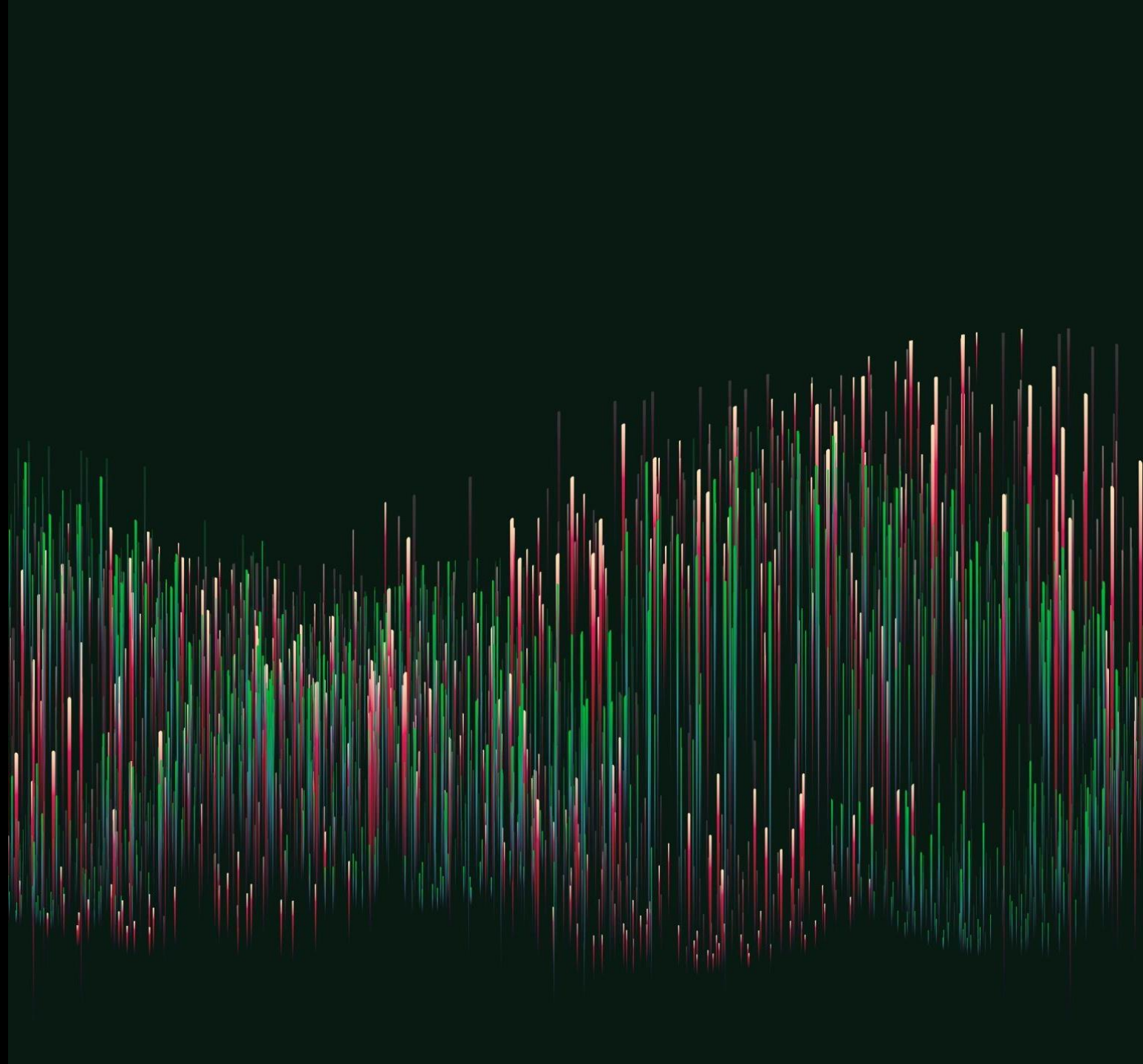

TARGETING THE VAGUS NERVE FOR WEIGHT LOSS AND IMPROVEMENTS IN CARDIOMETABOLIC HEALTH

Zachary Grunewald, PhD, RDN

July 27th, 2022



DISCLOSURES

- Nothing to disclose

OUTLINE

- Current state of obesity and weight loss interventions
 - Vagus nerve & hunger control
 - Vagus nerve and related interventions for weight loss
 - vBlock therapy
 - Cryoneurolysis of vagus nerve (Cryovagotomy)
 - GLP-1 and receptor antagonists
-

WHAT IS THE CURRENT STATE OF OBESITY?

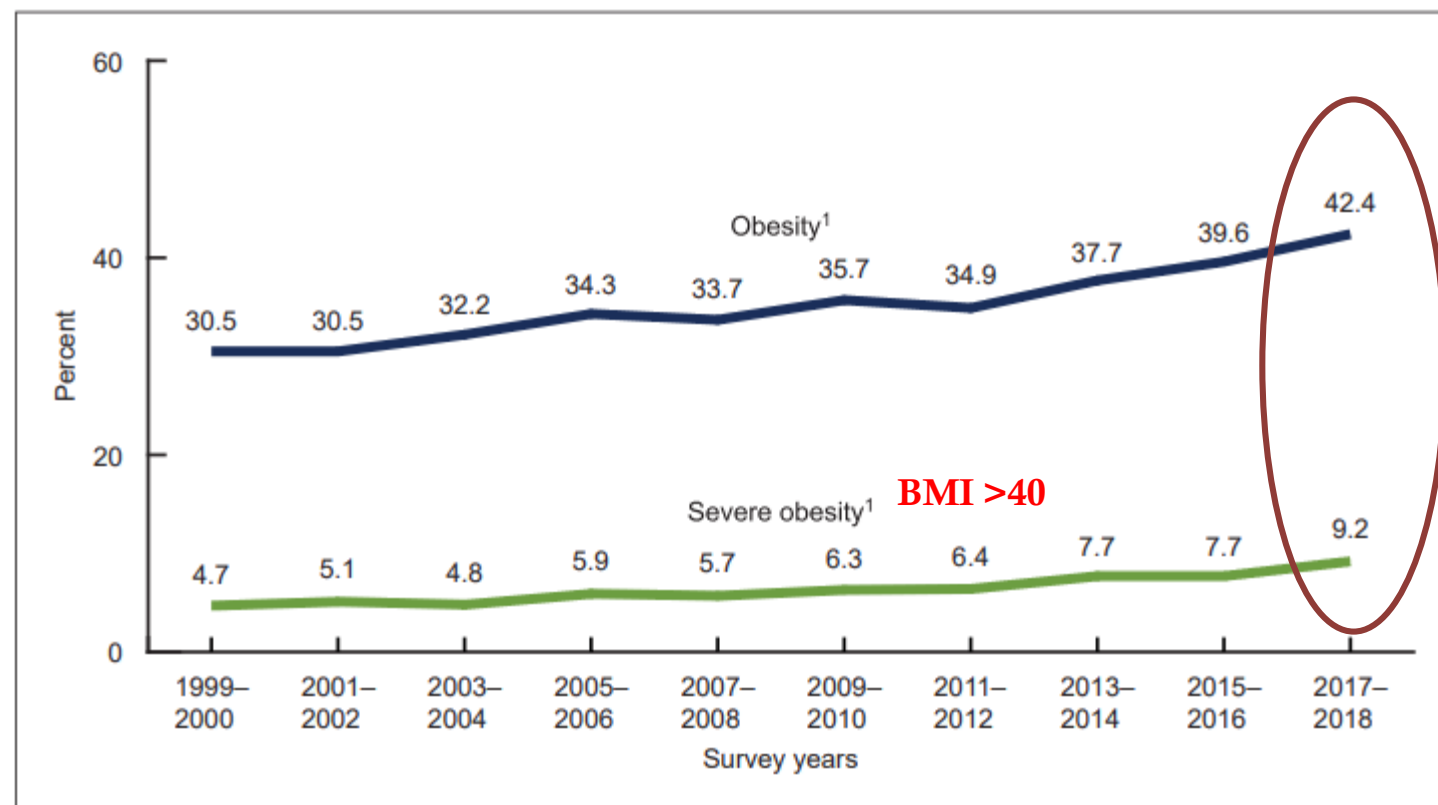
- Recent statistics that end in 2018 show that ~42% of American adults are obese (BMI > 30 kg/m²)
- Today the rate is unknown

What about the COVID-19 years?

What are the trends in obesity and severe obesity among adults?

From 1999–2000 through 2017–2018, the age-adjusted prevalence of obesity increased from 30.5% to 42.4%, and the prevalence of severe obesity increased from 4.7% to 9.2%. The observed changes in prevalence of obesity and severe obesity between 2015–2016 and 2017–2018 were not significant (Figure 4).

Figure 4. Trends in age-adjusted obesity and severe obesity prevalence among adults aged 20 and over: United States, 1999–2000 through 2017–2018



¹Significant linear trend.

NOTES: Estimates were age adjusted by the direct method to the 2000 U.S. Census population using the age groups 20–39, 40–59, and 60 and over. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db360_tables-508.pdf#4.

SOURCE: NCHS, National Health and Nutrition Examination Survey, 1999–2018.

PANDEMIC SURVEY

Slightly More Than 6 in 10 U.S. Adults (61%) Report Undesired Weight Change Since Start of Pandemic



Case Study: 170 lbs at 5'7" = 26.6 BMI

COVID-19 weight gain of 29 lbs = **31.2 BMI**

Is the obesity rate is likely closer to 50% in 2022?

What treatments or interventions exist to reduce weight?

WHAT ARE THE TOP WEIGHT LOSS STRATEGIES?

(For BMI >30 kg/m²)

1

Metabolic and Bariatric Surgery

25-50% weight loss

Up to 100% EWL

Shorter term –very effective
Long-term – 25%+ regain

2

Pharmacotherapies & minimally invasive procedures

Up to 25% weight loss

Requires sustained intervention

3

Diet & Exercise

Cornerstone of health

5-10% weight loss?

