The Skinny On Obesity Meds

Stacy M. Chronister, D.O.
Clinical Assistant Professor
Department of Internal Medicine
Oklahoma State University

THE MEAL IS NOT OVER WHEN I'M FULL

THE MEAL IS OVER WHEN I HATE MYSELF

Disclosures

- No financial disclosures
- Generic and branded names may be interchanged during the lecture
- Off-label use of medications will be discussed

Objectives

- Define Obesity
- Understand which patient is a candidate for weight loss medications
- Understand the new management approach to overweight and obesity
- Learn the MOA, risks, side effects, and potential efficacy of weight loss medications
- Recognition of common weight gaining medications

LONDON | Thu Jul 29, 2010

(Reuters) - British Public Health Minister has urged doctors to call overweight patients 'fat' rather than 'obese.'

"Doctors and health workers are too worried about using the term 'fat'", said the health minister, *"but doing so will motivate people to take personal responsibility for their lifestyles."*

"Calling them 'obese' does not provide sufficient motivation.
Just call them fat: Plain-speaking doctors will jolt people into losing weight."

DIAGNOSIS	ANTHROPO-METRIC COMPONENT	CLINICAL COMPONENT	Prevention/ Treatment
Normal	BMI < 25		**Primary**
Overweight Stage 0	BMI 25-29.9	No obesity-related complications	**Secondary**
Obesity Stage 0	BMI ≥ 30	No obesity-related complications	
Obesity Stage 1	BMI ≥ 25	Presence of 1 or more mild-to-moderate obesity-related complications	**Tertiary**
Obesity Stage 2	BMI ≥ 25	Presence of 1 or more severe obesity-related complications	

AMA, June 2013

“…..the view of obesity as a behavioral decision is debunked by biomedical evidence……..obesity is a primary disease, and the full force of our medical knowledge should be brought to bear on its prevention and treatment……”

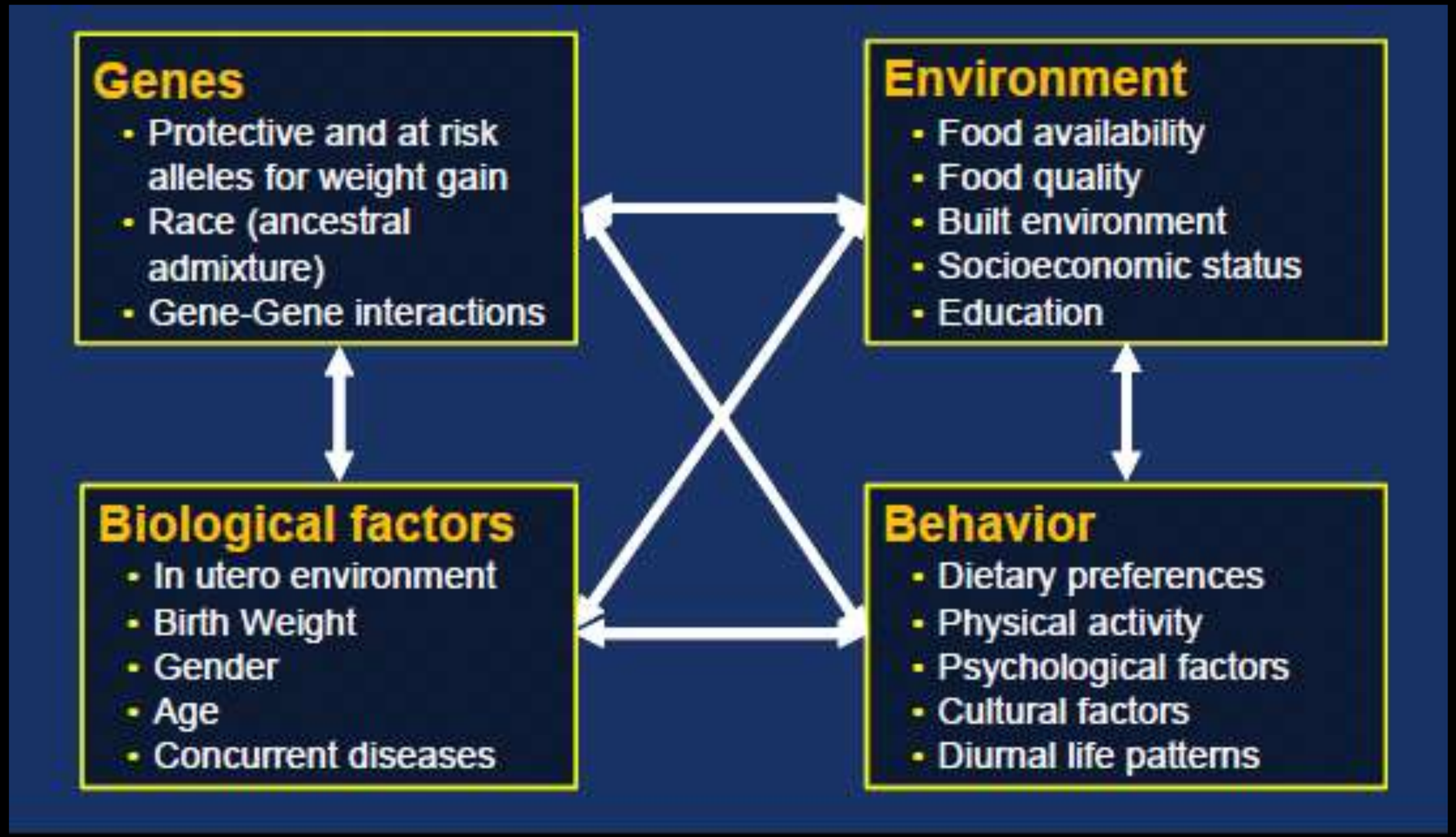
AMA: Essential Criteria of A Disease

1. Characteristic signs or symptoms
2. Impairment in the normal functioning of some aspect of the body
3. Results in harm or morbidity

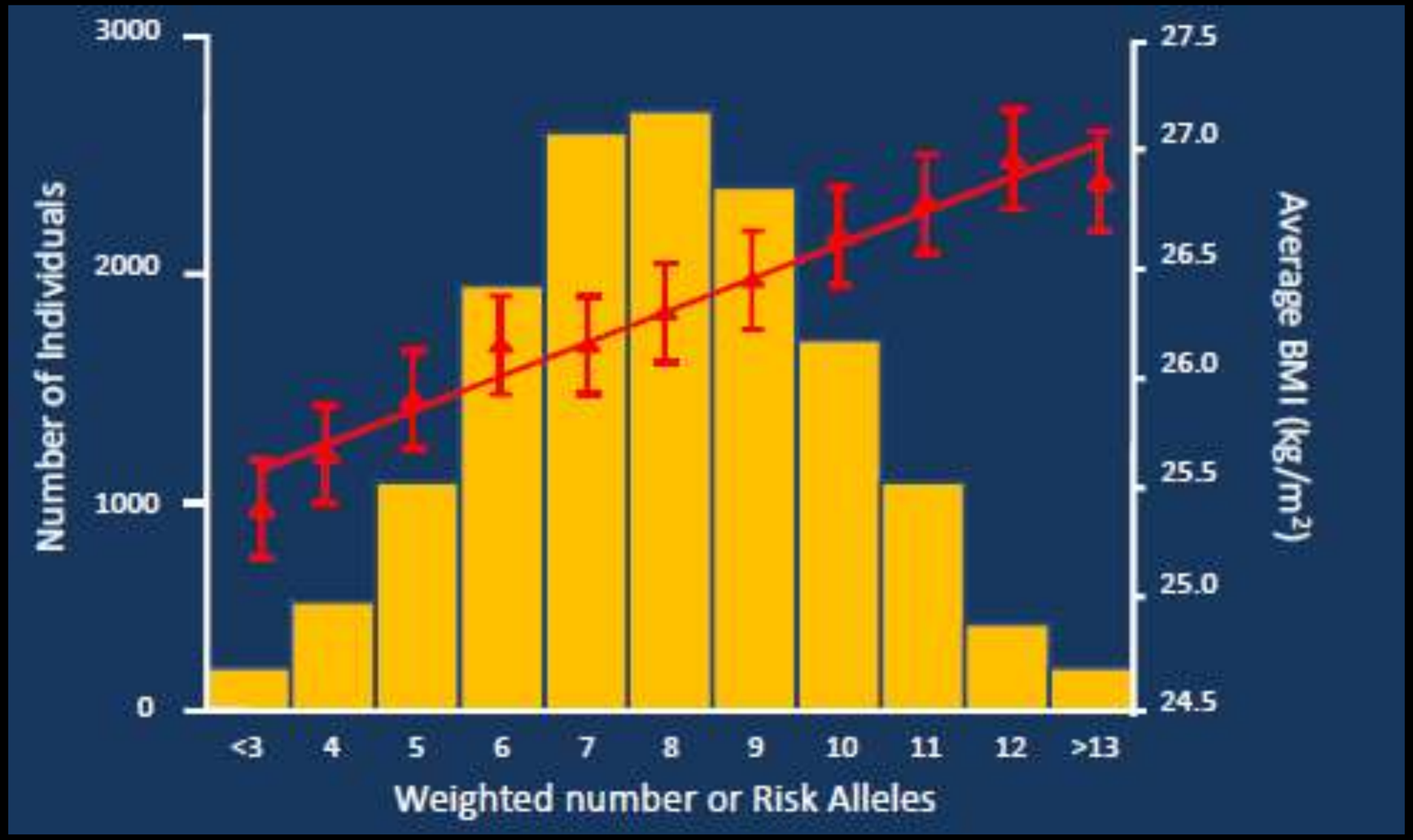
Obesity Definition

Obesity is a chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences.

Determinants of Obesity



BMI increases as the number of alleles increases




IT'S NATIONAL "GET YOUR $HIT TOGETHER DAY"
Unfortunately, it's the least celebrated holiday
imgflip.com

Old Treatment Paradigm
Treat Weight *LAST*

	Dys-lipidemia	HTN	IGT
Monitor	Lipid panels Lipoproteins subsets	Blood Pressure Ambulatory Blood Pressure	Blood sugar Glycosylated hemoglobin distribution
Diet	↓ Total fat ↓ Chol. ↑ Fiber	↓ Sodium ↑ K ++	↓ Sugar Distribute CHO, PRO, Fat
Meds	Statins Fibrates Resins Niacin	Central acting Renal effective Peripherally acting diuretics Thiazide diuretics	Insulin Sulfonylureas Glidizones Absorption agents

