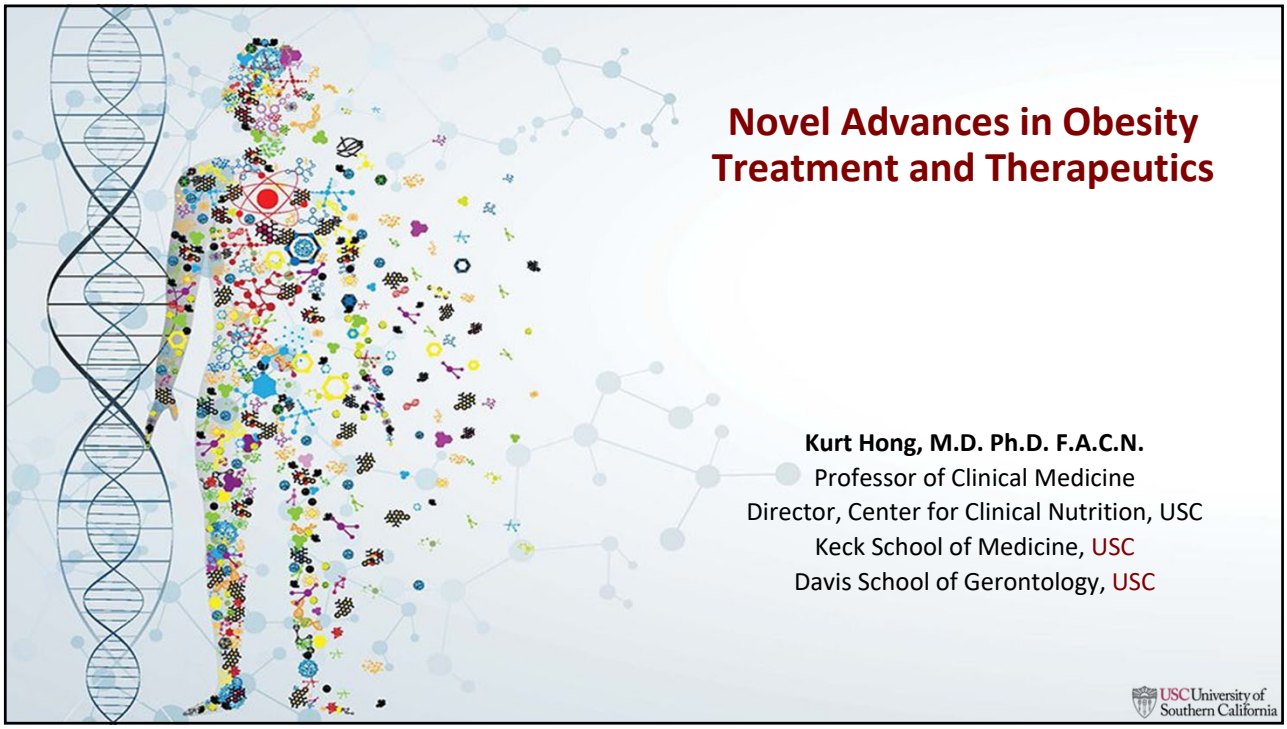

Novel Advances in Obesity Treatment and Therapeutics

Kurt Hong, M.D. Ph.D. F.A.C.N.
Professor of Clinical Medicine
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Davis School of Gerontology, USC

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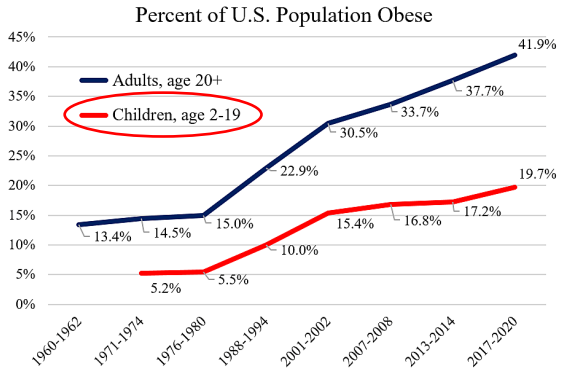
1

CONFLICT OF INTEREST

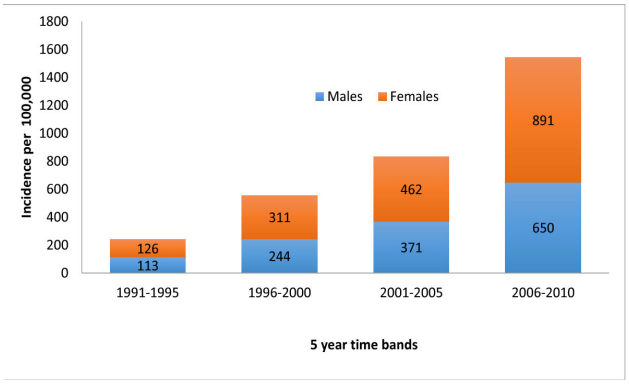
No conflict of interest to disclose.

2

The "Diabesity" Problem



Obesity Epidemic: (Adults, Children, Adolescents) - 1990-2020



Parallel Increase in Prevalence of Diabetes

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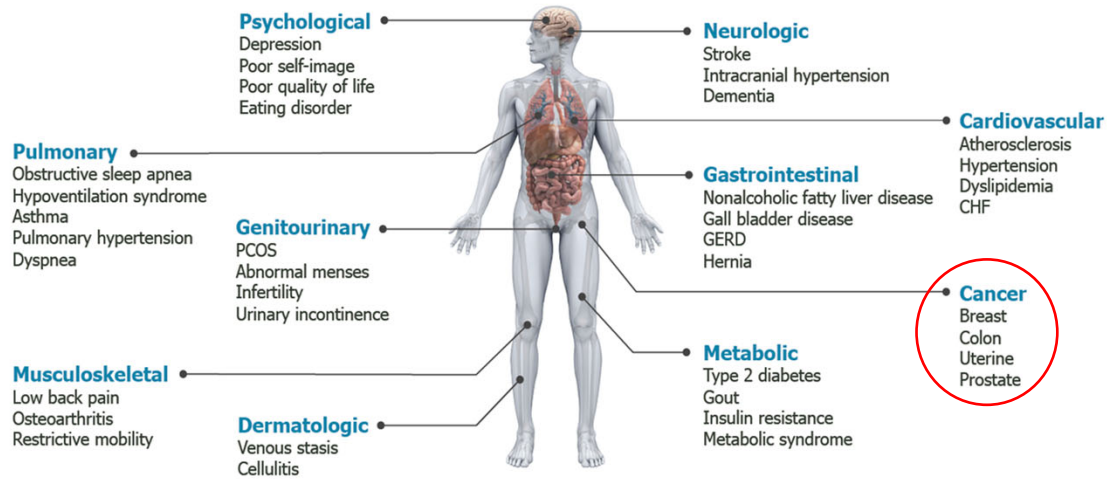
3

Obesity: A Major Contributor to Disease[1]



CHF=congestive heart failure; GERD=gastroesophageal reflux disease; PCOS=polycystic ovarian syndrome.
1. Catenacci VA et al. *Clin Chest Med.* 2009;30:415-444.

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4

Cultural, Linguistics and Implicit Bias in Treatment of Obesity

Obesity Is a Chronic Disease With a Complex Etiology[1-6]

Possible interrelated factors contributing to obesity:

1. Lean MEJ et al. *Int J Obes (Lond).* 2016;40:622-632. **2.** Yu YH et al. *Obes Rev.* 2015;16:234-247. **3.** National Heart, Lung, and Blood Institute. www.nhlbi.nih.gov/health/health-topics/topics/obe/causes#. Updated July 13, 2012. Accessed July 14, 2016. **4.** Moleres A et al. *Curr Obes Rep.* 2013;2:23-31. **5.** Sharma AM et al. *Obes Rev.* 2010;11:362-370. **6.** Chaput JP et al. *Obes Rev.* 2012;13:681-691.

