

Updates in the Medical Management of Obesity

Rekha B. Kumar, M.D., M.S.
Assistant Professor of Medicine
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ANNUAL

**CONTROVERSIES, PROBLEMS
& TECHNIQUES IN SURGERY**



Disclosures

- Shareholder

Vivus pharmaceuticals

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Myos corp.

- Speakers Bureau

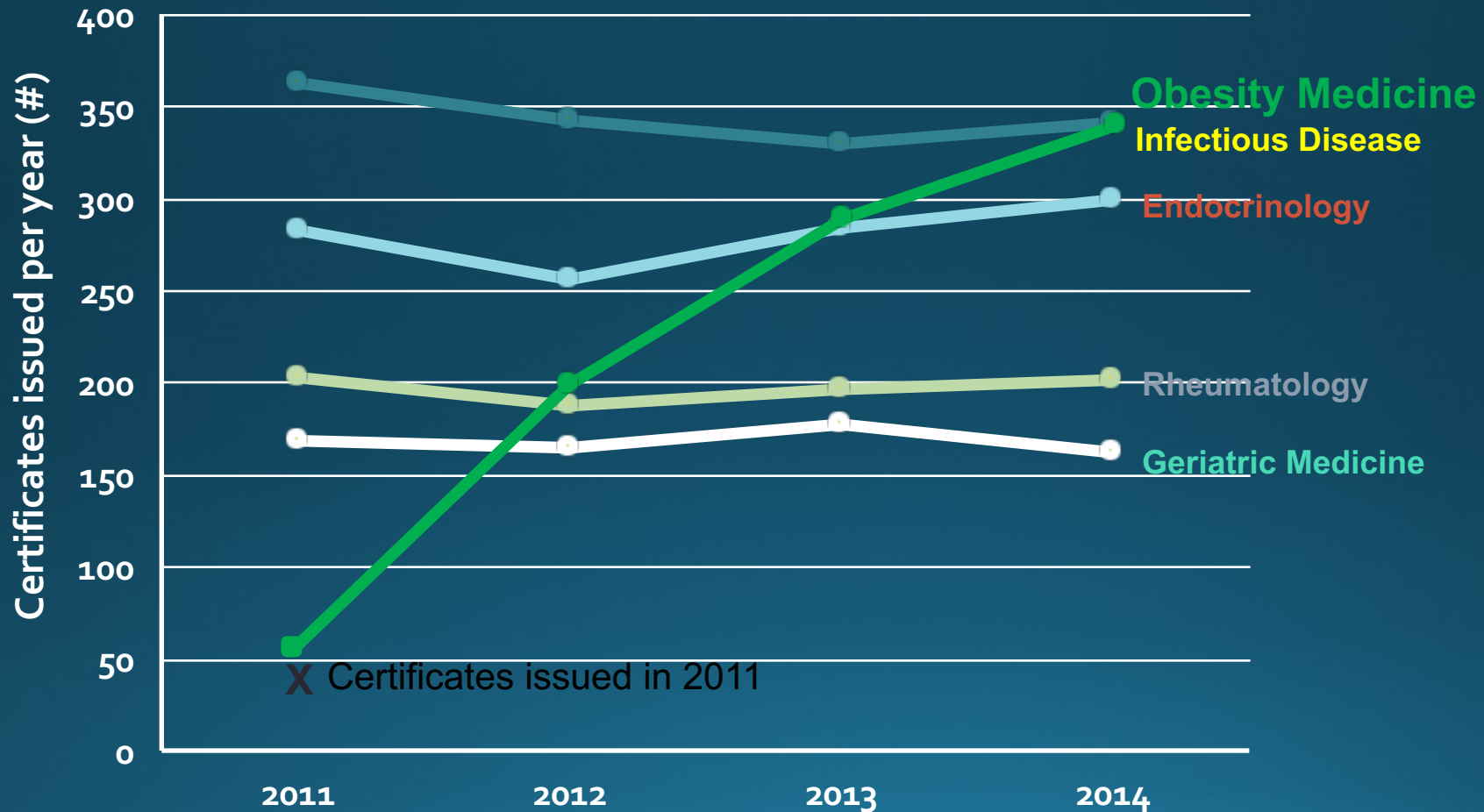
Jansen Pharmaceuticals



AMERICAN BOARD
of OBESITY MEDICINE

Obesity Medicine: The Newest Specialty in Medicine

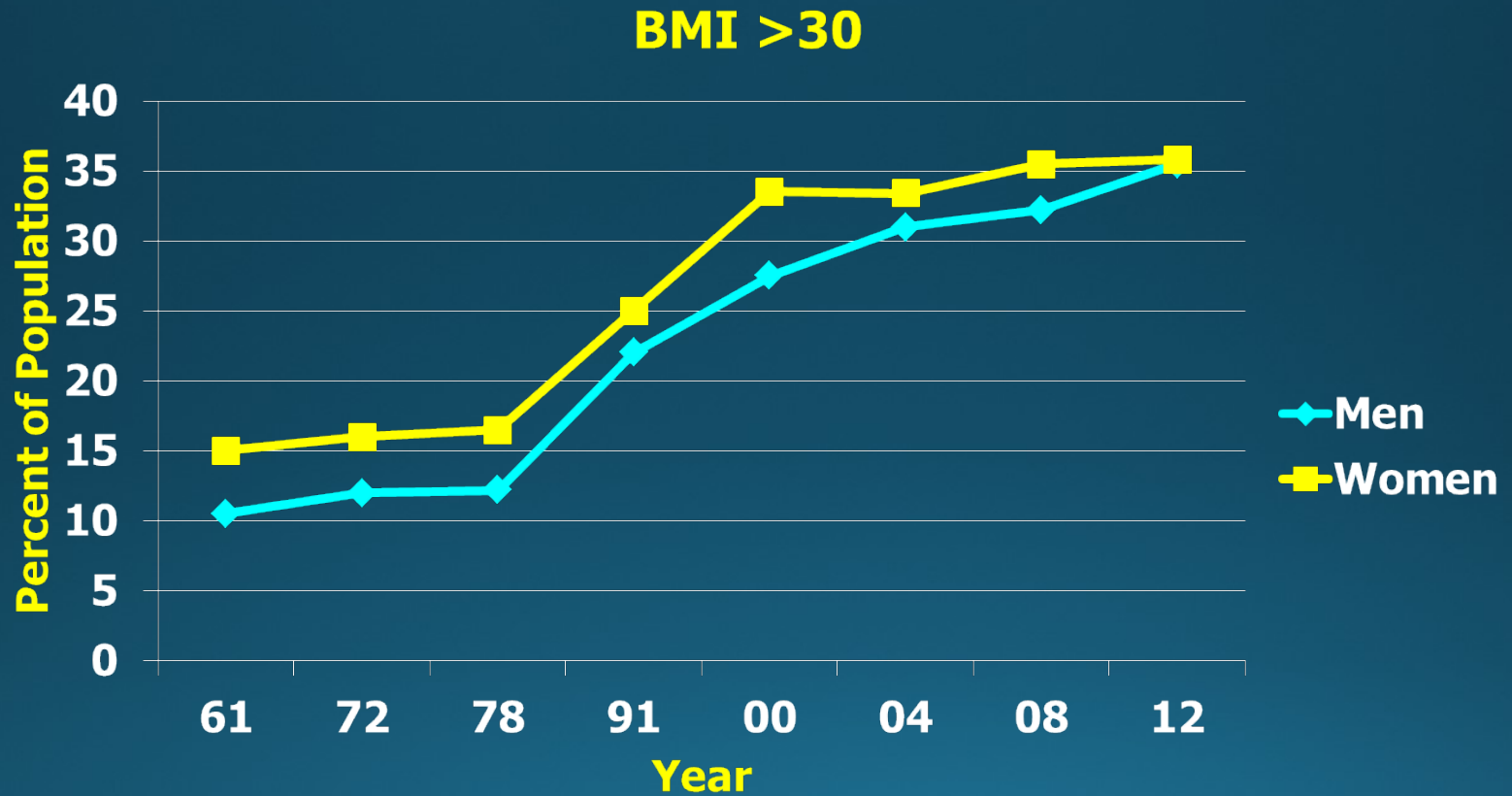
Number of Certificates Issued in Various Medical Specialties