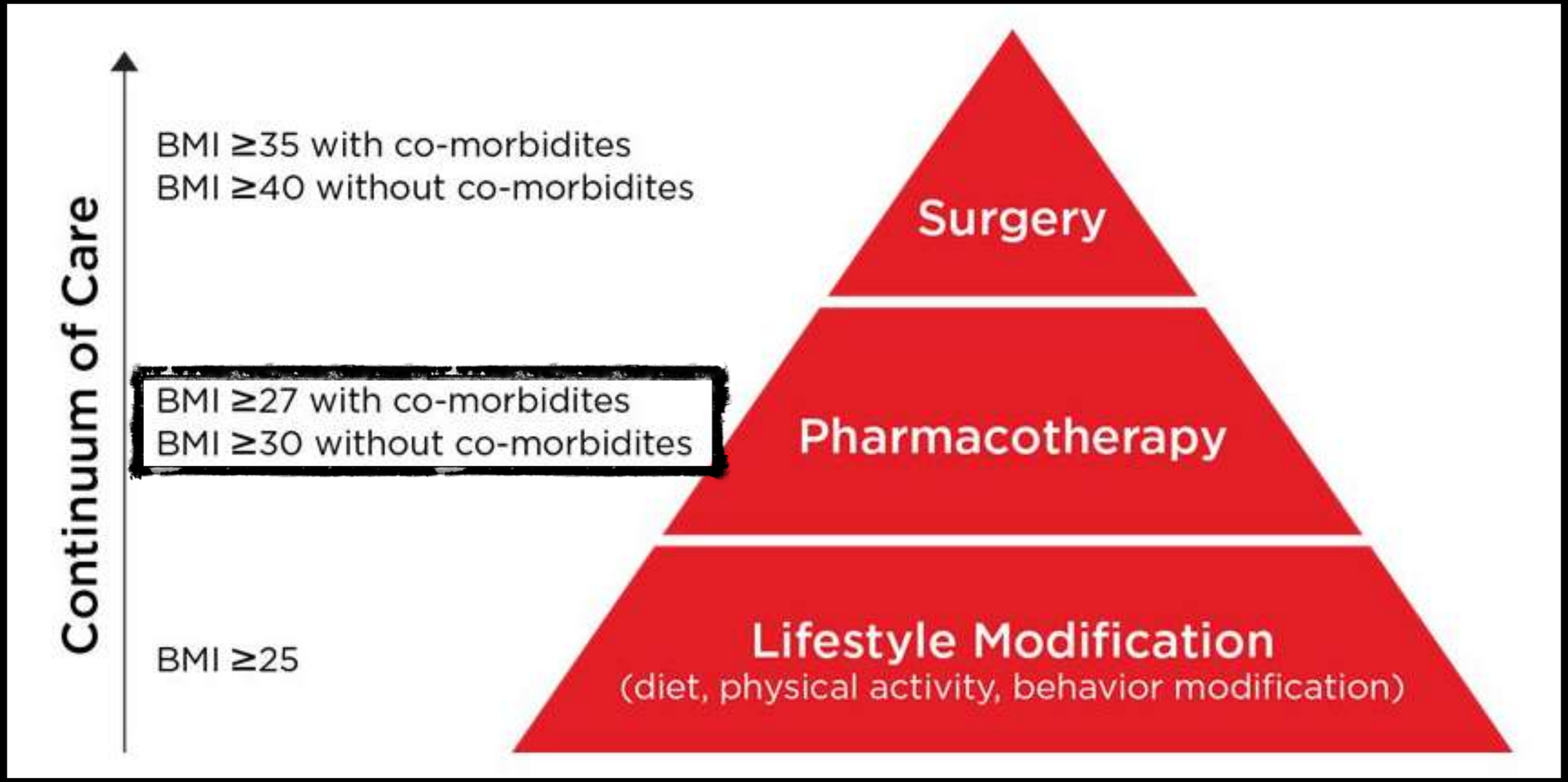
	Overweight/Obesity
Monitor	Weight and BMI
Diet	Any diet patient will adhere to
Exercise	150 minutes of moderate-intensity aerobic activity/wk and muscle-strengthening activities on ≥ 2 days/wk
Meds	Orlistat, phentermine, phentermine/topiramate, lorcaserin

CHANGING THE TREATMENT PARADIGM

New Treatment Paradigm
Treat Weight *FIRST*

	Overweight/Obesity
Monitor	Weight and BMI
Diet	Any diet patient will adhere to
Exercise	150 minutes of moderate-intensity aerobic activity/wk and muscle-strengthening activities on > 2 days/wk
Meds	Orlistat, phentermine, phentermine/topiramate, lorcaserin

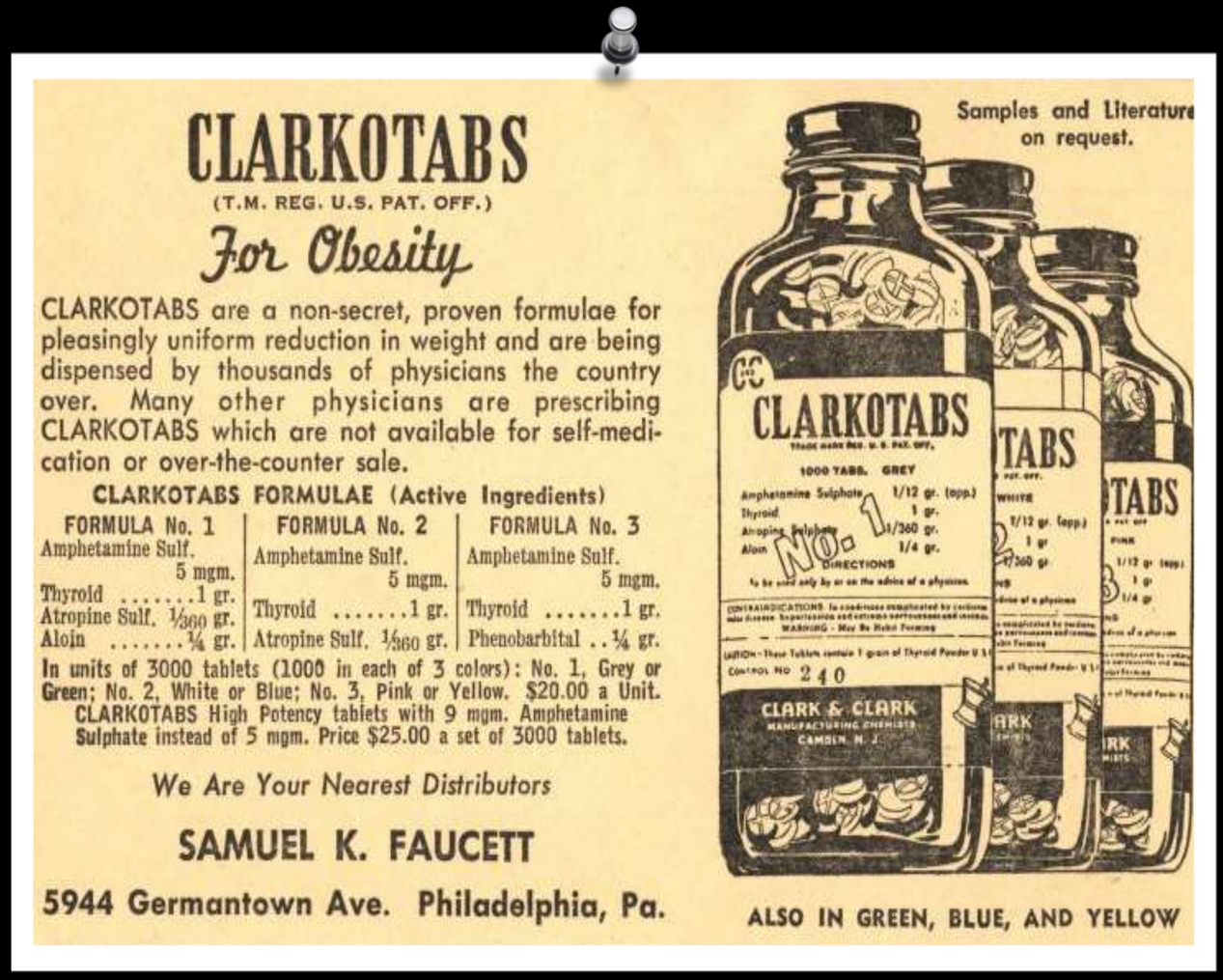
	Dys-lipidemia	HTN	IGT
Monitor	Lipid panels Lipoproteins subsets	Blood Pressure Ambulatory Blood Pressure	Blood sugar Glycosylated hemoglobin distribution
Diet	↓ Sat + trans fat ↑ Omega-3s ↑ MUFA ↓ Simple CHOs ↓ ETOH	DASH Diet ↓ Sodium ↓ ETOH	Glycemic index diet ↑ Fiber Diabetic diet
Meds	Statins Fibrates	ACE Inhibitors ARBs Thiazide diuretics	Metformin Exenatide Liraglutide



Treatment Pyramid

Use of Anti-Obesity Medications

- BMI: ≥30 or ≥27+comorbidity
- Combine with behavioral modification, physical activity, and nutrition for optimal results
- Continue medications only in responders
- Use combinations if mono therapy does not give desired results
- Long-term continuation if indicated



CLARKOTABS

(T.M. REG. U.S. PAT. OFF.)

For Obesity

CLARKOTABS are a non-secret, proven formulae for pleasingly uniform reduction in weight and are being dispensed by thousands of physicians the country over. Many other physicians are prescribing CLARKOTABS which are not available for self-medication or over-the-counter sale.

CLARKOTABS FORMULAE (Active Ingredients)

FORMULA No. 1	FORMULA No. 2	FORMULA No. 3
Amphetamine Sulf. 5 mgm.	Amphetamine Sulf. 5 mgm.	Amphetamine Sulf. 5 mgm.
Thyroid .....1 gr.	Thyroid .....1 gr.	Thyroid .....1 gr.
Atropine Sulf. 1/360 gr.	Atropine Sulf. 1/360 gr.	Phenobarbital ..¼ gr.
Aloin .....¼ gr.		

In units of 3000 tablets (1000 in each of 3 colors): No. 1, Grey or Green; No. 2, White or Blue; No. 3, Pink or Yellow. $20.00 a Unit.
CLARKOTABS High Potency tablets with 9 mgm. Amphetamine Sulphate instead of 5 mgm. Price $25.00 a set of 3000 tablets.

