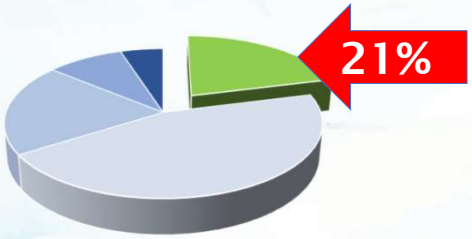


Type 2 Diabetes

5845 unique patients, Q1 2014

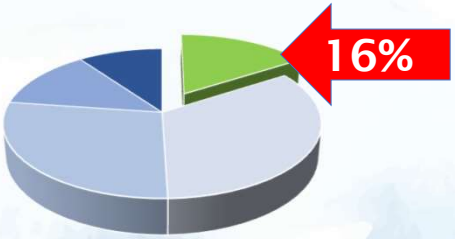
Hyperlipidemia

8577 unique patients, Q1 2014



Hypertension

9822 unique patients, Q1 2014



- = Normal Weight (BMI <25)
- = Overweight (BMI 25-30)
- = Obesity I (BMI 30-35)
- = Obesity II (BMI 35-40)
- = Obesity III (BMI >40)

Woodward S and Stoehr JP. Internal review of all patient medical visits to Virginia Mason Medical Center, q1 2014

Obesity: A Global Pandemic

- In 2014, >1.9 billion adults overweight
  > 600 million obese
- Worldwide prevalence of obesity has more-than doubled since 1980.
- Over 2.8 million people each year die as a result of being overweight or obese.
- Globally, more deaths are now attributable to overweight / obesity than to underweight.

World Health Organization, January 2015
http://www.who.int/mediacentre/factsheets/fs311/en/

Is a 5% weight reduction clinically meaningful for patients?

Established Health Benefits of a 5% Weight Reduction

- Prevention of Diabetes
  - Knowler WC et al. *NEJM* 2002. 346:394
- Improved Glycemic Control, in patients with DM2
  - Wycherley et al. *J Diab Obes Met*, 2008.
- Improvement in Sleep-Disordered Breathing
  - Peppard PE et al. *JAMA* 2000. 284:3015
  - Foster et al. *Arch Int Med* 2009. 169:1619.
- Improved Blood Pressure, LDL Cholesterol
  - Van Gaal LF et al. *Eur Heart J Suppl* 2005. 7:L21-26

US Surgeon General, Institutes of Medicine, NHLBI, NIDDK, Centers for Disease Control and Prevention

Established Health Benefits of a 5% Weight Reduction

- Improved joint pain / stiffness and function, in Osteoarthritis
  - Felson DT. *J Rheumatol* 1995. 43:7.
  - Christensen et al. *Osteoarthritis and Cartilage* 2005. 12(1):20-27
- Improved HR-QOL
  - Blaine BE et al. *J Health Psychology* 2007. 12:66
- Improved Reproductive Function, Fertility
  - Pasquali R et al. *Human Reprod* 2003. 9:359

US Surgeon General, Institutes of Medicine, NHLBI, NIDDK, Centers for Disease Control and Prevention

Clinical Practice Guidelines AHA/ACC/The Obesity Society

- Measure height and weight and **calculate BMI** at annual visits.... Measure waist circumference annually. Use BMI standards.

- Advise overweight / obese adults that the greater the BMI, the greater the risk of CVD, type 2 diabetes, and all-cause mortality.

http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437739.71477.ee.citation

Clinical Practice Guidelines AHA/ACC/The Obesity Society

- Counsel overweight / obese adults with CV risk factors that lifestyle changes that produce even modest, **sustained weight loss of 3%-5%** produce clinically meaningful health benefits, and greater weight losses produces greater benefits.

- Advise overweight and obese individuals… to participate for ≥6 months in a **comprehensive lifestyle program**.

- Prescribe on site, high-intensity (e.g. ≥14 sessions in 6 months) comprehensive weight loss interventions…

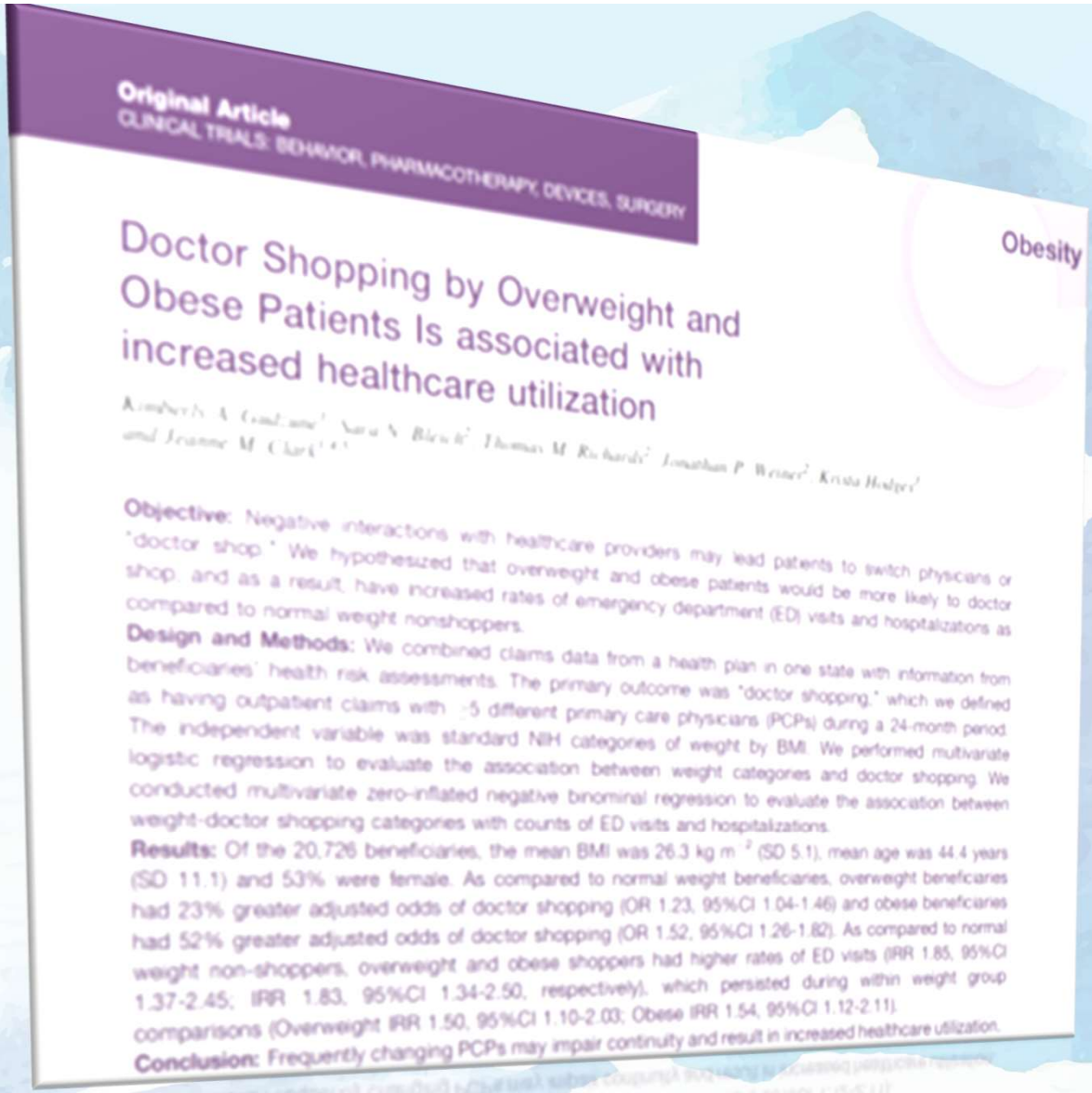
http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437739.71477.ee.citation

Where to begin?

Inability to Properly Address Weight Concerns

leads to

Doctor Shopping



Original Article
CLINICAL TRIALS: BEHAVIOR, PHARMACOTHERAPY, DEVICES, SURGERY

Obesity

Doctor Shopping by Overweight and Obese Patients Is associated with increased healthcare utilization

Kimberly A. Gudzune[1], Sara N. Bleich[2], Thomas M. Richards[1], Jonathan P. Weiner[2], Krista Hodges[1] and Jeanne M. Clark[1,2]

Objective: Negative interactions with healthcare providers may lead patients to switch physicians or "doctor shop." We hypothesized that overweight and obese patients would be more likely to doctor shop, and as a result, have increased rates of emergency department (ED) visits and hospitalizations as compared to normal weight nonshoppers.

Design and Methods: We combined claims data from a health plan in one state with information from beneficiaries' health risk assessments. The primary outcome was "doctor shopping," which we defined as having outpatient claims with ≥5 different primary care physicians (PCPs) during a 24-month period. The independent variable was standard NIH categories of weight by BMI. We performed multivariate logistic regression to evaluate the association between weight categories and doctor shopping. We conducted multivariate zero-inflated negative binominal regression to evaluate the association between weight-doctor shopping categories with counts of ED visits and hospitalizations.