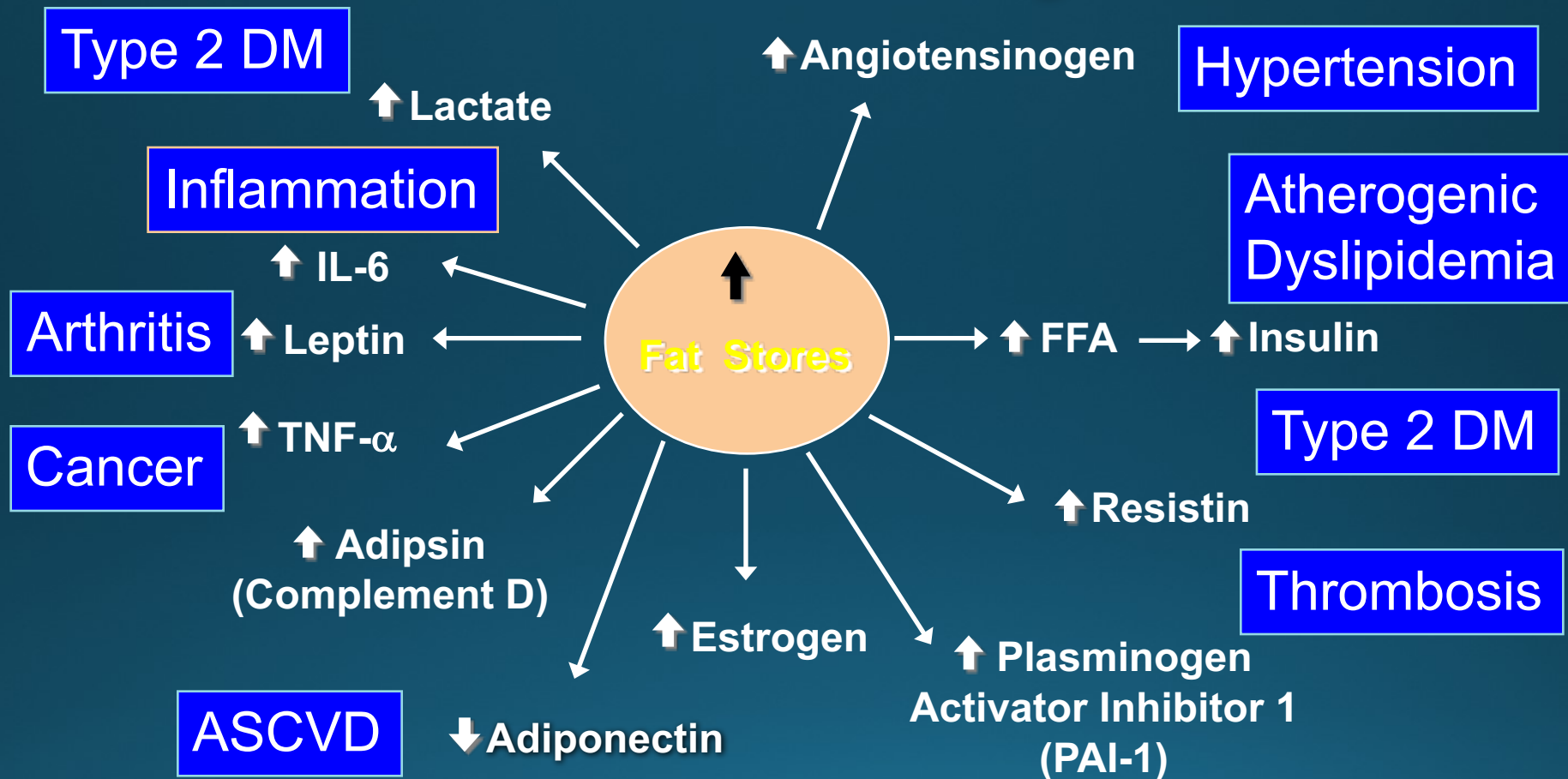
Definition of Obesity

- Obesity is defined as an excess of body fat
- Body fat is difficult to measure quickly and cheaply
- For people with average lifestyles, Body Mass Index (BMI) has been the measure of obesity
- $BMI = \text{Wt in Kg} \div \text{height in M squared}$
- BMI has been divided into categories
- 18-25 is normal, 25-30 is overweight, 30-35 is class I, 35-40 is class II, >40 is class III

NHANES – Prevalence of Obesity 1961-2012



How Obesity Causes Disease: The Fat Cell—A Multiendocrine Organ



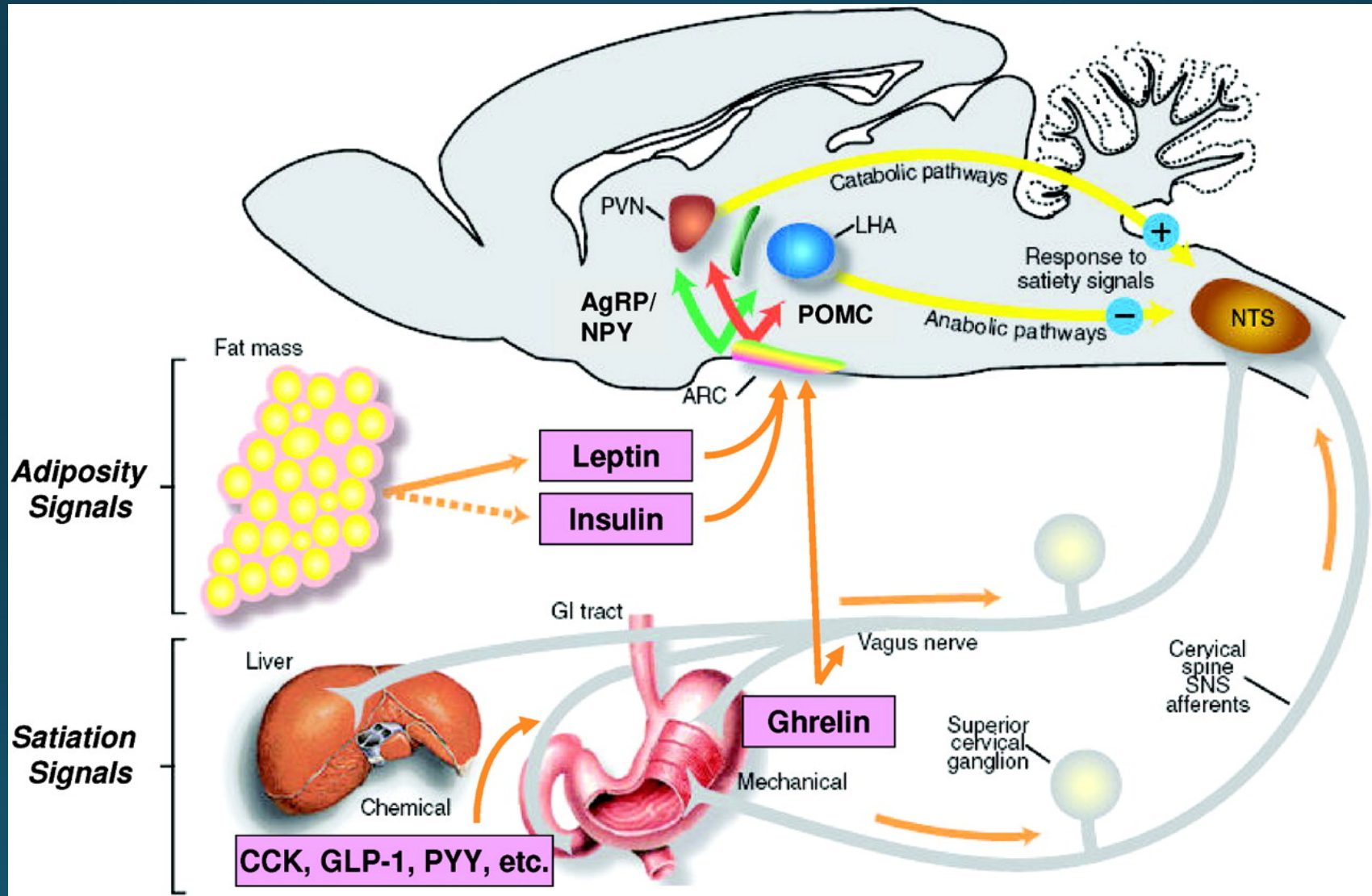
DM=diabetes mellitus; FFA=free fatty acid; PAI-1=plasminogen activator inhibitor-1; TNF α =tumor necrosis factor-alpha; IL-6=interleukin 6; ASCVD=atherosclerotic cardiovascular disease.

Bray, G. J Clin Endocrinol Metab. 2004;89:2583-2589.

Eckel RH, et al. *Lancet*. 2005;365:1415-1428.

Slide: Aronne LJ After Dr. G. Bray.

Model Summarizing Different Levels of Control Over Appetite Regulation



ORIGINAL ARTICLE

Long-Term Persistence of Hormonal Adaptations to Weight Loss

Priya Sumithran, M.B., B.S., Luke A. Prendergast, Ph.D.,
Elizabeth Delbridge, Ph.D., Katrina Purcell, B.Sc., Arthur Shulkes, Sc.D.,
Adamandia Kriketos, Ph.D., and Joseph Proietto, M.B., B.S., Ph.D.

15% Weight Loss:

Reduced

Leptin – 65%

Peptide YY

Cholecystokinin

Insulin

Amylin

Increased

Ghrelin

Gastric inhibitory polypeptide

Pancreatic polypeptide

**The net result of these hormonal changes =
WEIGHT GAIN!**

Clinical Evaluation of the Obese Patient

- Is the patient actually obese?

BMI, Ethnicity, Waist Circumference, Body dysmorphic disorder.

- Do they have the stigmata of any medical/endocrine diseases that might be causing obesity

Hypothyroidism, Cushing's Syndrome, PCOS, Acromegaly, Lipodystrophy (HIV patients)

Before Prescribing, Look for Medications that Cause Weight Gain

Drug-Associated Weight Change Reference			Alternatives That Cause Less Weight Gain, Weight Loss, or are Weight Neutral
Therapeutic Category	Drug Class	May Cause Weight Gain	
Psychiatry	Antipsychotic	<ul style="list-style-type: none"> • Clozapine • Risperidone • Olanzapine • Quetiapine • Other 	<ul style="list-style-type: none"> • Ziprasidone • Aripiprazole
	Antidepressants and Mood Stabilizers	<ul style="list-style-type: none"> • Citalopram • Escitalopram • Fluvoxamine • Lithium • MAOIs 	<ul style="list-style-type: none"> • Bupropion • Nefazodone • Fluoxetine (short term: <1 year) • Sertraline (short term: <1 year)
Neurology	Anticonvulsants	<ul style="list-style-type: none"> • Carbamazepine • Gabapentin • Valproate 	<ul style="list-style-type: none"> • Lamotrigine • Topiramate • Zonisamide
Endocrinology	Diabetes Treatments	<ul style="list-style-type: none"> • Insulin • Sulfonylureas • Thiazolidinedione 	<ul style="list-style-type: none"> • Metformin • Acarbose • Miglitol • Pramlintide • Exenatide • Sitagliptin
Obstetrics & Gynecology	Oral Contraceptives	<ul style="list-style-type: none"> • Progestational steroids • Hormonal contraceptives containing progestational steroids 	<ul style="list-style-type: none"> • Barrier methods • IUDs
	Endometriosis Treatment	<ul style="list-style-type: none"> • Depot leuprolide acetate 	<ul style="list-style-type: none"> • Surgical methods
Cardiology	Antihypertensives	<ul style="list-style-type: none"> • α-blocker • β-blocker 	<ul style="list-style-type: none"> • ACE inhibitors • Calcium channel blockers
Infectious Disease	Antiretroviral Therapy	<ul style="list-style-type: none"> • Protease inhibitors 	<ul style="list-style-type: none"> • None
General	Steroid Hormones	<ul style="list-style-type: none"> • Corticosteroids • Progestational steroids 	<ul style="list-style-type: none"> • NSAIDs
	Antihistamines/ Anticholinergics	<ul style="list-style-type: none"> • Diphenhydramine • Doxepin • Cyproheptadine • Other potent antihistamines 	<ul style="list-style-type: none"> • Decongestants • Steroid inhalers