We Are Your Nearest Distributors

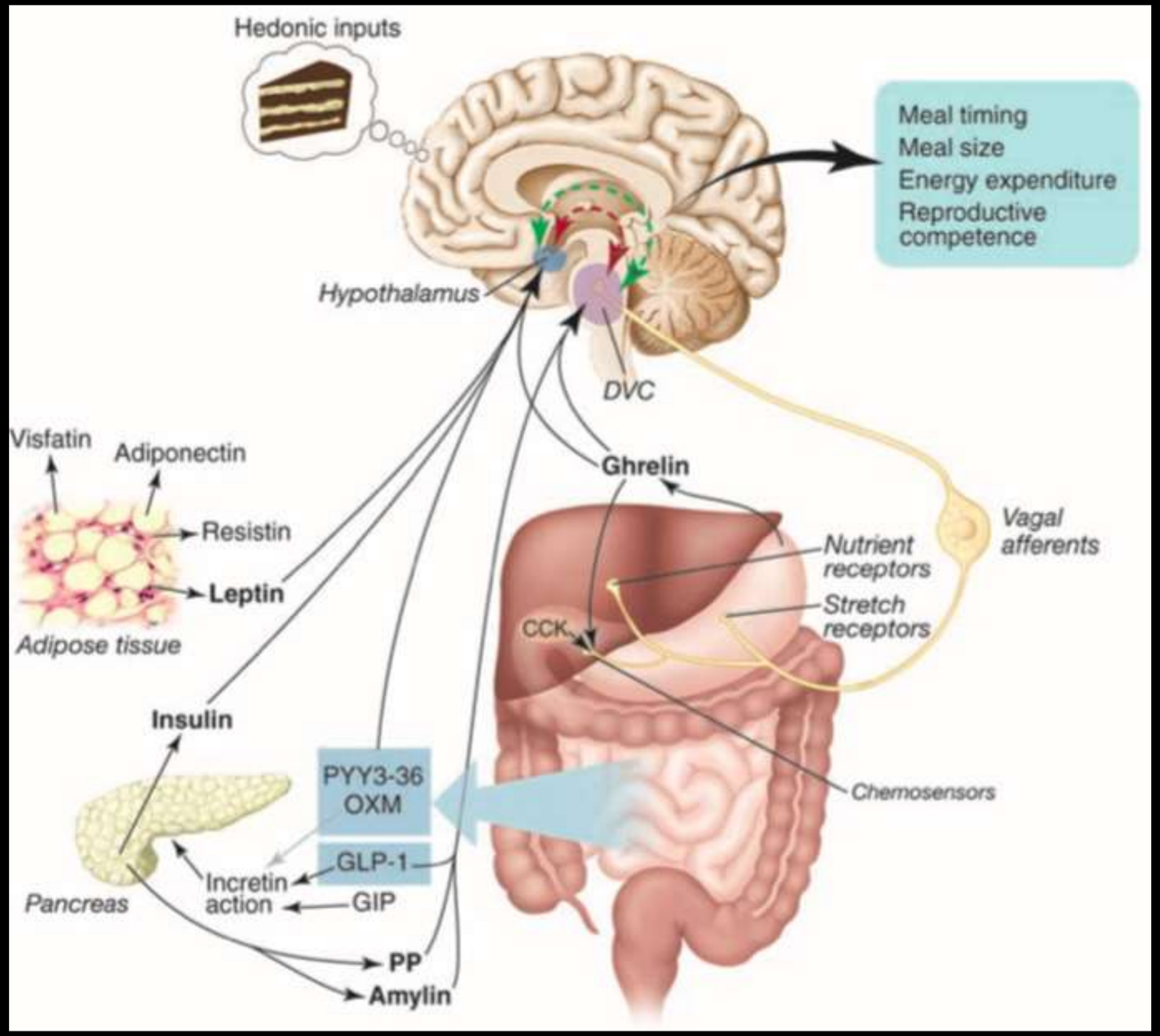
SAMUEL K. FAUCETT

5944 Germantown Ave. Philadelphia, Pa.

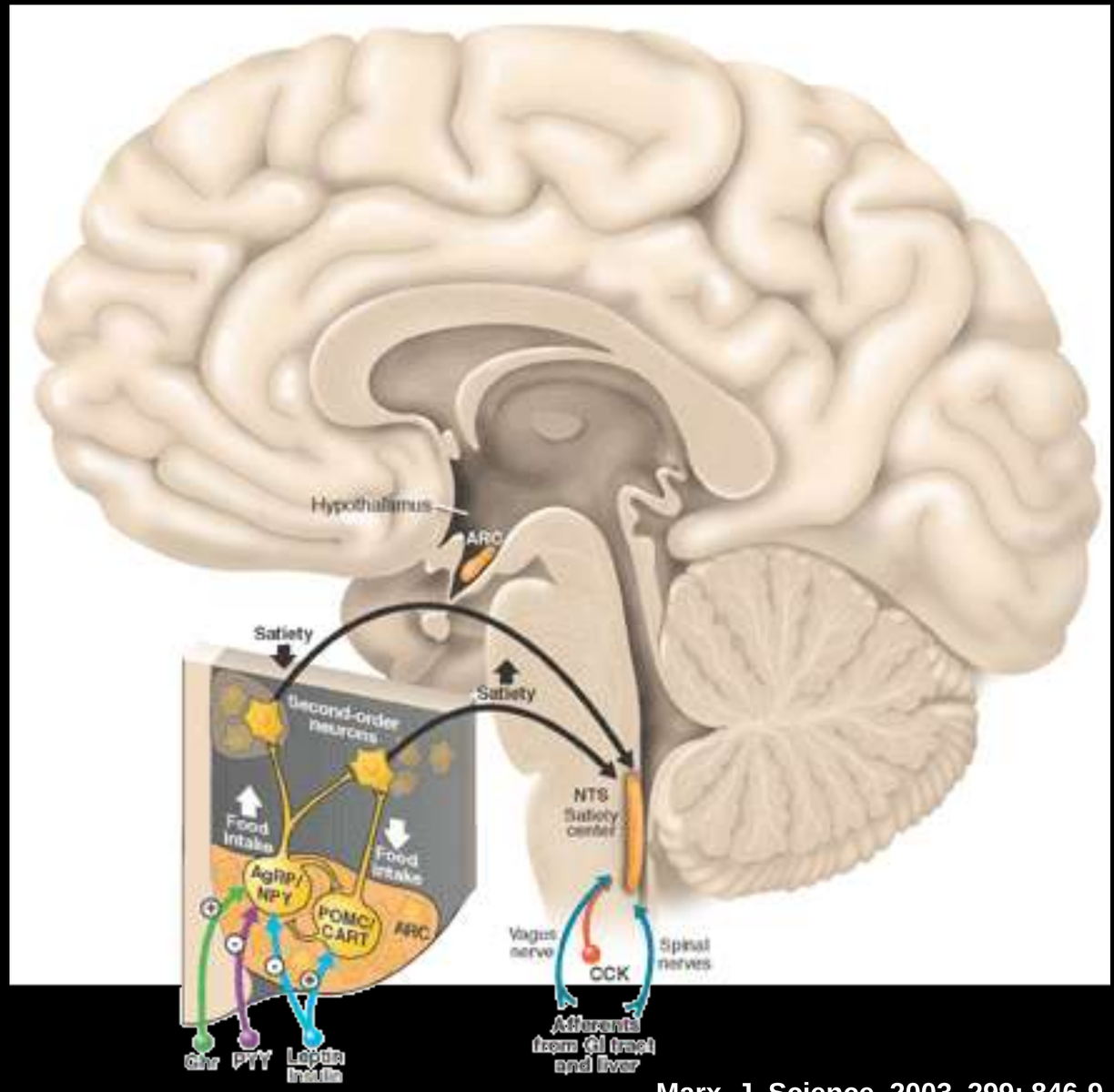
Samples and Literature on request.

ALSO IN GREEN, BLUE, AND YELLOW

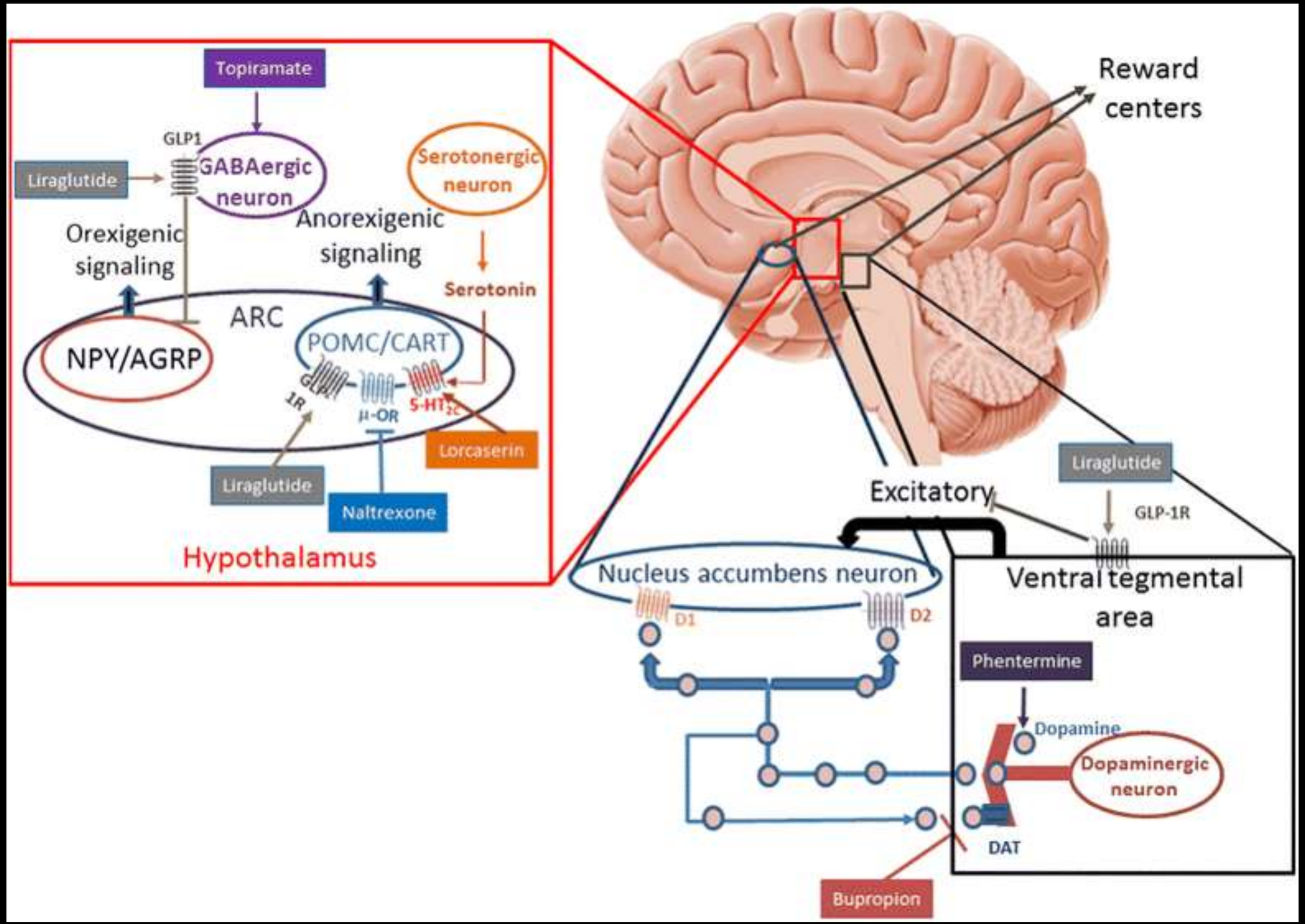
Interacting Pathways of Energy Regulation



Badman, MK. Science 2005, 307:1909-1914

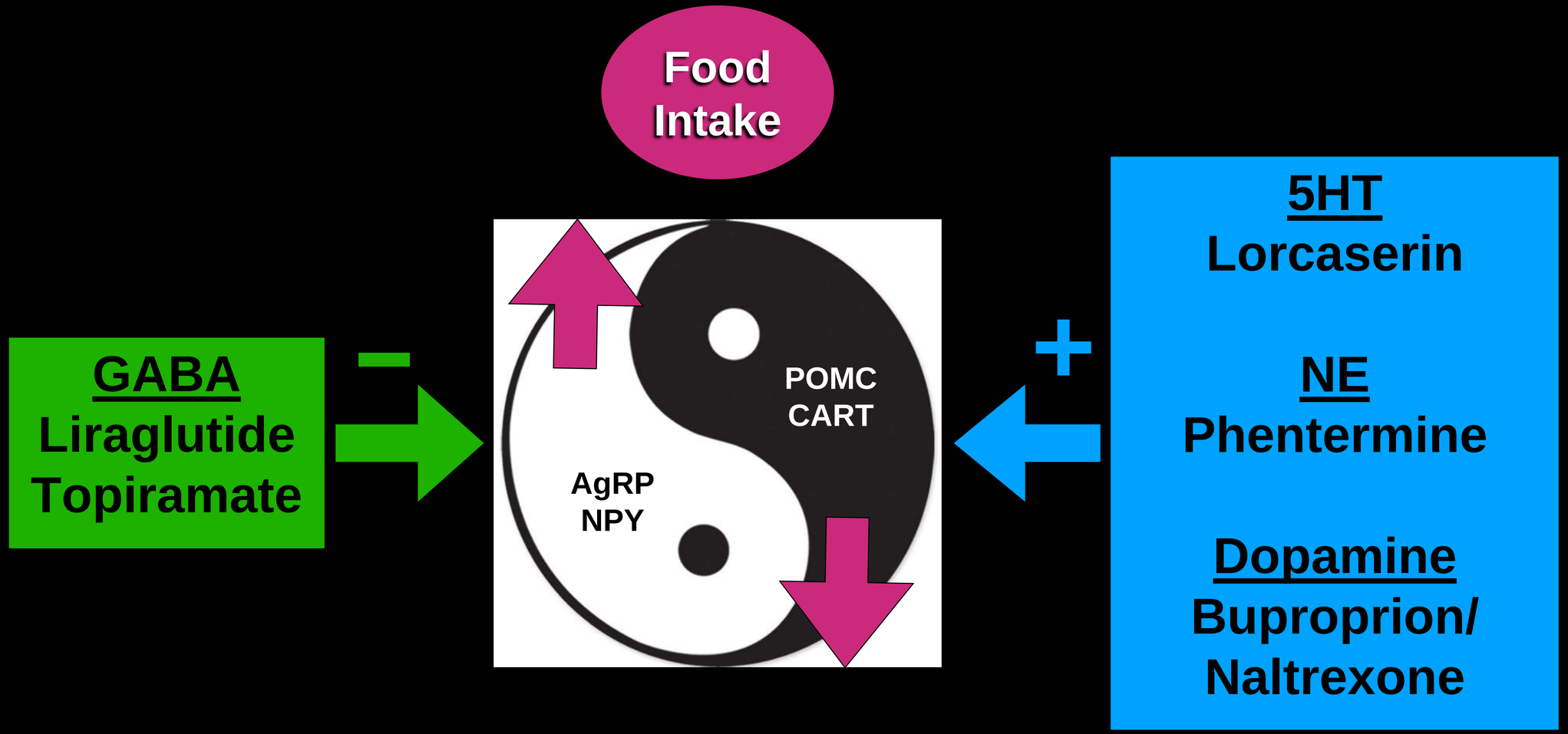


Marx, J. Science. 2003, 299: 846-9



Diabetes Metab Syndr 2017; 9-44

Central Mechanisms of Action



POMC=ProOpioMelanoCortin
CART=Cocaine and Amphetamine Regulated Transcript
NPY=Neuropeptide Y
AgRP=Agouti-Related Peptide

