8 Common Pitfalls of Treating Obesity

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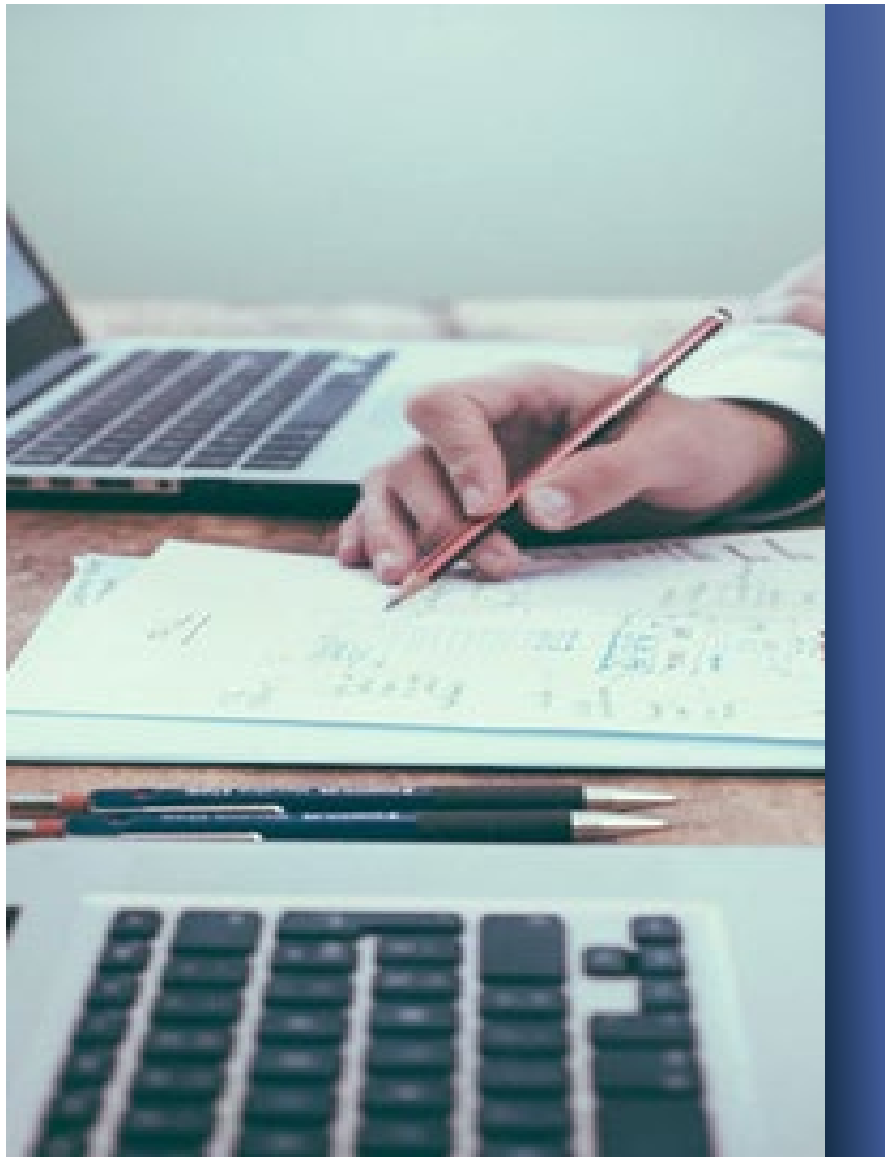


Disclosures

- Speaker for Rhythm Pharmaceuticals
- Advisory Board for Madrigal Pharmaceuticals

Objectives

- Address common misconceptions about weight loss and pitfalls to avoid
- Give a framework for approaching obesity medicine in practice
- Review recent literature relating to obesity

8 Common Pitfalls of Treating Obesity

1. Lack of Setting Expectations
2. Worsening/Missing Disordered Eating & Poor Population Selection
3. Missing Underlying Pathology
4. Worsening Physical Health
5. Ignoring Behavioral Lifestyle Change: Exercise and Nutrition
6. Failing to explain the science or only CICO
7. Emphasizing One Diet or Medication Over Another
8. Recommending “Compounded” Medication Without Evidence to Support It