Very poor compliance

Foundation – Weight Maintenance

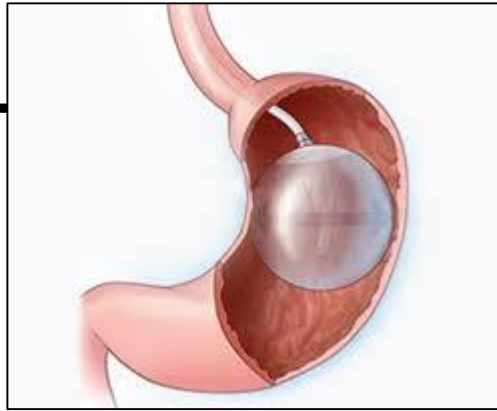
Diet Variety Moderate Physical Activity Mental Health/Sleep Healthcare Access Education

2

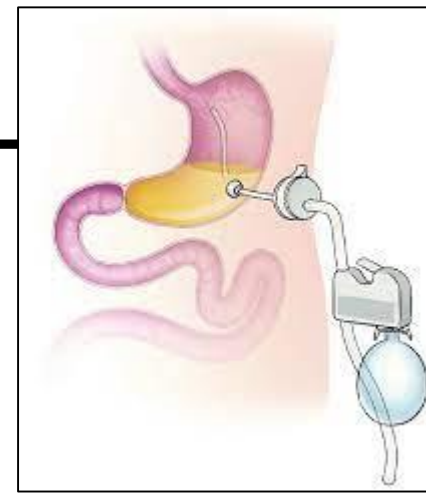
Pharmacotherapies & minimally invasive procedures

Up to 25% weight loss

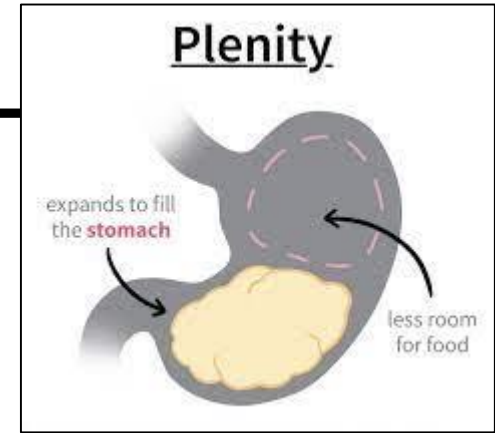
Requires sustained intervention



Intragastric balloons

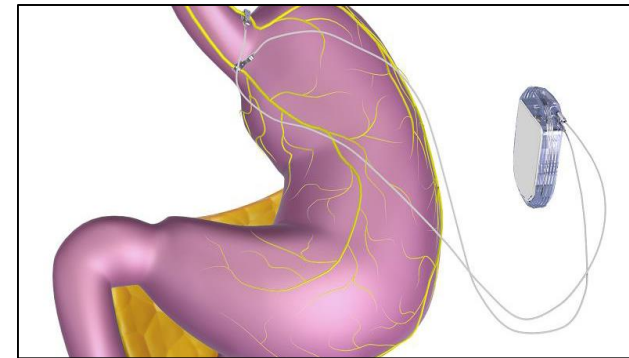


Aspire aspiration devices



Gastric filling water absorbent capsules

Vagus nerve interventions



vBlock device



Vagotomy

Pharmacotherapies

- Phentermine/Topiramate
- Orlistat (Alli)
- GLP-1 receptor agonists

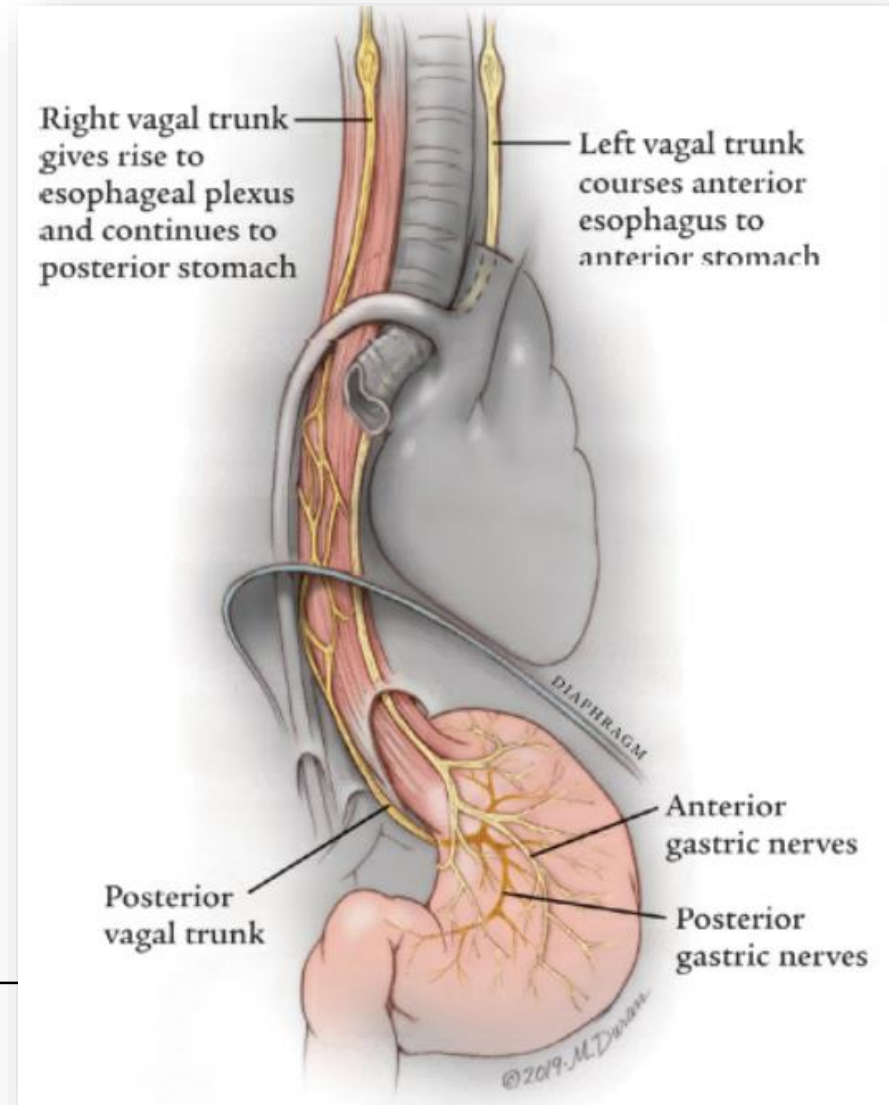
*Not an exhaustive list of therapies

VAGUS NERVE AND RELATED INTERVENTIONS FOR WEIGHT LOSS

1. vBlock therapy
 2. Cryoneurolysis of vagus nerve
 3. Glucagon-like peptide (GLP)-1 receptor agonists
-

VAGUS NERVE (CRANIAL NERVE X)

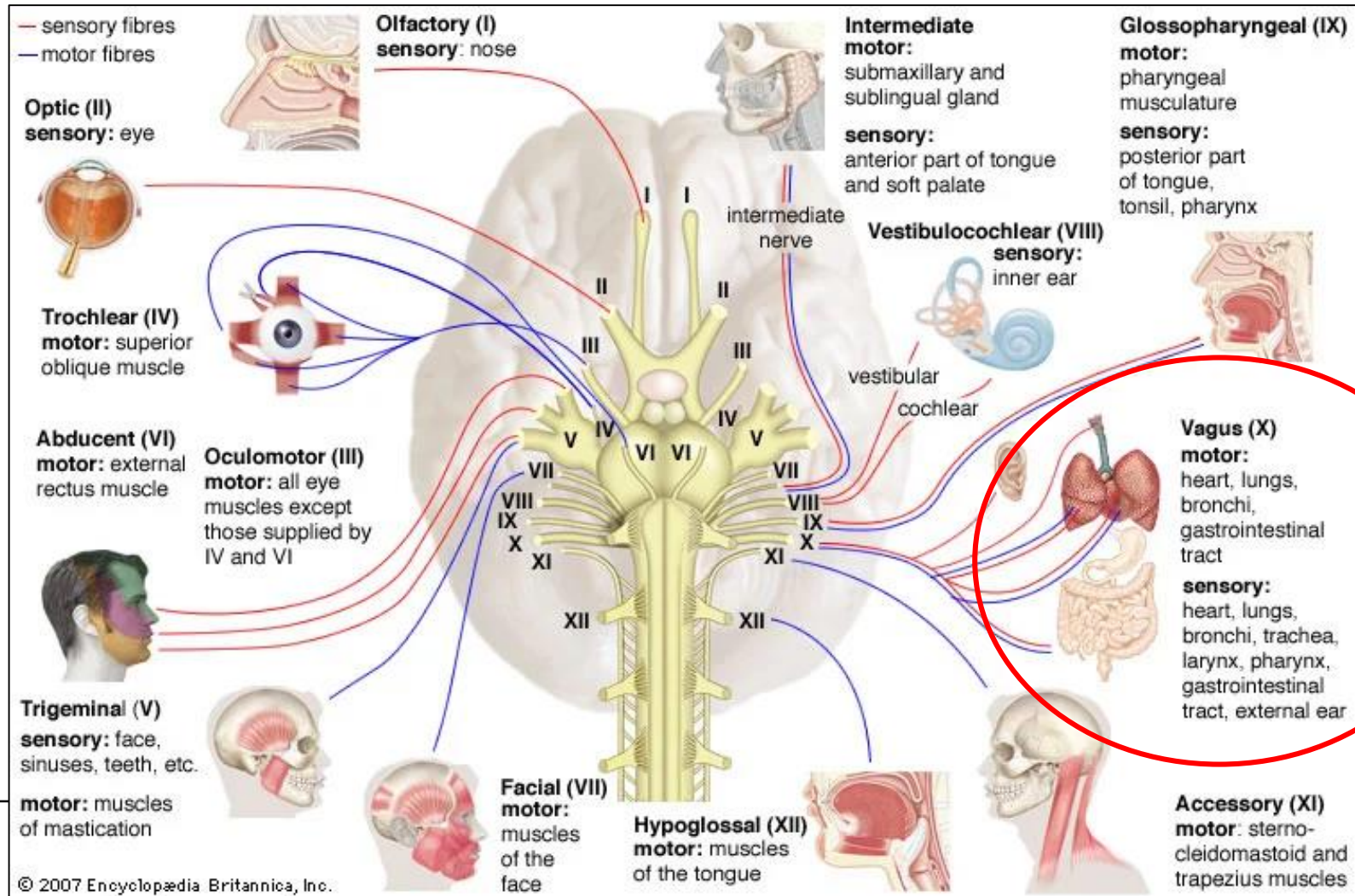
- Most extensive innervation sites of all cranial nerves (the wanderer)
- 80% composition of nerve is reported to be **afferent** (from periphery to brain) - **Sensory**
- Parasympathetic in nature
- **Rest and Digest nerve**
 - Opposite of fight or flight
- **Breed and Feed**