Current Anti-Obesity Medications

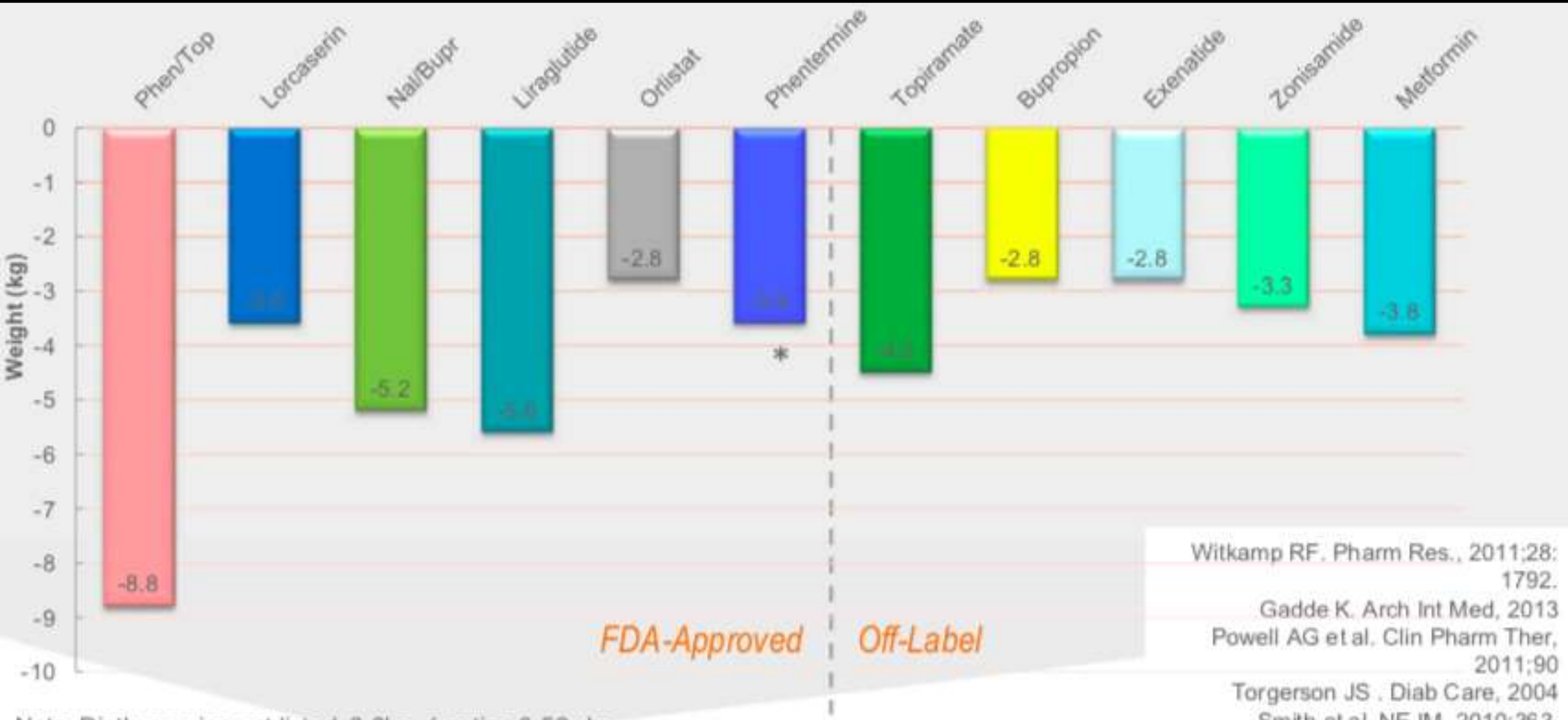
FDA approved

- **Phentermine**
- **Diethylproprion**
- **Phendimetrazine**
- **Orlistat**
- **Lorcaserin**
- **Phentermine/Topiramate**
- **Naltrexone/Bupropion**
- **Liraglutide**

Off Label Use

- **Metformin**
- **Exenatide (and other GLP-1s)**
- **Canagliflozin (and other SGLT-2is)**
- **Pramlintide**
- **Topiramate**
- **Zonisamide**
- **Bupropion**

Average Weight Loss with Anti-Obesity Meds

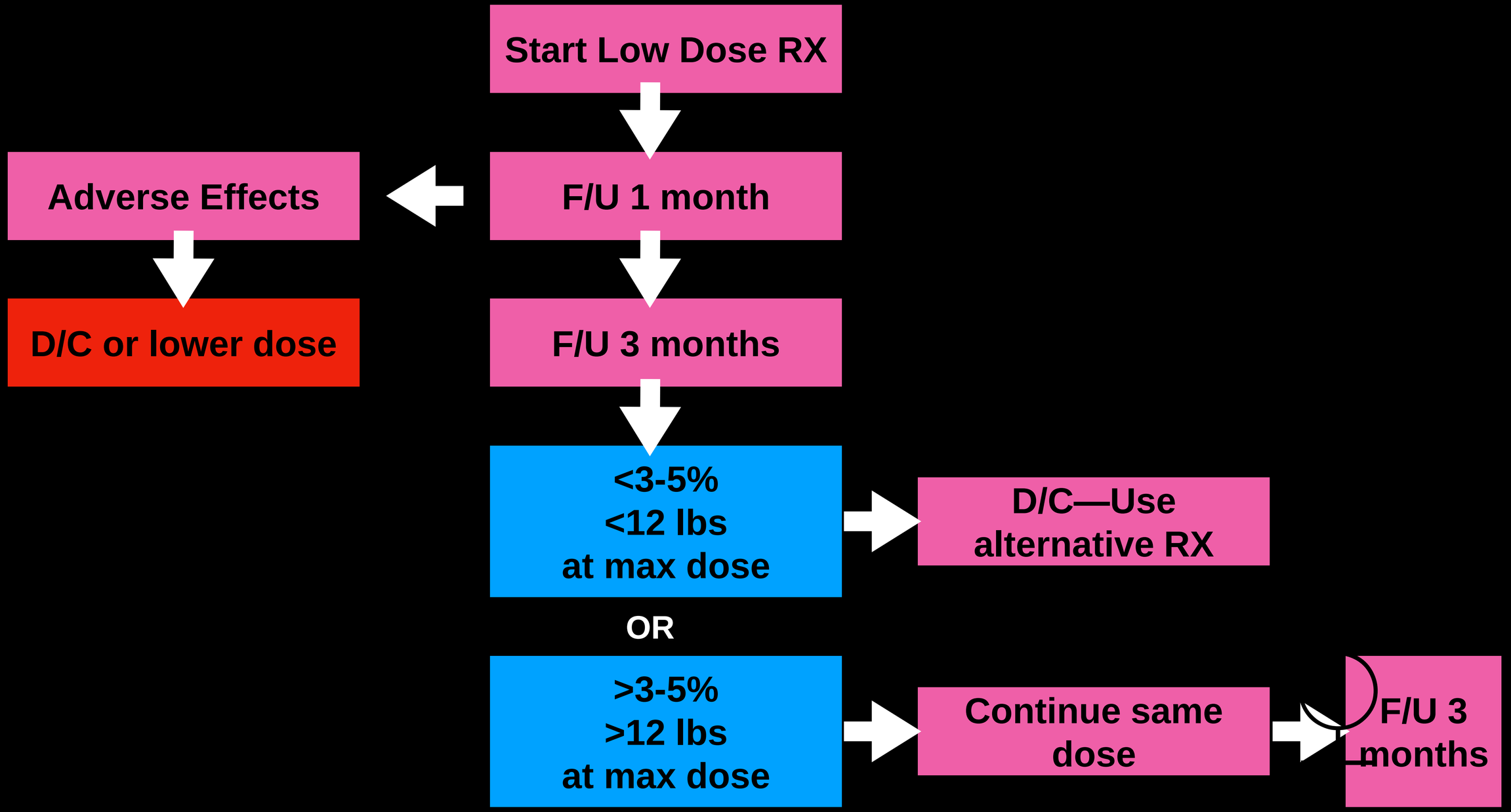


Witkamp RF. Pharm Res., 2011;28: 1792.
Gadde K. Arch Int Med, 2013
Powell AG et al. Clin Pharm Ther, 2011;90
Torgerson JS . Diab Care, 2004
Smith et al. NEJM, 2010;363.
Garvey WT. AJCN. 2012.

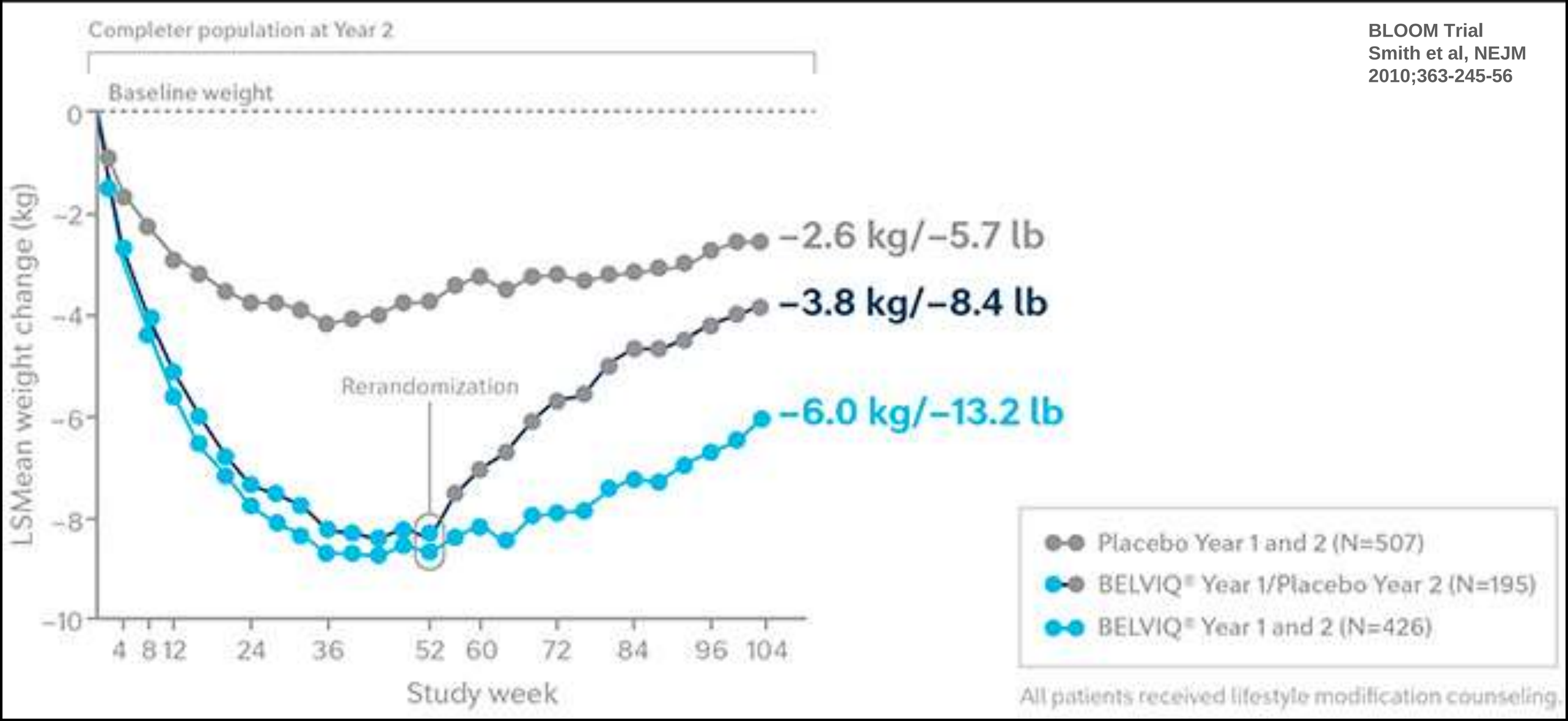
Note: Diethypropion not listed, 3.0kg, duration 6-52wks