PITFALL 1: Failing to Set Expectations

Expectation Setting: Longevity of Weight Loss Results

- A meta-analysis of US studies showed that ~60% of those that lost at least 5% of their weight were unable to sustain this threshold of loss 5 years later. Average loss was 3% at 5 years.[1]
- The Biggest Loser Study found 36% of subjects were within 1% of original starting weight. And 57% maintained >10% weight loss. Average loss 11.9%.[2]
- The Diabetes Prevention Program (DPP) found that 37% maintained 7% of their weight loss at a 3-year follow-up.[3]
- The Look AHEAD Study showed 27% of participants maintained 10% weight loss at 8-year follow-up.[4]
- NHANES study performed 1999-2006 demonstrated that 1 in 6 adults with overweight and obesity reported maintaining weight loss of at least 10% for 1 year at any point in their lives. [5]

Expectation Setting:
Time-frame, Rate, Total

- Faster rates of weight loss may result in more fat-free mass and less fat mass being lost.[6]
- Gradual weight loss promoted greater reductions in fat mass and body fat percentage. Gradual weight loss significantly preserved RMR compared with rapid weight loss.[7]
- Metabolic adaptation: The Biggest Loser" study starting average RMR was 2607 ± 649 kcal/day. At the end of the 30-week competition it was 1996 ± 358 kcal/day. 6 years later it was 1903 ± 466 kcal/day, 704 ± 427 kcal/day below the baseline but not significantly different from the RMR at the end of the competition [8]
- Men vs Women: Men lose more weight than women during weight loss attempts, although it is possible that this is due to the greater baseline weight of men.[9]
- Percentage of FFM loss typically 25%.[10]
- NWCR: Total 66 lb over 5.5 years.[11]

Body Weight Planner | Balancing Your Food and Activity

Starting Information — Advanced Controls: OFF

Weight	300	lbs
Sex	Female	
Age	40	yrs
Height	5 ft. 6 in.	feet
Physical Activity Level	1.2	Estimate Your Level

Goal Weight | **Lifestyle Change** — Advanced Controls: OFF

Change your calories (intake) or activity (expenditure) to see how your weight will change.

Change 1 — On / Off

Change starts on day 1 with an intake of 1529 Calories/day.

Change your physical activity by 0 % — Estimate

Change 2 — On / Off

Change starts on day 90 with an intake of 1800 Calories/day.

Change your physical activity by 23 % — Estimate

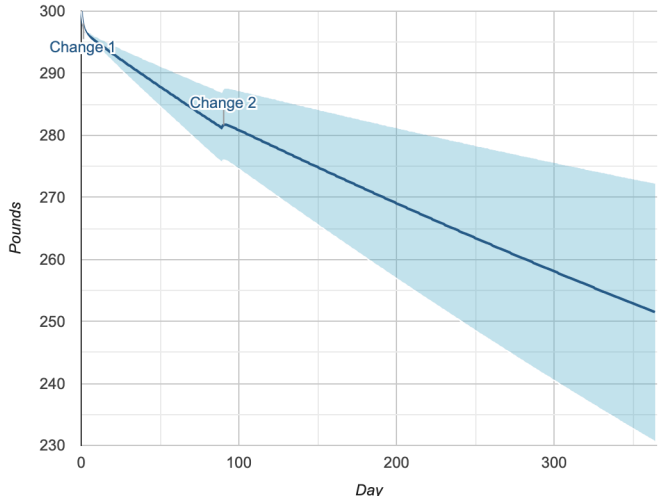
Simulation Displayed

Length of Simulation: 365 days

Initial Weight (lbs):	300	Initial % Fat:	58.6	Initial BMI:	48.4
Final Weight (lbs):	251.5	Final % Fat:	53.9	Final BMI:	40.6