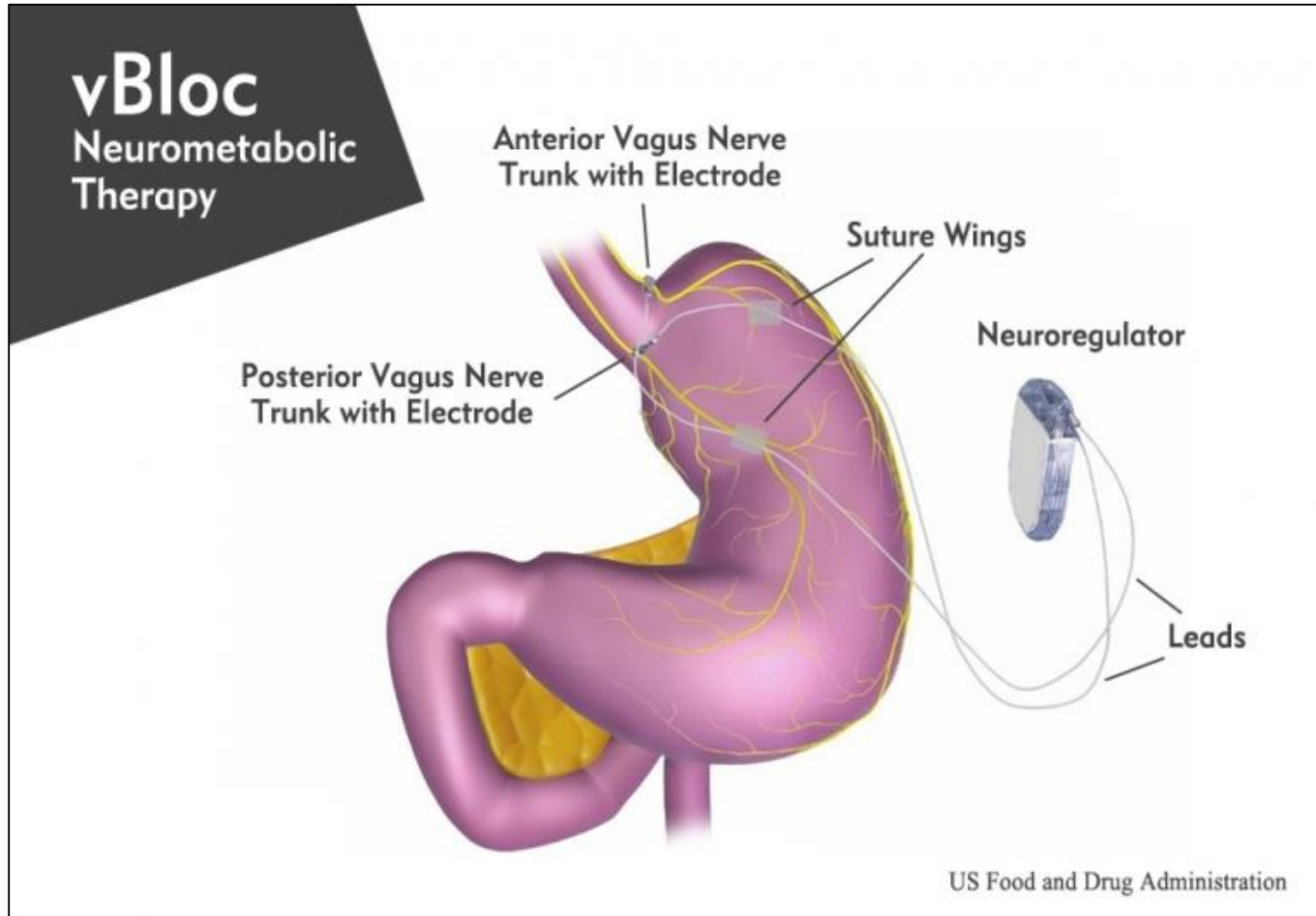
WHY INTERVENE AT THE VAGUS NERVE?

- Vagus nerve is one of the largest nerves in the body
 - Plays a critical role in the “**gut-brain axis**”
 - Communicates nutrient intake to the brain
 - Responds to gastric distension (stretching/expansion of stomach)
 - Influenced by microbiota
 - Directly responsible for regulating central control of food intake (appetite/satiety)
 - **Effective, cost-effective, and safe therapies for significant weight loss**
 - Does not involve intensive surgery or recovery
-

VAGUS NERVE

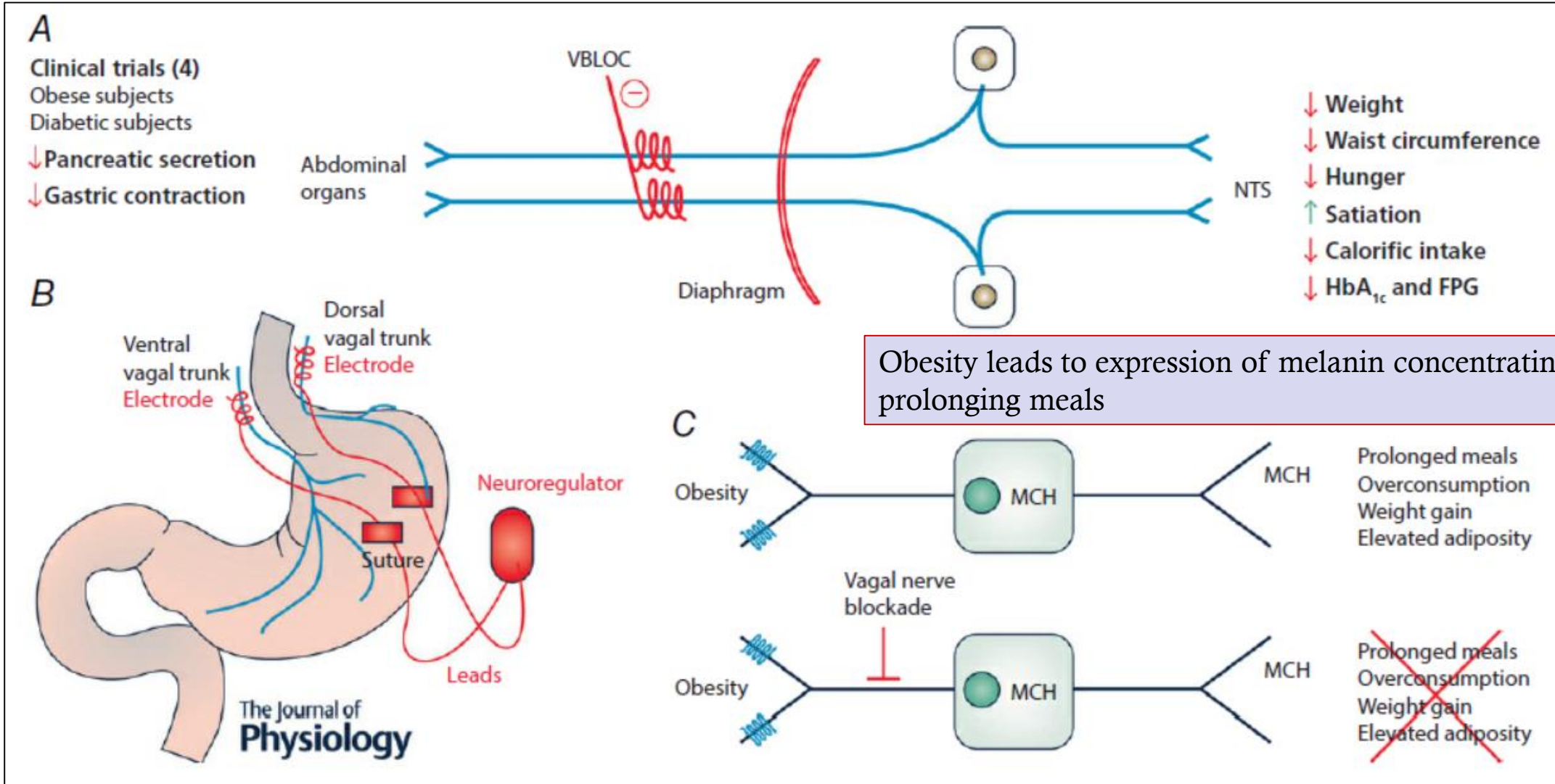


VBLOCK THERAPY FOR WEIGHT LOSS



- Intermittent vagal blocking with external vagal device
- FDA approved device in 2016
- Appears safe and effective for two-years following implantation
- Leads to ~8% total weight loss and ~21% excess weight loss

EFFECT OF VBLOCK ON VAGUS NERVE



VBLOCK STUDIES

OBES SURG (2017) 27:169–176
DOI 10.1007/s11695-016-2325-7

ORIGINAL CONTRIBUTIONS

Two-Year Outcomes of Vagal Nerve Blocking (vBloc) for the Treatment of Obesity in the ReCharge Trial

Caroline M. Apovian¹ · Sajani N. Shah² · Bruce M. Wolfe³ · Sayeed Ikramuddin⁴ · Christopher J. Miller⁵ · Katherine S. Tweden⁶ · Charles J. Billington⁷ · Scott A. Shikora⁸

~8% weight loss at two years

Clinical Study

Vagal Blocking Improves Glycemic Control and Elevated Blood Pressure in Obese Subjects with Type 2 Diabetes Mellitus

S. Shikora,¹ J. Toouli,² M. F. Herrera,³ B. Kulseng,⁴ H. Zulewski,⁵
R. Brancatisano,⁶ L. Kow,² J. P. Pantoja,³ G. Johnsen,⁴ A. Brancatisano,⁶
K. S. Tweden,⁷ M. B. Knudson,⁷ and C. J. Billington⁸

CARDIOMETABOLIC EFFECTS OF VBLOCK THERAPY

TABLE 1: % EWL and change in glycemic parameters (mg/dL) and blood pressure (mmHg) from baseline over 12 months.