Results: Of the 20,726 beneficiaries, the mean BMI was 26.3 kg m^{-2} (SD 5.1), mean age was 44.4 years (SD 11.1) and 53% were female. As compared to normal weight beneficiaries, overweight beneficiaries had 23% greater adjusted odds of doctor shopping (OR 1.23, 95%CI 1.04-1.46) and obese beneficiaries had 52% greater adjusted odds of doctor shopping (OR 1.52, 95%CI 1.26-1.82). As compared to normal weight non-shoppers, overweight and obese shoppers had higher rates of ED visits (IRR 1.85, 95%CI 1.37-2.45; IRR 1.83, 95%CI 1.34-2.50, respectively), which persisted during within weight group comparisons (Overweight IRR 1.50, 95%CI 1.10-2.03; Obese IRR 1.54, 95%CI 1.12-2.11).

Conclusion: Frequently changing PCPs may impair continuity and result in increased healthcare utilization.

How to Initiate a Conversation about Weight?

- Ask PERMISSION to discuss the issue.
- Express genuine CONCERN.
- Ask OPEN ENDED QUESTIONS and provide AFFIRMATION.

How to help patients achieve weight loss?

Medications associated with Weight Gain

Anti-diabetes Agents

- Insulin
- Glipizide, Glyburide
- Pioglitazone

Corticosteroids

- Prednisone
- Dexamethasone
- Inhaled / Articular

Psychiatric Meds

- Dopamine Antagonists
- Atypical Antipsychotics
- Tricyclics
- Lithium

Anticonvulsants

- Valproic Acid
- Carbamazepine
- Gabapentin

Antihypertensives

- Beta Blockers

Hormones

- Estrogen
- Progestins

Returning to Case Vignette…

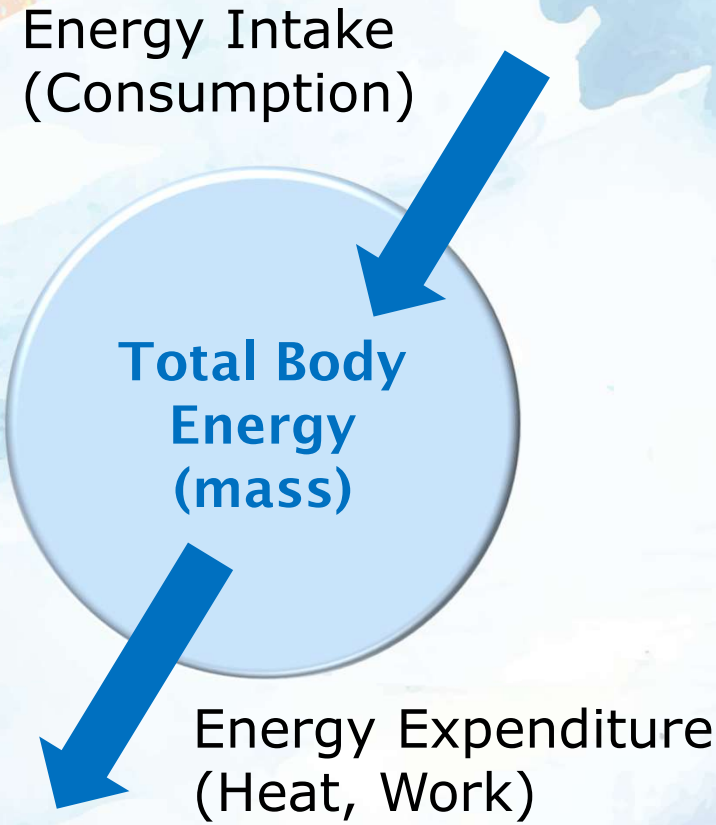
- **HPI:** 55 y/o woman presents for review of abnormal lab findings (fasting glucose 155). She denies polydipsia / polyuria, but is frustrated at her inability to lose weight despite increases in walking and water aerobics, and attention to diet.
- **PMH:** Hyperlipidemia, HTN, plantar fasciitis
- **MEDS**: Loestrin, Atenolol

Treatment of Peptic Ulcer Disease, ca 1970

Lifestyle Modification	→	No Effect Progressive Disease
Medical Therapy	→	Modest Improvement
Surgery	→	Significant Improvement Chance for Cure

1970's Approach to the Obese Patient

Obesity as a disorder of personality

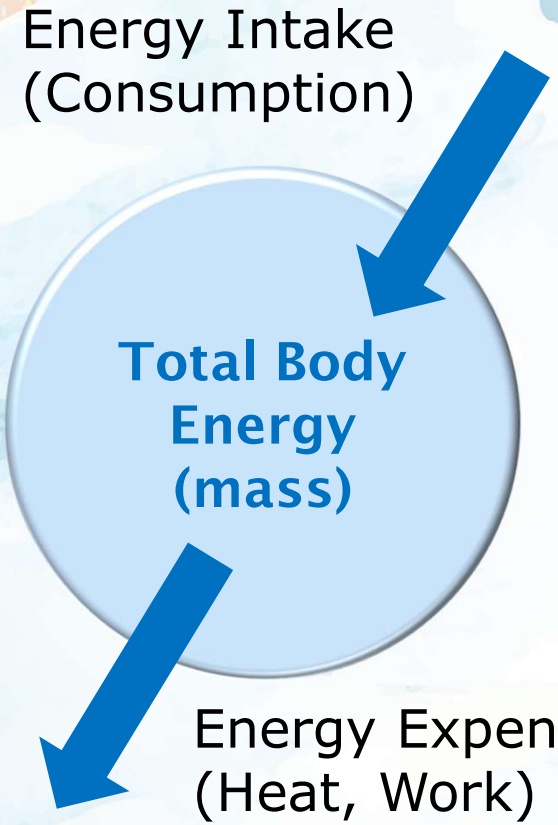


Obesity caused by lack of self control (over-consumption), laziness (sedentary lifestyle), poor impulse control (cravings).

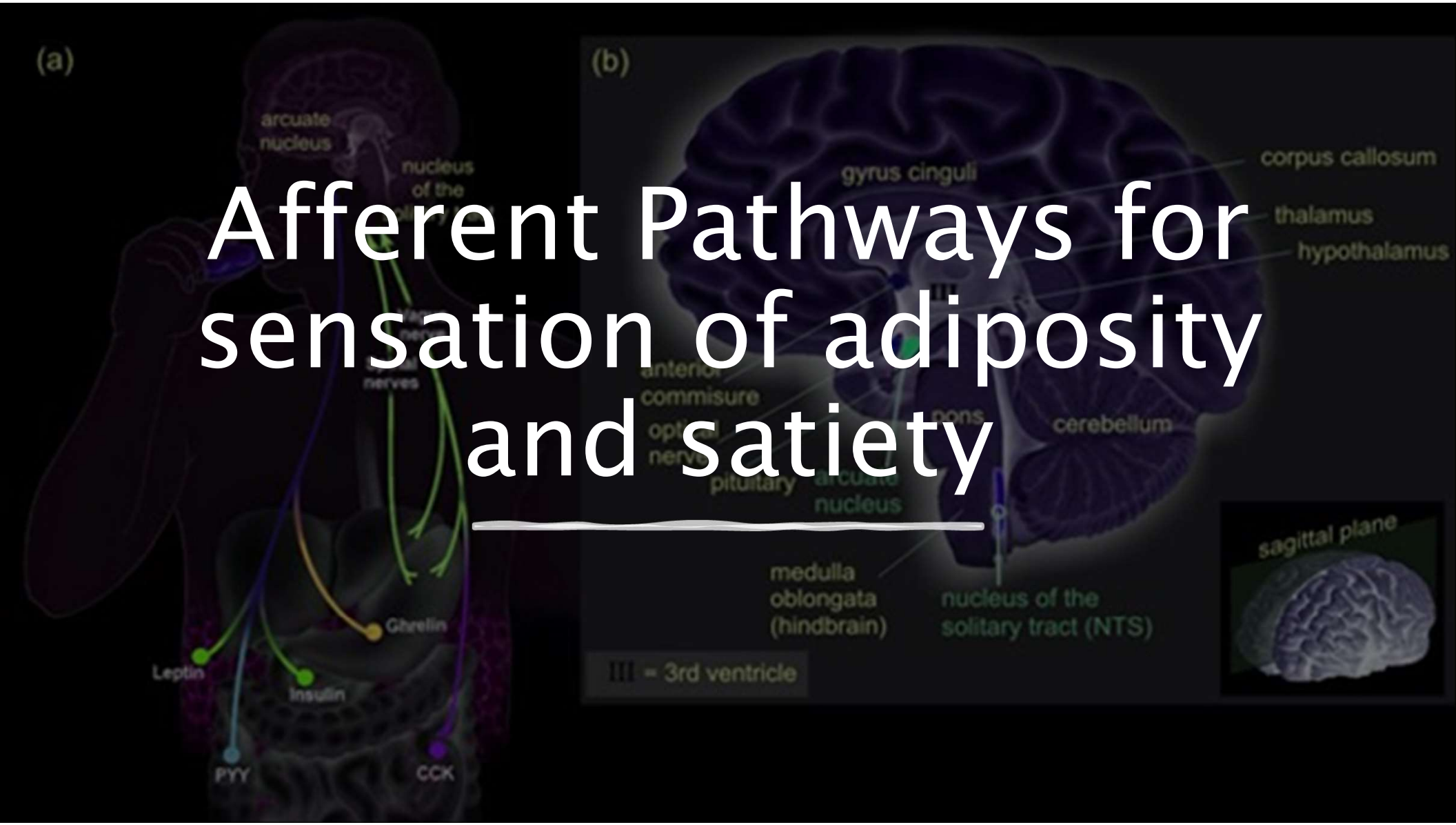
Pejorative.
Harms Dr-Pt relationship.
No clinical utility