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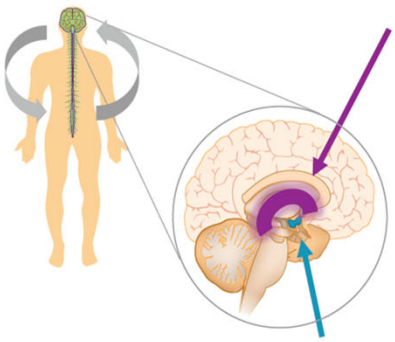
5

Two Centers of the Brain Are Involved in Food Intake and Energy Balance



Mesolimbic Reward System[1,2]

- Region of the brain that controls the **motivation, reward,** and **reinforcement** associated with survival activities (eg, eating, reproduction)
- **Dopamine** and **opioid** signaling known to play important roles
- Activity is seen to be altered in obese population

Mesolimbic reward system
can override the
hypothalamic hunger system
increasing the consumption of highly palatable foods[3]

Hypothalamic Hunger System[4]

- Detection and integration of peripheral signals of hunger, fullness, and fat stores to **modulate feeding behavior** and **energy balance** (eg, appetite suppression by leptin [adipose], appetite stimulation by ghrelin [stomach]).
- Signals can be altered in obesity (eg, leptin resistance)

1. Morton GJ et al. *Nature.* 2006;443:289-295. **2.** Billes SK et al. *Pharmacol Res.* 2014;84:1-11. **3.** Volkow ND et al. *Obes Rev.* 2013;14:2-18. **4.** Yu JH et al. *Diabetes Metab J.* 2012;36:391-398.

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Weight Loss Is Difficult to Achieve and Maintain[1]

Weight regain approached **50%**
after 1 year of diet alone or with exercise[a]

	Baseline weight (kg)[b]	Initial weight loss (kg)[b]	Weight loss after 1 year (kg)[b]
Diet + Exercise (n=265)	97.4 ± 16.1	-13 ± 10.4	-6.7 ± 8.3
Diet alone (n=142)	97.8 ± 10.7	-9.9 ± 9.6	-4.5 ± 11.3

[a]A meta-analysis of 6 randomized controlled trials assessed the efficacy of diet, exercise, or both for short-term and long-term weight loss in overweight or obese adults; diet was defined as any type of caloric restriction, and exercise included any type of exercise that could be quantified.
[b]Mean ± standard deviation.
1. Curioni CC et al. *Int J Obes.* 2005;29:1168-1174.

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Treatment Options: 2012

Diet
- Meal replacements, VLCDs, standard low calorie diets

Exercise
- Combination of cardio and resistance training is better

MEDICATIONS:

1. Phentermine
- Short term appetite suppressant

2. Orlistat
- Lipase inhibitor with limited efficacy and well known side effects

3. Bariatric surgery
- Lap band
- RYGastric bypass

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Treatment Options: 2024

Medications:

1st Gen "Appetite Suppressants" & Lipase inhibitors

- Phentermine
- Diethylpropion
- Phendimetrazine
- Orlistat (Xenical)

"Newer" therapies (Since 2013)

- Phentermine/Topiramate ER (Qsymia)*
- Bupropion SR/ Naltrexone SR (Contrave)
- ~~Lorcaserin (Belviq)~~
- Liraglutide (Saxenda)*
- Semaglutide (Wegovy)*
- Tirzepatide (Zepbound)

** Approved for adolescents aged 12 and up*

Bariatric Surgery:

- RYGastric Bypass
- Laparoscopic Sleeve Gastrectomy
- Adjustable Gastric Banding

Endoscopic Bariatric Therapy

- Intra-Gastric Balloon
  - ORBERA – Fluid filled
  - OBALON-Gas filled
- Intragastric "Botox" Injection
- Endoscopic Sleeve Gastroplasty

Others: (Minimally invasive procedures):

- Plenity (Cellulose gel cap)
- Aspire Assist (Gastric Content Drainage)

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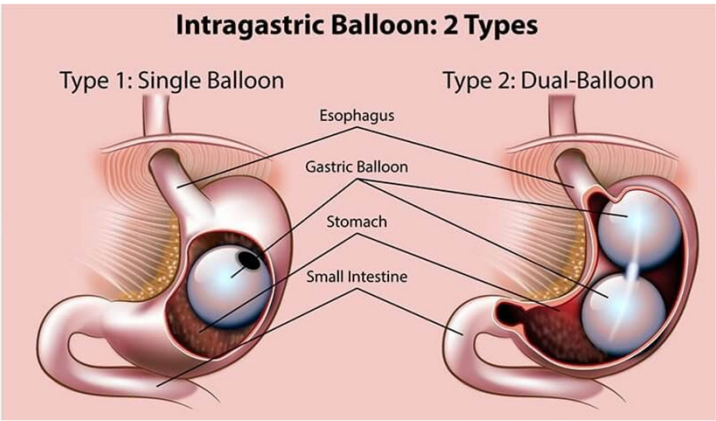
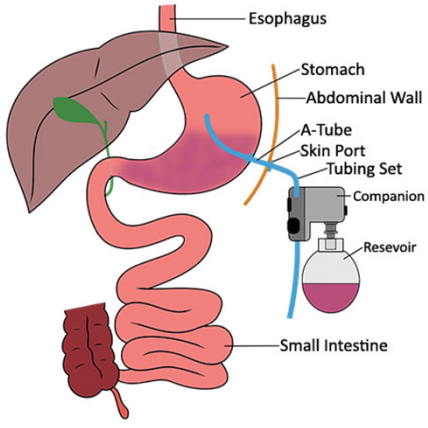
IntraGastric Ballons



Aspire Assist® Device



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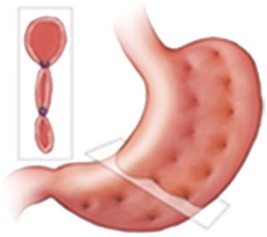
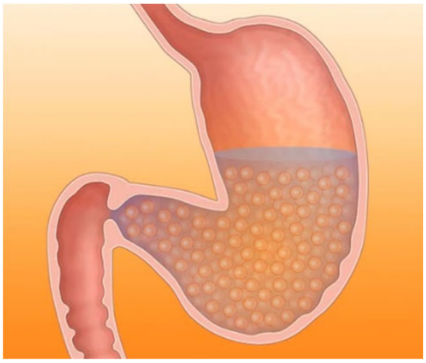
Endoscopic Sleeve Gastroplasty

Surgical Sleeve Gastrectomy



Endoscopic Sleeve Gastroplasty

Gelesis (Plenity)



Ingested, Transient, Space Occupying Device

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ASSESSMENT & OFFICE EVALUATION

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Degree of Overweight or Obesity: Adult

Classification	BMI (kg/m^2)
Healthy weight	18.5–24.9
Overweight	25–29.9
Obesity I	30–34.9
Obesity II	35–39.9
Morbid Obesity (Obesity III)	40-59
Super Morbid Obesity	60 or more
Use clinical judgement when interpreting BMI	

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During the Office Visit

- Measure weight, height (BMI calculation), waist circumference, body composition (% BF, if available)
- Assess co-morbid conditions
- Communicate to the patient your interest in their undertaking lifestyle change to lose weight and "be healthier"
- Outline trigger foods and a simple (yet specific) meal plan for the patient
- Provide follow-up and support lifestyle change

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Utility and Limitations of BMI

- Permits population-based studies of trends in obesity and is used for clinical guidelines.
- Does not correlate well with fat mass in both over-muscled (athletic) and under-muscled (sarcopenic) patients.
- Does not reveal differences in fat distribution (visceral vs. subcutaneous).
- Does not measure fat directly but correlates with body fat over thousands of average patients.
- At any given BMI, women have more fat than men.