Waist Circumference



- Waist circumference measurements are most useful for overweight to class I obesity (BMI 25-35 kg/m^2) for further risk assessment
- Waist circumference indicates increased cardiometabolic risk

Men > 40 inches (>102 cm)

Women > 35 inches (>88 cm)

- ? Ethnic specific values

Obstructive Sleep Apnea

- Daytime hypersomnolence
- Snoring
- Morning headaches
- Irritability
- Disturbed sleep
- Hypertension and right sided heart failure
- Neck circumference > 17 inches

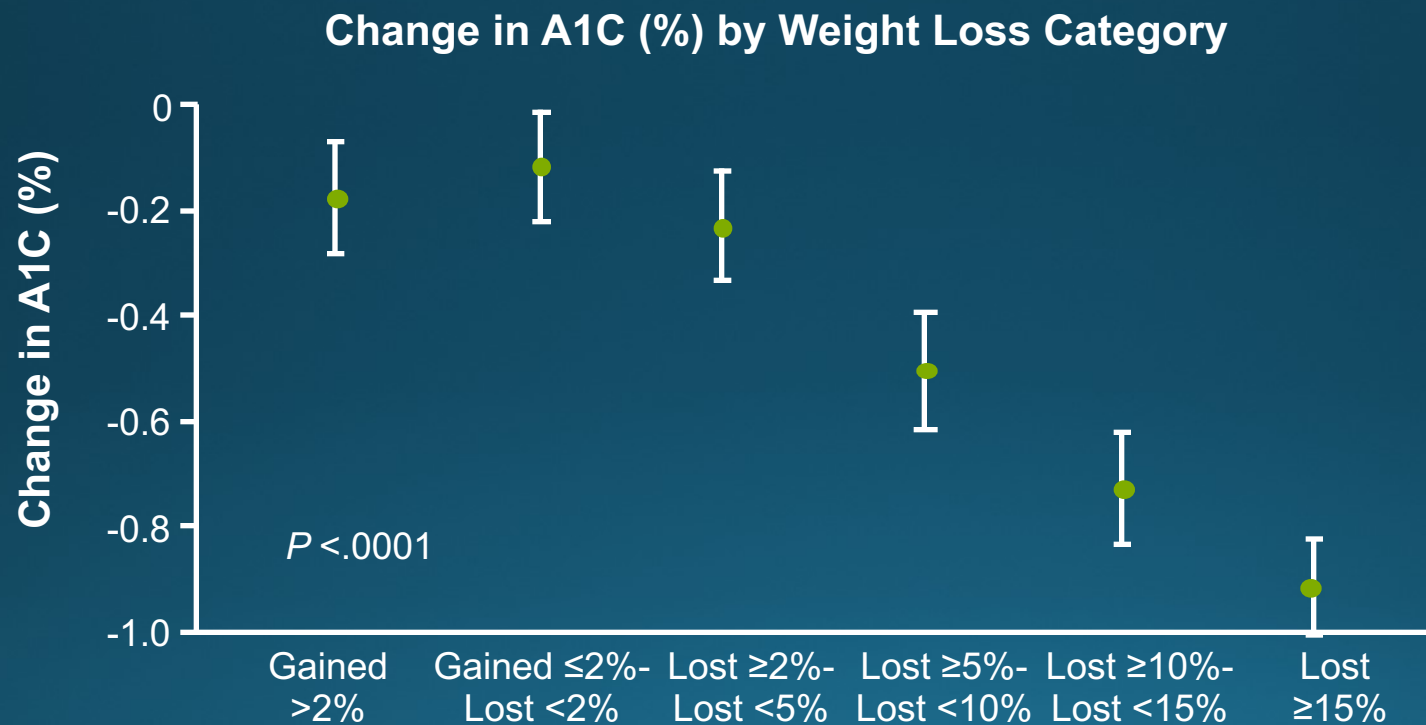


Weight Management is Moving into the Workplace and Mainstream of Healthcare

- **Screening for Obesity in Adults.** The US Preventive Services Task Force recommends that clinicians screen all adult patients for obesity and offer intensive counseling and behavioral interventions to promote sustained weight loss for obese adults (Grade B recommendation)
- Medicare now covers behavioral treatment of obesity

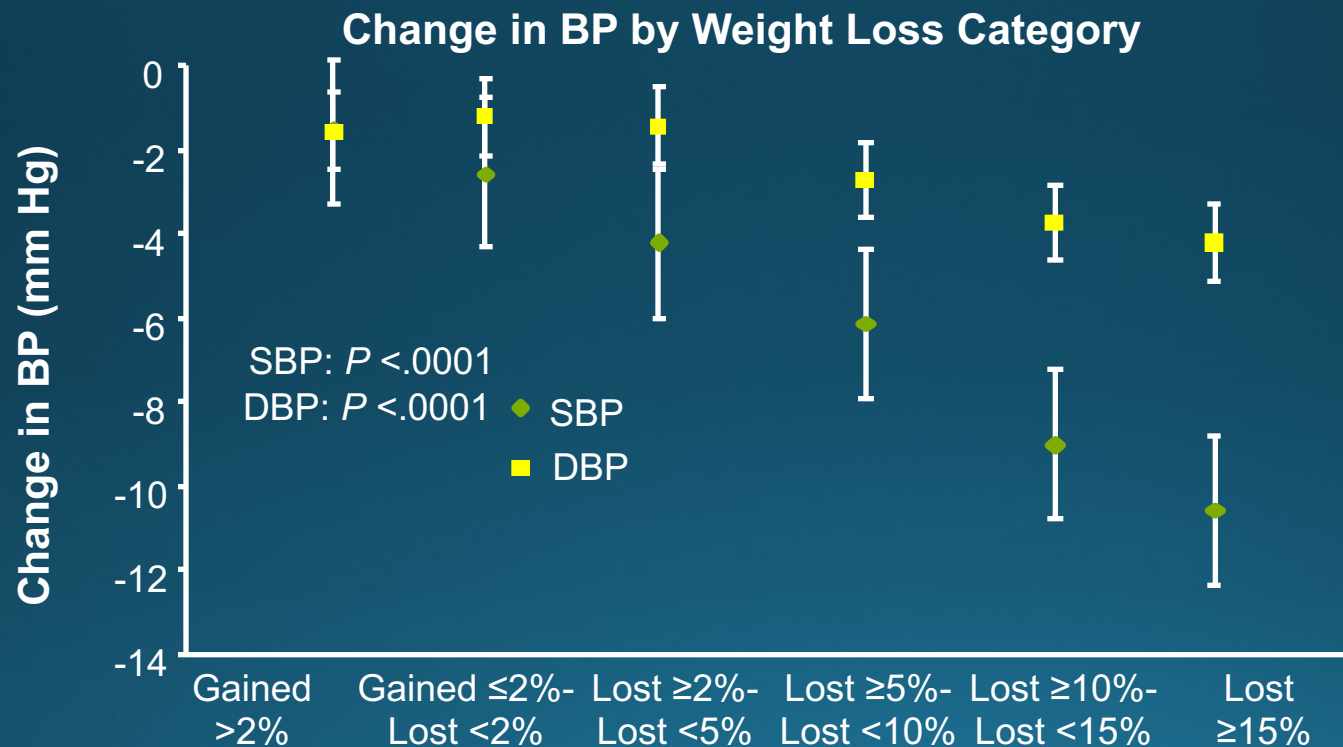
How Much Weight Loss Is Needed to Improve Glycemic Control in T2DM?

Improvement Begins With >2% Weight Loss



How Much Weight Loss Is Needed to Improve BP in T2DM?

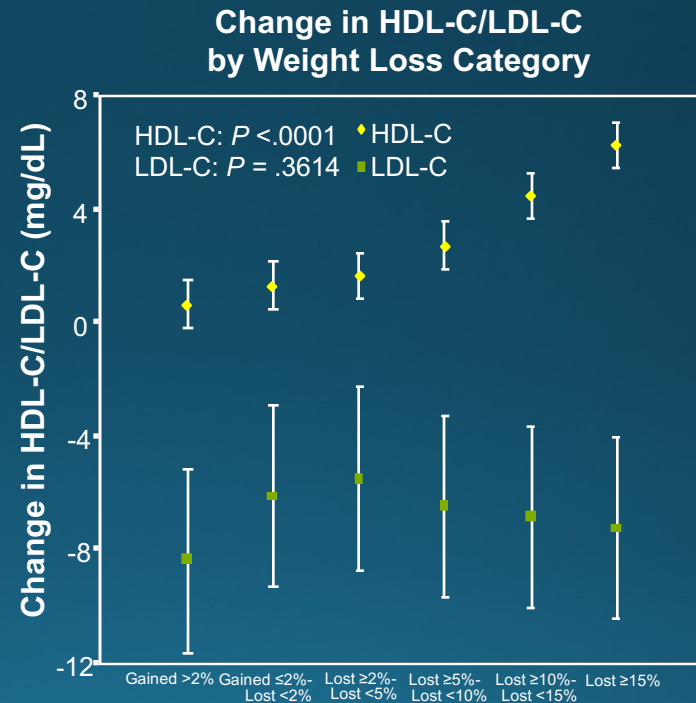
Effect of Amount of Weight Loss on SBP and DBP: Direct and Linear



DBP = diastolic BP; SBP = systolic BP.

How Much Weight Loss Is Needed to Improve Lipids in T2DM?