* Most trials are ≥ 1 year (*except Phentermine, 2-24wks, meta-analysis of trials, weight range 0.6-6.0kg)

Med Continuation: *High Responders lose >5% in 3 months*



Medications are needed for long durations

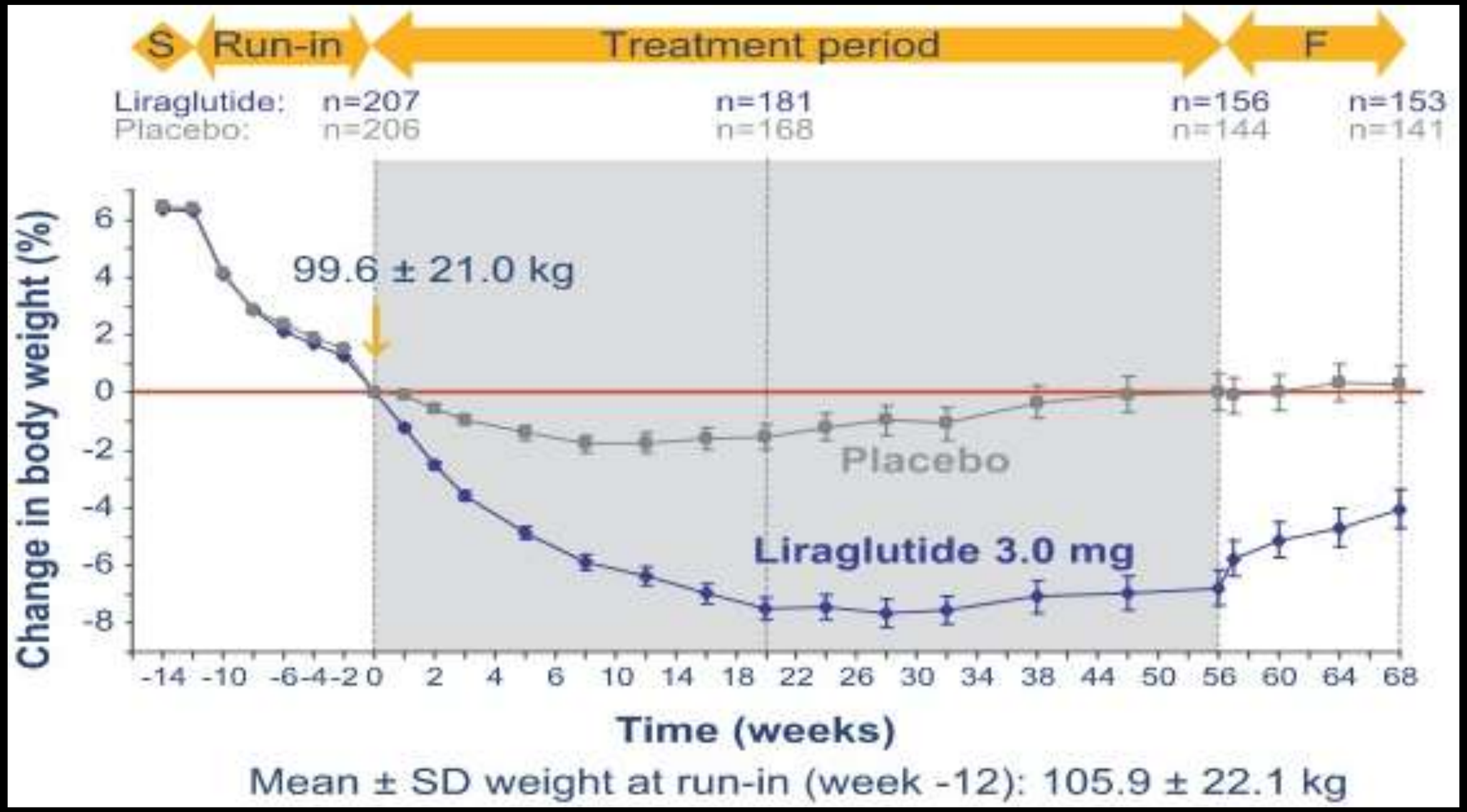


BLOOM Trial
Smith et al, NEJM 2010;363-245-56

Medications are needed for maintenance

The SCALE Maintenance randomized study

International Journal of Obesity (2013) 37, 1443-1451



Anti-Obesity Medications

Potential Targets

Contraindications*

***Not a complete list**

Common Adverse Effects

Mechanism of Action:

Dosing:

Advice/Precautions:

Orlistat

+

Hypercholesterolemia
Low risk medication

CI

Cholestasis
Chronic malabsorption syndrome

AE

Flatulence, diarrhea, bloating, cramping, abd pain
Increase urinary oxalate
Fat soluble vitamin deficiency

Mechanism of Action:

- Pancreatic lipase inhibitor—Blocks ~30% of fat intake

Dosing:

- Start 120mg daily
- Range: 120mg/d—120mg TID
- Alli is an OTC available in 60mg

Advice/Precautions:

- Advise daily multivitamin
- Monitor fat-soluble vitamins (A,D,E,K)
- Decrease levels of cyclosporin if co-administered
- No causal relationship with liver failure


Please
Excuse Me
From Being
Late.
I HAVE
Explosive
Diarrhea.
-K

alli™

Phentermine

+

Increased hunger
Low metabolic rate

CI

Active CV disease
Poorly controlled HTN
Cardiac arrhythmias
Hyperthyroidism
Glaucoma

AE

Dry mouth
Constipation
Insomnia
Palpitations, HA, Irritability

Mechanism of Action:

- Inhibits Na-dependent NE transporter to reduce NE uptake
- Inhibits serotonin and dopamine reuptake

Dosing:

- 15-30mg capsule, 37.5mg tablet QD-BID
- 8mg TID
- 1/2 of 37.5mg tablet

Advice/Precautions:

- *Schedule IV controlled substance*
- Monitor BP, awareness of caffeine intake
- ***NO*** evidence of addiction, withdrawal
- ***NO*** established relationship related to cardiac valvulopathy or pulmonary hypertension

Why you shouldn’t be afraid of phentermine

- Phentermine is the most widely used anti-obesity drug in the U.S.
- Warnings of adverse CV and psychiatric effects are included in FDA labeling. However, the few clinical reports of such adverse effects are anecdotal.
- When phentermine was approved (1959) the expectations were that it would prove to be addictive. Due to the structural similarities between phentermine and amphetamine and on evidence in rats that phentermine stimulated spontaneous activity. No evidence suggesting the drug had human addiction potential appeared in clinical trials conducted prior to approval.
- After 60 years, there is no evidence in peer-reviewed medical literature to support the hypothesis that phentermine has significant human addiction potential.
- One retrospective study investigated symptoms occurring when patients treated with long-term phentermine ceased taking it. The study found that patients on long-term phentermine who ceased phentermine abruptly by their choice did not have an amphetamine-like withdrawal symptom complex. Significantly, **there was no evidence of phentermine cravings**.

Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Safety and Effectiveness of Longer-Term Phentermine Use: Clinical Outcomes from an Electronic Health Record Cohort

Kristina H. Lewis [1,2], *Heidi Fischer*[3], *Jamy Ard* [1], *Lee Barton*[3], *Daniel H. Bessesen*[4], *Matthew F. Daley*[5], *Jay Desai*[6], *Stephanie L. Fitzpatrick*[7], *Michael Horberg*[8], *Corinna Koebnick*[3], *Caryn Oshiro*[9], *Ayae Yamamoto*[3], *Deborah R. Young*[3], *and David E. Arterburn*[10]

Conclusions: Greater weight loss without increased risk of incident CVD or death was observed in patients using phentermine monotherapy for longer than 3 months. Despite the limitations of the observational design, this study supports the effectiveness and safety of longer-term phentermine use for low-risk individuals.

Obesity (2019) **27**, 591-602. doi:10.1002/oby.22430

Topiramate (Topamax ®)

+

Migraines, seizures, binge eating, excessive cravings (carbs), on mood stabilizers (sub/alt), on phentermine

CI

Severe depression
Pregnancy
Kidney Stones

AE

WARNING: Acute angle glaucoma, SI, pregnancy

Parasthesias, somnolence, kidney stones, cognitive impairment, taste aversion

Mechanism of Action: *Unclear*

- AMPA, Glutamate receptor
- Carbonic anhydrase
- GABA-A (isozymes II, IV)
- Voltage-dependent sodium channels

Dosing:

- Start 25mg daily
- Range: 25-200mg/day

Advice/Precautions:

- Take at night if trouble with drowsiness
- Interaction with OCPs
- Use BIRTH CONTROL d/t increased risk of cleft lip and palate
- Hyperchloremic NAGMA

Try zonisamide if cognitive impairment or dyspepsia is intolerable

Phentermine/Topiramate CR (Qysmia®)

+

Non-child bearing pt
Excessive hunger
Mild SE with phentermine

CI

Active CV Disease
Uncontrolled HTN
Hyperthyroidism
Glaucoma
Kidney Stones
During or within one day of MAOI

AE

Dry mouth, restlessness, insomnia, palpitations, HA, constipation
Parasthesias, dysgeusia, somnolence, cognitive impairment

Mechanism of Action:

- Sympathomimetic (NE) release in hypothalamus decreases hunger
- AMPA, GABA receptor—decreases cravings