Parameter	Time following device activation—change from baseline						P value
	Baseline	1 week	4 weeks	12 weeks	6 months	12 months	
EWL %, <i>n</i> = 28	0	9 ± 1	14 ± 2	21 ± 3	24 ± 4	25 ± 4	<.0001
HbA _{1c} (%), <i>n</i> = 28	7.8 ± 0.2	-0.3 ± 0.1	-0.7 ± 0.1	-0.9 ± 0.2	-0.9 ± 0.2	-1.0 ± 0.2	.02
FPG (mg/dL), <i>n</i> = 28	151 ± 7	-21 ± 6	-19 ± 7	-27 ± 8	-29 ± 8	-28 ± 8	.01
MAP, all subjects (mmHg), <i>n</i> = 28	95 ± 2	-4 ± 2	-5 ± 2	-5 ± 2	-8 ± 2	-3 ± 2	.04 [#]
SBP, all subjects (mmHg), <i>n</i> = 28	125 ± 2	-3 ± 3	-7 ± 3	-6 ± 3	-8 ± 3	-4 ± 3	.04 [^]
DBP, all subjects (mmHg), <i>n</i> = 28	80 ± 2	-5 ± 2	-4 ± 2	-4 ± 2	-8 ± 2	-2 ± 2	.04 ^{&}
MAP elevated (mmHg), <i>n</i> = 15	100 ± 2	-7 ± 3	-9 ± 3	-9 ± 2	-13 ± 2	-8 ± 3	.04
SBP elevated (mmHg), <i>n</i> = 8	140 ± 4	-10 ± 9	-12 ± 10	-13 ± 5	-16 ± 8	-12 ± 9	.03 [*]
DBP elevated (mmHg), <i>n</i> = 12	88 ± 2	-10 ± 2	-10 ± 3	-9 ± 1	-14 ± 2	-10 ± 3	.009

[#] At 1, 4, and 12 weeks and 6 months; [^] at 4 weeks, 12 weeks and 6 months; [&] at 1 week, 12 weeks and 6 months; ^{*} at 12 weeks.

FPG: fasting plasma glucose, MAP: mean arterial pressure, SBP: systolic blood pressure, and DBP: diastolic blood pressure.

SUMMARY OF VBLOCK THERAPY

- Shown to have moderate/reasonable weight loss after ~2-years of intervention (8% body weight)
 - Not intended for long-term or lifetime use
 - Requires surgery with anesthesia
 - Largely helps with proof of concept that vagus nerve blockade in obese individuals can lead to weight loss
 - Long-term efficacy and mechanisms of action remain to be fully elucidated
-


CRYONEUROLYSIS OF THE VAGUS NERVE (CRYOVAGOTOMY)

Original Article

CLINICAL TRIALS AND INVESTIGATIONS

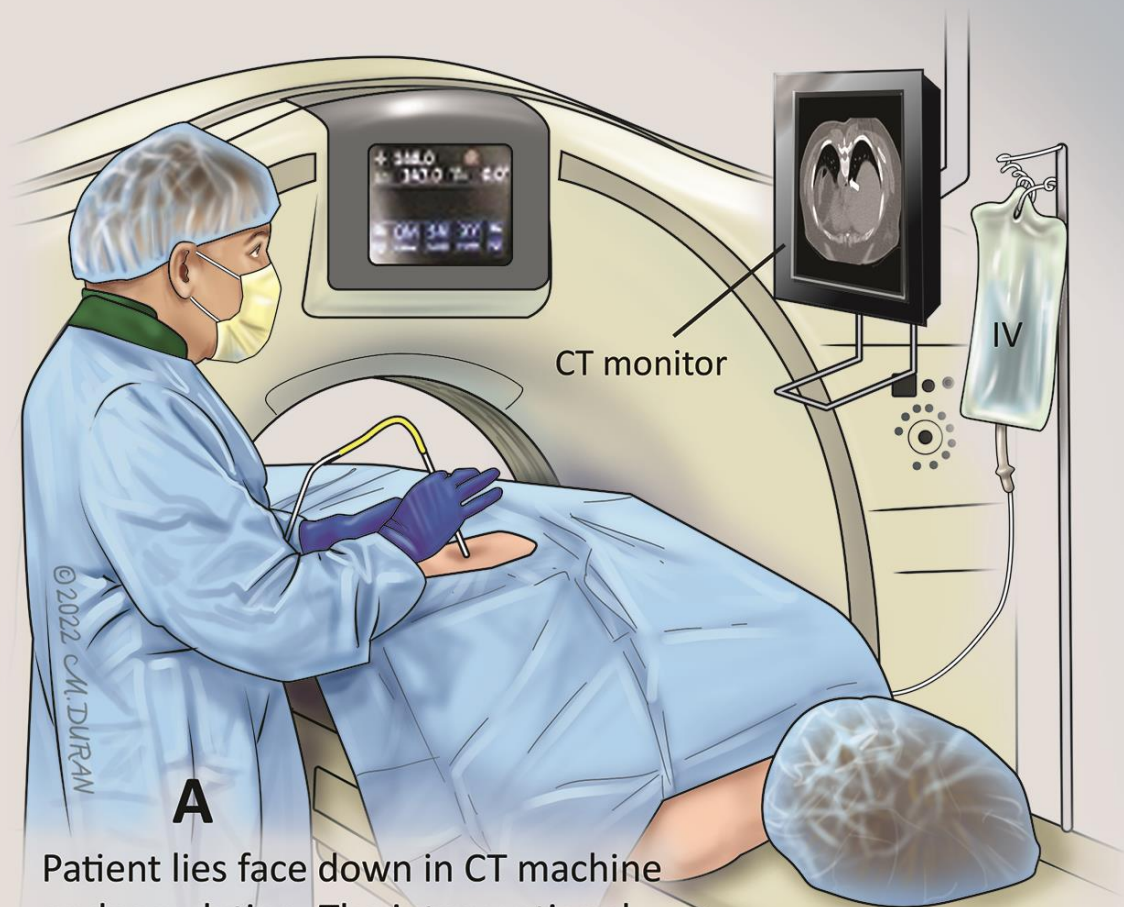
Obesity

Percutaneous CT-Guided Cryovagotomy in Patients with Class I or Class II Obesity: A Pilot Trial

J. David Prologo ¹, *Edward Lin*², *Sharon Horesh Bergquist*³, *Jackie Knight*⁴, *Hazem Matta*⁵, *Marjin Brummer*¹, *Arvinpal Singh*⁶, *Yogi Patel*⁷, and *David Corn*⁸

CATCH PROCEDURE

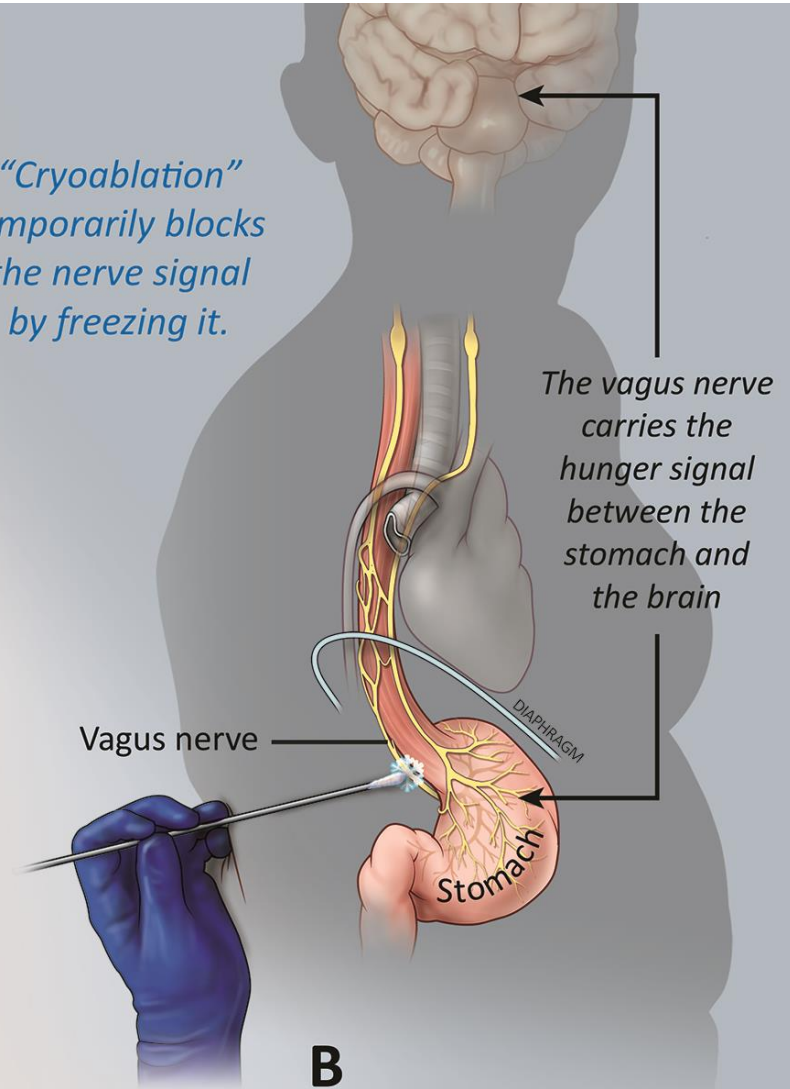
CryoAblation To Curb Hunger



A

Patient lies face down in CT machine under sedation. The interventional radiologist looks at the monitor to guide the probe to the nerve.

"Cryoablation" temporarily blocks the nerve signal by freezing it.