Effect of Amount of Weight Loss on HDL-C and TGs Is Direct and Linear; Effect on LDL-C Is Less Pronounced

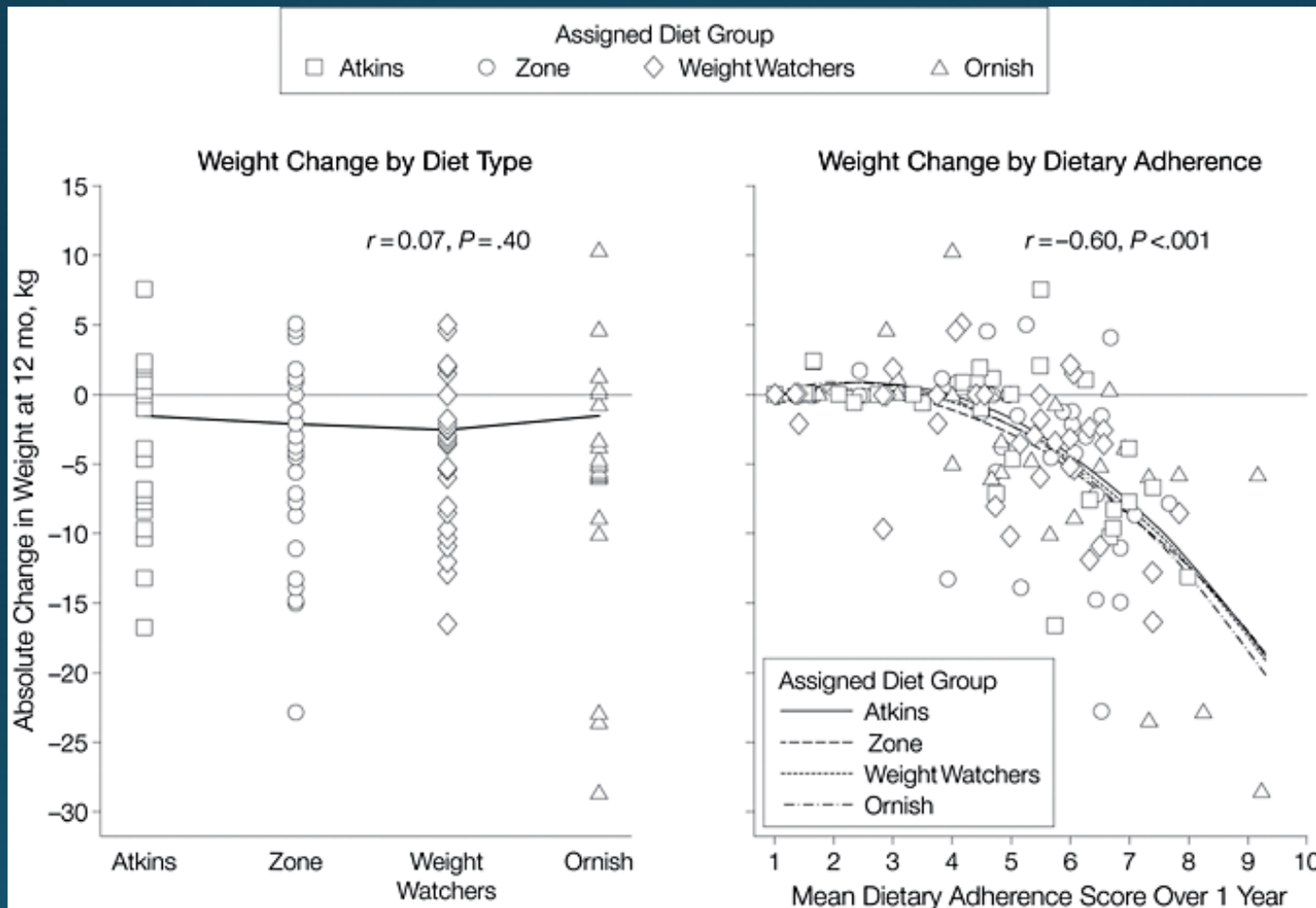


HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TGs = triglycerides.

Adherence to the diet and not the diet predicts success.

“The Best Diet is the One You Like Best”

Provide Different Options!



Diet Type does not predict weight loss

Adherence Score predicts weight loss

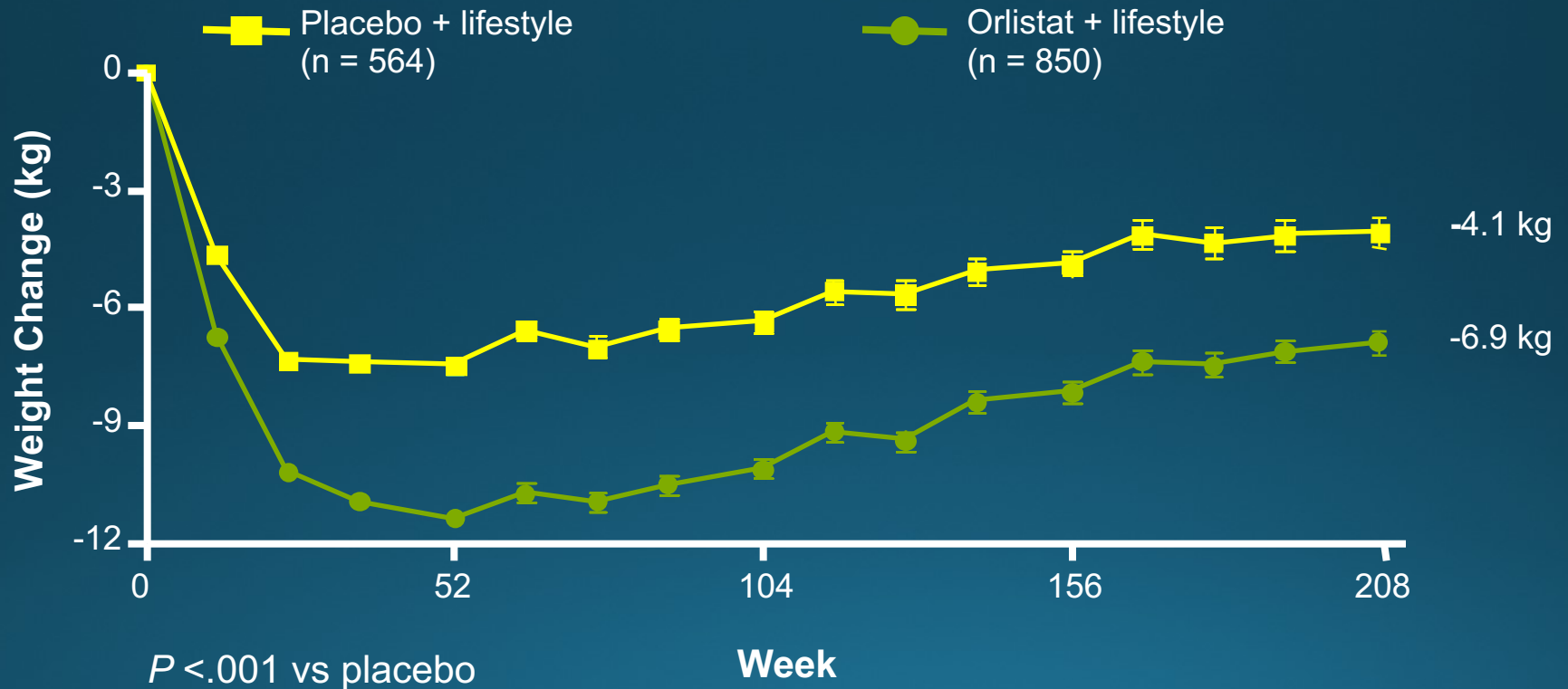
Dansinger, M. L. et al. JAMA 2005;293:43-53.

Use of Pharmacotherapy

- The goal of treatment is not only to reduce weight, but more importantly to improve the comorbid conditions associated with obesity, such as hyperglycemia, hyperlipidemia, and heart disease.
- Efficacy of the current medication options is limited to 5-10% body weight loss in the majority of successful patients.
- As an adjunct to healthy lifestyle changes, including an increase in activity and calorie-deficit diet.
- Pharmacotherapy can also be considered an adjunct to bariatric surgery when additional weight loss is required or to prevent weight regain after weight loss surgery.

Effect of Long-term Treatment With Orlistat: XENDOS Study

Completers Data



XENDOS = XENical in the Prevention of Diabetes in Obese Subjects.
Torgerson JS, et al. *Diabetes Care*. 2004;27:155-161.

Phentermine

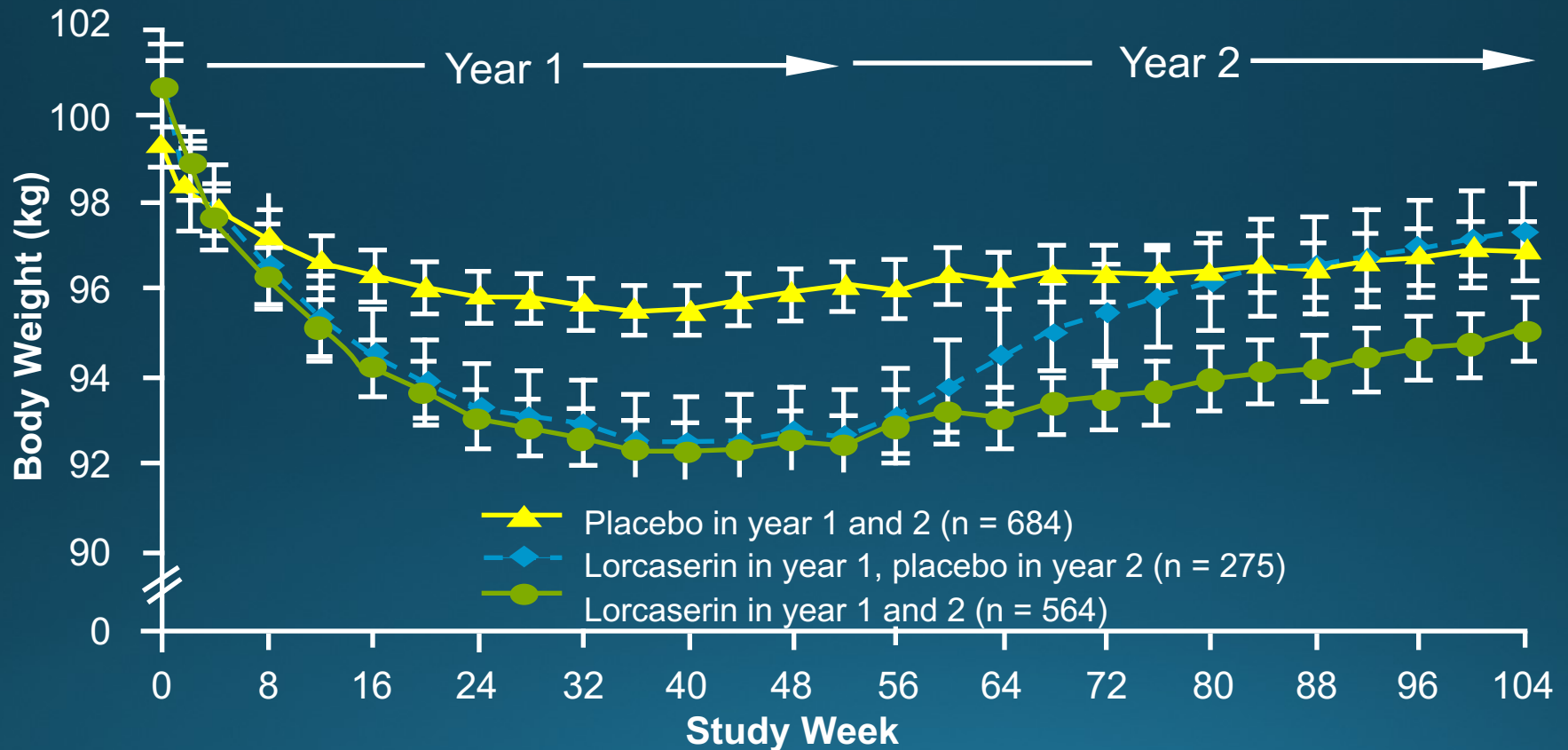
- Phentermine resin (15-30 mg/d) approved in 1959 for short-term (12 wk) weight management
- Mechanism: noradrenergic, sympathomimetic amine: decreases appetite
- Most common AEs: tachycardia, increase in BP, tremor, overstimulation of central nervous system, dry mouth, constipation
- Notes
 - Generic; most commonly prescribed/least expensive option
 - Phentermine HCl salt easily dissociates in gastrointestinal tract, resulting in immediate release of phentermine drug; absorbed ~3× faster than resin
 - DEA Schedule IV drug
 - Pregnancy category X