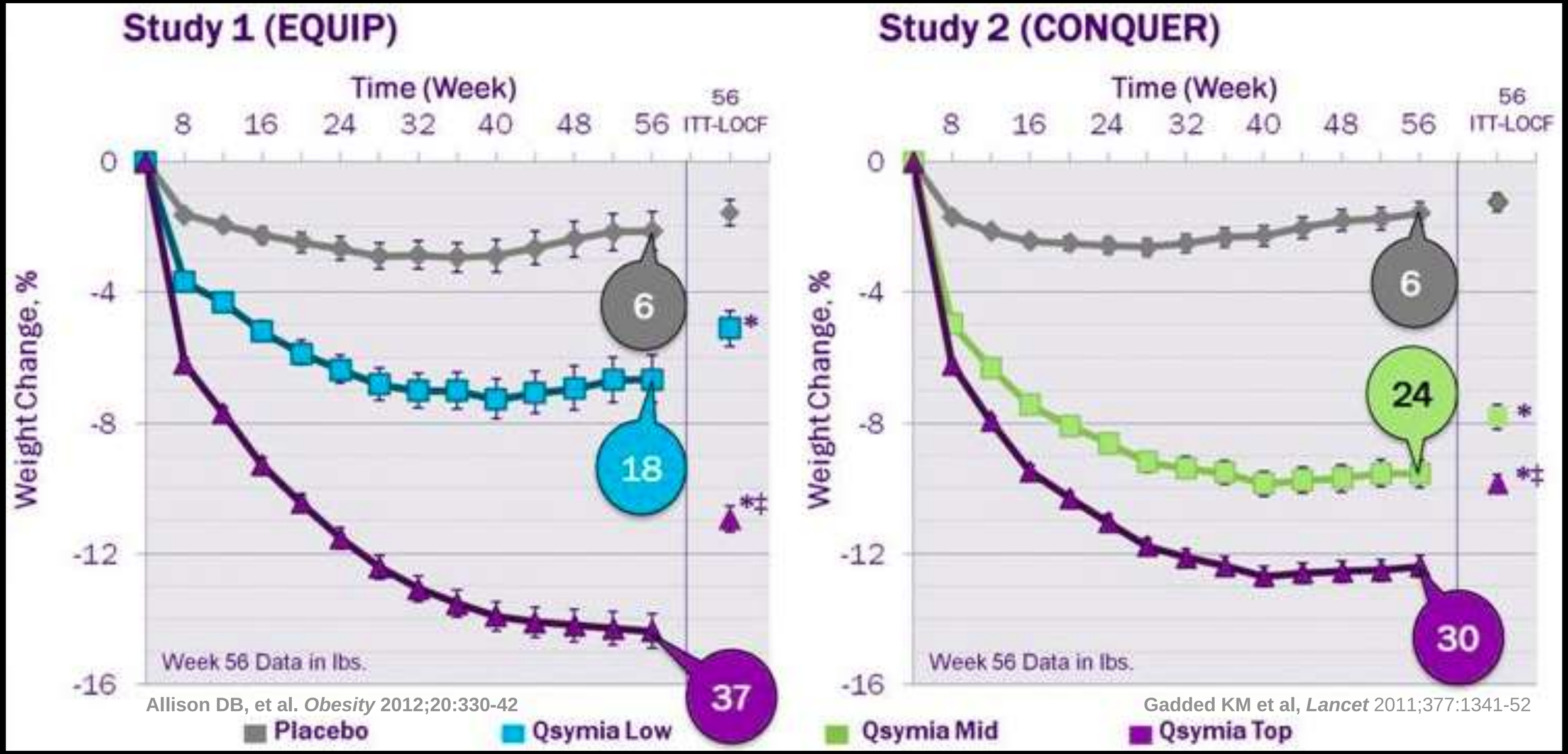
Dosing:

- Start 3.75/23mg x14d then 7.5/46mg
- Range 3.75/23mg—15/92mg/day

Advice/Precautions:

- Schedule IV controlled substance
- counsel on use of BIRTH CONTROL due to increased risk of cleft lip and palate
- Pregnancy test prior to start then MONTHLY
- Increase hydration
- 1/4 cup lemon/lime juice for paresthesias

Responders to Phentermine/Topiramate (Qsymia)



Allison DB, et al. *Obesity* 2012;20:330-42

Gadded KM et al, *Lancet* 2011;377:1341-52

3.75/23mg/d **7.5/46mg/d** **15/92mg/d**

Lorcaserin (Belviq ®)

Unable to tolerate phentermine
Older pt on multiple meds
Diabetes
Night eating

Pregnancy

Headache, nausea
dizziness, dry mouth, fatigue,
nasopharyngitis
priapism

Mechanism of Action:

- Selective serotonin 5HT2c receptor agonist
- Increases satiety via alpha-MSH and POMC neuron activation

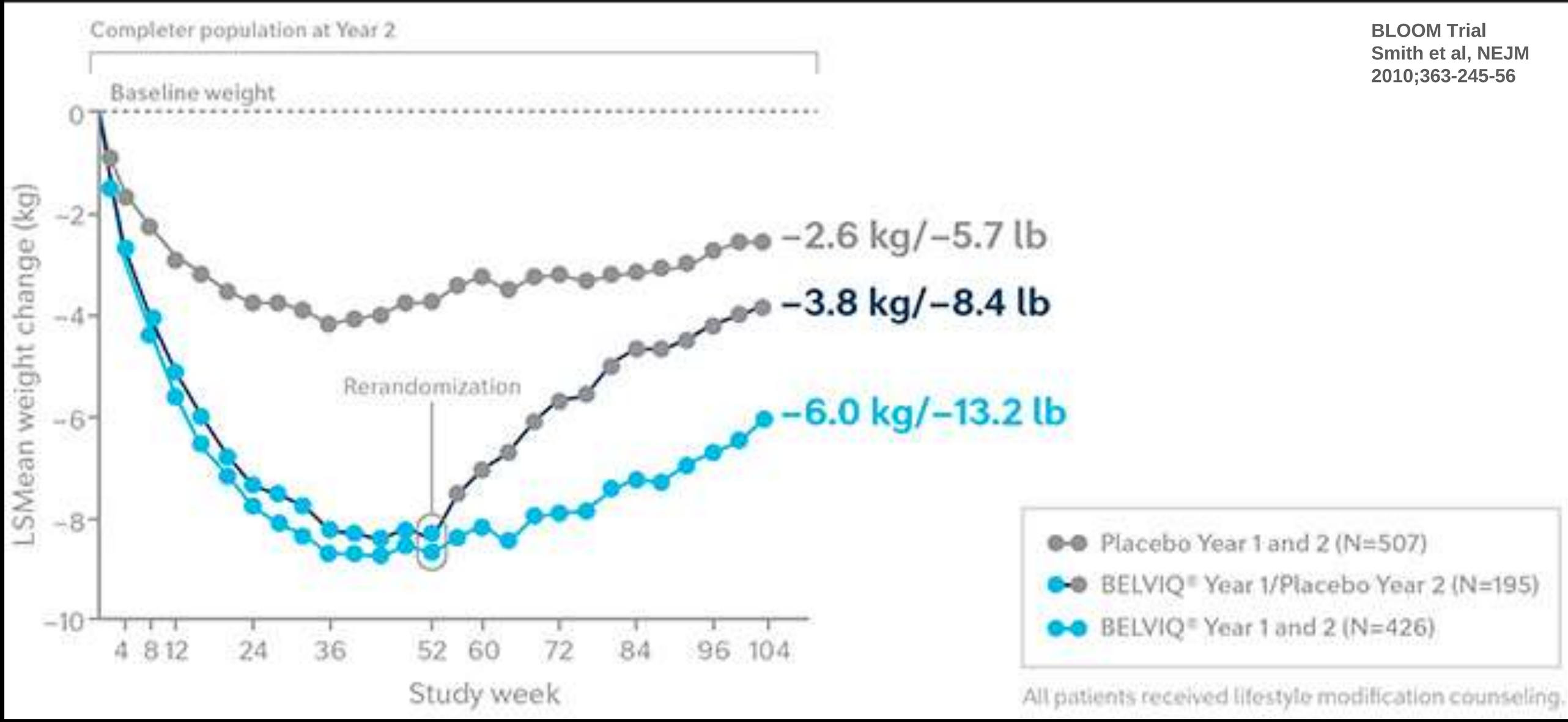
Dosing:

- 10mg BID or 20mg XR daily
- Can use QD daily in evening as combination

Advice/Precautions:

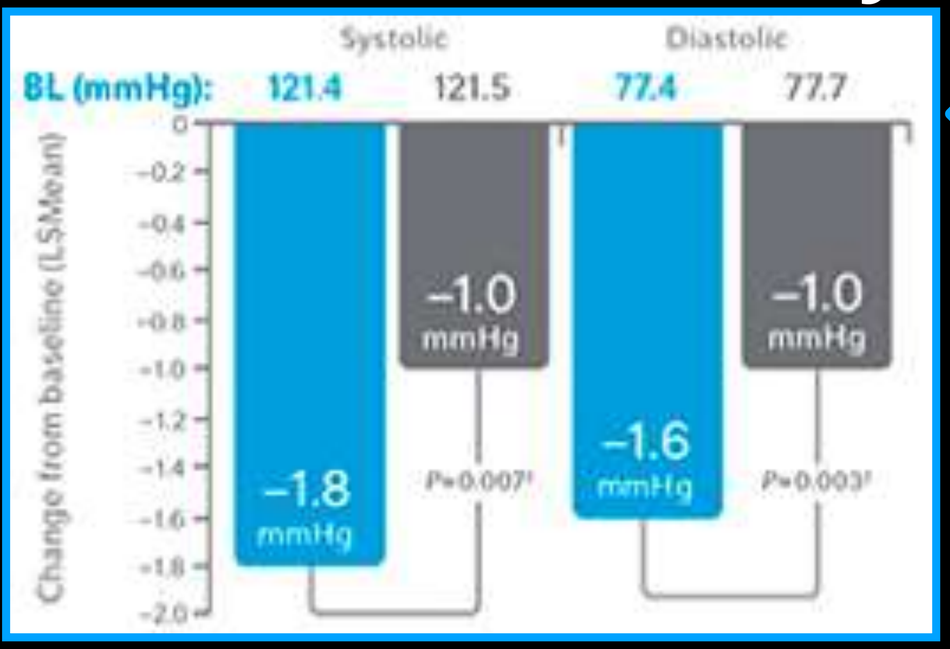
- Schedule IV controlled substance
- Watch co-administration with SSRIs, bupropion or concern about serotonin syndrome
- Caution with congestive heart failure
- No concern about combo with phentermine