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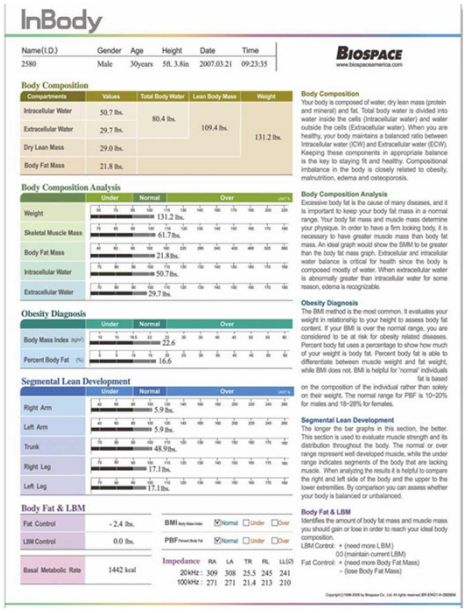
Bioelectrical Impedance Analysis


InBody

Name(I.D.) 2580 | Gender Male | Age 30years | Height 5ft. 3.8in | Date 2007.03.21 | Time 09:23:35

BIOSPACE www.biospaceamerica.com

Body Composition

Compartments	Values	Total Body Water	Lean Body Mass	Weight
Intracellular Water	50.7 lbs.	80.4 lbs.	109.4 lbs.	131.2 lbs.
Extracellular Water	29.7 lbs.			
Dry Lean Mass	29.0 lbs.			
Body Fat Mass	21.8 lbs.			

Body Composition Analysis

	Under	Normal	Over
Weight			131.2 lbs.
Skeletal Muscle Mass			61.7 lbs.
Body Fat Mass			21.8 lbs.
Intracellular Water			50.7 lbs.
Extracellular Water			29.7 lbs.

Obesity Diagnosis

	Under	Normal	Over
Body Mass Index (kg/m²)		22.6	
Percent Body Fat (%)		16.6	

Segmental Lean Development

	Under	Normal	Over
Right Arm			5.9 lbs.
Left Arm			5.9 lbs.
Trunk			48.9 lbs.
Right Leg			17.1 lbs.
Left Leg			17.1 lbs.

Body Fat & LBM

Fat Control	- 2.4 lbs.
LBM Control	0.0 lbs.
Basal Metabolic Rate	1442 kcal

BMI (Body Mass Index) ☑Normal ☐Under ☐Over

PBF (Percent Body Fat) ☑Normal ☐Under ☐Over

Impedance	RA	LA	TR	RL	LL(Ω)
20kHz :	309	308	25.5	245	241
100kHz :	271	271	21.4	213	210

Body Composition
Your body is composed of water, dry lean mass (protein and mineral) and fat. Total body water is divided into water inside the cells (Intracellular water) and water outside the cells (Extracellular water). When you are healthy, your body maintains a balanced ratio between Intracellular water (ICW) and Extracellular water (ECW). Keeping these components in appropriate balance is the key to staying fit and healthy. Compositional imbalance in the body is closely related to obesity, malnutrition, edema and osteoporosis.

Body Composition Analysis
Excessive body fat is the cause of many diseases, and it is important to keep your body fat mass in a normal range. Your body fat mass and muscle mass determine your physique. In order to have a firm looking body, it is necessary to have greater muscle mass than body fat mass. An ideal graph would show the BMM to be greater than the body fat mass graph. Extracellular and intracellular water balance is critical for health since the body is composed mostly of water. When extracellular water is abnormally greater than intracellular water for some reason, edema is recognizable.

Obesity Diagnosis
The BMI method is the most common. It evaluates your weight in relationship to your height to assess body fat content. If your BMI is over the normal range, you are considered to be at risk for obesity related diseases. Percent body fat uses a percentage to show how much of your weight is body fat. Percent body fat is able to differentiate between muscle weight and fat weight, while BMI does not. BMI is helpful for 'normal' individuals fat is based on the composition of the individual rather than solely on their weight. The normal range for PBF is 10~20% for males and 18~28% for females.

Segmental Lean Development
The longer the bar graphs in this section, the better. This section is used to evaluate muscle strength and its distribution throughout the body. The normal or over range represent well developed muscle, while the under range indicates segments of the body that are lacking muscle. When analyzing the results it is helpful to compare the right and left side of the body and the upper to the lower extremities. By comparison you can assess whether your body is balanced or unbalanced.

Body Fat & LBM
Identifies the amount of body fat mass and muscle mass you should gain or lose in order to reach your ideal body composition.
LBM Control: + (need more LBM) 0 (maintain current LBM)
Fat Control: + (need more Body Fat Mass) - (lose Body Fat Mass)

Sample BIA Report

TEST RESULTS

Percent Body Fat: 22.1%
Fat Body Weight: 44.2 lbs
Lean Body Weight: 155.8 lbs
Basal Metabolic Rate: 2150 kcal/day

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Is one diet better than others for weight loss?

Meta-analysis - Comparisons of Weight Loss Among Named Diet Programs in Overweight and Obese Adults

Johnston BC, Kanter S, Bandayrel K, Wu, P, et al.

JAMA: Sept 3, 2014. Volume 312:9. Pages 923-933.

Original Investigation

Comparison of Weight Loss Among Named Diet Programs in Overweight and Obese Adults

A Meta-analysis

Bradley C. Johnston, PhD; Steve Kanters, MSc; Kristofer Bandayrel, MPH; Ping Wu, MBBS, MSc; Faysal Naji, BHSc; Reed A. Siemieniuk, MD; Geoff D. C. Ball, RD, PhD; Jason W. Busse, DC, PhD; Kristian Thorlund, PhD; Gordon Guyatt, MD, MSc; Jeroen P. Jansen, PhD; Edward J. Mills, PhD, MSc

IMPORTANCE Many claims have been made regarding the superiority of one diet or another for inducing weight loss. Which diet is best remains unclear.

OBJECTIVE To determine weight loss outcomes for popular diets based on diet class (macronutrient composition) and named diet.

DATA SOURCES Search of 6 electronic databases: AMED, CDSR, CENTRAL, CINAHL, EMBASE, and MEDLINE from inception of each database to April 2014.

STUDY SELECTION Overweight or obese adults (body mass index ≥25) randomized to a popular self-administered named diet and reporting weight or body mass index data at 3-month follow-up or longer.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted data on populations, interventions, outcomes, risk of bias, and quality of evidence. A Bayesian framework was used to perform a series of random-effects network meta-analyses with meta-regression to estimate the relative effectiveness of diet classes and programs for change in weight and body mass index from baseline. Our analyses adjusted for behavioral support and exercise.

MAIN OUTCOMES AND MEASURES Weight loss and body mass index at 6- and 12-month follow-up (±3 months for both periods).

RESULTS Among 59 eligible articles reporting 48 unique randomized trials (including 7286 individuals) and compared with no diet, the largest weight loss was associated with low-carbohydrate diets (8.73 kg [95% credible interval (CI), 7.27 to 10.20 kg] at 6-month follow-up and 7.25 kg [95% CI, 5.33 to 9.25 kg] at 12-month follow-up) and low-fat diets (7.99 kg [95% CI, 6.01 to 9.92 kg] at 6-month follow-up and 7.27 kg [95% CI, 5.26 to 9.34 kg] at 12-month follow-up). Weight loss differences between individual diets were minimal. For example, the Atkins diet resulted in a 1.71 kg greater weight loss than the Zone diet at 6-month follow-up. Between 6- and 12-month follow-up, the influence of behavioral support (3.23 kg [95% CI, 2.23 to 4.23 kg] at 6-month follow-up vs 1.08 kg [95% CI, −1.82 to 3.96 kg] at 12-month follow-up) and exercise (0.64 kg [95% CI, −0.35 to 1.66 kg] vs 2.13 kg [95% CI, 0.43 to 3.85 kg], respectively) on weight loss differed.