DEA = Drug Enforcement Administration; HCl = hydrochloride.

Lorcaserin

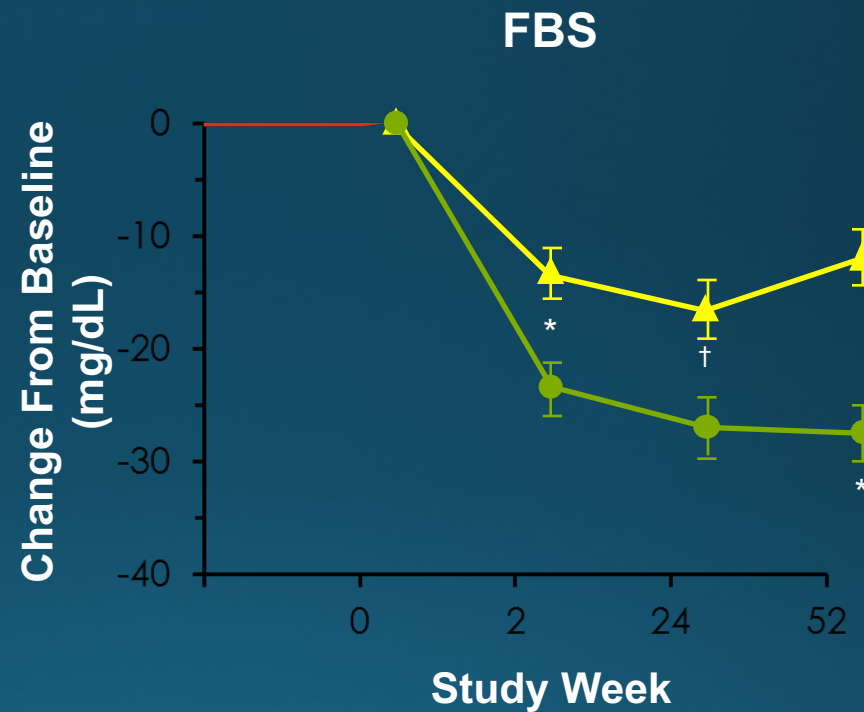
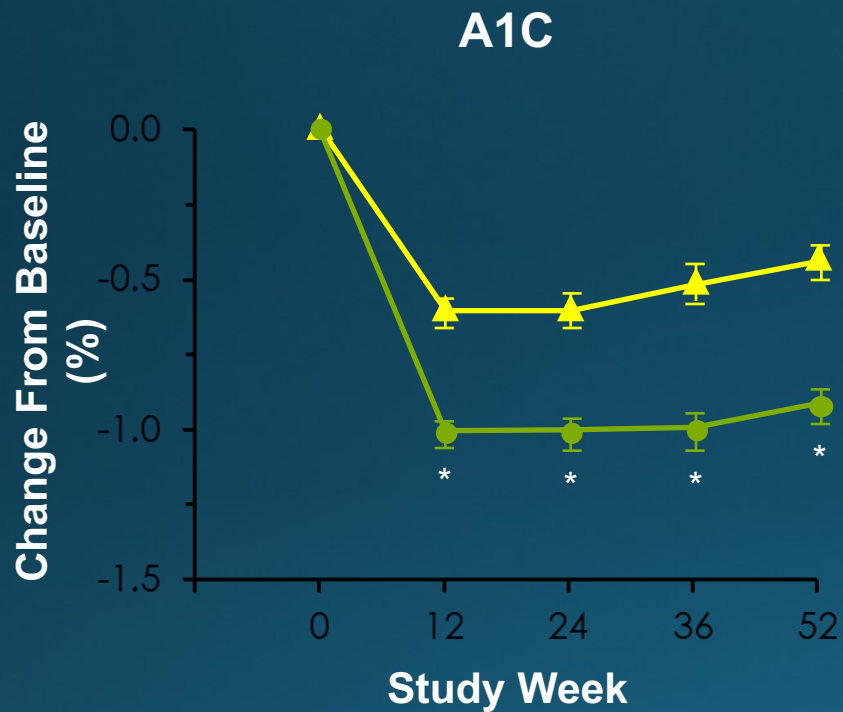
- Approved in 2012 (10 mg twice daily) for long-term weight management
- Mechanism: selective 5-HT_{2C} receptor agonist: increases satiety
- Most common AEs: headache, nausea, dizziness, fatigue, dry mouth, constipation
- Notes
 - Discontinue if 5% weight loss is not achieved by week 12
 - Discontinue for evaluation if signs or symptoms of valvular heart disease occur
 - DEA Schedule IV
 - Pregnancy category X

BLOOM Study: Body Weight Over Years 1 and 2



BLOOM = Behavioral Modification and Lorcaserin for Overweight and Obesity Management.

BLOOM-DM: Change in Glycemic Parameters



● Lorcaserin 10 mg twice a day

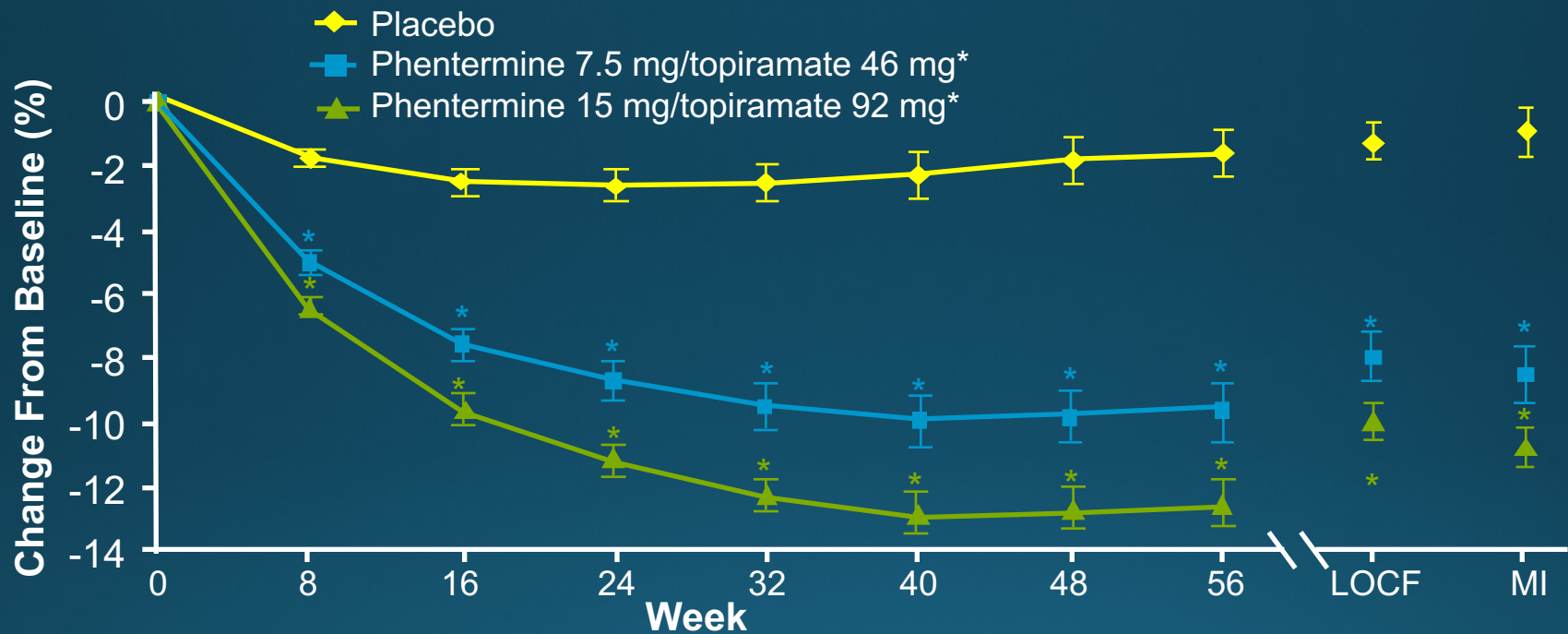
▲ Placebo

* $P < .001$; † $P < .05$; LS mean change \pm standard error of the mean.
BLOOM-DM = BLOOM in Diabetes Mellitus; LS = least squares.