Weight | Body Fat % | Intake & Expenditure | Tabular

Click and drag to zoom — Reset View — Download Chart as Image



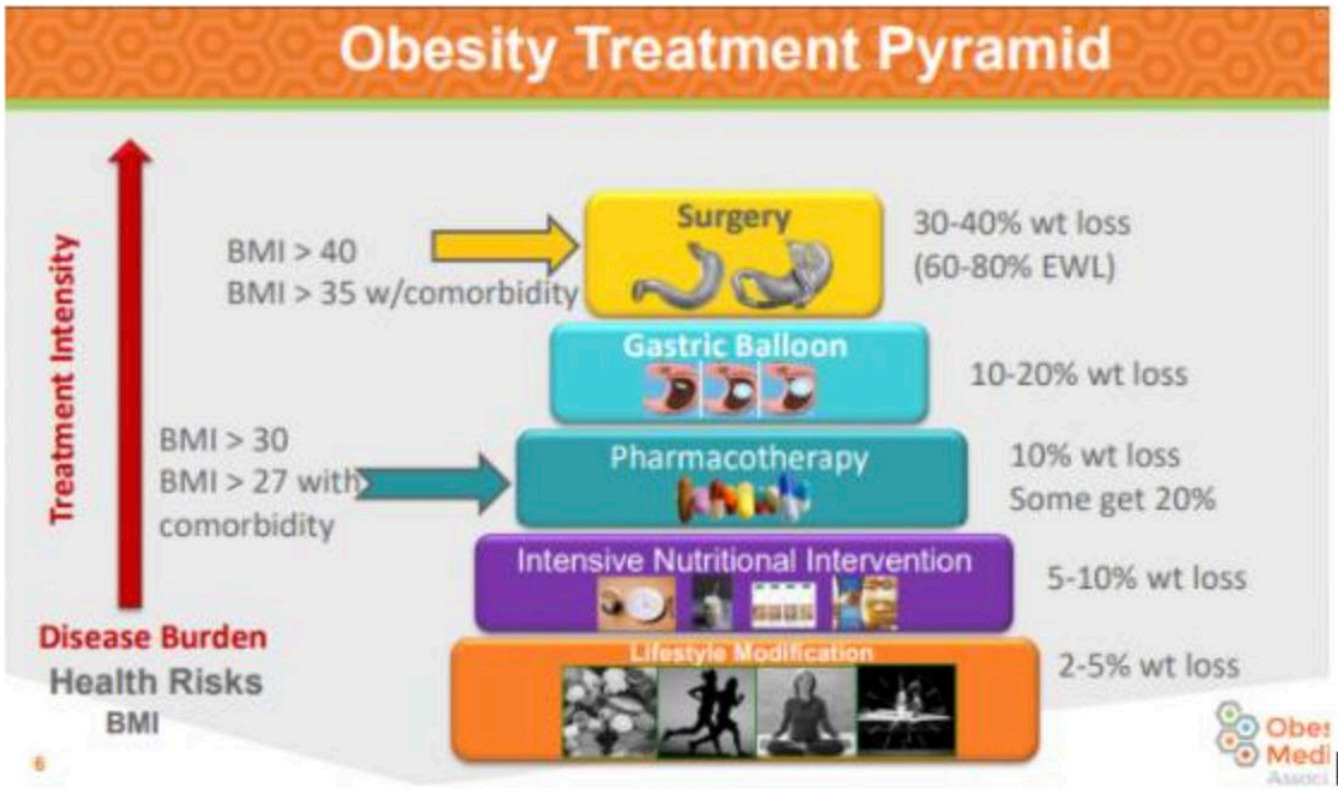
Export Charts Data (CSV Format)

Day	Date	Weight (lbs)	High Weight (lbs)	Low Weight (lbs)
0	12/31/23	300	300	300
1	1/1/24	298	298	297.9
2	1/2/24	297.1	297.2	296.9
3	1/3/24	296.6	296.8	296.4
4	1/4/24	296.3	296.5	296
5	1/5/24	296	296.4	295.7
6	1/6/24	295.8	296.2	295.4
7	1/7/24	295.6	296.1	295.2
8	1/8/24	295.4	295.9	294.9
9	1/9/24	295.2	295.8	294.6
10	1/10/24	295	295.7	294.4
11	1/11/24	294.8	295.5	294.1
12	1/12/24	294.6	295.4	293.9
13	1/13/24	294.4	295.3	293.6
14	1/14/24	294.3	295.2	293.4

Body Weight Planner: National Institute of Diabetes and Digestive and Kidney Diseases (https://www.niddk.nih.gov/bwp)

Expectation Setting:
Frequency of Visits, Surgery

- DPP: 22 sessions over a year.[12]
- Look Ahead: 42 visits over a year.[13]
- RNY: Mean pre-operative BMI of 54.7 kg/m2, max 39.0% TBWL at 1.7 years post-surgery. 10-year %TBWL at 5 and 10 years were 33.3% and 31.0%, respectively.[14]
- LSG: 10-year weighted mean %TWL was 24.4%; remission rates from TD2M to HTN were 45.6% and 41.4%, respectively.[15]