CONCLUSIONS AND RELEVANCE Significant weight loss was observed with any low-carbohydrate or low-fat diet. Weight loss differences between individual named diets were small. This supports the practice of recommending any diet that a patient will adhere to in order to lose weight.

JAMA. 2014;312(9):923-933. doi:10.1001/jama.2014.10397

Editorial page 900
Author Audio Interview at jama.com
Supplemental content at jama.com
CME Quiz at jamanetworkcme.com and CME Questions page 958

Author Affiliations: Author affiliations are listed at the end of this article.
Corresponding Author: Edward J. Mills, PhD, MSc, Stanford University School of Medicine, 1265 Welch Rd, Stanford, CA 94305 (millsej@stanford.edu).

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Study Design & Results

Diet Classes Based on Macronutrient Composition

Type of Diet	Branded Diets[a]	Carbohydrates, % kcal	Protein, % kcal	Fat, % kcal
Low carbohydrate	Atkins, South Beach, Zone	≤40	Approximately 30	30-55
Moderate macronutrients	Biggest Loser, Jenny Craig, Nutrisystem, Volumetrics, Weight Watchers	Approximately 55-60	Approximately 15	21-≤30
Low fat	Ornish, Rosemary Conley	Approximately 60	Approximately 10-15	≤20

[a] The Lifestyle, Exercise, Attitudes, Relationships, and Nutrition (LEARN) diet was applied as both a low-fat diet (2 trials) and a moderate macronutrient diet (5 trials) among the 7 included trials having used the LEARN diet (Table 2).

Slimming World was excluded from the diet class analyses because it does not fit any of the definitions above.

- 48 unique randomized trials (7286 individuals)
- Largest weight loss was associated with
  - Low-carbohydrate diets (6 months - 8.73 kg; 12 months - 7.25kg)
  - Low-fat diets (6 months - 7.99 kg; 12 months - 7.27 kg)
- Weight loss differences between individual diets were minimal.
  - For example, the *low-carb* Atkins diet resulted in similar weight loss as *low-carb* Zone diet (at 6, 12 months)

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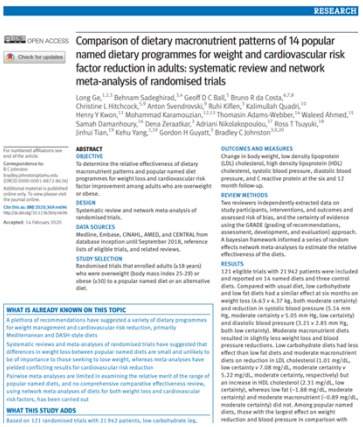
2020: British Medical Journal

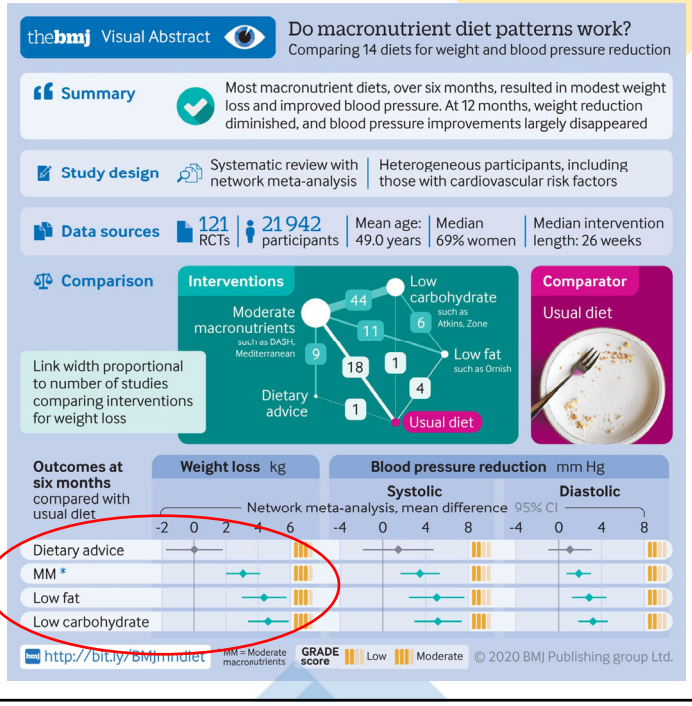
- ~22K participants in meta analysis
- Weight loss similar after 6 months between MM, LF, LC groups
- BP reduction similar



RESEARCH

OPEN ACCESS

Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials



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PHARMACEUTICAL THERAPIES

20

A Guide to Selecting Obesity Treatment

	BMI Category (kg/m^2)				
Treatment	**25-26.9**	**27-29.9**	**30-34.9**	**35-39.9**	**≥ 40**
Diet & Lifestyle Therapy	+	+	+	+	+
Pharmacotherapy		+ (with comorbidity)	+	+	+
Endoscopic Bariatric Therapy		+/?	+	+	+
Bariatric Surgery			+ (with comorbidity)	+	+

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Assess Medications That May Cause Weight Gain

- Psychotropic medications
  - Tricyclic antidepressants
  - Atypical antidepressants (mirtazapine)
  - Specific SSRIs (citalopram)
  - Atypical antipsychotics (quetiapine)
  - Lithium
  - Specific anticonvulsants (gabapentin, cabamazepine)
- Diabetes medications
  - Insulin
  - Sulfonylureas
  - Thiazolidinediones
- HIV Medications
- Anti-estrogen (tamoxifen)
- Glucocorticoids
- *β*-adrenergic receptor blockers (older generation, atenolol)

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Overview: Anti-obesity Drugs Presently on the Market

	FDA-Approved Drug	~$/month (US)	Mechanism of Action	Comments
60% market!	**Phentermine**	$35	Norepinephrine/dopamine releasing stimulator	Schedule III drug, approved 1961 for short-term use
	Phendimetrazine/ Diethylpropion	$25	Noradrenaline/dopamine releasing stimulator	Schedule IV drug, approved 1973 for short-term use
	Orlistat	$110	Pancreatic lipase inhibitor	Approved for long-term use in 1999
	Phentermine/Topiramate	$98	Noradrenaline releasing + modulator of ɣ aminobutyric acid (GABA)	Approved July 2012
	Bupropion/Naltrexone	$98	Inhibitor of dopamine and noradrenaline reuptake + μ opiate antagonist	Approved September 2014 (Non-Schedule)
	Liraglutide (3mg)	$1200	GLP-1 agonist	Approved 2014 (adults) **Approved 2020 (adolescents 12-17)**
New!	**Semaglutide (2.4mg)**	$1200	GLP-1 agonist	Approved June 2021 **(Approved 2021 for adolescents 12-17)**
New!	**Tirzepatide (15mg)**	$1200	GLP-1/GIP agonists	Approved December 2023

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Phentermine/Phendimetrazine/Diethylpropion

Type: Sympathomimetics

Mechanism of action: Stimulates the hypothalamus to suppress appetite

Cost: ~$25-$30/month

FDA approved indication: Short-term (< 12 weeks) adjunct to exercise and caloric restriction for BMI ≥ 30 or ≥ 27 in the presence of other risk factors such as hypertension, diabetes or hyperlipidemia

Efficacy: 2-3.5 kg mean weight loss beyond that achieved by placebo at 2-24 weeks

Adverse effects: Risk of dependence and abuse, hypertension, dry mouth, insomnia, tremor, GI disturbance, valvular heart disease (rare)

Contraindications: History of CV disease, MAOIs, hyperthyroidism, glaucoma, history of drug abuse, pregnancy, breastfeeding