Phentermine/Topiramate

- Immediate-release phentermine HCl/controlled-release topiramate approved for weight management in 2012 (titrated in AM up to 7.5/46 mg/d; max 15/92 mg/d)
- Mechanism: phentermine—decreases short-term appetite; topiramate—decreases longer-term appetite and may have glycemic effects
- Most common AEs: paresthesia, dizziness, cognitive dysfunction, dysgeusia, insomnia, constipation, dry mouth, metabolic acidosis, elevated creatinine
- Notes
 - Schedule IV drug
 - May contribute to secondary angle-closure glaucoma
 - If full/max dose discontinued, it should be done gradually to prevent seizures
 - Pregnancy category X (cleft palate)

CONQUER: Weight Loss Over Time



Patients	Placebo	Mid	Full
Completers (% of randomized)	557 (57%)	338 (69%)	625 (64%)

*Weight change for either dose vs placebo, $P < .0001$.

LOCF = last observation carried forward; MI = multiple imputation.

REMS for Phentermine/Topiramate ER

Risk Evaluation and Mitigation Strategy (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks. The FDA has required a REMS for Qsymia.

The purpose of the Qsymia REMS is to inform prescribers and females of reproductive potential about the:

- Increased risk of congenital malformation, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy
- Importance of pregnancy prevention for females of reproductive potential receiving Qsymia
- Need to discontinue Qsymia immediately if pregnancy occurs

Healthcare Provider Training Program

The Qsymia REMS includes a healthcare provider training program.

Complete the Qsymia Healthcare
Provider Training Program

START

Counseling Females on *Risk of Birth Defects with Qsymia*

- Counsel females of reproductive potential at initial and all follow-up visits on the increased risk of orofacial clefts in infants exposed to Qsymia during the first trimester of pregnancy
- Counsel females of reproductive potential to have a pregnancy test before starting Qsymia and monthly thereafter during therapy
- Discuss the need for consistent use of effective contraception during therapy
- Make use of the REMS tools supporting patient education that are available on this Web site

Dispensed to Patients Through Certified Pharmacies

Qsymia is available only through certified pharmacies. [Click Here](#) to learn more.

- Addresses risk of teratogenicity
- Modified REMS approved April 2013: may be dispensed through certified retail pharmacies in addition to network of certified mail-order pharmacies

REMS = Risk Evaluation and Mitigation Strategy.

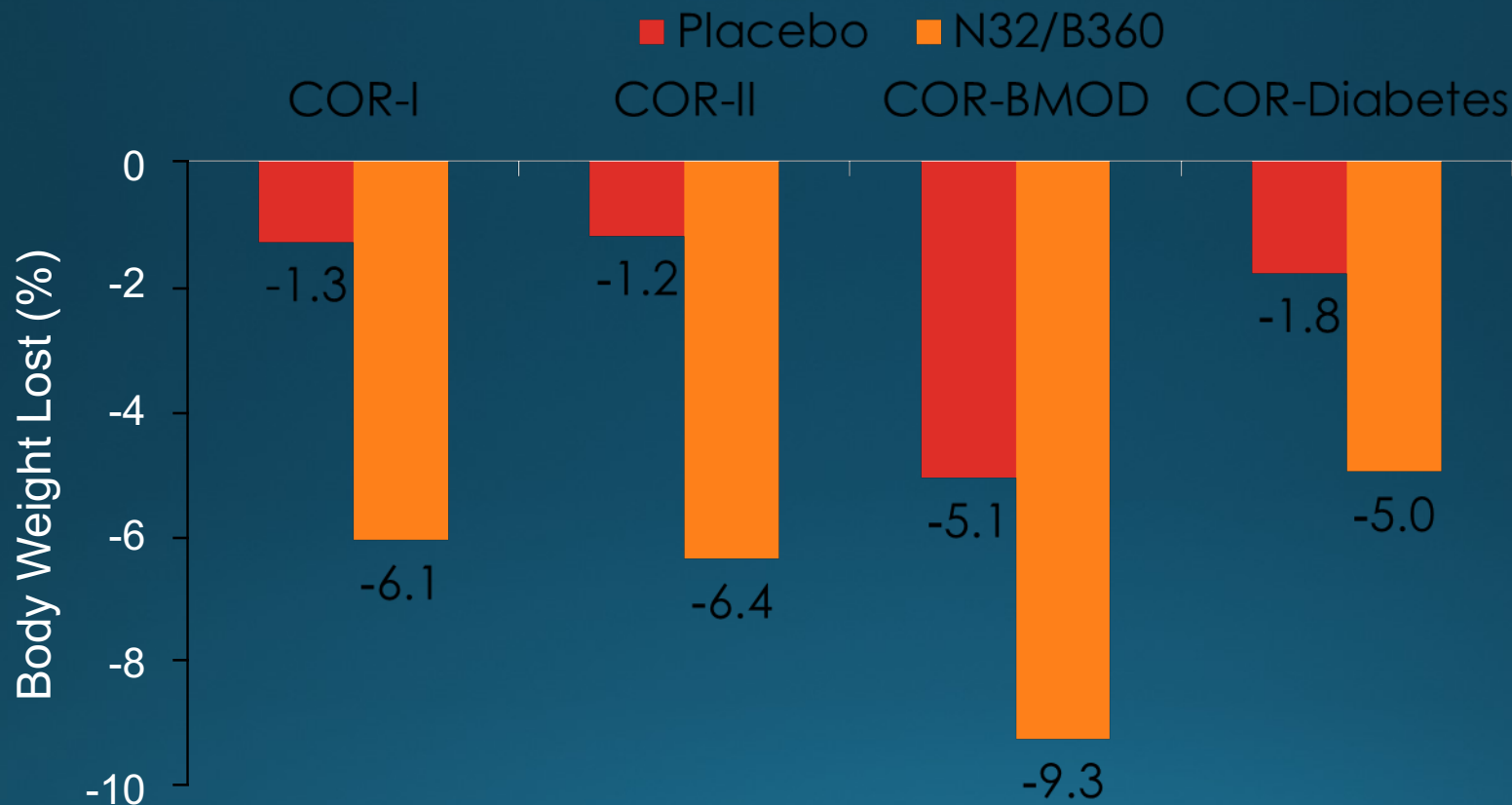
VIVUS Inc. <http://www.qsymiarems.com>. Accessed October 3, 2014.

Bupropion ER/Naltrexone ER

- Approved for weight loss September 2014
- Bupropion: primary mechanism of action thought to be dopaminergic and/or noradrenergic
 - Does not inhibit MAO or reuptake of serotonin
 - Metabolites inhibit reuptake of norepinephrine
 - Appears to decrease the “reward system” that various foods can induce
- Naltrexone mechanism of action: pure opioid antagonist
 - An opioid pathway is known that tries to stop or slow weight loss—naltrexone blocks this pathway

MAO = monoamine oxidase.

COR Studies: Weight Loss With Bupropion/Naltrexone at 56 Weeks



BMOD = intensive behavioral modification; COR = Contrave Obesity Research; N32/B360 = naltrexone 32 mg/bupropion 360 mg.

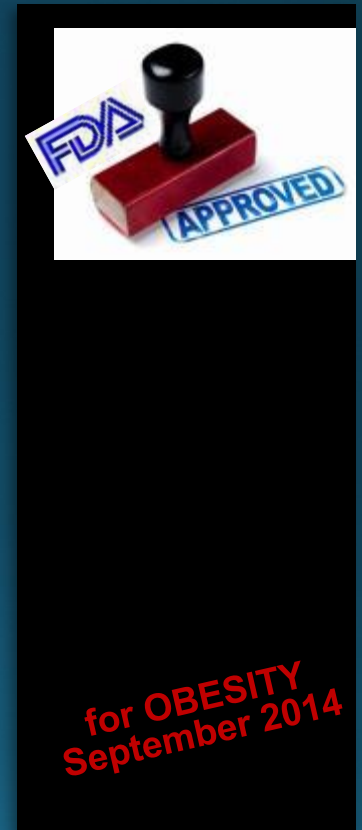
Rueda-Clausen CF, et al. *Nat Rev Endocrinol*. 2013;9:467-478.

Bupropion/Naltrexone Tolerability Data

AE	Bupropion/Naltrexone 360 mg/32 mg (n = 2545), %	Placebo (n = 1515), %
Nausea	32.5	6.7
Constipation	19.2	7.2
Headache	17.6	10.4
Vomiting	10.7	2.9
Dizziness	9.9	3.4
Insomnia	9.2	5.9
Dry mouth	8.1	2.3
Diarrhea	7.1	5.2
Anxiety	4.2	2.8
Hot flush	4.2	1.2
Fatigue	4.0	3.4
Tremor	4.0	0.7