Weight Loss Over 2 Years

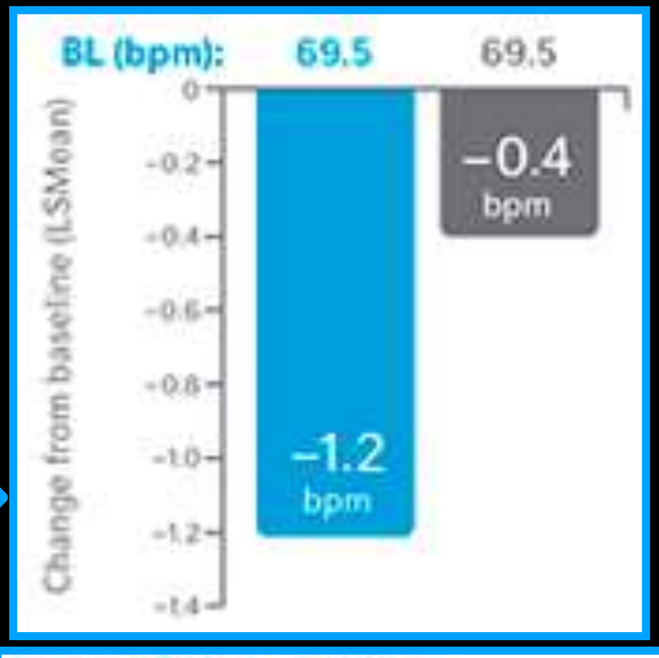


BLOOM Trial
Smith et al, NEJM 2010;363-245-56

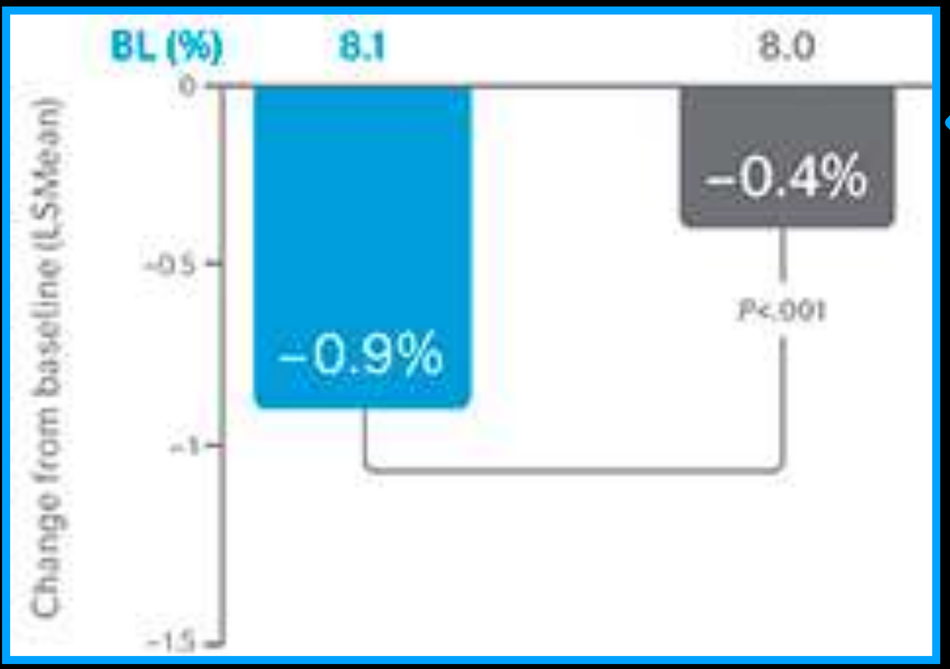
Secondary End-Points of Lorcaserin



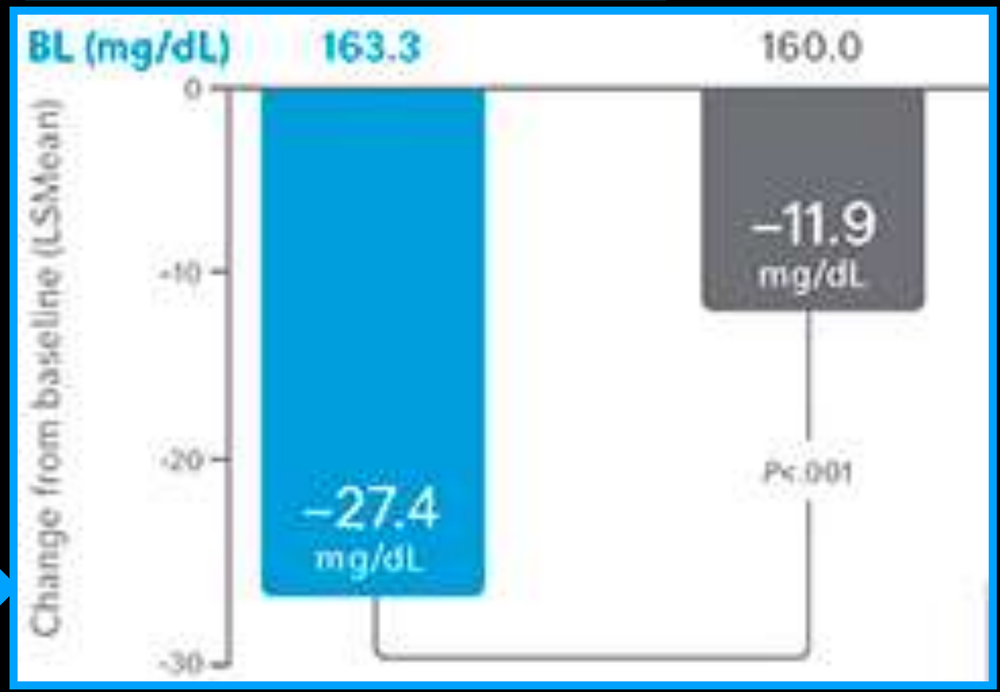
Blood Pressure



Resting Heart Rate



HbA1c%



Fasting Glucose

Naltrexone/Bupropion (Contrave ®)

+

Excessive hunger and cravings
Patients who smoke
On bupropion already

CI

Seizures, uncontrolled HTN
Bulimia
Chronic Opioid Use
Upcoming surgery

AE

WARNING: Neuropsychiatric rxns, SI, behavior changes nausea, headache, insomnia, dizziness, dry mouth

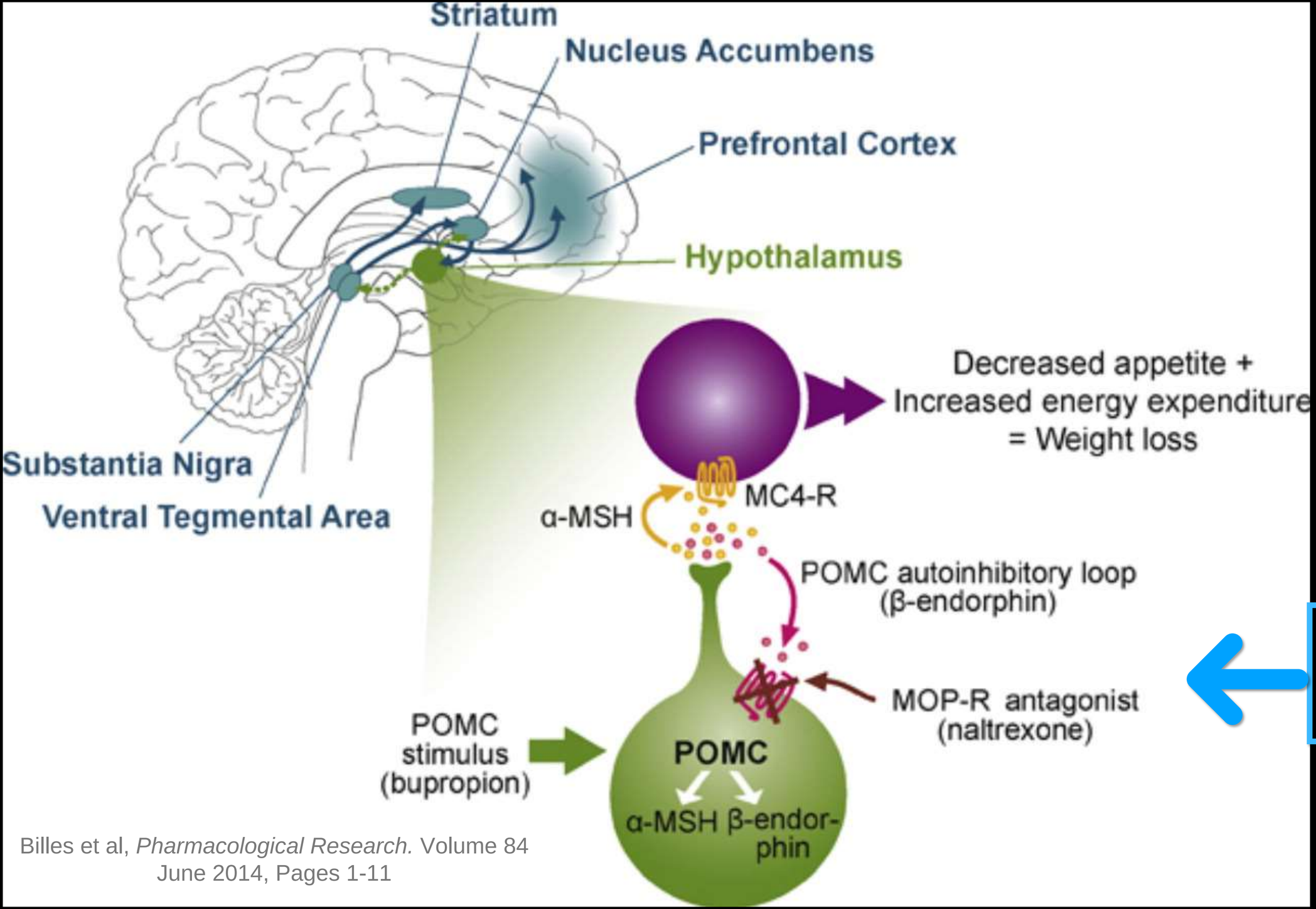
Mechanism of Action:

- Reuptake inhibitor DA and NE activity increases POMC activity
- Naltrexone blocks B-endorphin, POMC auto inhibitor

	Morning dose	Evening dose
Starting: Week 1	1	
Week 2	1	1
Week 3	2	1
Week 4-onward	2	2

Advice/Precautions:

- **Avoid opioid use, ask about surgery!**
- **Results of LIGHT trial (2016) do NOT show reduction in CV events**
- **Avoid high fat diet (increases bioavailability)**



Reduces the probability that compensatory pathways mitigate drug benefits over time!

Billes et al, *Pharmacological Research.* Volume 84
June 2014, Pages 1-11

Liraglutide (Saxenda ®)

+

Diabetes or Prediabetes
(Not indicated for diabetes tx)
Pts with insurance coverage

CI

Medullary thyroid CA (including FHx)
MEN type II
Hx of pancreatitis

AE

Nausea, HA, Angioedema
Gastroparesis
Cannot be combined with DPP4i

Mechanism of Action:

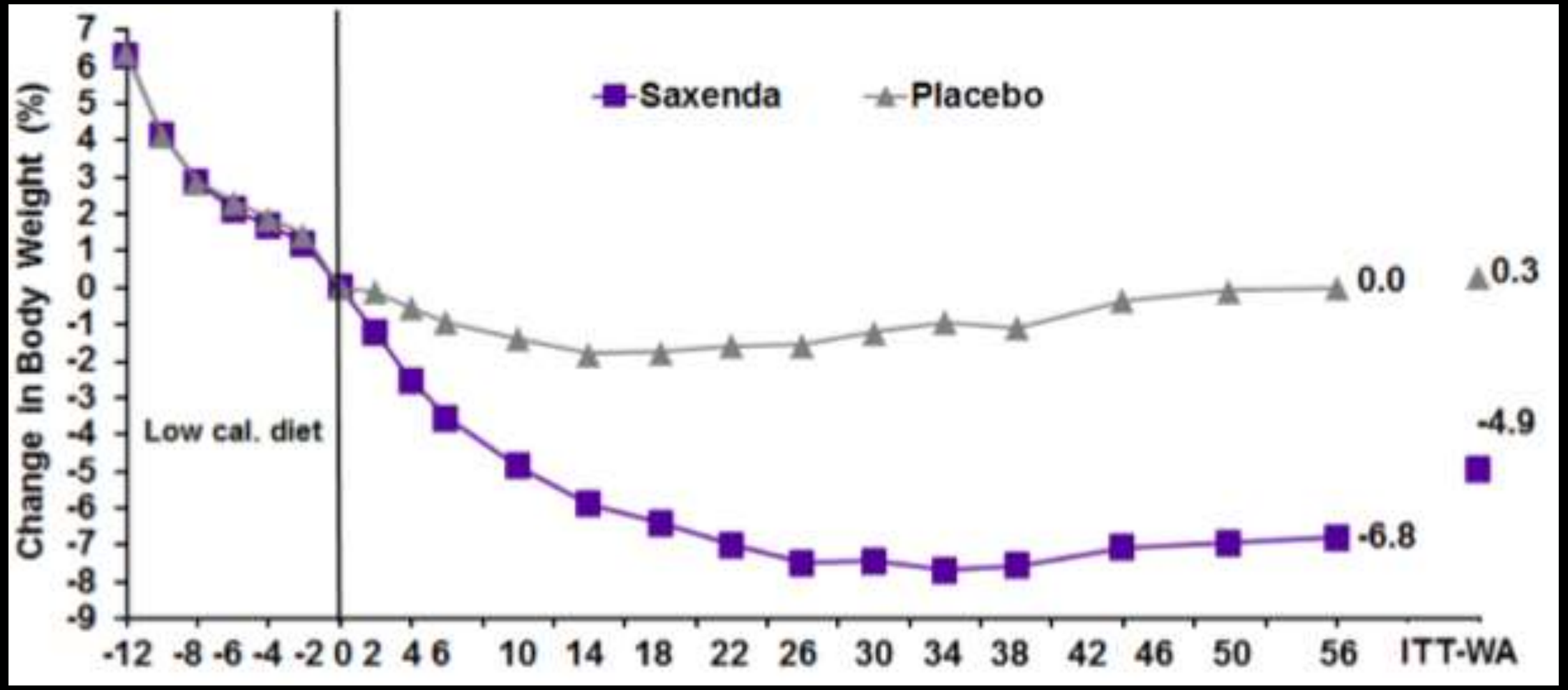
- GLP-1 receptor agonist
- Increase satiety, decreases gastric emptying
- 97% homologous to human GLP-1
- Central acting by inhibition of NPY/AgRP