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Orlistat

Type: Lipase inhibitor

Mechanism of action: Inhibits the breakdown of triglycerides into absorbable free fatty acids by lipase enzymes in the stomach and pancreas, resulting in less fat being absorbed

Year of approval: 1999 (Prescription strength: 120 mg TID),
2007 (OTC 60 mg; $80/month)

FDA approved indication: Efficacy: 2.9 kg mean weight loss (Xenical) beyond that achieved by placebo at one year (meta-analysis of 15 trials; *Ann Intern Med* 2005;142:532-46)

Adverse effects: Significant diarrhea, fecal incontinence, oily spotting, flatulence, bloating, dyspepsia (all can be reduced with avoidance of fat-rich foods), reduced absorption of fat-soluble vitamins, serious liver injury (rare)

Contraindications: Malabsorption, cholestasis, impaired liver function, pancreatic disease, pregnancy (added in 2012)

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Phentermine/Topiramate

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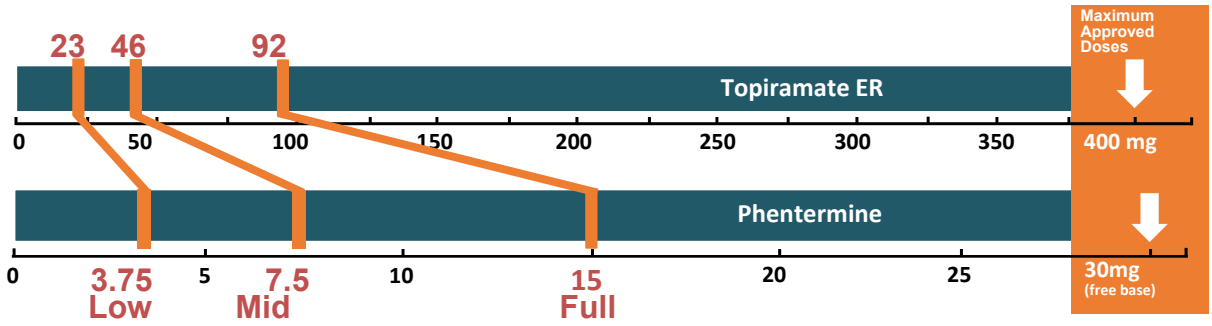
Phentermine/Topiramate ER

- Once-a-day, oral, extended release topiramate
- Low doses of previously approved medications to minimize side effects



DOSING

- Begin with low dose for 2 wks phentermine 3.75/ topiramate ER
- Advance to treatment dose phentermine 7.5/ topiramate ER 46
- If <3% weight loss after 12 wks, either discontinue or advance to full dose phentermine 15/ topiramate ER 92 (transition dose phentermine 11.25/ topiramate ER 69 for 2 wks)
- If <5% weight loss after 12 wks on full dose, discontinue (take every other day for one wk)

Phentermine and topiramate extended-release [package insert]. Mountain View, CA: Vivus; 2012.

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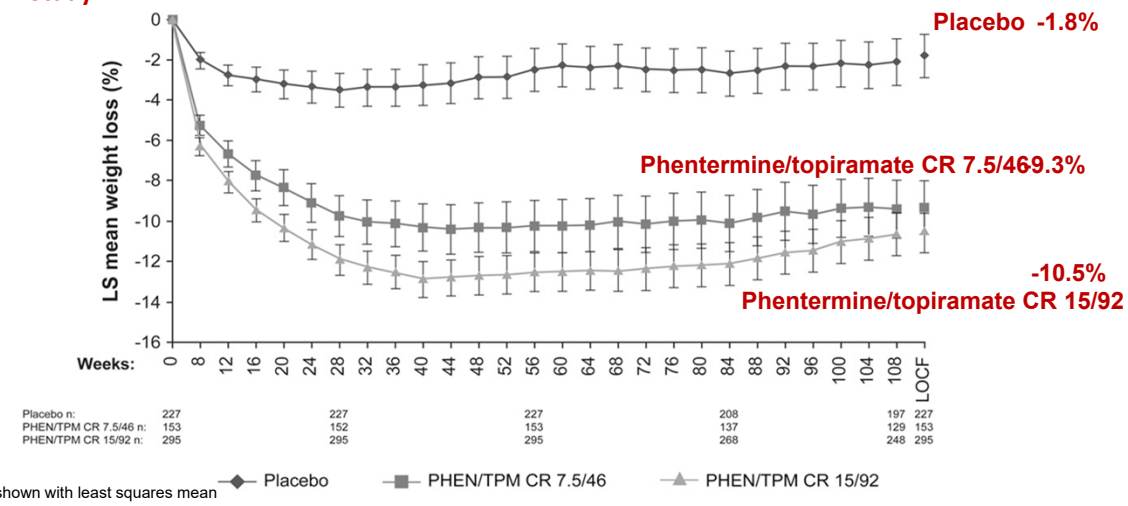
Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 2 Years

SEQUEL Study



* Data are shown with least squares mean (95% CI).

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

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Phentermine/Topiramate ER Improves Cardiometabolic Risk factors: CONQUER Study

Changes from baseline to week 56 in secondary endpoints

Variable		Phentermine 7.5mg/ Topiramate 46 mg ER	Placebo	*P* value
Waist circumference (cm)	↓	-7.6	-2.4	<0.0001
Systolic BP (mm Hg)	↓	-4.7	-2.4	0.0008
Diastolic BP (mm Hg)		-3.4	-2.7	0.1281
Triglycerides (%)	↓	-8.6	4.7	<0.0001
LDL–C (%)		-3.7	-4.1	0.7391
HDL–C (%)	↑	5.2	1.2	<0.0001
CRP (mg/L)	↓	-2.49	-0.79	<0.0001
Adiponectin (µg/mL)	↑	1.40	0.33	<0.0001

Gadde KM, et al. *Lancet*. 2011;377(9774):1341-1352.

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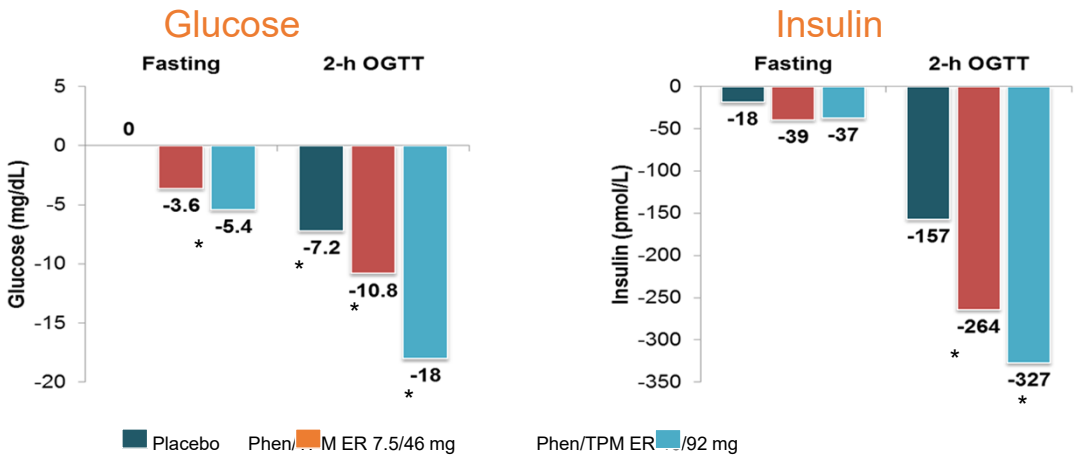
1

Metabolic Effects of Phentermine/Topiramate ER in Non-Diabetic Patients: SEQUEL Study



*$P \leq 0.005$ vs placebo.
Phen/TPM CR, phentermine/topiramate controlled release.