2022 Approach to the Obese Patient

Understanding Altered Physiology

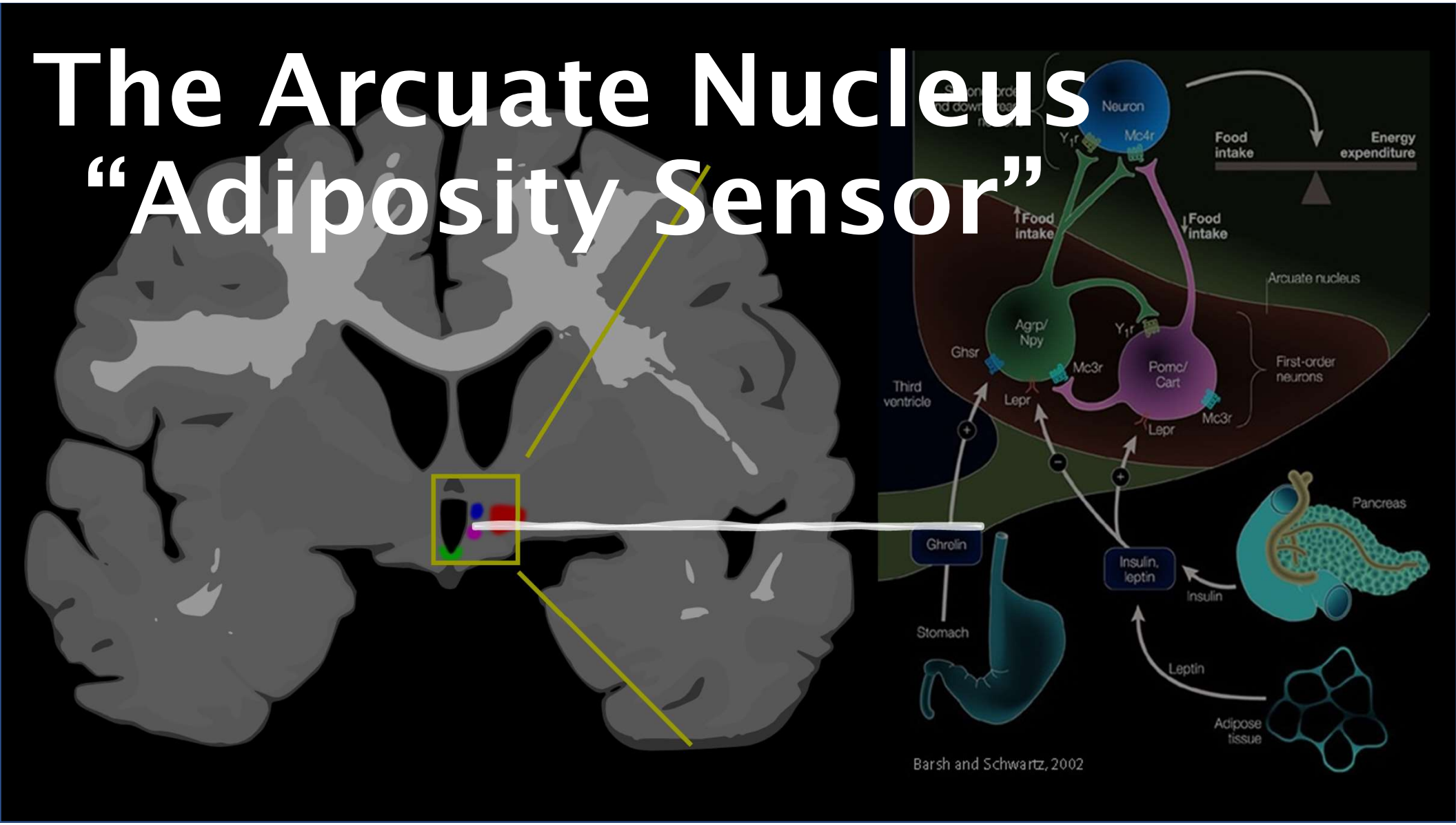


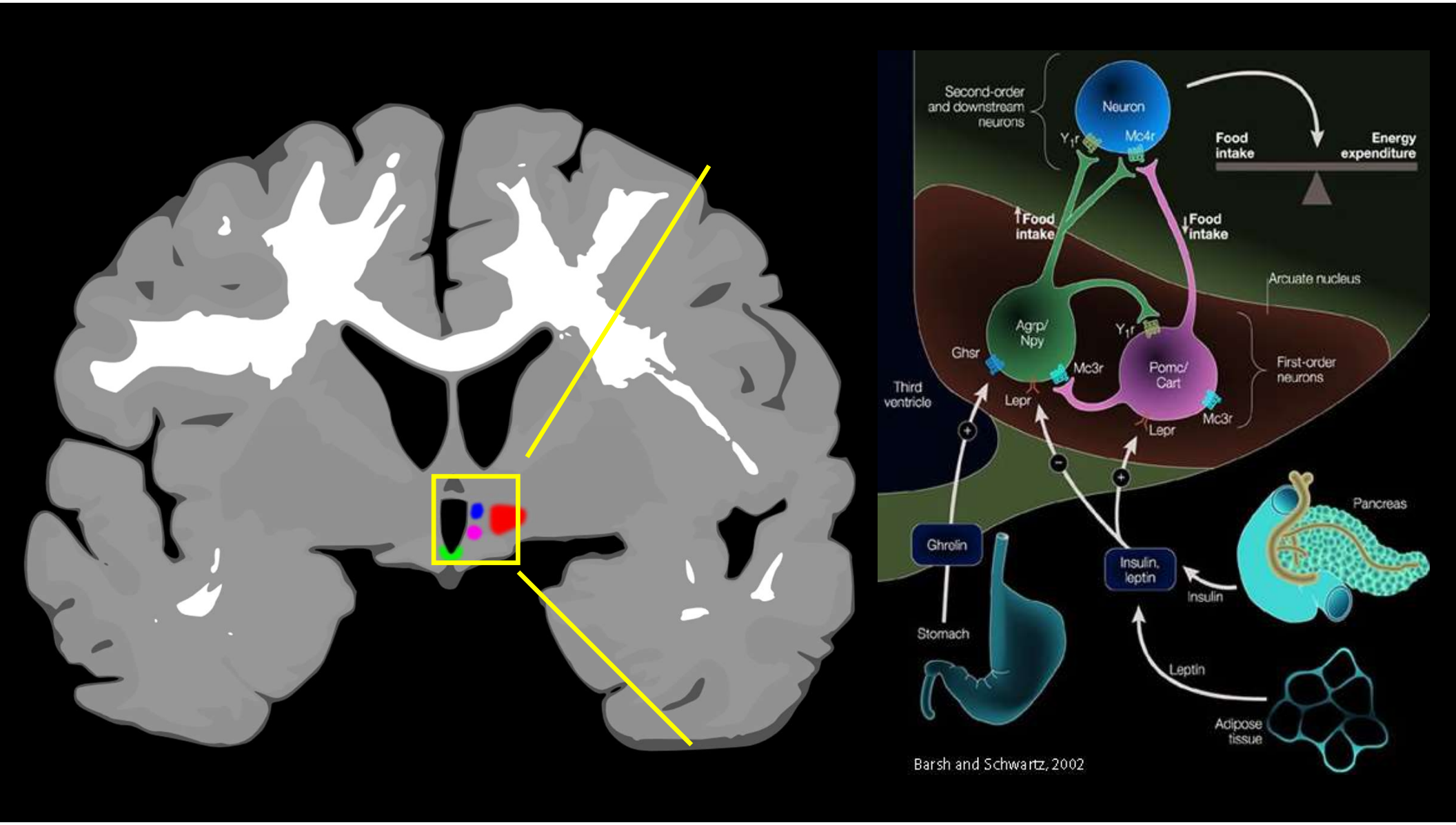
Food intake and energy expenditure are NOT totally under voluntary control, but reflect the effects of a neural network control system that measures and regulates body composition.