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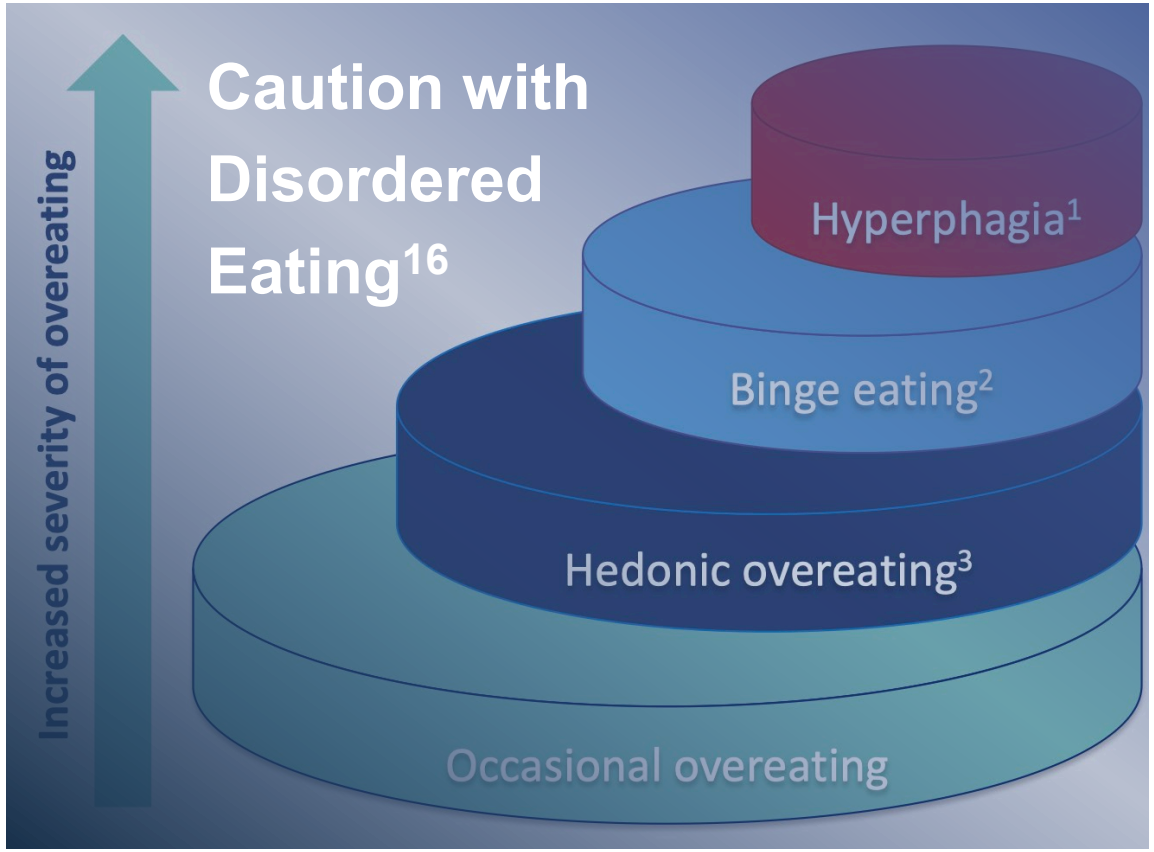
Pitfall 2: Worsening or Missing Disordered Eating &/or Poor Population Selection

ED History

Obtaining a Dietary History

- Using MI to inquire on prior dietary efforts
- Past attempts at CICO
- If positive questionnaire (e.g. SCOFF), assessing h/o BN/AN



Binge-Eating Disorder

- BED7, BES

ARFID

- Lack of interest/avoidance
- Social/wt loss/Nutrition

Food Addiction

- YFAS 2.0
- Not in DSM
- Dieting, Food Insec.