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

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Slide 30

1 check if this is this from day 1 to day 730, 2 years?
Weill Cornell Medical College, 3/15/2014

Phentermine/Topiramate ER: EQUIP and CONQUER
Most Commonly Reported Treatment Emergent Adverse Events

Adverse Event (%) (N=3749)	Placebo	PHEN/TPM ER 3.75/23	PHEN/TPM ER 7.5/46	PHEN/TPM ER 15/92
Paresthesia	1.9	4.2	13.7	19.9
Dry mouth	2.8	6.7	13.5	19.1
Constipation	6.1	7.9	15.1	16.1
Upper respiratory tract infection	12.8	15.8	12.2	13.5
Headache	9.3	10.4	7.0	10.6
Dysgeusia	1.1	1.3	7.4	9.4
Nasopharyngitis	8.0	12.5	10.6	9.4
Insomnia	4.7	5.0	5.8	9.4
Dizziness	3.4	2.9	7.2	8.6
Sinusitis	6.3	7.5	6.8	7.8
Nausea	4.4	5.8	3.6	7.2
Back pain	5.1	5.4	5.6	6.6
Fatigue	4.3	5.0	4.4	5.9
Blurred vision	3.5	6.3	4.0	5.4
Diarrhea	4.9	5.0	6.4	5.6

Ref: Phentermine and topiramate extended-release (Package insert). Mountain View, CA: Vivus; 2012.

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Naltrexone SR/Bupropion

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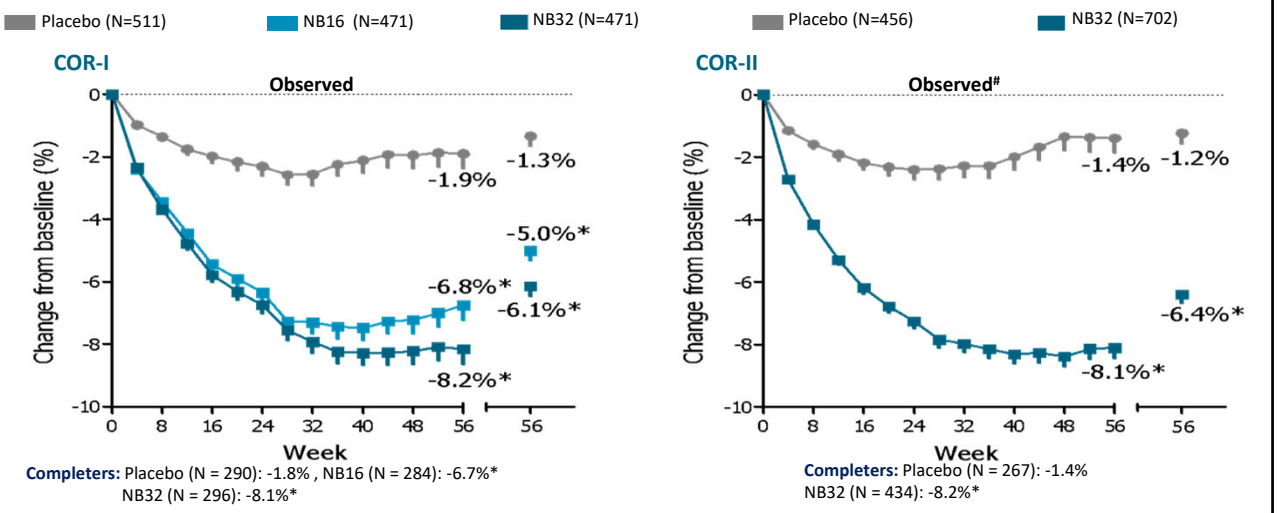
COR-I, II: % Change in Body Weight



Completers: Placebo (N = 290): -1.8% , NB16 (N = 284): -6.7%*
NB32 (N = 296): -8.1%*

Completers: Placebo (N = 267): -1.4%
NB32 (N = 434): -8.2%*

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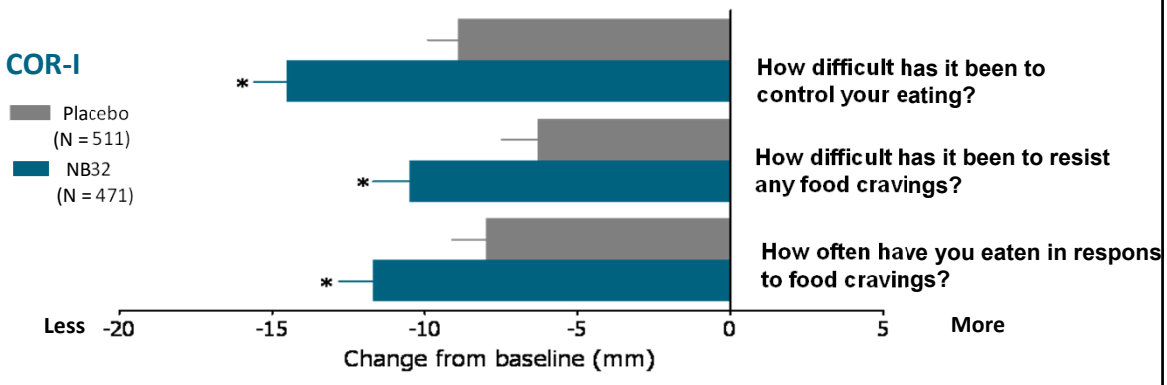
Improvements in Control of Eating, ITT-LOCF



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COR-I, II: Most Common Treatment-Emergent Adverse Events (TEAE)

	COR-I			COR-II	
	Placebo N=569	NB16 N=569	NB32 N=573	Placebo N=492	NB32/48 N=992
Nausea	5.3%	27.2%*	29.8%*	6.9%	29.2%*
Headache	9.3%	16.0%*	13.8%*	8.7%	17.5%*
Constipation	5.6%	15.8%*	15.7%*	7.1%	19.1%*
Dizziness	2.6%	7.7%*	9.4%*	3.7%	6.9%*
Vomiting	2.5%	6.3%*	9.8%*	2.0%	8.5%*
Dry mouth	1.9%	7.4%*	7.5%*	2.6%	9.1%*
Patients discontinuing due to a TEAE	**9.8%**	**21.4%***	**19.5%***	**13.8%**	**24.3%***
Nausea	0.4%	4.6%*	6.3%*	0.2%	6.0%*
Dizziness	0.5%	2.3%*	1.2%	0.2%	1.0%
Headache	0.7%	1.6%	0.9%	0.8%	2.6%*
Vomiting	0.2%	0.7%	0.9%	0%	0.8%
Insomnia	0.2%	0.7%	0.7%	1.0%	0.8%

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2015, 2021, 2023

GLP-1 and GLP-1/GIP Receptor Agonists: Liraglutide, Semaglutide, Tirzepatide

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Glucagon-like Peptide-1 (GLP-1) and Gastric Inhibitory Polypeptide (GIP) Receptor Agonists

- **Liraglutide:**
  - Approved in 2010 for treatment of type 2 diabetes (up to 1.8 mg/day)
  - Approved for obesity management with dose up to 3.0mg/day (adults in 2014, Adolescents 2020)
- **Semaglutide:**
  - Approved in 2014 for treatment of type 2 diabetes (up to 1.0 mg/week)
  - Approved for obesity management with dose up to 2.4mg/week (adolescents/adults in 2022)
- **Tirzepatide**
  - Approved in 2022 for treatment of type 2 diabetes (up to 15 mg/week)
  - Approved for obesity management with dose up to 15 mg/week (December 2023)

Mechanism of Action:

- Endocrine: Delays gastric emptying, increase glucose uptake in muscle, stimulate glucose dependent insulin release, increased satiety due to direct actions on hypothalamus