Afferent Pathways for sensation of adiposity and satiety

The Arcuate Nucleus "Adiposity Sensor"

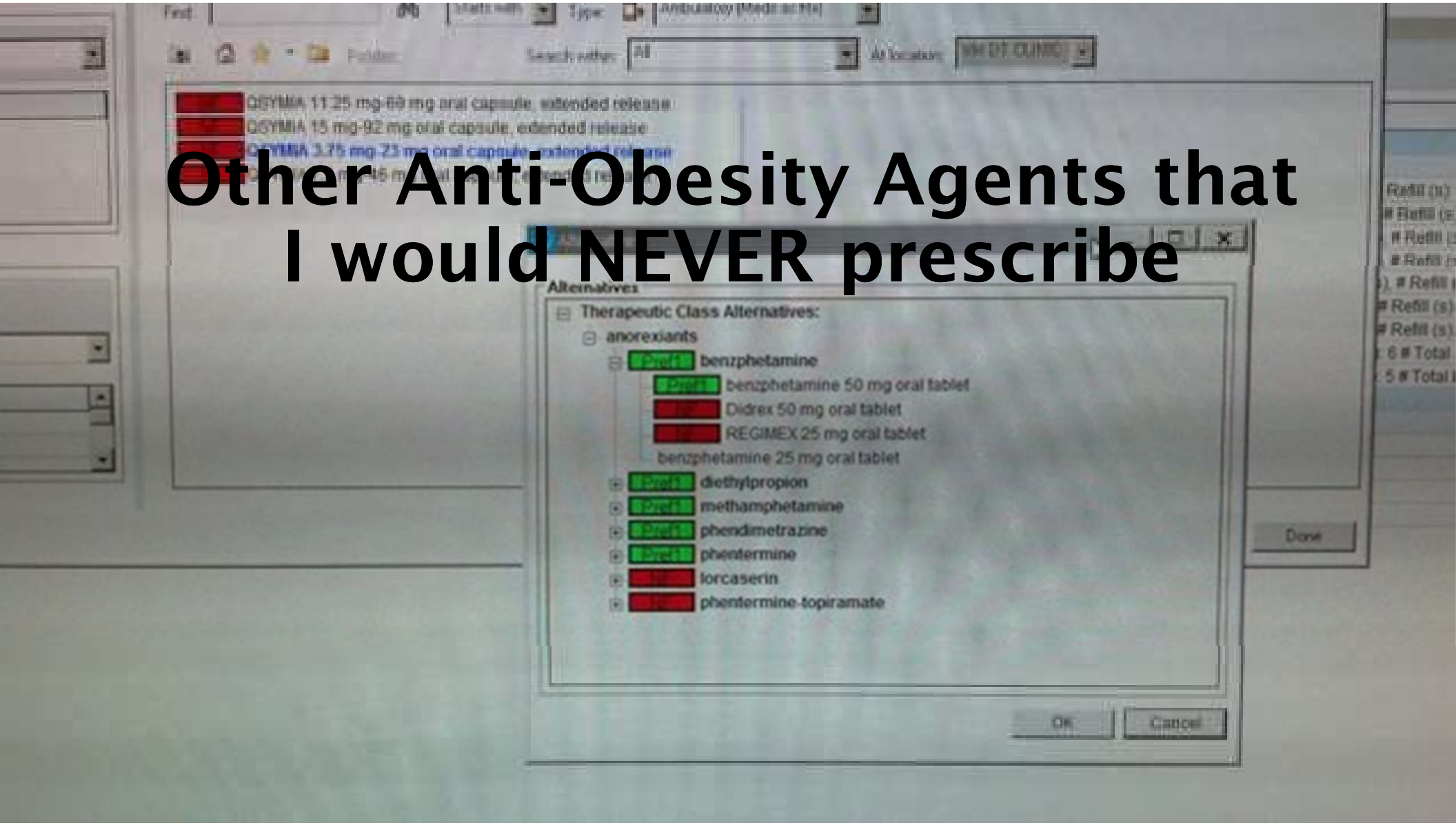



Second-order and downstream neurons
Neuron
Y1r
Mc4r
Food intake
Energy expenditure
↑Food intake
↓Food intake
Arcuate nucleus
Agrp/ Npy
Y1r
Ghsr
Mc3r
Pomc/ Cart
First-order neurons
Third ventricle
Lepr
Mc3r
Lepr
Pancreas
Ghrelin
Insulin, leptin
Insulin
Stomach
Leptin
Adipose tissue
Barsh and Schwartz, 2002

Phentermine (Adipex-P®, generic)

- **FDA Indications:** Obesity (1959)
- **Dosing:** 37.5mg PO QAM
- **Efficacy:** Mean 1-year placebo-adjusted weight loss of 3.6kg, by 2005 meta analysis.
- **ADRs:** Insomnia, HTN, irritability, dry mouth, dizziness, CV Events.
- **Status:** Approved for 12-week treatment based on original clinical trial duration. Schedule IV controlled substance.

Ann Intern Med 2005; 142: 532-546



Other Anti-Obesity Agents that I would NEVER prescribe

Phentermine/Topiramate (Qsymia®) for Obesity

Clinical Trials: Phentermine/Topiramate

PHASE 3: EQUIP

- BMI >35 with no weight complications
  - Excluded: FPG >110, BP >140/90, TG >200
- 1267 patients, 56 weeks
- Primary Endpoint: weight loss

PHASE 3: CONQUER

- BMI 27-45 with 2 weight complications
  - Included: Patients with controlled HTN, DM (metformin).
  - Excluded: Uncontrolled HTN, DM on other meds
- 2487 patients, 56 weeks
- Primary Endpoint: weight loss
- SEQUEL: 2-year extension study

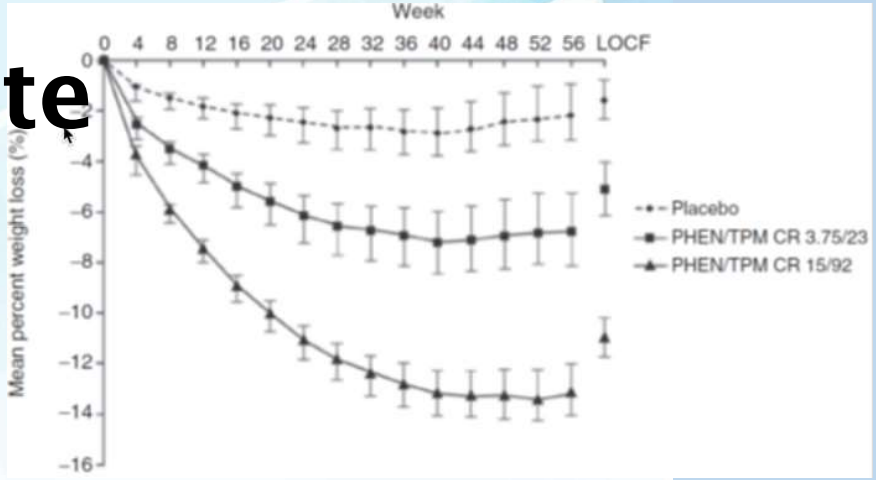
EQUIP: Phase 3 Trial Phentermine/Topiramate

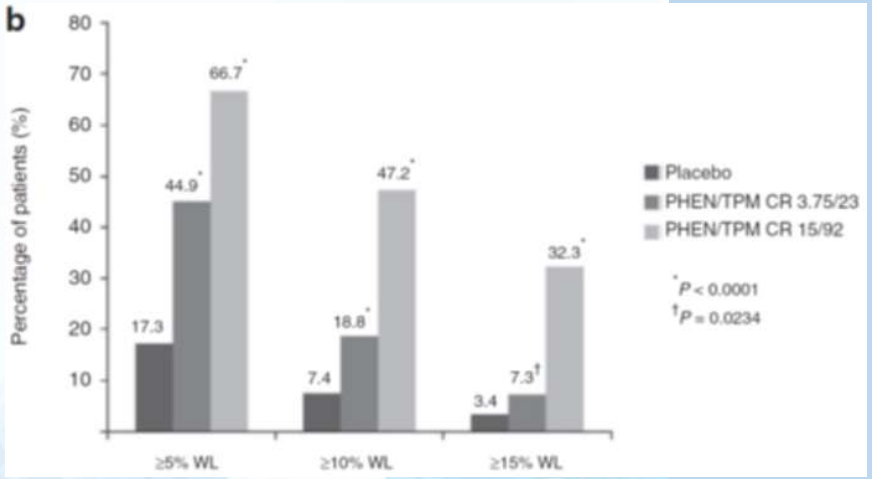
1-Year Placebo-Controlled RCT

Subjects: 1267 Patients with BMI >35 AND no complications

Intervention: Phentermine / Topiramate 3.75/23mg daily, 15/92mg daily, or Placebo