ED History

- AN/BN, SCOFF
- Weight over health

Binge Eating Disorder

- Relationship with ADHD
- Outcomes: Symptoms, Behavior, and Rx[17]
- Most common ED in the US[18]
- May not present as in image above
- May present differently after bariatric surgery

Food Addiction & Avoid Restrictive Food Intake Disorder

Food Addiction

1. Consuming more food than intended, especially highly palatable foods, over a longer duration than planned.
2. Repeated unsuccessful efforts to reduce or control the consumption of certain foods.
3. Spending much time obtaining specific foods, eating them, or recovering from overeating. (e.g. driving to gas station for it)
4. Intense cravings for certain foods that are hard to resist.
5. Food consumption interferes with daily responsibilities and roles.
6. Continuing to consume certain foods despite it causing social or interpersonal problems.
7. Abandoning or reducing engagement in important activities due to food consumption.
8. Eating in a manner that is physically dangerous, such as binge eating despite health issues.
9. Continuing to consume specific foods despite knowing it worsens physical or psychological problems.
10. Needing more of the food to achieve the desired effect or experiencing diminished effect with continued use of the same amount.
11. Experiencing withdrawal symptoms when cutting down or stopping the intake of certain foods similarly seen with substance use disorders.

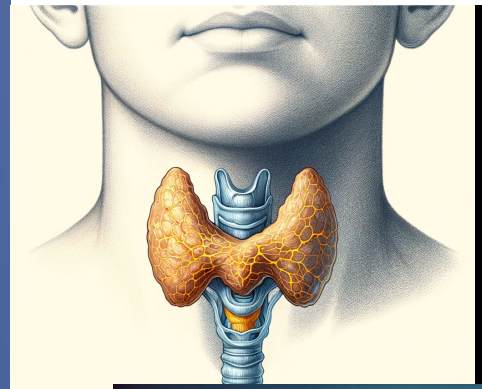
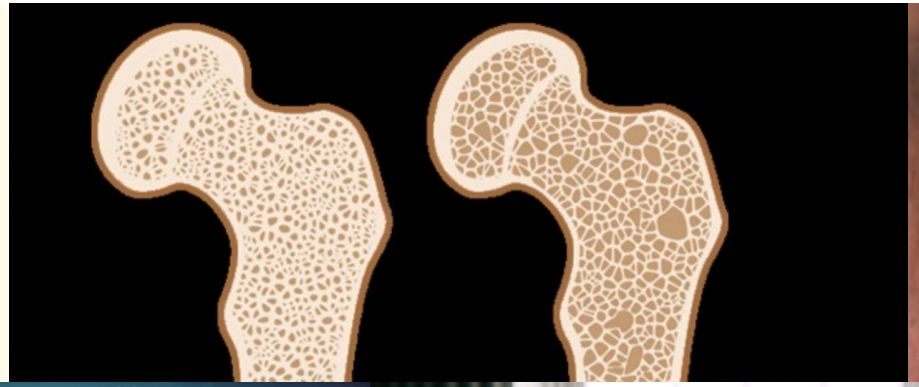
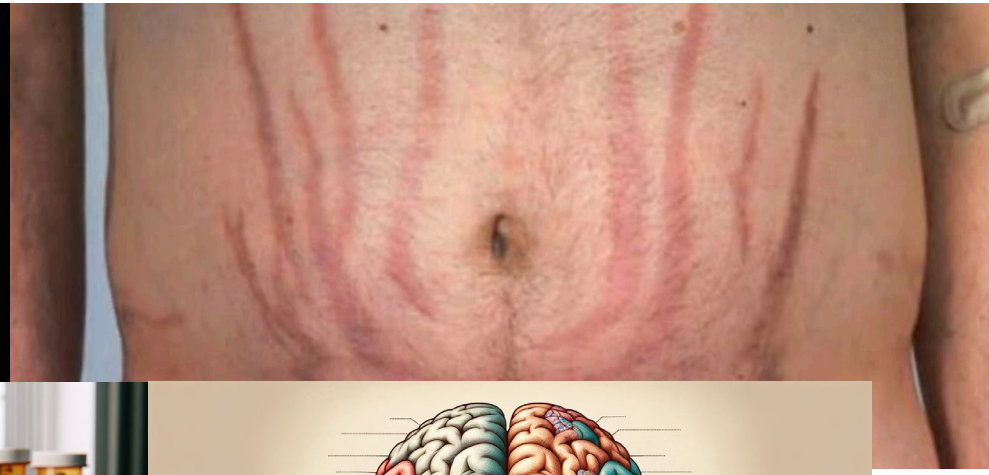
ARFID