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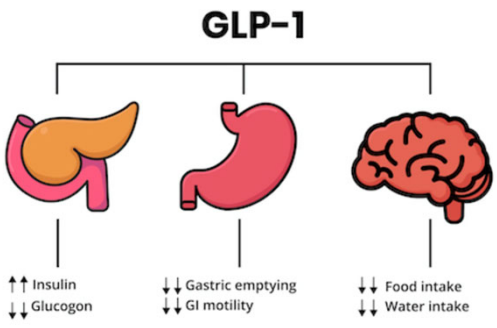
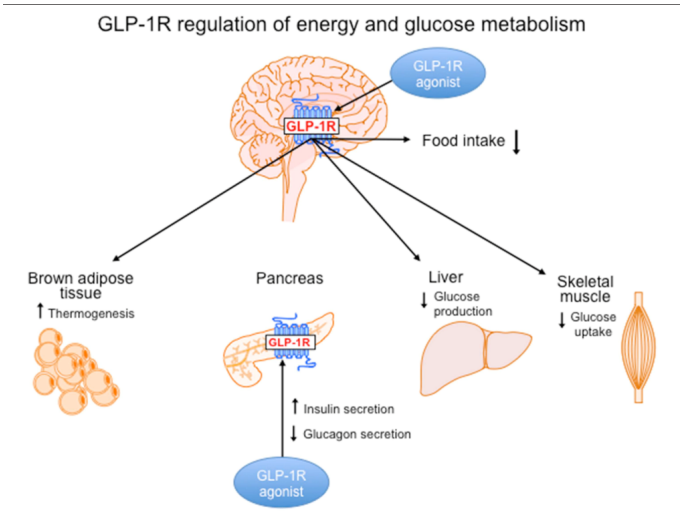
GLP-1 and GIP: Mechanism of Action and Physiologic Effect



Impact on decreased dietary intake



Impact on improved energy and carbohydrate metabolisnm

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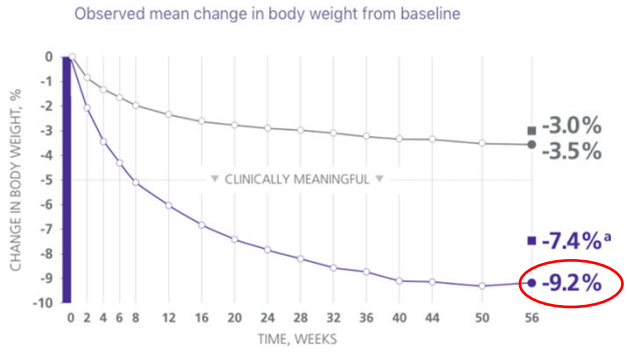
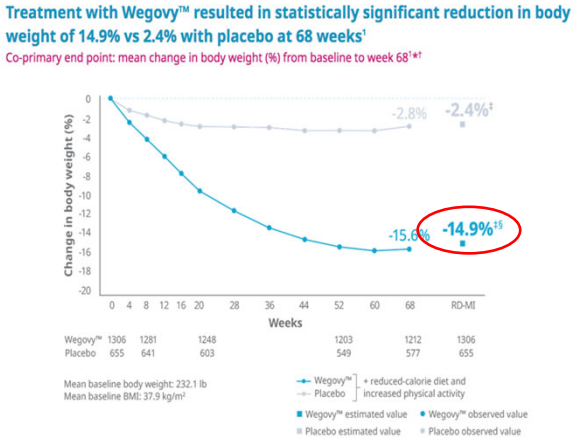
Effects of Liraglutide and Semaglutide in Obese Adults



Weight loss with Liraglutide



Weight loss with Semaglutide

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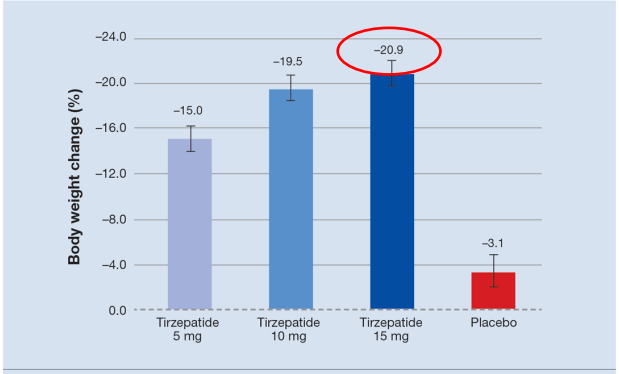
Semaglutide: Effect of 2.4mg Injection vs Placebo

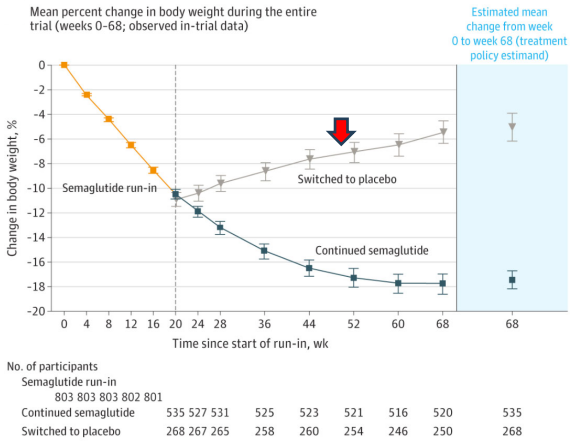
Weight Loss with Tirzepatide

Weight loss with SC tirzepatide once-weekly over 72 weeks in overweight adults[a]



[a]Based on findings reported by and figure adapted from Jastreboff et al[10]
SC: subcutaneous

What Happens When you Stop?



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GLP-1 Agonists: Contraindications, Warnings, Adverse Effects

Contraindications

- Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
- Pregnancy
- History of pancreatitis

Warnings

- Thyroid tumors seen in rodent models
- Acute pancreatitis or gallbladder disease
- Hypoglycemia if used with sulfonylurea or glinide (in patients with T2D)
- Heart rate increase
- Renal impairment
- Hypersensitivity reactions
- Suicidal behavior or ideation
- Do not use with insulin or to treat T2D

Adverse Effects

- GI: nausea, diarrhea, constipation, vomiting, decreased appetite, dyspepsia, abdominal pain
- Headache, fatigue
- Dizziness
- Increased lipase

T2D = type 2 diabetes.

Saxenda prescribing information. Plainsboro, NJ: NovoNordisk Inc.

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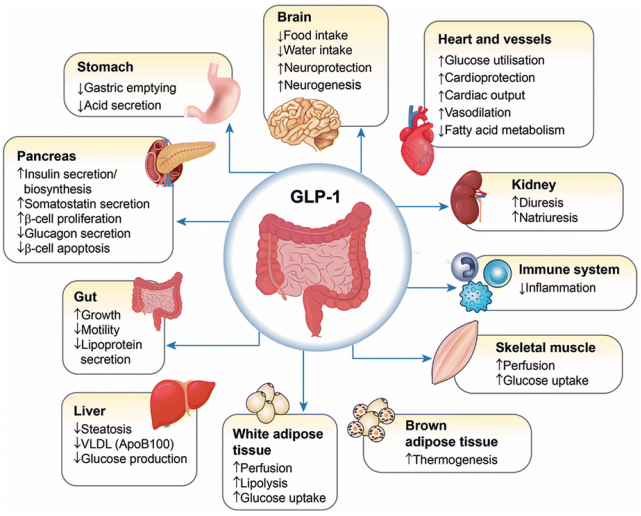
On the Horizon:
Role of GLP-1/GIP Agonists Beyond DM and Weight Management



THERAPEUTIC TARGETS

- **March 8 2024:**

U.S. Food and Drug Administration approved semaglutide to reduce the risk of cardiovascular death, heart attack and stroke in adults with cardiovascular disease and either obesity or overweight.