Outcomes:
Weight loss at 1-year
Cardiovascular Parameters, ADRs





EQUIP: Other Effects Phentermine/Topiramate

Improved CV Risk Markers

- WAIST CIRC. (-10.9CM)

- SYSTOLIC BP (-2.9MMHG)
- DIASTOLIC BP (-1.5MMHG)

- CHOLESTEROL (-6.0%)
- LDLC (-8.4%)
- HDLC (+6.8%)

- FASTING GLUCOSE

Adverse effects

- PARESTHESIA (4%-18%)
- DRY MOUTH (7%-17%)
- CONSTIPATION (8%-14%)
- HEADACHE (10%-12%)
- DYSGEUSIA (1%-8%)
- INSOMNIA (5%-8%)
- DIZZINESS (3%-6%)
- ANXIETY (3%-4%)
- IRRITABILITY (1%-5%)
- INATTENTION (1%-4%)

Obesity 2011; 20: 330-42

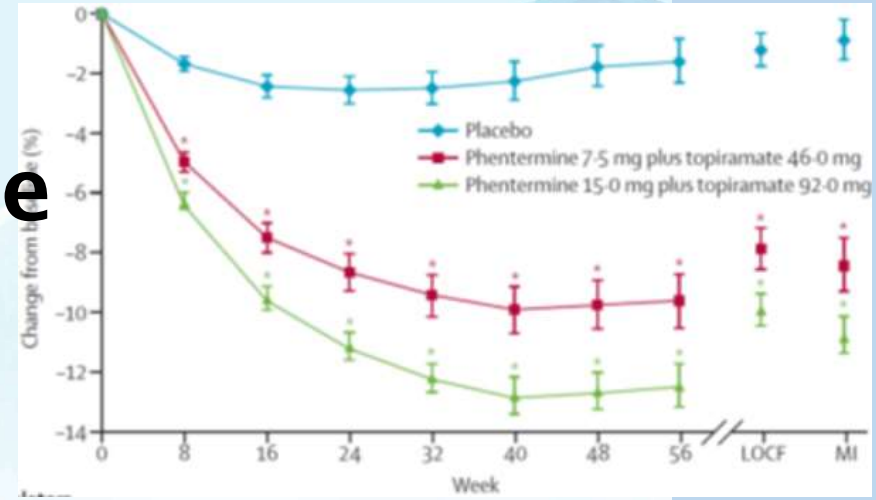
CONQUER: Phase 3 Trial Phentermine/Topiramate

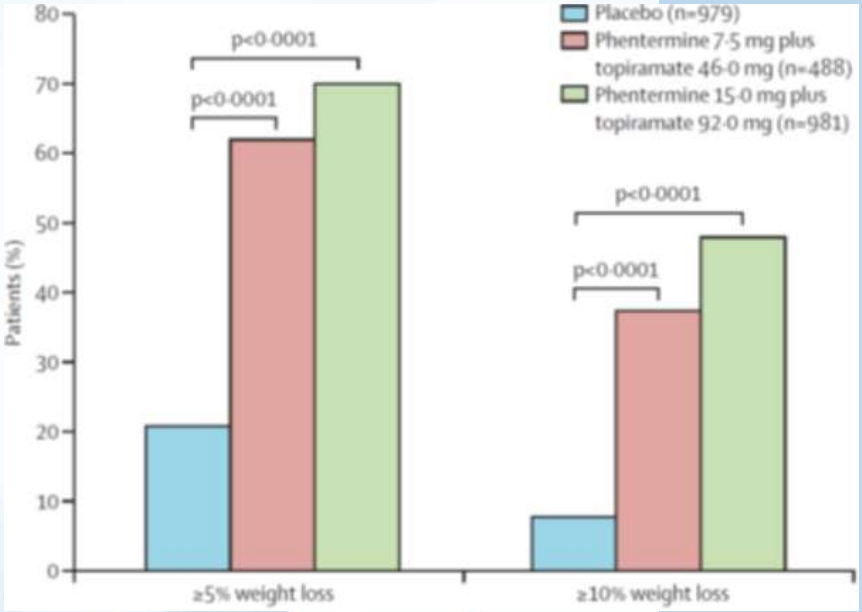
1-Year Placebo-Controlled RCT

Subjects: 2487 Patients with BMI 27-45 AND >2 Comorbidities

Intervention: Phentermine / Topiramate 7.5/46mg daily, 15/92mg daily, or Placebo

Outcomes:
Weight loss at 1-year
Cardiovascular Parameters
ADRs





CONQUER: Other Effects Phentermine/Topiramate

Improved CV Risk Markers

WAIST CIRC. (-9.2CM)

- SYSTOLIC BP (-5.6MMHG)
- DIASTOLIC BP (-3.8MMHG)

- CHOLESTEROL (-6.3MG/DL)
- LDLC (-6.9MG/DL)
- HDLC (+6.8MG/DL)
- TRIGLYCERIDES (-10.3MG/DL)

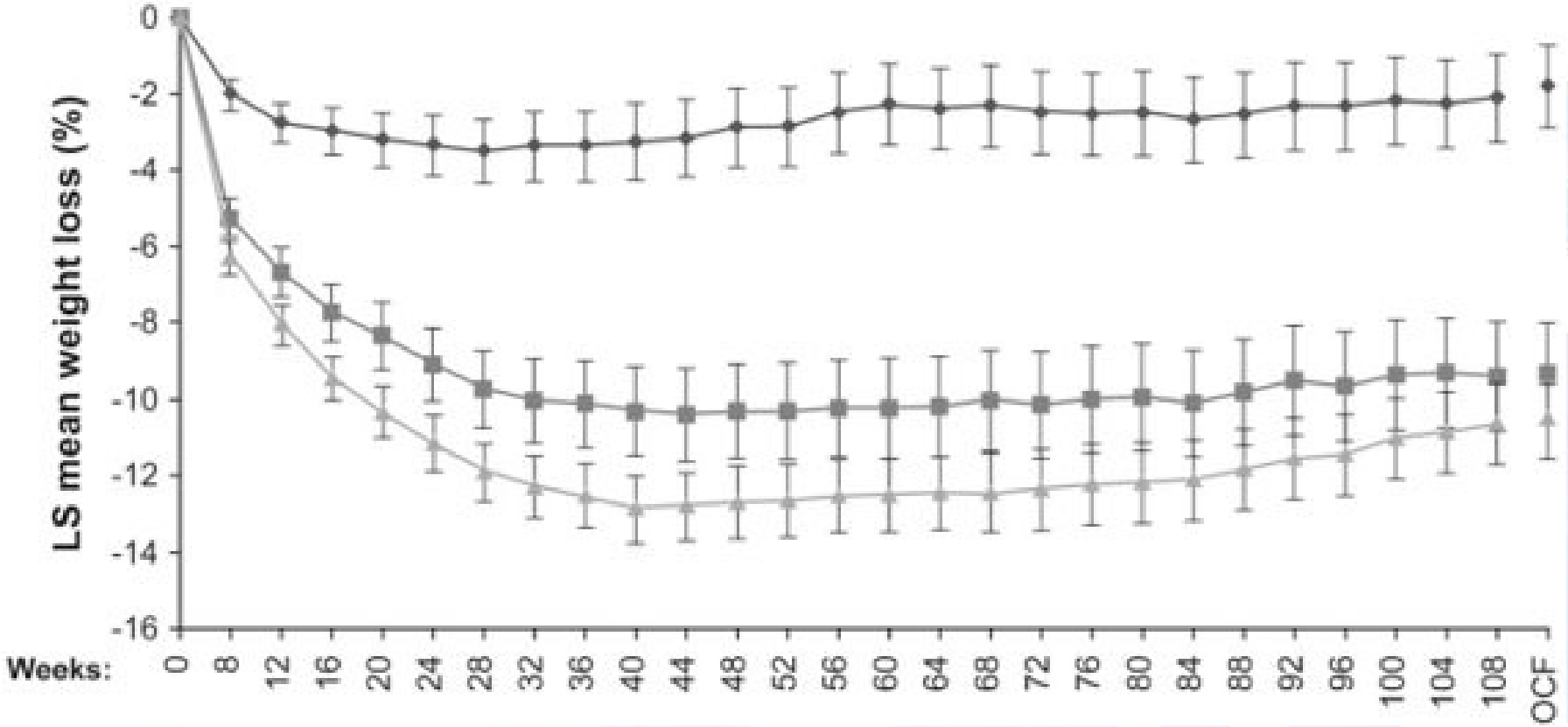
- INSULIN, HOMA-IR, ADIPONECTIN, HS-CRP

Adverse effects

- PARESTHESIA (14%-21%)
- DRY MOUTH (13%-21%)
- CONSTIPATION (15%-17%)
- DIZZINESS (7%-10%)
- DYSGEUSIA (7%-10%)
- HEADACHE (7%-10%)
- INSOMNIA (6%-10%)
- ANXIETY (2%-4%)
- IRRITABILITY (3%)
- INATTENTION (2%-4%)

Lancet 2011; 377: 1341

SEQUEL: Weight Loss is durable over 2 Years Study Duration



Am J Clin Nutr 2012;95:297

Prescribing Issues: Teratogenicity with Topiramate

Registry Data: Infants exposed to topiramate in utero have higher rates of cleft lip / palate.