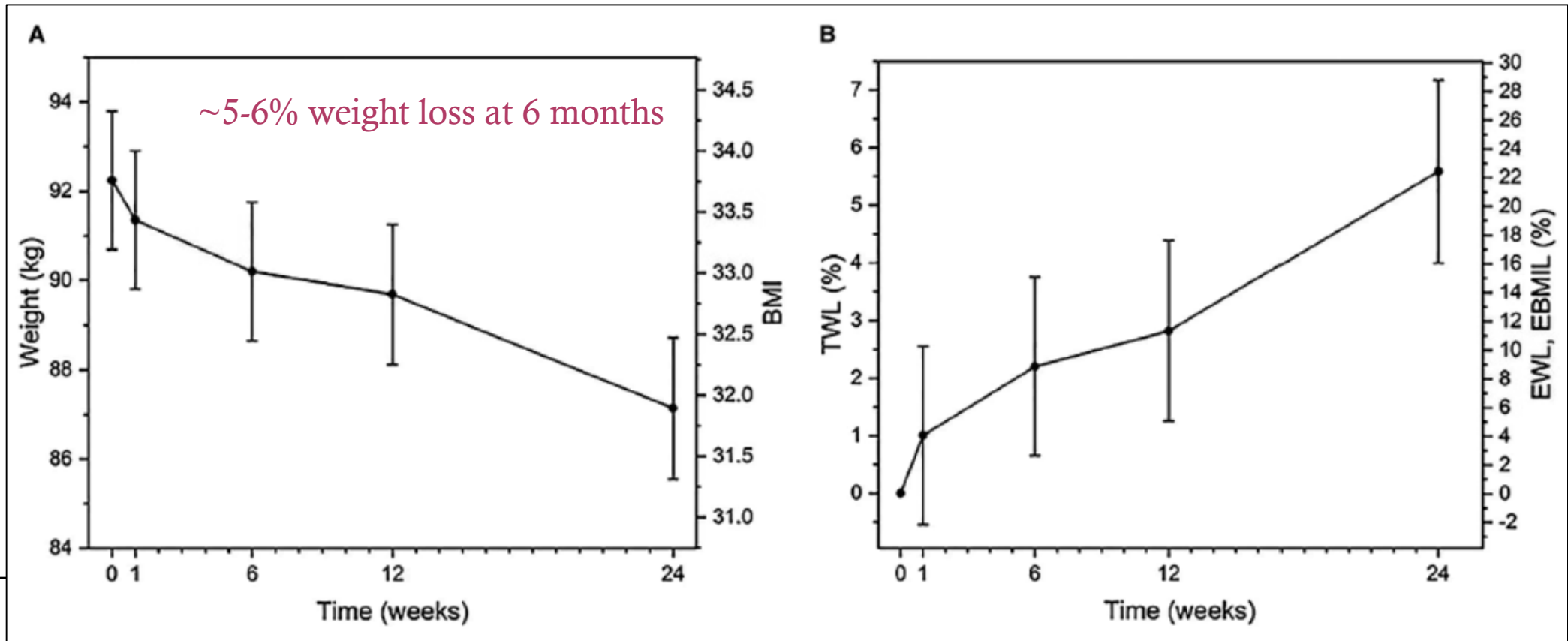


The vagus nerve carries the hunger signal between the stomach and the brain

B

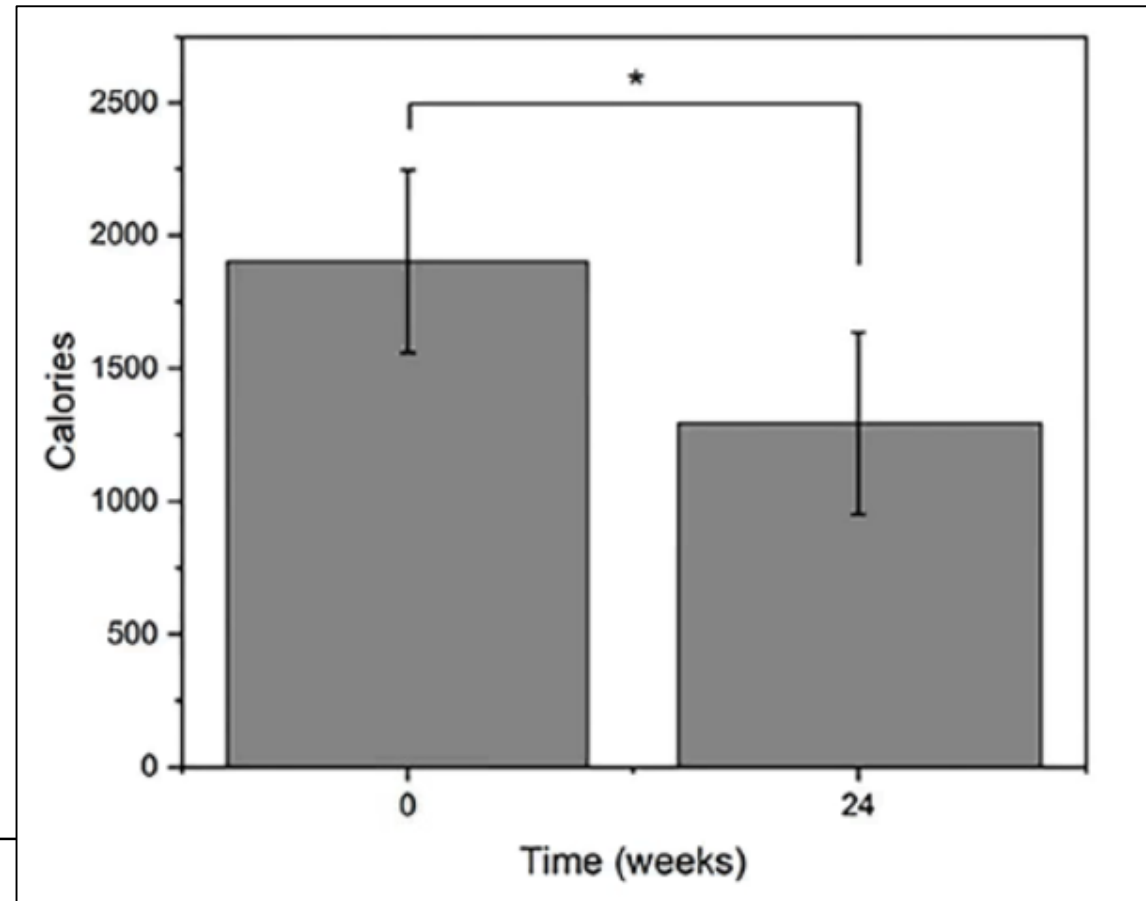
A small probe is inserted into the back. The icy tip touches and freezes the nerve for up to 5 minutes. Afterwards, a small bandage is applied to the skin

CRYOVAGOTMY LEADS TO GRADUAL WEIGHT LOSS AT 6 MONTHS

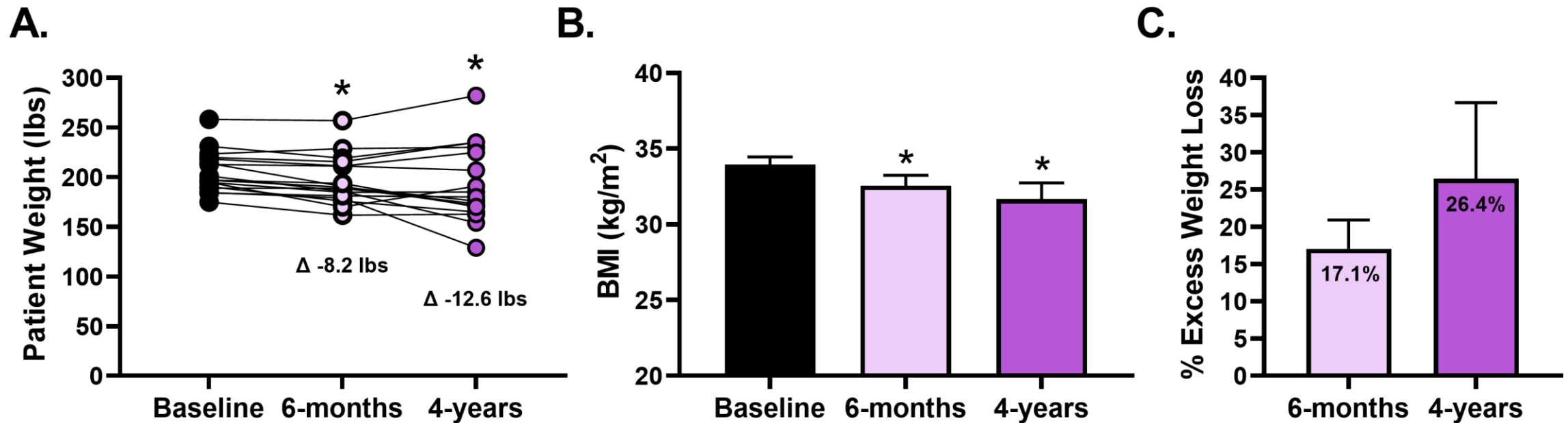


CRYOVAGOTOMY IS ASSOCIATED WITH REDUCTION IN CALORIC INTAKE

- Reduction in ~400-500 calories consumed per day
- Patients report greater feelings of fullness and satiation in questionnaire
- Exact mechanisms for weight loss are largely unknown
 - May slow gastric emptying rate leading to enhanced feelings of fullness
 - May increase GLP-1 action



CRYOVAGOTOMY IS ASSOCIATED WITH SUSTAINED WEIGHT LOSS AFTER 4 YEARS

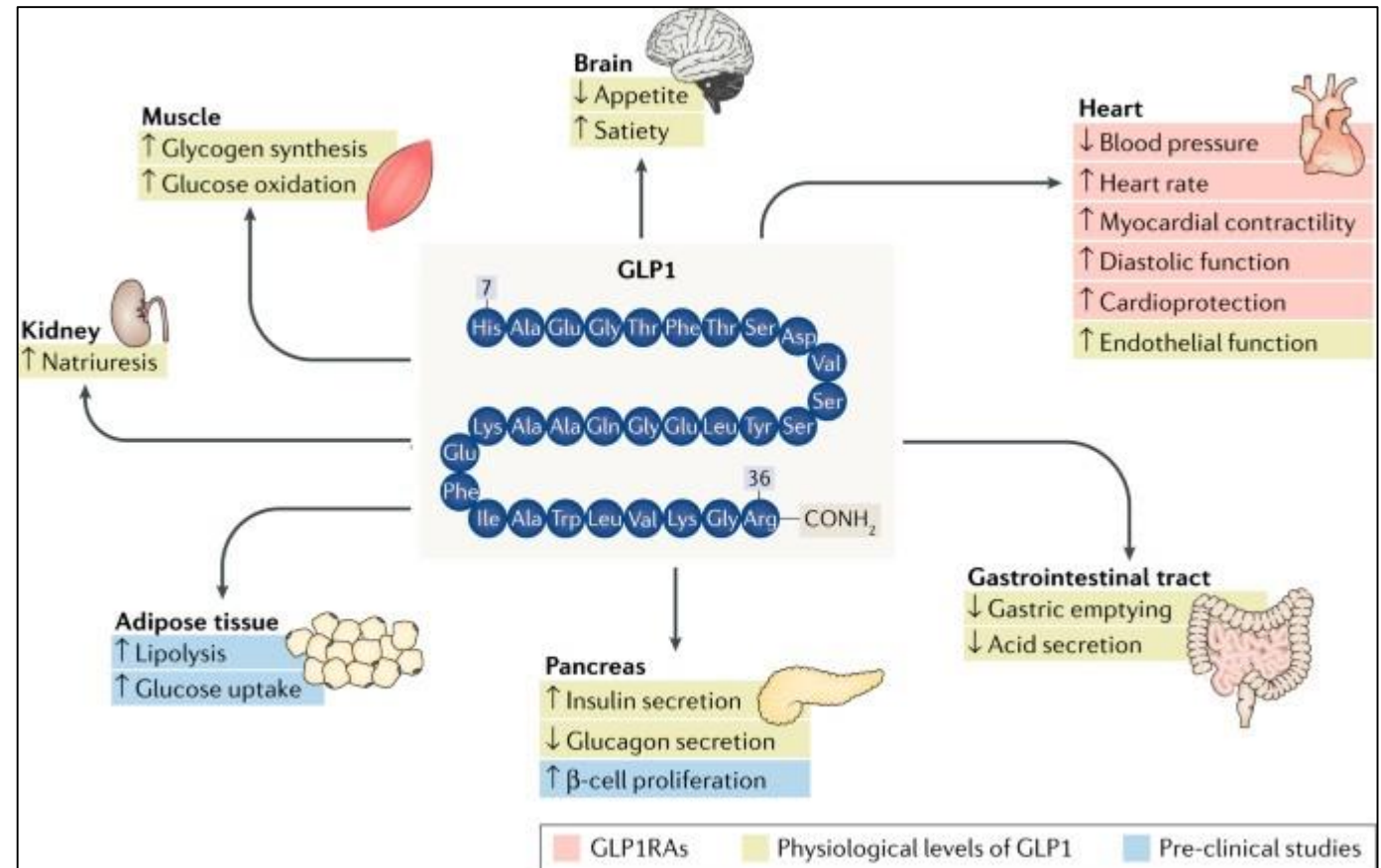


SUMMARY OF CRYOVAGOTOMY

- Shown to have moderate/reasonable weight loss after 6 months to 4-years of intervention (26% excess weight loss)
 - Minimally invasive, does not require surgery, does not require long-term management
 - *Procedure can be performed multiple times*
 - Designed to help treat binge eating and chronic hunger
 - Long-term efficacy and mechanisms of action remain to be studied
-