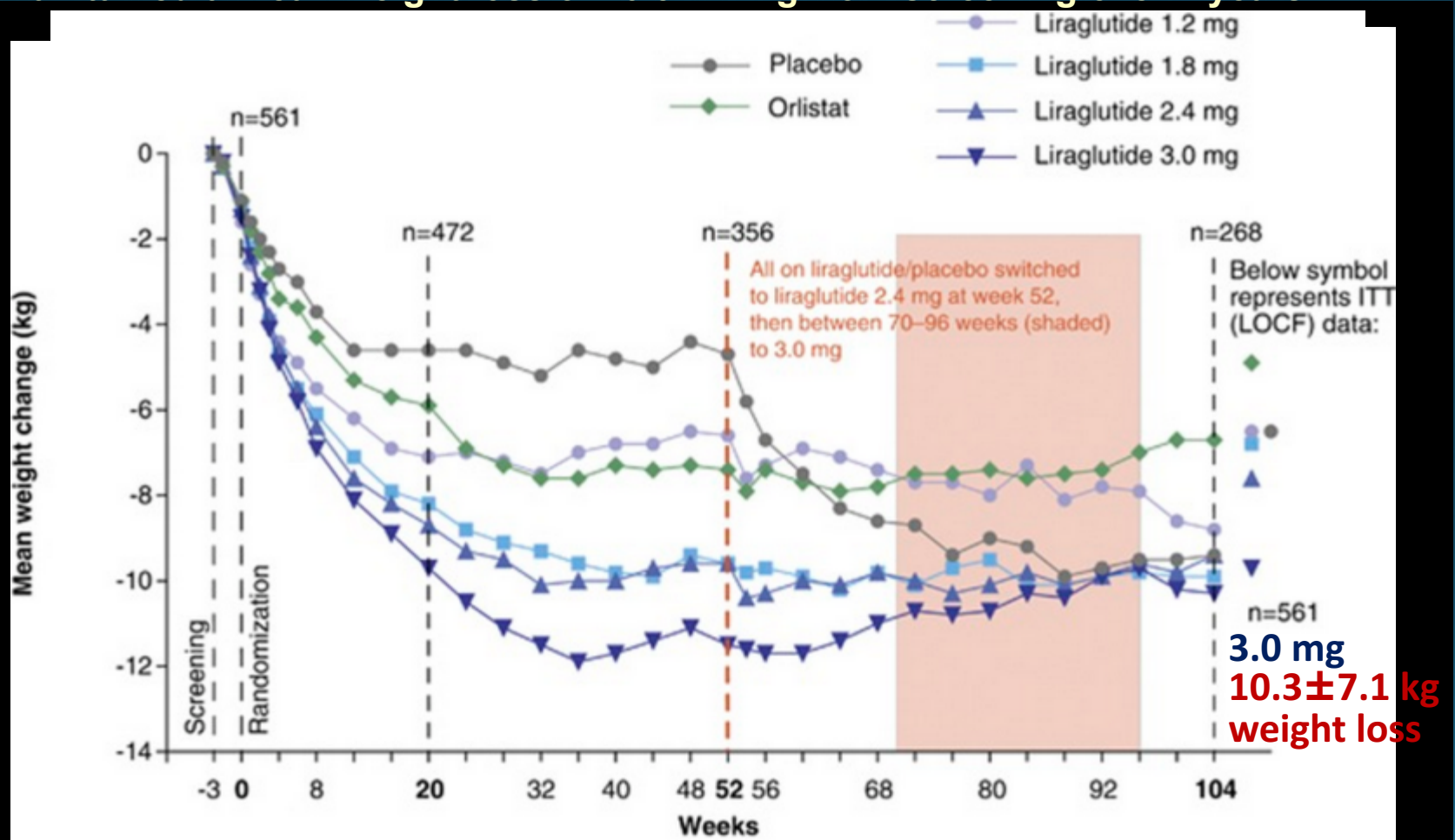
Liraglutide

- Glucagon-Like Peptide 1 (GLP-1) receptor agonist approved in 2010 for treatment of type 2 diabetes (1.8 mg/day)
- Appetite effect mediated by both the activation of GLP-1 receptors expressed in the hypothalamus
- Affects appetite, food preference, and cardiovascular biomarkers in patients with type 2 diabetes
- Approved under obesity indication at 3 mg dose



Liraglutide Weight Loss: Two Years

Liraglutide 3.0 mg for 1 year (and then maintained on 2.4/3.0 mg for the second year) maintained a mean weight loss of 10.3 ± 7.1 kg from screening over 2 years



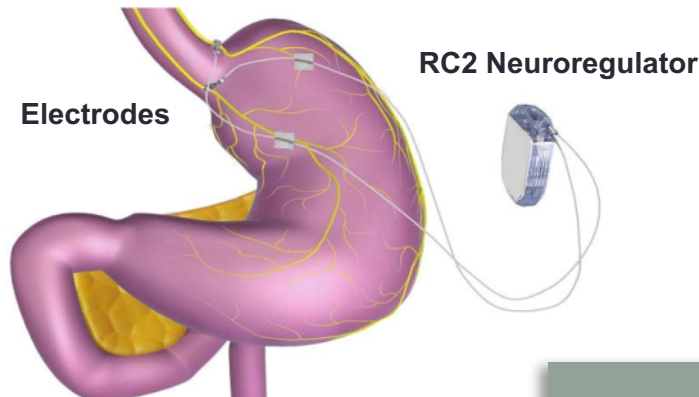
Liraglutide: Adverse Events

- Generally well tolerated and improved quality of life
- Adverse events mostly mild or moderate
- Gastrointestinal events (particularly nausea and vomiting), consistent with the known physiological effects of GLP-1, were more frequent than with placebo
- 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
- Injection regimen did not impair adherence or cause significant withdrawal during treatment or run-in



Devices

Vagal Blocking Therapy

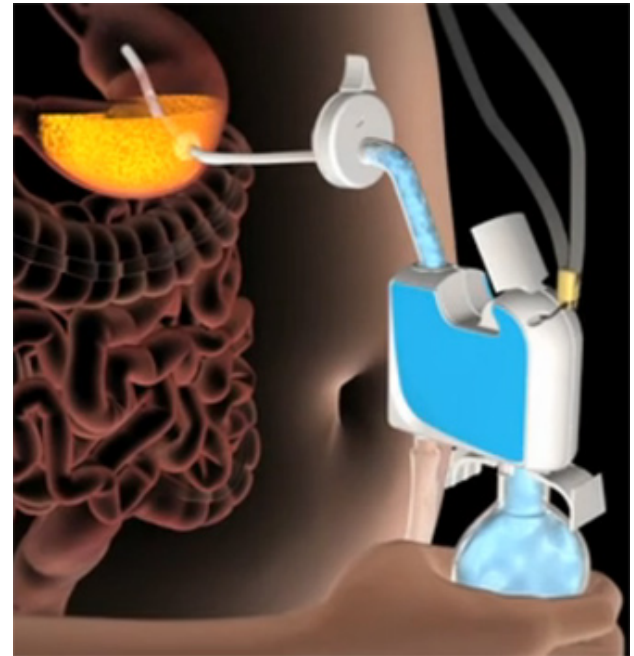


- Pacemaker-like device designed to control hunger and fullness by blocking the vagus nerve to affect the perception of hunger and fullness
- Satiation by delaying food processing and gastric emptying

%EWL achieved	VBLOC	
	12 months (N=147)	24 months (N=103)
≥5.0%	67%	58%
≥7.5%	56%	45%
≥10.0%	39%	34%
≥12.5%	32%	27%
≥15.0%	22%	21%

Recently Approved: Aspire Assist

- Removable device
- 20 minute procedure is performed under conscious sedation – no general anesthesia is required
- Removes ~30% of food from stomach before calories are absorbed, causing weight loss
- Thin tube connects inside of stomach directly to a discreet Skin-Port on outside of abdomen. Valve on port valve controls flow of stomach contents
- Aspiration process is performed ~20 minutes after entire meal is consumed and takes 5 to 10 minutes to complete, 3x/day

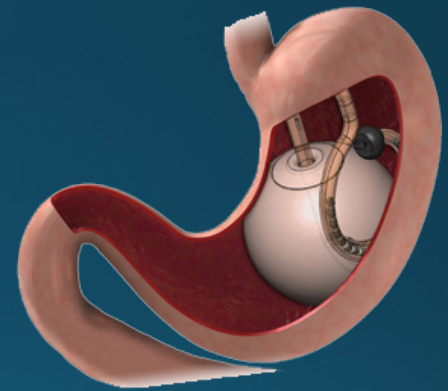


16 weeks mean weight reduction:
– 12.4 kg, 32.2% Excess Weight Loss

Procedure for Endocrine and Obesity Medicine ?

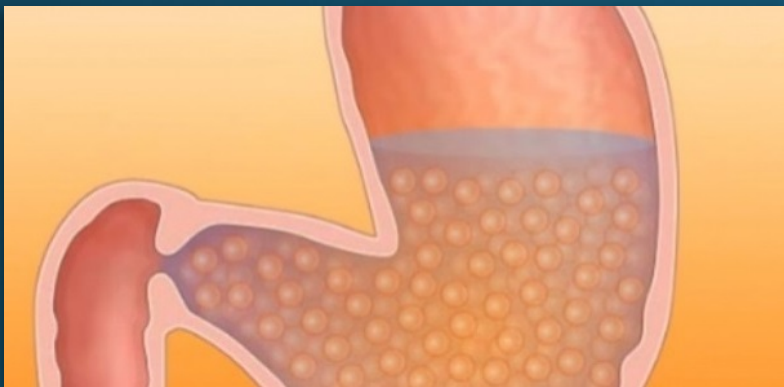
Swallowable Balloon Devices

Name	Procedure	Time	Weight Loss
Obalon Balloon Pill Obalon	Attached to lightweight catheter; swallow with water; deflates in stomach and passes	3 mos	50.2% Excess Weight Loss 8.3% Total Body Weight Loss and 2.8 point reduction in BMI in 3 months (n=110)
The Elipse Allurion Technologies	"Procedure-less" Swallowed and excreted without surgery, endoscopy, or anesthesia	3 mos	13% Excess Weight Loss at 6 weeks 3.0 kg total body weight loss 6 weeks



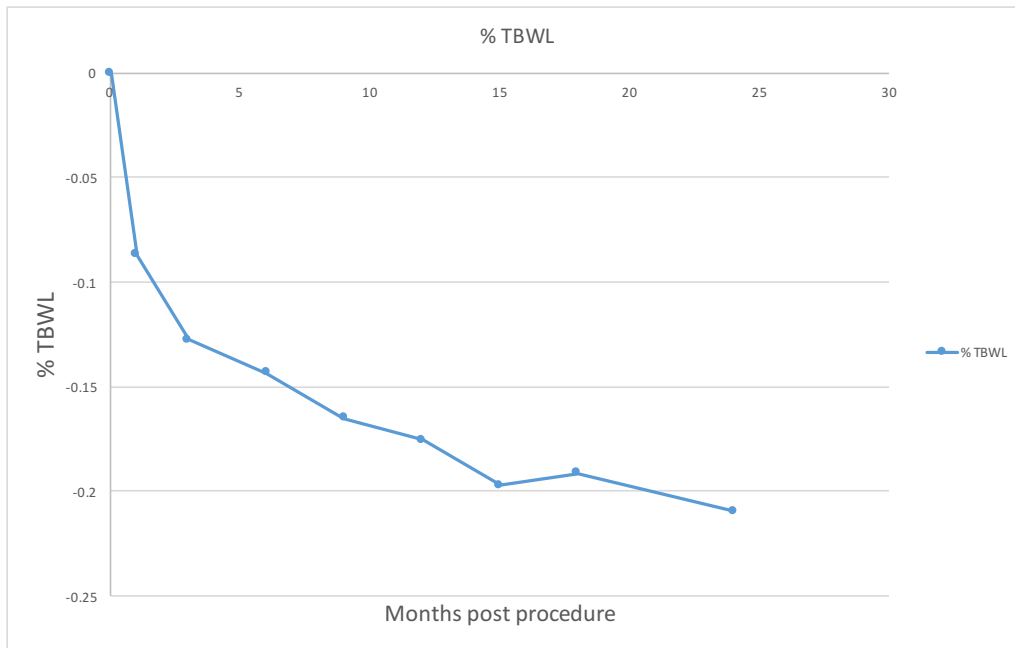
Devices in Trial: GELESIS₁₀₀ Polymer

- Superabsorbent hydrogel capsules taken orally prior to a meal
- Contain small particles that expand ~100 times when hydrated in the stomach and small intestine, triggering several important satiety and glycemic control mechanisms
- Mean \pm SD body weight percent change from baseline to the end of 12 week treatment were $-6.1 \pm 5.1\%$ ($P=0.026$) with Gelesis100 2.25 g



Endoscopic Gastroplasty - WCMC

- 96 patients underwent ESG (mean age 41 years, 67% female).