Animal Models: clinically relevant doses associated with craniofacial defects and lower birth weight.

Incomplete Cleft Lip or "Notch"

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Prescribing Issues: Teratogenicity with Topiramate

FDA Recommendation: AVOID in pregnant women, or women of childbearing age that are not practicing **effective contraception.**

Regular pregnancy tests, counseling. Males and postmenopausal females need counseling too.

Incomplete Cleft Lip or "Notch"

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Bupropion / Naltrexone (Contrave®) for Obesity

Clinical Trials: Bupropion/Naltrexone

PHASE 3: COR-I

- BMI 30-45, or 27-45 with HTN/HLD
- 1742 patients, 56 weeks
- Primary Endpoint: weight loss

PHASE 3: COR-II

- BMI 30-45, or 27-45 with HTN/HLD
- 1496 patients, 56 weeks
- Primary Endpoint: weight loss

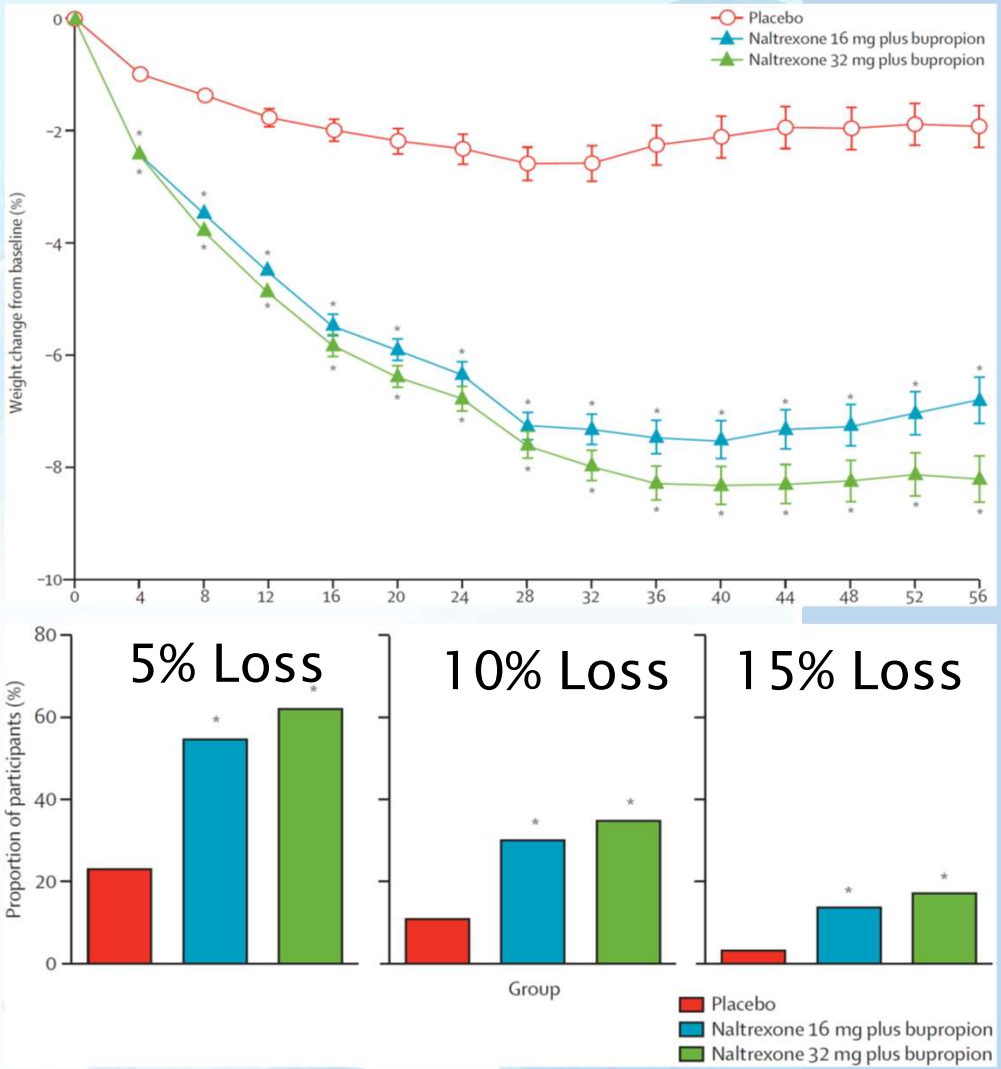
COR-I: Phase 3 Trial Bupropion/Naltrexone

56-week double-blind Placebo-Controlled RCT

Subjects: 1742 Patients with BMI 30-45 or
BMI 27-45 with HLD/HTN

Intervention: Bupropion / Naltrexone 360/32mg daily, 360/16mg daily, or Placebo

Outcomes:
Weight loss at 1-year
Cardiovascular Parameters
ADRs



Lancet 2010; 376: 595-605

COR-I: Other Effects Bupropion/Naltrexone

Improved CV Risk Markers

WAIST CIRC. (-6.2CM)

- LDLC (-2%)
- HDLC (+8%)
- TRIGLYCERIDES (-12.7%)

- FASTING GLUC. (-2%)
- FASTING INS. (-17%)
- HOMA-IR (-20%)

- IWQOL-LITE (+12.7)

Adverse effects

- NAUSEA (28-30%)
- HEADACHE (14-16%)
- CONSTIPATION (15%)
- URI (8-9%)
- DIZZINESS (8-9%)
- INSOMNIA (6-7%)
- VOMITING (6-10%)
- DRY MOUTH (7%)
- HOT FLASH (2-5%)

Lancet 2010; 376: 595-605

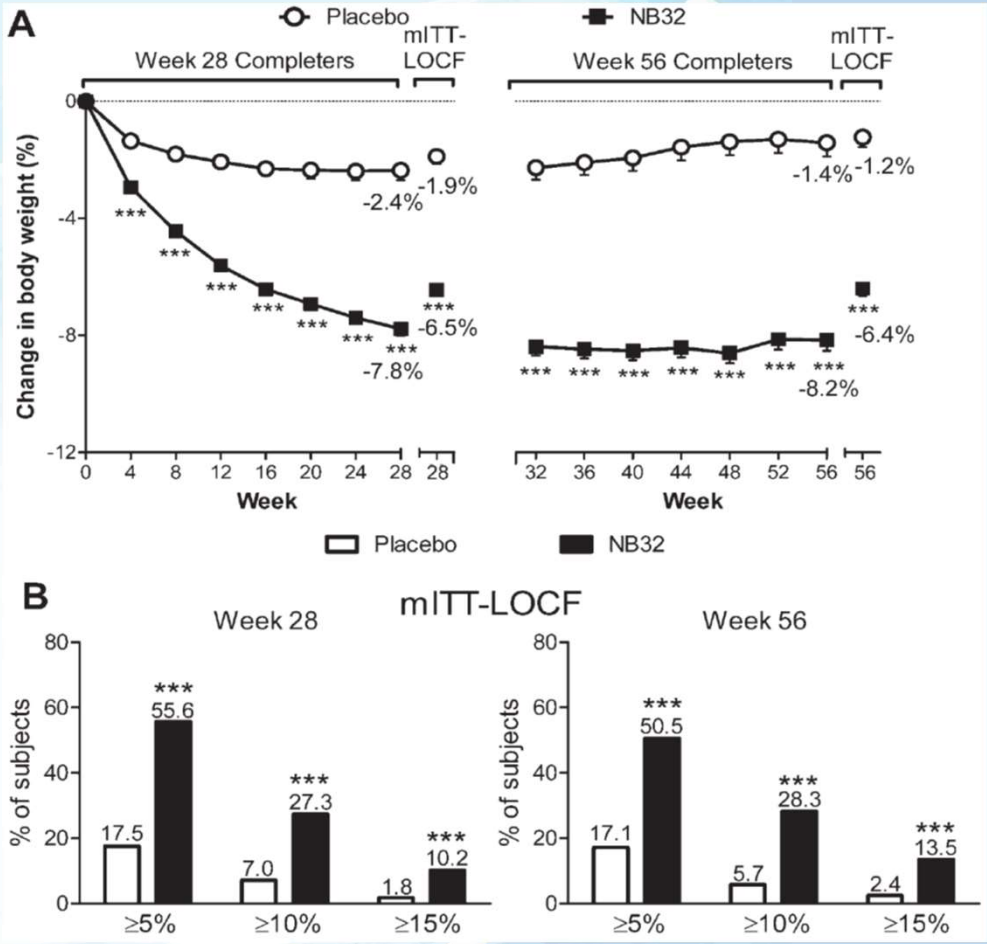
COR-II: Phase 3 Trial Bupropion/Naltrexone