GLUCAGON-LIKE PEPTIDE 1 (GLP-1)

- Incretin gut hormone that plays a critical role in insulin sensitivity, nutrient utilization, and hunger control
- Signals via GLP-1 receptors found on numerous tissues



Review Article | Published: 04 May 2018

Glucagon-like peptide 1 in health and disease

Andreas Andersen, Asger Lund, Filip K. Knop & Tina Vilsbøll 

Nature Reviews Endocrinology 14, 390–403 (2018) | [Cite this article](#)

WHAT INCREASES GLP-1 PRODUCTION?

- Produced by L-cells along GI tract (ileum)
- Presence of glucose in intestine
 - GLP-1 action is known to be glucose-dependent

Review > Mol Metab. 2019 Dec;30:72-130. doi: 10.1016/j.molmet.2019.09.010. Epub 2019 Sep 30.

Glucagon-like peptide 1 (GLP-1)

T D Müller¹, B Finan², S R Bloom³, D D'Alessio⁴, D J Drucker⁵, P R Flatt⁶, A Fritsche⁷, F Gribble⁸, H J Grill⁹, J F Habener¹⁰, J J Holst¹¹, W Langhans¹², J J Meier¹³, M A Nauck¹⁴, D Perez-Tilve¹⁵, A Pocai¹⁶, F Reimann⁸, D A Sandoval¹⁷, T W Schwartz¹⁸, R J Seeley¹⁷, K Stemmer¹⁹, M Tang-Christensen²⁰, S C Woods²¹, R D DiMarchi²², M H Tschöp²³

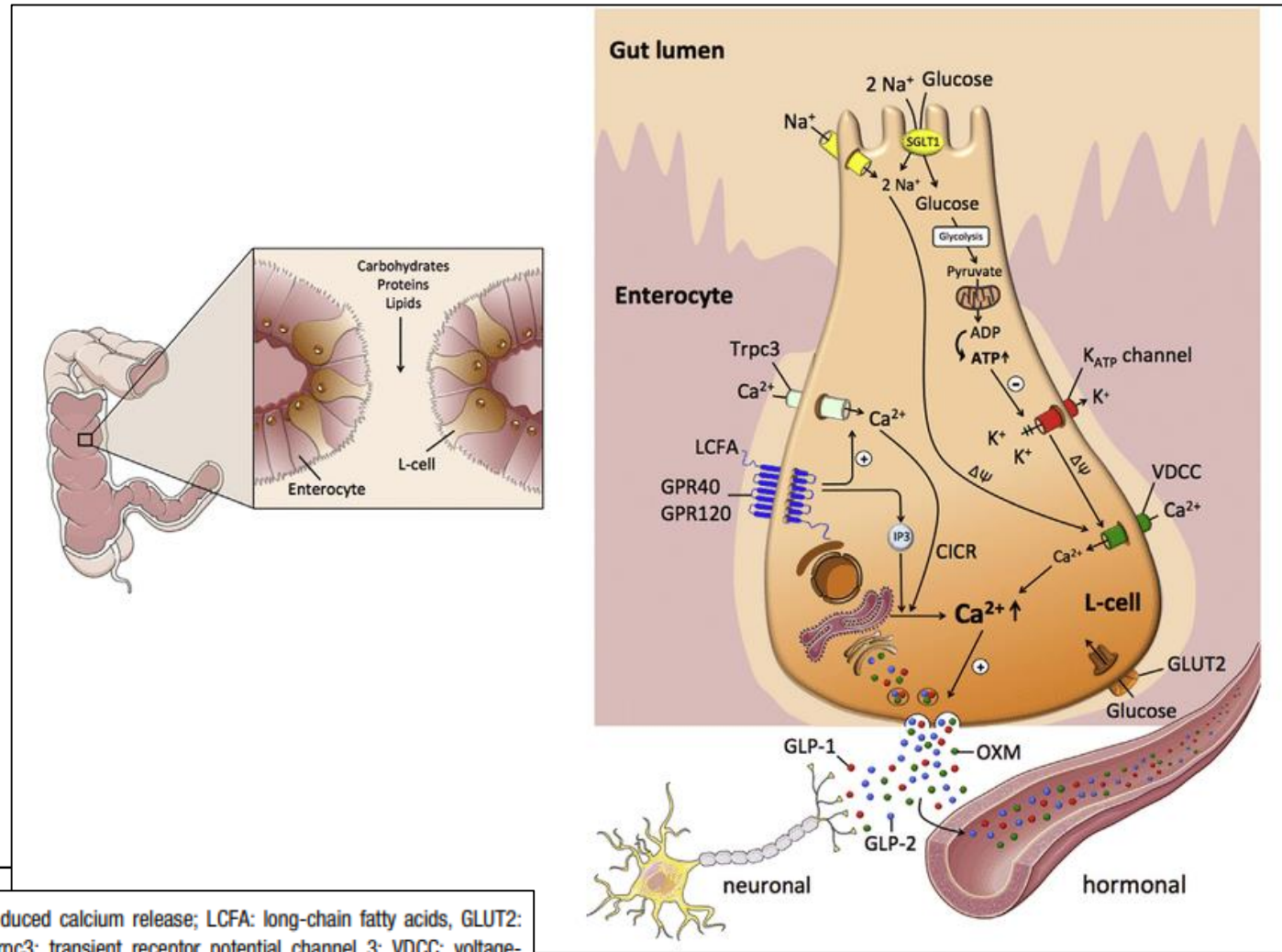
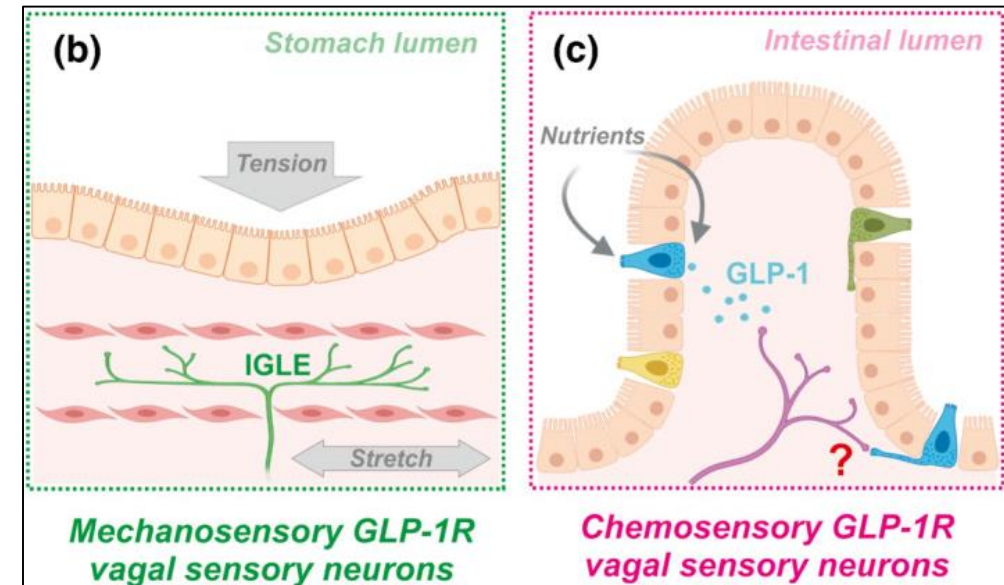
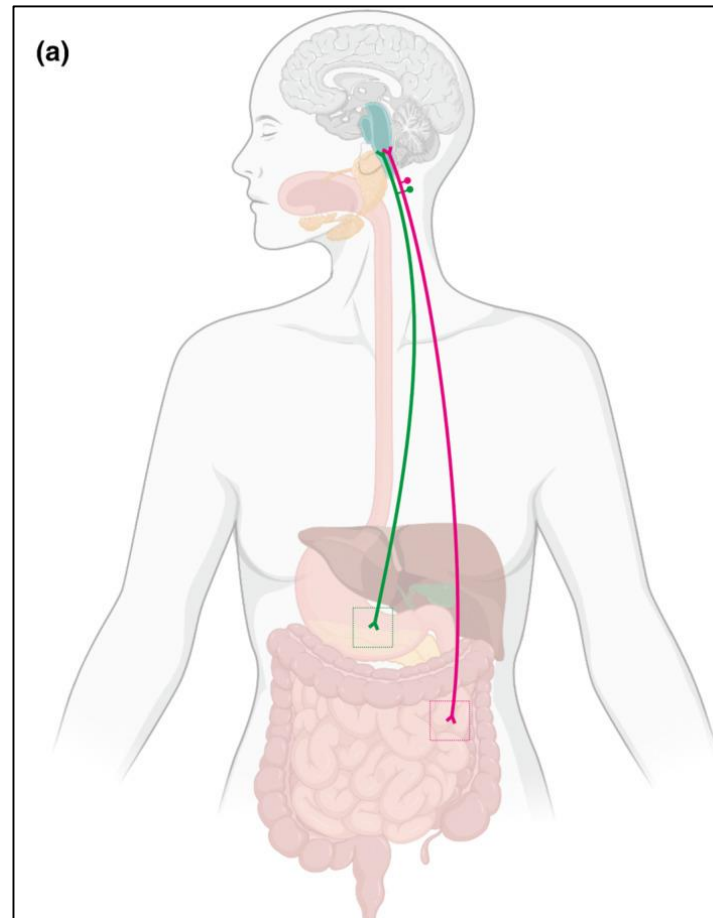


Figure 3: Schematic on the nutrient-induced stimulation of GLP-1 secretion in the L-cell. CICR: calcium-induced calcium release; LCFA: long-chain fatty acids, GLUT2: glucose transporter 2; GLP-1: glucagon-like peptide-1; GLP-2: glucagon-like peptide-2; OXM: oxyntomodulin; Trpc3: transient receptor potential channel 3; VDCC: voltage-dependent calcium channel; SGLT1: sodium/glucose co-transporter 1. For further explanations, please see text.