Dosing: Daily SC injections

Advice/Precautions:

- Nausea may improve with time
- No data to support reports on increased risk of pancreatic ductal neoplasia and pancreatic cancer

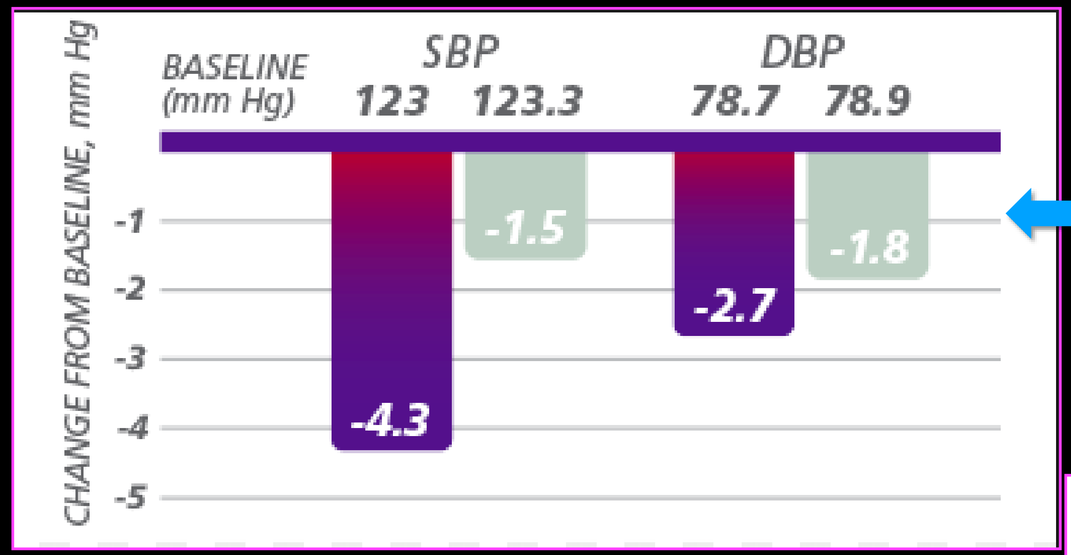
Average Weight Loss With Liraglutide 3mg



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

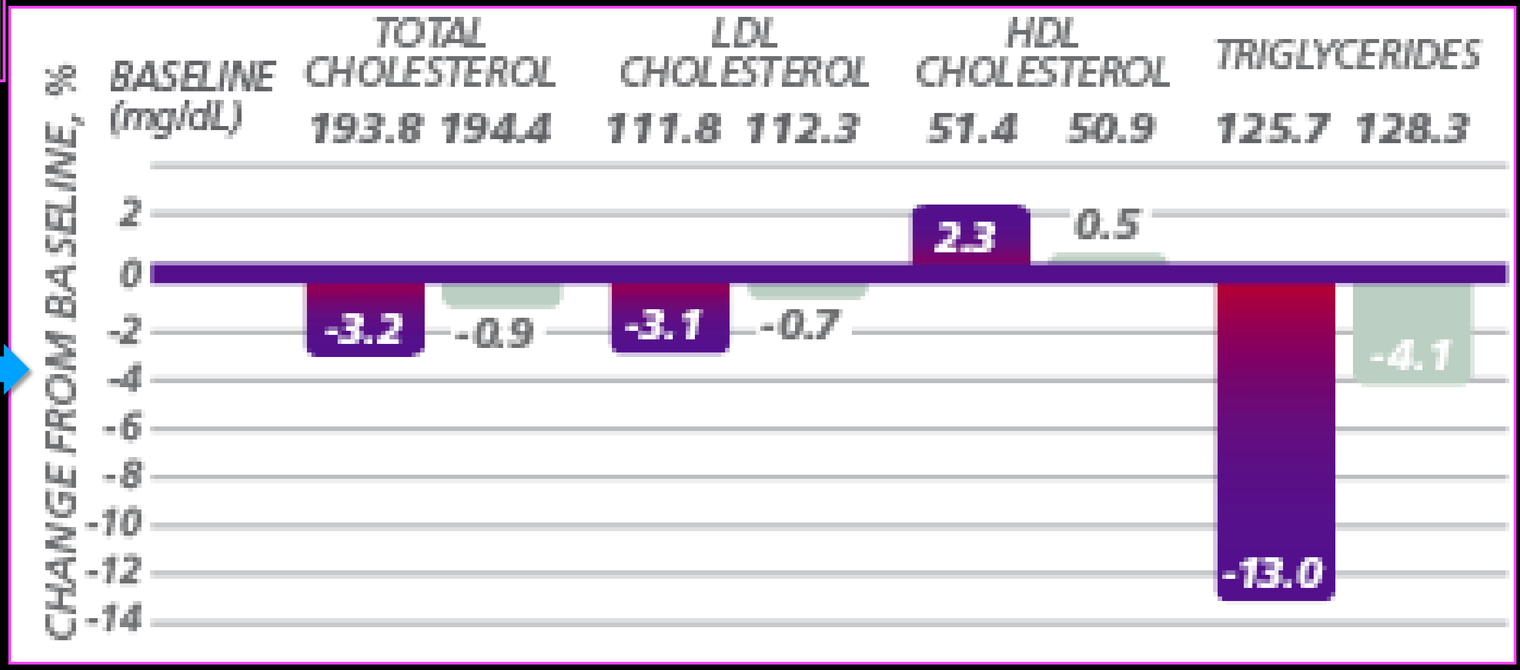
Wadden TA, et al. the SCALE study. Int J Obes (Lond) 2013; 37: 1443–1451.

Improvements in Secondary End-Points with Liraglutide 3mg

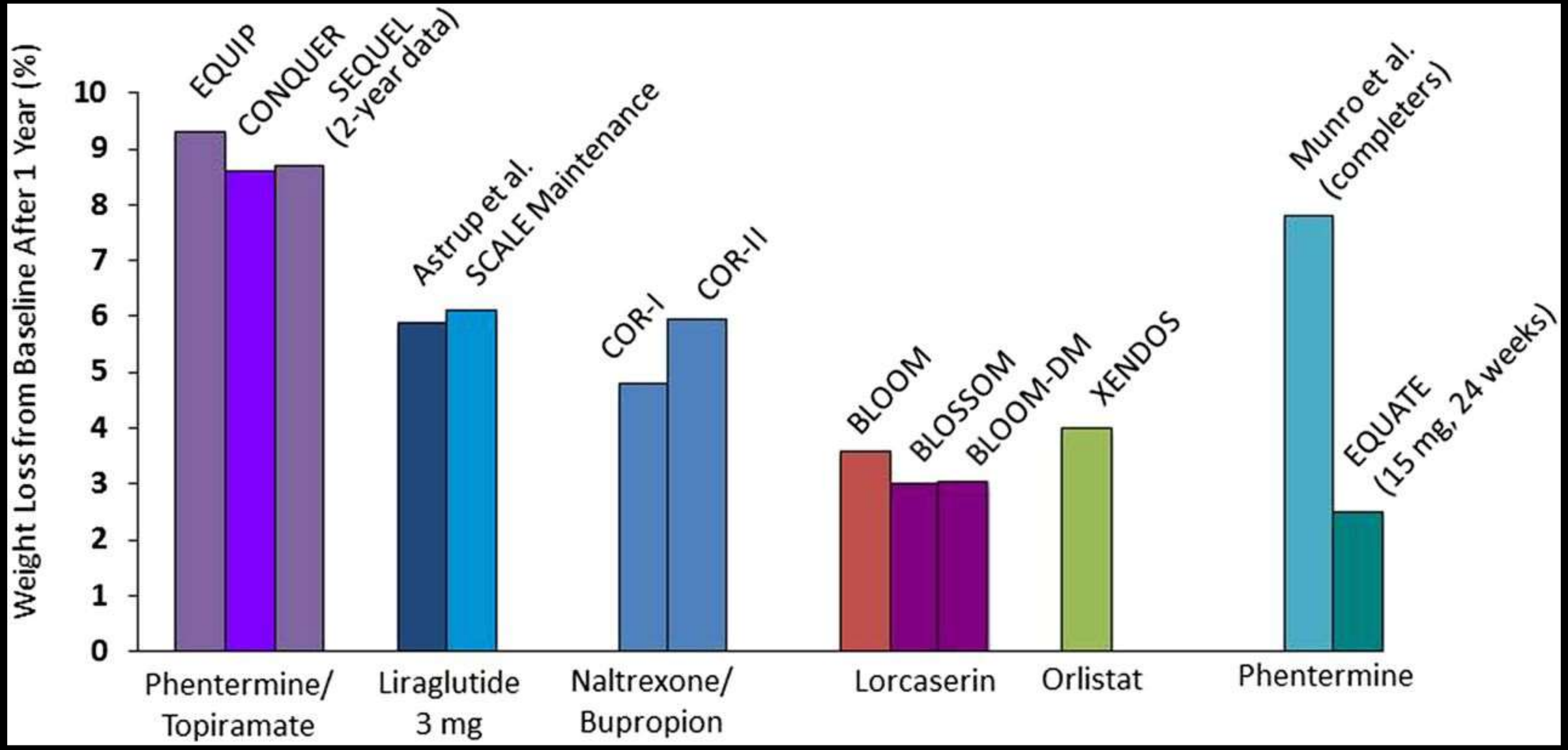


Blood Pressure

Lipids



Comparison of Anti-Obesity Medications



Before Adding A Med…

Determine if a med is the cause!

Weight Gain Promoting Medications	Alternate Agents
<u>Diabetes Treatments:</u> Insulin Sulfonylureas Thiazolidinediones	Amylin analog—pramlintide GLP-1 agonists metformin SGLT-2 inhibitors DPP4 inhibitors
<u>Glucocorticoids</u> Prednisone, Methyl-prednisolone, etc	Immunosuppressive agents DMARDs
<u>Contraceptives</u> Depo-provera	Non-hormonal contraception OCPs
<u>Beta-Blockers</u> Propranolol, Metoprolol, Atenolol	Other anti-hypertensives such as ACEi Third generation BBs have less weight gain (carvediolol, nebivolol)
<u>Anti-Histamines</u> Diphenhydramine, Hydroxyzine, Cetirizine, Fexofenadine	Loratadine

Weight Gain Promoting Medications	Alternate Agents
<u>Atypical Antipsychotics:</u> clozapine, olanzapine, quetiapine, risperidone, aripiprazole	ziprasidone
<u>Anti-Depressants:</u> Tricyclics: nortriptyline, amitriptyline SSRIs: paroxetine, citalopram, escitalopram Others: trazodone, mirtazipine, venlafaxine	bupropion sertraline CBT memantine or ketamine L-methylfolate (Deplin ®)
<u>Anti-Epileptics</u> gabapentin, valproic acid	topiramate zonisamide lamotrigine
<u>Mood Stabilizers</u> lithium	topiramate zonisamide lamotrigine cariprazine (Vraylar ®)

Want to know more?

Sign up for a roundtable event

Questions?

stacy.chronister@okstate.edu

Obesity Medicine Association

CLINICAL LEADERS IN OBESITY MEDICINE ®

Join OMA | Academy Login | Member Login

Home | About | Membership | Clinician Resources | Conferences | CME | Corporate Relations | Foundation

Learn about available clinical obesity treatment tools at our Fundamentals of Obesity Treatment Course!

View Course Dates and Cities

Feb. 2 | Portland, OR

Feb. 16 | Dallas, TX

March 2 | Chicago, IL

May 4 | Cleveland, OH

Oct. 19 | San Francisco, CA

obesitymedicine.org