56-week double-blind Placebo-Controlled RCT

Subjects: 1496 Patients with BMI 30-45 or BMI 27-45 with HLD/HTN

Intervention: Bupropion / Naltrexone 360/32mg daily, or Placebo. Non-responders randomly assigned to 360/48mg @ Wk 28

Outcomes: Weight loss at 1-year Cardiovascular Parameters, ADRs



Obesity 2013; 21: 935-43

COR-II: Other Effects Bupropion/Naltrexone

Improved CV Risk Markers

WAIST CIRC. (-6.7CM)

- LDLC (-6.2MG/DL)
- HDLC (+3.6MG/DL)
- TRIGLYCERIDES (-9.8%)

- FASTING GLUC. (-2.8MG/DL)
- FASTING INS. (-11%)
- HOMA-IR (-14%)

- IWQOL-LITE (+10.9)

Adverse effects

- NAUSEA (29%)
- CONSTIPATION (19%)
- HEADACHE (17%)
- INSOMNIA (10%)
- DRY MOUTH (9%)
- URI (8%)
- VOMITING (8.5%)
- DIZZINESS (7%)

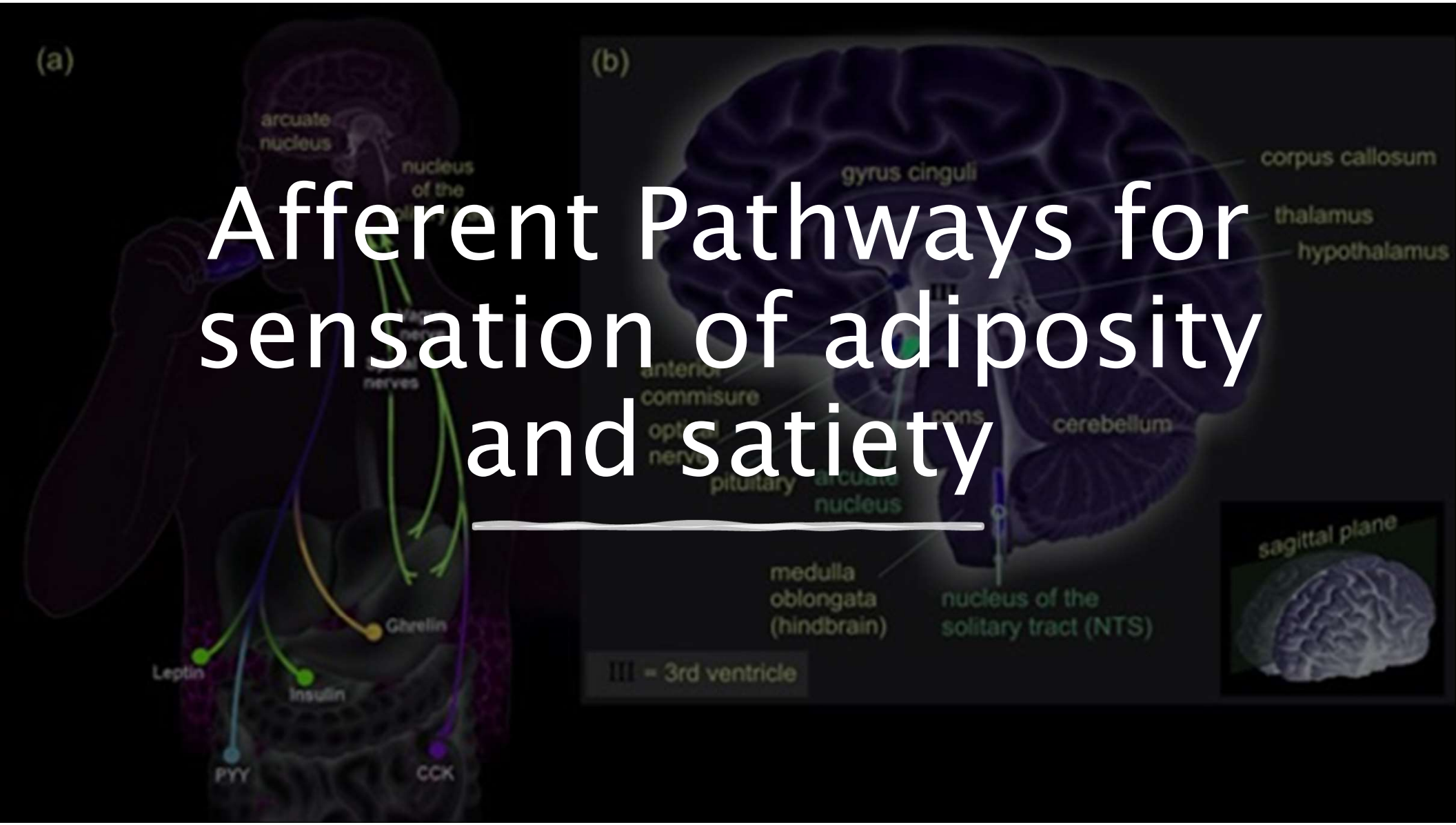
Obesity 2013; 21: 935-43

Prescribing Issues: Bupropion/Naltrexone

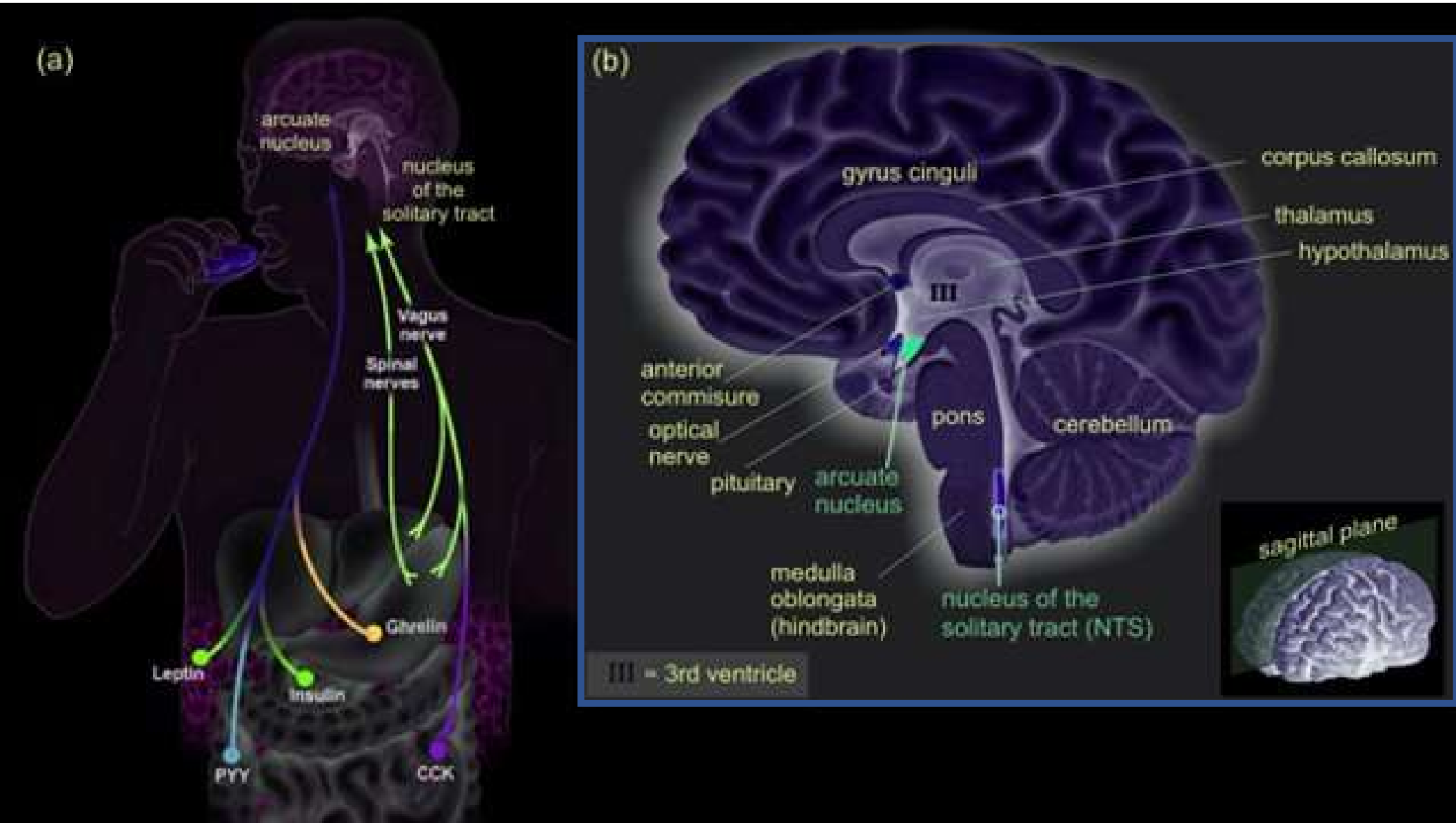
- **Opioid Antagonist:** AVOID in patients taking chronic opiates or other potent mu-opioid agonists.
- **Severe Depression:** Bupropion associated with suicidality in children, adolescents and young adults.
- Contraindicated in pregnancy.