ACTION OF GLP-1 ON VAGUS SIGNALING

FIGURE 1 Mechanosensory and chemosensory GLP-1 receptor (GLP-1R)-expressing vagal sensory neuron populations. (a) Vagal sensory neurons which express the GLP-1 receptor comprises of distinct mechanosensory and chemosensory subpopulations. (b) Mechanosensory neurons predominantly innervate the stomach and detect gastric distension via intraganglionic laminar endings (IGLEs), (c) while chemosensory neurons predominantly innervate the intestinal mucosa and detect GLP-1 released from enteroendocrine L-cells. Nutrient sensing by L-cells occurs primarily via post-absorptive mechanisms that include receptors and transporters on their basolateral surface, but some nutrients may also be directly sensed via apical projections into the gut lumen. Nutrient detection triggers release of GLP-1 from L-cells, which can bind GLP-1 receptors on local terminals of chemosensory vagal sensory neurons. Direct synaptic signalling between L-cells and vagal sensory neurons may also occur via neuropod projections present on a subset of L-cells; however, the physiological role of this signalling pathway remains unclear



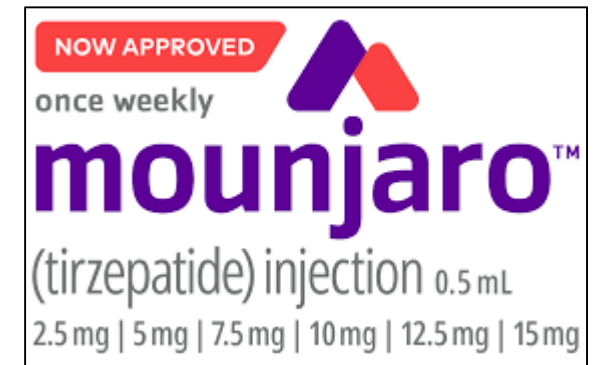
Review > Br J Pharmacol. 2022 Feb;179(4):584-599. doi: 10.1111/bph.15603. Epub 2021 Jul 31.

Reappraising the role of the vagus nerve in GLP-1-mediated regulation of eating

Daniel I Brierley¹, Guillaume de Lartigue²

COMMON GLP-1 RECEPTOR AGONISTS

- Liraglutide – 5-10% wt loss
 - Saxenda (high dose)
 - Victoza (low dose)
- Semaglutide – 10-15% wt loss
 - Ozempic (low dose)
 - Wegovy (high dose)
- Tirzepatide* – Up to 25% wt loss



*also a glucose-dependent insulintropic polypeptide (GIP)

- Mounjaro - approved for weight loss with diabetes diagnosis in May 2022

*Considered safe for use before and after bariatric surgery

Intended for BMI >30 or BMI >27 with HTN, diabetes

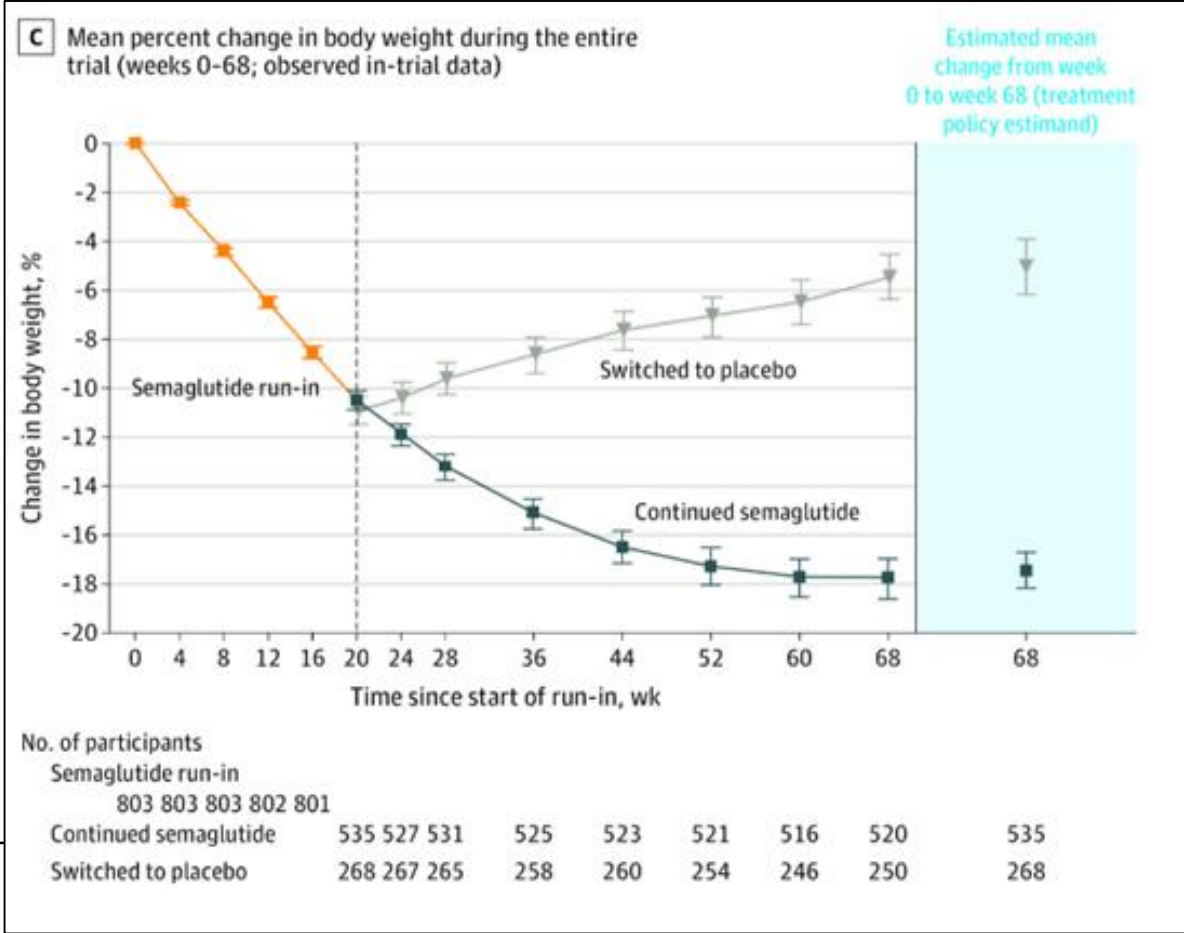
WEIGHT LOSS MEDICATIONS MUST BE TAKEN LONG-TERM

Avg. weight loss medication is taken for only ~84 days

Clinical Trial > JAMA. 2021 Apr 13;325(14):1414-1425. doi: 10.1001/jama.2021.3224.

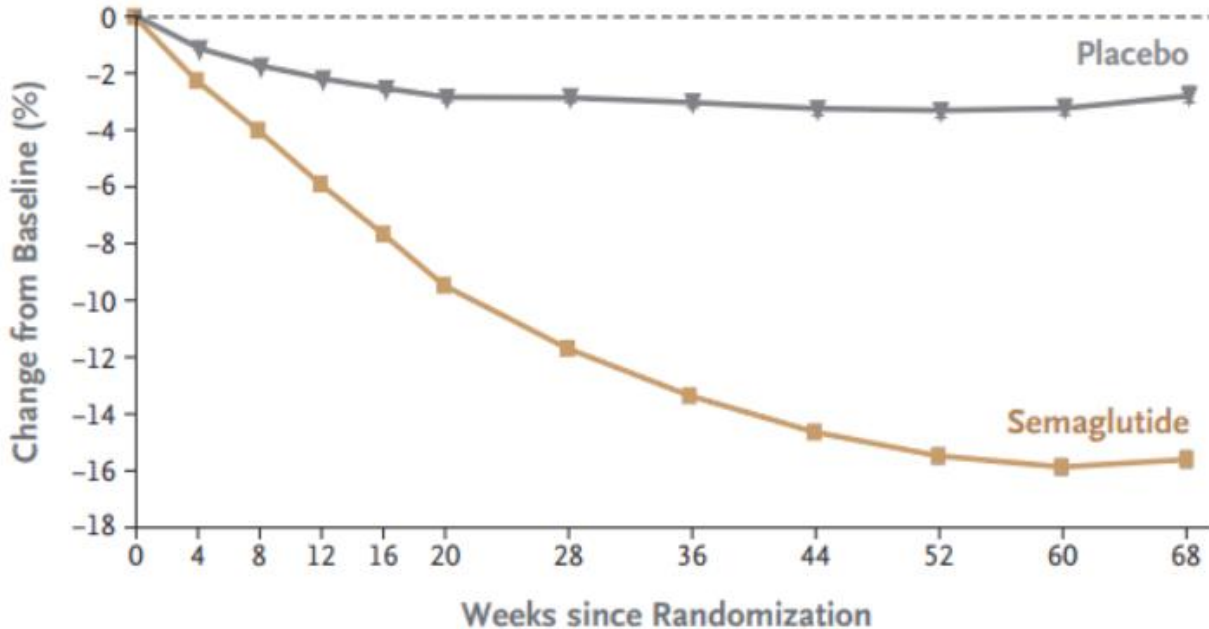
Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial

Domenica Rubino ¹, Niclas Abrahamsson ², Melanie Davies ^{3, 4}, Dan Hesse ⁵, Frank L Greenway ⁶, Camilla Jensen ⁵, Ildiko Lingvay ⁷, Ofri Mosenzon ⁸, Julio Rosenstock ⁹, Miguel A Rubio ¹⁰, Gottfried Rudofsky ¹¹, Sayeh Tadayon ⁵, Thomas A Wadden ¹², Dror Dicker ¹³, STEP 4 Investigators



WEGOVY ADMINISTRATION LEADS TO SIGNIFICANT WEIGHT LOSS

Body Weight Change from Baseline by Week, Observed In-Trial Data



No. at Risk

Placebo	655	649	641	619	615	603	592	571	554	549	540	577
Semaglutide	1306	1290	1281	1262	1252	1248	1232	1228	1207	1203	1190	1212

CONCLUSIONS

Adults without diabetes who were overweight or obese had clinically relevant weight loss with weekly injections of semaglutide (2.4 mg) added to lifestyle changes.