- Current clinical trials ongoing for use of GLP-1 in MASLD and MASH therapy

Hurdles in Clinical Practice:

- Costs/Insurance coverage
- Inventory/Supply issues
- Medication wean protocol
- Compounded/generic GLP-1s
- Long-term adverse risks

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BARIATRIC SURGERY

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General Criteria for Weight Loss Surgery

- BMI 35-40 with at least one co-morbidities BMI > 40 without co-morbidities
- Previous unsuccessful attempts at weight loss
- Age >18-65 with few exceptions
- Medically cleared for surgery
- Mentally & emotionally prepared and motivated
  - No substance abuse, no active eating disorder
  - Support system in place
  - Realistic expectation regarding outcomes
- Has good understanding of the procedure and dedicated to lifestyle change

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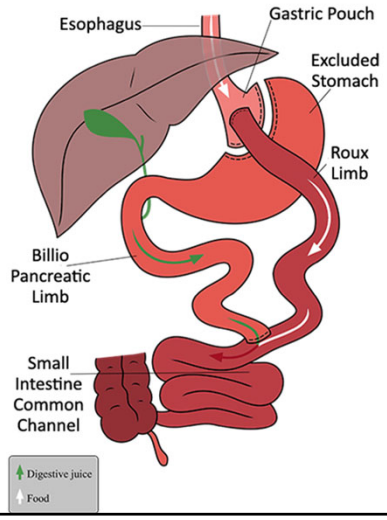
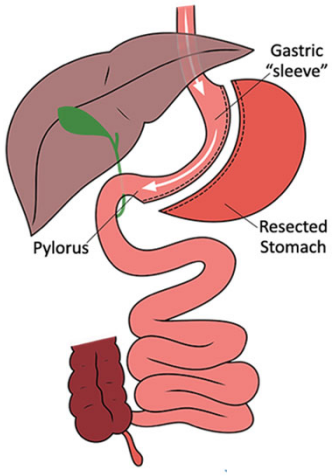
Surgical Options

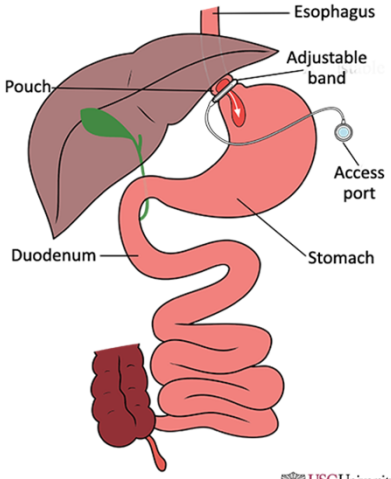
(Roux-en-Y) Gastric Bypass



Laparoscopic Sleeve Gastrectomy



Adjustable Gastric Banding



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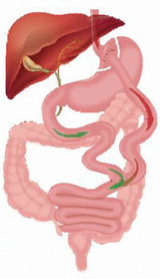
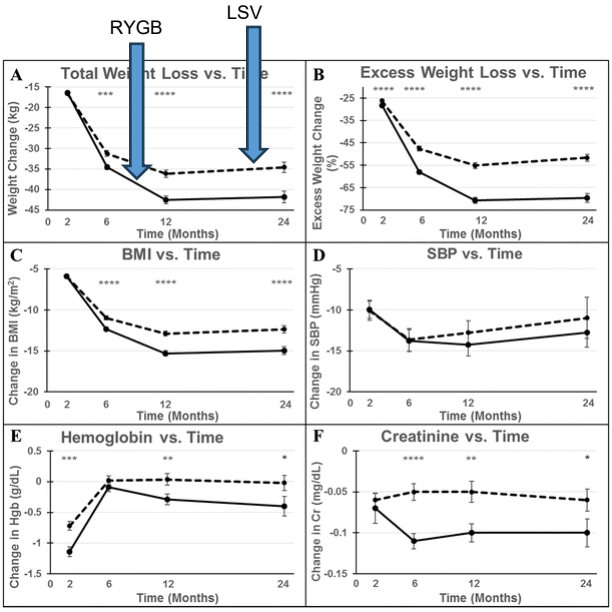
RYGB vs LSV: Impact on Physiology and Change in Metabolic Profile Over Time



RYGB

+	Calorie restriction	+
↑	Vagal nerve signaling	↑
+	Taste and smell changes	+
+	Food aversions	+
↓	Ghrelin	↓↓
↑	Bile acid secretion	↑
↑	Intestinal glucose uptake	
+	Fat malabsorption	
↑↑	GLP-1	↑
↑↑	PYY3-36	↑
↓	GIP	
↑	Oxyntomodulin	
↑↑	FGF-19	↑
↑	CCK	↑
↓	Gastrin	↑
↑	Neurotensin	

SG



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Schedule for Clinical Monitoring Following Different Bariatric Procedures

Blood Test	Laparoscopic Adjustable Gastric Band	Laparoscopic Sleeve Gastrectomy	Laparoscopic Roux - en-Y Gastric Bypass
Complete Blood Count	Annually	3,6,12 month after surgery, then annually	3,6,12 month after surgery, then annually
Complete Metabolic Panel	Annually	3,6,12 month after surgery, then annually	3,6,12 month after surgery, then annually
Calcium, Vitamin D, Parathyroid Hormone	N/A	3,6,12 month after surgery, then annually	3,6,12 month after surgery, then annually
Ferritin, Folate	N/A	3,6,12 month after surgery, then annually	3,6,12 month after surgery, then annually
Vitamin B12	N/A	6,12 month after surgery, then annually	6,12 month after surgery, then annually
Vitamin A	N/A	If clinically indicated	Annually
Zinc, Copper	N/A	If clinically indicated	Annually
Selenium	N/A	If clinically indicated	If clinically indicated

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Nutritional Supplementation after Different Bariatric Procedures

Nutritional supplement	RYGB	Sleeve gastrectomy	LAGB
Calcium with vitamin D	Calcium citrate, 500 mg × 3/d	Calcium citrate, 500 mg × 3/d	Calcium citrate, 500 mg × 3/d, or carbonate, 1200 mg/d
Vitamin B_{12}	Intramuscular, 1000 µg/month; oral, 100–300 µg/d; or sublingual, 500 µg/d	Oral, 100–300 µg/d; or sublingual, 500 µg/d	Not required unless low
Vitamin B complex with thiamine	1 tablet/d	1 tablet/d	1 tablet/d
Multivitamin tablet to replace	1 tablet/d	1 tablet/d	1 tablet/d
Vitamin A	1 mg/d	1 mg/d	1 mg/d
Vitamin D	5 µg/d	5 µg/d	5 µg/d
Vitamin E	100–300 mg/d	100–300 mg/d	100–300 mg/d
Vitamin K	65–80 µg/d	65–80 µg/d	65–80 µg/d
Iron	45–60 mg/d	45–60 mg/d	45–60 mg/d
Vitamin C	500 mg/d	500 mg/d	500 mg/d
Zinc	15 mg/d	15 mg/d	15 mg/d
Biotin	3000 µg/d	3000 µg/d	3000 µg/d

Other "clinical pearls":

- Don't forget to address protein malnutrition
- Pharmacotherapy still an option post endoscopic intervention or surgery
- Support for continuing behavioral therapy and exercise prescription

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Summary: Therapeutic Goals

- *Explain goals, assess readiness*
- *Tailor individual programs, using BIA*
- *Categorize clinical obesity subtype*
- *Recommend options for a hypocaloric dietary approach*
- *Exercise prescription*
- *Treat co-morbidities*
- *Use pharmacotherapy where appropriate*
- *Morbid obese patients – consider surgery when appropriate*
- *Current ongoing studies: Intermittent fasting for weight management and metabolic health?*

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