Contrave Prescribing Information, rev Sept 2014

Liraglutide (Saxenda®) For Obesity



Afferent Pathways for sensation of adiposity and satiety


(a)
arcuate nucleus
nucleus of the solitary tract
Vagus nerve
Spinal nerves
Ghrelin
Leptin
Insulin
PYY
CCK
(b)
gyrus cinguli
corpus callosum
thalamus
hypothalamus
III
anterior commisure
optical nerve
pituitary
arcuate nucleus
pons
cerebellum
medulla oblongata (hindbrain)
nucleus of the solitary tract (NTS)
III = 3rd ventricle
sagittal plane

Clinical Trials: Liraglutide for Obesity

PHASE 2:

- BMI 30-40
  - Excluded: Diabetes
- 2487 patients
- 20 weeks blinded, 2 years open-label extension.
- Primary Endpoint: weight loss

PHASE 3: SCALE

- BMI >30, or >27 with HTN or dyslipidemia
  - Excluded: diabetes, bariatric surgery
- 3731 patients, 56 weeks
- Primary Endpoint: weight loss

SCALE Other Effects
Liraglutide 3.0mg/d

Improved CV Risk Markers

WAIST CIRC. (-8.2CM)

- LDLC (-3%)
- HDLC (+2%)
- TRIGLYCERIDES (-13%)

- FASTING GLUC. (-7.1MG/DL)
- FASTING INS. (-13%)
- HOMA-IR (-14%)

- SYSTOLIC BP (-4.2 MMHG)
- DIASTOLIC BP (-2.6 MMHG)

Adverse effects

- NAUSEA (40%)
- DIARRHEA (21%)
- CONSTIPATION (20%)
- VOMITING (16%)
- DYSPEPSIA (10%)
- UPPER ABD PAIN (5%)
- HEADACHE (13%)
- DIZZINESS (6%)

- CHOLELITHIASIS (0.8%)
- PANCREATITIS (0.2%)

N Engl J Med 2015; 373: 11-22

Semaglutide (Wegovy®) For Obesity

Clinical Trials: Semaglutide for Obesity

PHASE 2:

- BMI >30 without diabetes
- 957 patients
- Semaglutide vs. Liraglutide vs. Placebo
- 52 weeks blinded
- Primary Endpoint: weight loss

PHASE 3: STEP1 Trial

- BMI >30, or >27 with >1 weight-related condition
- 1961 patients, 68 weeks
- Semaglutide vs. Placebo
- Primary Endpoint: weight loss

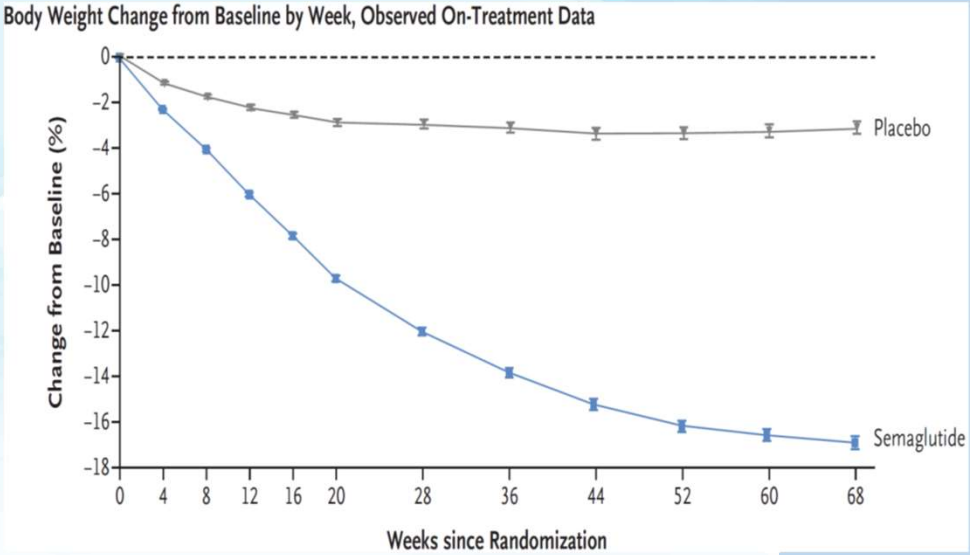
STEP1: Phase 3 Trial Semaglutide

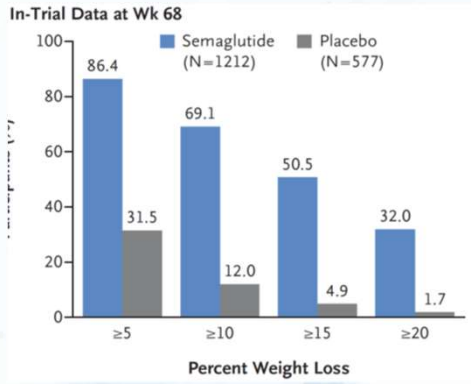
68-week double-blind Placebo-Controlled RCT

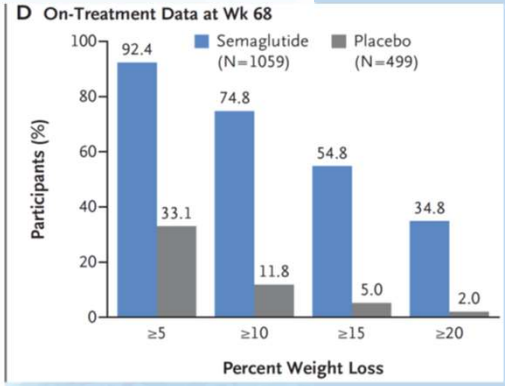
Subjects: 1961 Patients with BMI >30 or BMI >27 with >1 weight comorbidity

Intervention: Semaglutide 2.4mg weekly vs. Placebo. All patients received intensive lifestyle intervention.

Outcomes: Weight loss at 1-year Cardiovascular Parameters, ADRs







NEJM 2021; 384: 989-1002

STEP1 Trial: Other Effects of Semaglutide

Improved CV Risk Markers

WAIST CIRC. (-13.5CM)

- LDLC (-3%)
- HDLC (+5%)
- TRIGLYCERIDES (-22%)

- FASTING GLUC. (-8.4MG/DL)

- SYSTOLIC BP (-6.2 MMHG)
- DIASTOLIC BP (-2.8 MMHG)

- IWQOL-LITE +14.7

Adverse effects

- NAUSEA (44%)
- DIARRHEA (31%)
- CONSTIPATION (23%)
- VOMITING (25%)
- DYSPEPSIA (10%)
- UPPER ABD PAIN (10%)
- HEADACHE (15%)
- NASOPHARYNGITIS (21%)

- CHOLELITHIASIS (1.8%)
- PANCREATITIS (0.2%)

NEJM 2021; 384: 989-1002

Prescribing Issues: Liraglutide and Semaglutide

- **C-cell hyperplasia in rodents:** AVOID in patients with MEN2 or medullary thyroid cancer.
- **Pancreatitis:** rare hemorrhagic pancreatitis. More common: gallstones.
- Contraindicated in pregnancy.

Saxenda Prescribing Information, rev Jan 2015

Summary

- **Clinical Practice Guidelines** emphasize counseling all overweight and obese patients about the health benefits of modest weight loss.
- Emerging medical treatments for obesity are directed at the neural network that senses and regulates body composition.
- Multiple new drug classes are FDA approved, with large-scale clinical trial data showing sustained, clinically meaningful weight reduction.
  - **Phentermine / Topiramate (Qsymia®)**
  - **Bupropion / Naltrexone (Contrave®)**
  - **Liraglutide (Saxenda®, Victoza®)**
  - **Semaglutide (Wegovy®, Ozempic®)**

Treatment of Peptic Ulcer Disease, ca 1970

Lifestyle Modification	→	No Effect Progressive Disease
Medical Therapy	→	Modest Improvement
Surgery	→	Significant Improvement Chance for Cure

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