TIRZEPATIDE ADMINISTRATION LEADS TO SIGNIFICANT WEIGHT LOSS

> N Engl J Med. 2022 Jun 4. doi: 10.1056/NEJMoa2206038. Online ahead of print.

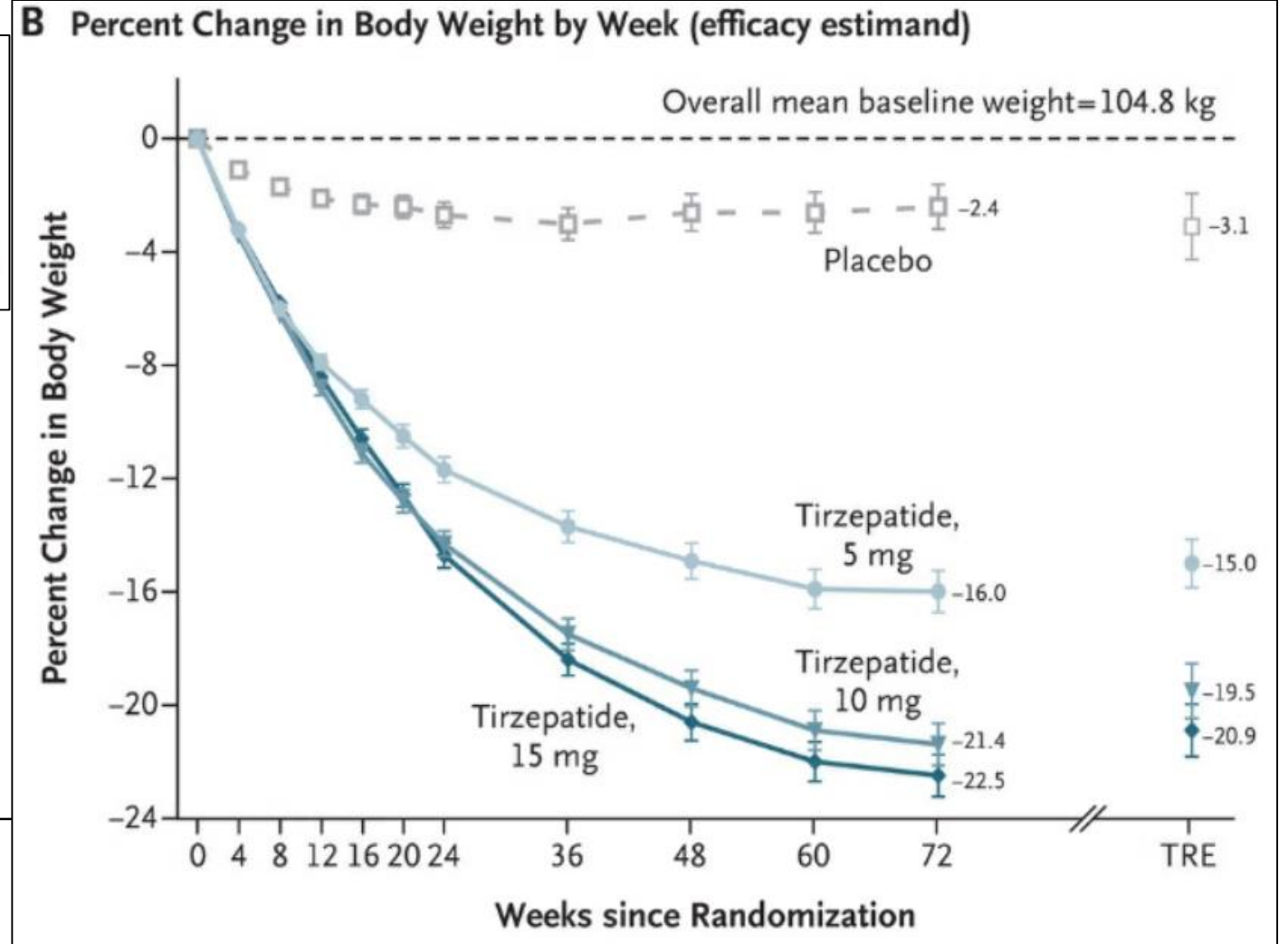
Tirzepatide Once Weekly for the Treatment of Obesity

Ania M Jastreboff¹, Louis J Aronne¹, Nadia N Ahmad¹, Sean Wharton¹, Lisa Connery¹, Breno Alves¹, Arihiro Kiyosue¹, Shuyu Zhang¹, Bing Liu¹, Mathijs C Bunck¹, Adam Stefanski¹, SURMOUNT-1 Investigators

*Dual Action Drug

Tirzepatide is a GLP-1 receptor agonist + glucose-dependent insulinotropic polypeptide (GIP)

GIP is produced by K-cells in intestine and target the beta cells of the pancreas to stimulate insulin secretion



SUMMARY OF GLP-1 RECEPTOR AGONISTS

- Shown to be promising highly effective for weight loss (up to 25% total body weight loss)
 - Variety of options – good for insurance coverage
 - **Can be costly** (\$1000+ per month if able to obtain)
 - Considered safe for long-term use
 - Much of the action of GLP-1 receptor agonists for weight loss may be related to their impact on the vagus nerve
-

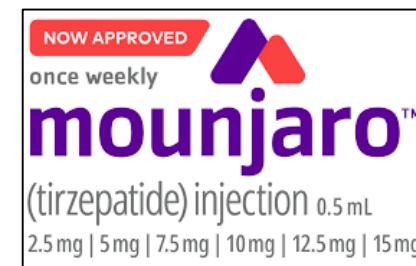
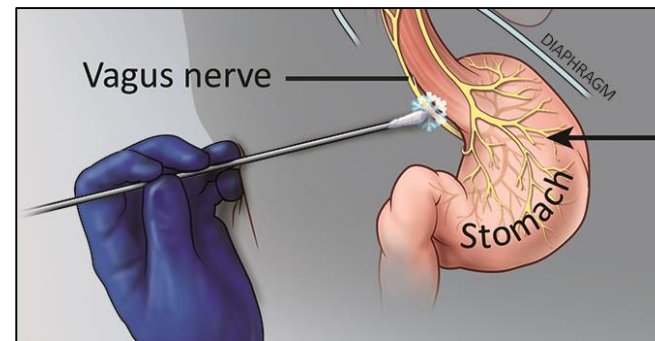
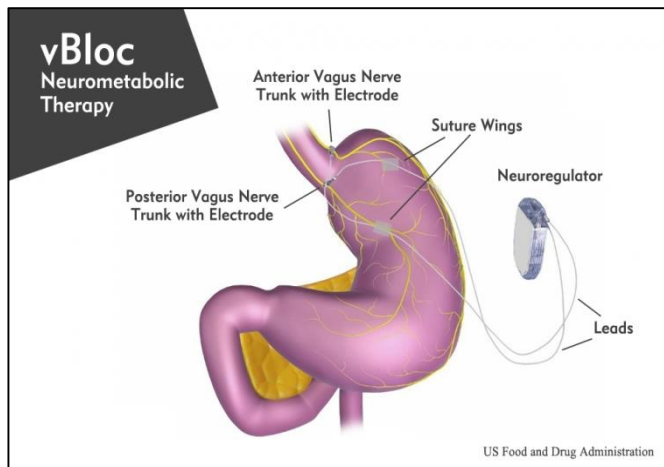
BUILDING ON OUR FOUNDATION WITH THE VAGUS NERVE

Foundation – Weight Maintenance

Diet Variety Moderate Physical Activity Mental Health/Sleep Healthcare Access Education

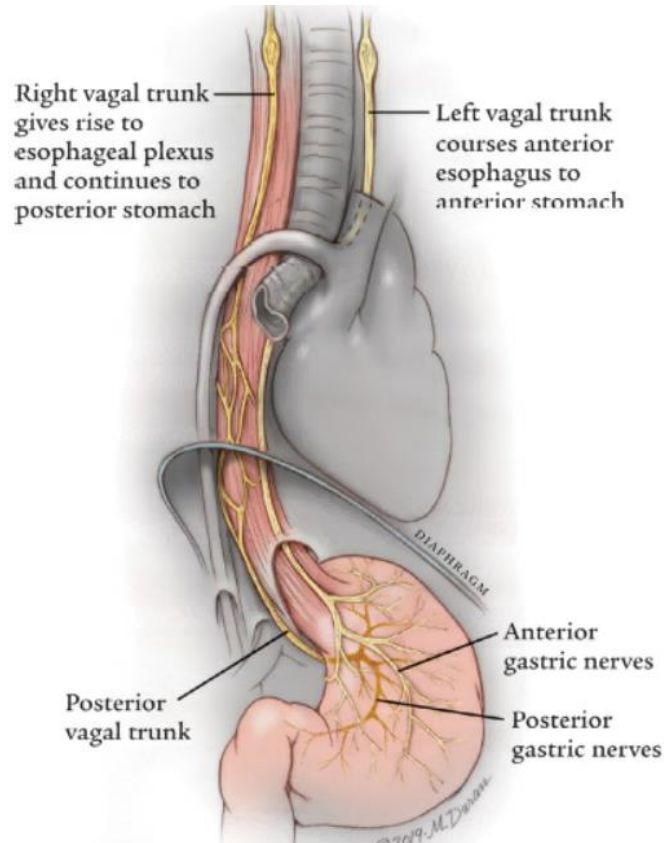


If BMI >30 kg/m² and looking for weight loss



Combination of therapies can lead to greater and more sustained results

VAGUS NERVE INTERVENTIONS SUMMARY



- **vBlock produces moderate weight loss over two-years**
 - Likely not intended for long-term use
 - Demonstrates efficacy of vagus nerve interventions for weight loss
- **Cryovagotomy demonstrated to have longer term efficacy, is safe, and treatment is temporary**
- **GLP-1 receptor agonists are commonly available and effective**
 - Must be taken long term (beyond 1 year)
 - Can become costly
 - Demand for use is very high (may experience supply shortages)

Exploring the vagus nerve interventions for weight loss is an exciting field; more data and research is needed!

THANK YOU!

We are enrolling patients in our cryovagotomy weight loss program!

Connect on LinkedIn!

<https://www.linkedin.com/in/zigrunewald>

Zach Grunewald, PhD, MS, RDN, LD

Zachary.grunewald@emoryhealthcare.org