Months	0	6	p value
Waist CM	141.5	119.8	0.0002
BMI	45.2	40.3	0.0001
LDL mg/dl	132	112	0.01
HbA1c	6.8	5.6	0.03

Increasing age and black race were independent predictors for worse outcomes

Months	0	1	3	6	9	12	15	18	24
% TBWL	0	-9%	-13%	-14%	-17%	-18%	-20%	-19%	-21%

Sharaiha, RZ, et al



New York Society for
Gastrointestinal Endoscopy
39th Annual
New York Course

We use weight loss medications after bariatric surgery

Review of patients treated at MGH and WCMC

Table 4. Mean Weight Change after Treatment by Subgroup

Subgroup	Weight Change		P-value
	(lbs)	(%) [^]	
All patients (n=317)*	-17.8 (SD=21.1)	-7.6 (SD=7.8)	
Patients prescribed medication at weight plateau (n=68, 21.5%)~	-15.8 (SD=27.8)	-6.9 (SD=8.8)	0.486 ^a
Patients prescribed medication at weight regain (n=249, 78.5%)~	-18.3 (SD=19.0)	-7.7 (SD=7.6)	
Surgery Type			
Sleeve Gastrectomy (n=61)	-9.8 (SD=13.5)	-4.3 (SD=5.7)	0.0001 ^a
Roux-En-Y Gastric Bypass (n=256)	-19.7 (SD=22.2)	-8.3 (SD=8.1)	
Patients who lost ≥ 5% total body weight with treatment (n=172, 54%)	-29.7 (SD=21.9)	-12.6 (SD=7.2)	
Patients who lost ≥ 10% total body weight with treatment (n=96, 30.3%)	-40.7 (SD=23.7)	-17.1 (SD=6.7)	
Patients who lost ≥ 15% total body weight with treatment (n=49, 15.4%)	-52.9 (SD= 27.7)	-22.02(SD=6.2)	

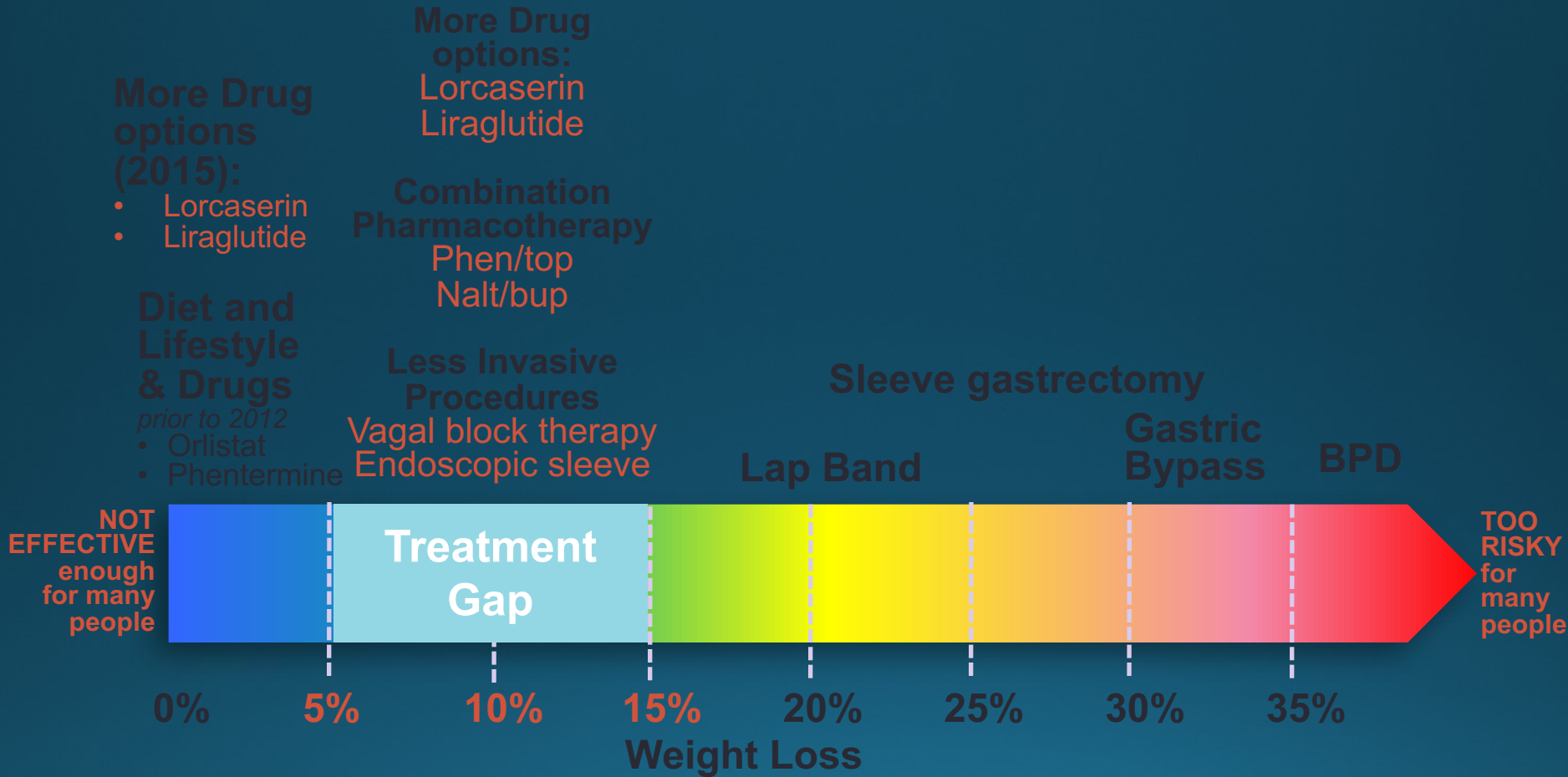
~ Plateau defined as weight that is within 3% above or below nadir weight postoperatively before medication. If above 3% patient defined as starting medication at weight regain

[^]Calculated this number as [(weight at nadir post medications) – (weight at start of medication)]/ (weight at start of medication)

- **RNYGB weight loss > Sleeve**
- **Same wt loss but TBWL > if meds started at plateau than weight regain**
- **54% lost ≥ 5%, 30% lost ≥ 10%**

Treatment Gap in Mid-BMI Range

New drugs and devices can reduce weight and weight-related comorbidities



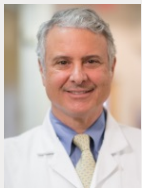
The gap is being filled

Summary

- The obesity epidemic continues to grow at an alarming rate
- Causes can be attributed to a combination of genetic factors, environmental issues, as well as sedentary lifestyle and diet.
- Effort toward prevention is the optimal approach but once a person has become obese, there are many challenges and barriers to losing weight due to the complex regulation of appetite/feeding/weight maintenance.
- A combination of behavioral intervention, plus medicine, and maybe even surgery would be the span of options available to treat a patient.
- There are several promising medications currently in clinical trials that induce weight loss through several separate mechanisms. Ultimately obesity will most likely be treated with combinations of medications, similar to other chronic diseases such as heart disease, hypertension, and diabetes



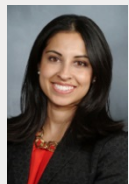
Comprehensive Weight Control Center



Louis J. Aronne, MD, FACP, FTOS, DABOM
Sanford I. Weill Professor of Metabolic Research
Medical Director, Comprehensive Weight Control Center



Jonathan A. Waitman, MD
Assistant Professor of Medicine
Internal Medicine, Clinical Nutrition, Obesity Medicine



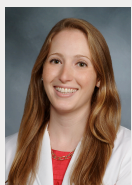
Rekha B. Kumar, MD, MS
Assistant Professor of Medicine
Endocrinologist



Leon I. Igel, MD
Assistant Professor of Clinical
Medicine
Endocrinologist



Alpana P. Shukla, MD, MRCP (UK)
Assistant Professor of Research
Medicine
Endocrinologist



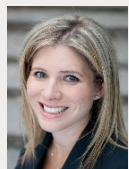
Katherine H. Saunders, MD
Instructor in Medicine
Internal Medicine, Obesity
Medicine



Joy Pape, MSN RN FNP-C
CDE WOCN CFCN FADE
Clinical Nurse Practitioner



Wanda Truong, MS
Clinical Research Coordinator



Rachel A. Lustgarten, MS, RD,
CDN
Clinical Dietitian



Janet L. Feinstein, MS, RD,
CDN
Clinical Dietitian



Anthony J. Casper, BS
Senior Research Aide



Devika Umashanker, MD
Clinical Fellow in Obesity
Medicine



Jeselin Andono, MS
Graduate Student (IHN)



Samir Touhamy, MS
Graduate Student (IHN)