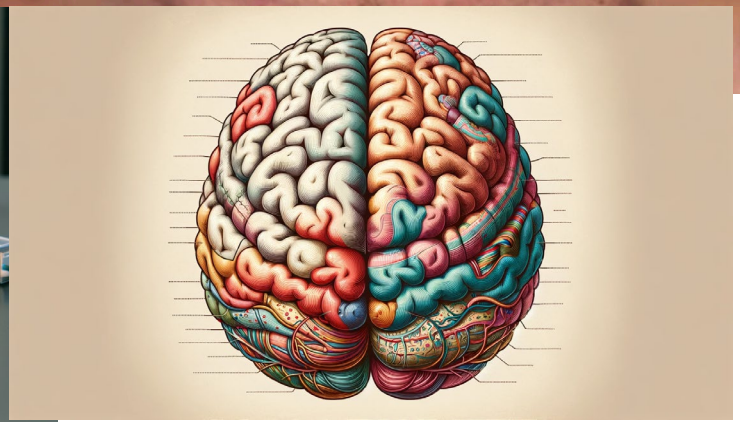
1. A food disturbance (e.g. lack of interest in eating; avoidance of food based on the sensory characteristics; concern about aversive consequences of eating) as manifested by persistent failure to meet appropriate nutritional and/or energy needs associated with one (or more) of the following:
    1. Significant weight loss (or faltering growth in children).
    2. Significant nutritional deficiency.
    3. Dependence on enteral feeding or oral nutritional supplements.
    4. Marked interference with psychosocial functioning.
2. Not explained by lack of available food or cultural practice.
3. There is no AN/BN/body dysmorphia/medical condition.

NuSHs

- FDA approved for BMI ≥27 with co-morbid conditions or BMI ≥30 kg/$m^{2.}$
- Considered HeAOM (Highly Effective Anti-Obesity Medication)[38]

Pitfall 3: Missing Underlying Pathology

- Endocrine issues, Sleep, Rx-induced, Fluid (cardiac/renal/hepatic), Genetic, Psychologic
- Renal dosing
- Rx-Rx interactions, Effects of surgery
- Side-effect profile

Case Study 1

- 42 yo F with NES, MDD, BED, ADHD, MASLD, MetS, POTS, RLS, Migraines, PTSD, chronic fatigue, excessive daytime sleepiness
- On Doxepin and Gabapentin for sleep and Propranolol for POTS, all of which cause weight gain and can worsen fatigue
- Gets poor sleep due to pain + insomnia + RLS; Fluoxetine worsened RLS in past.
- On Duloxetine which can help with pain, but also affect HR and sleep and MDD uncontrolled
- On low-dose D-A/Amphetamine but has sleep issues
- On Semaglutide (Wegovy) from PCP, but has constipation and tachycardia (Post-Mark., 5-10% in Zepbound)

Considerations

- Carvedilol or Nebivolol instead of Propranolol
- May want to avoid Wellbutrin with Cymbalta and POTS
- Can’t do Lisdexamfetamine (Vyvanse) b/c of severity of miBED and concurrent use of D-A/Amphetamine and tachycardia
- Trazodone + Lemborexant for insomnia instead of Doxepin and Gabapentin; Trazodone can worsen PTSD if nightmares. Withdrawal of Gabapentin may worsen RLS and pain.
- Changing Duloxetine to Sertraline for NES but could worsen RLS with Prozac history
- Could do bromocriptine (Cyloset) for RLS and insulin resistance (off-label), but not recommended with concurrent Bupropion (if considering starting).
- Topiramate could worsen fatigue and depression
- Could consider Modafinil for sleepiness, but also on D-A/Amphetamine and has tachycardia and prehypertension.

Results

- Weaning off Gabapentin, Propranolol, and Doxepin. Trazodone + Lemborexant for insomnia, Sertraline for depression. Changed Wegovy to Zepbound. Bromocriptine for RLS led to 37.1 lb (18.2%) weight loss over 10 months.

Case Study 2

- 40-year-old male who presents with history of blindness, heart failure, diabetes mellitus, dyslexia, MASLD, DLD, CKDG3aA1.
- Central adiposity present and high arched palate
- Weight gain began at age of 9 and he was already 300 lb at age 12. Presenting BMI 50.5 kg/m2.

Considerations

- Anyone with hyperphagia + obesity before age 10 + BMI >40 needs to be evaluated for monogenetic causes of obesity.
- Fiancé would supplement history that patient was going to say otherwise was normal (e.g. he had OT and special education classes as a child, dentist commenting on small dental roots)
- Additional testing and exam showed high arched palate, hypogonadism

Results

- Met 4 primary and and 3 minor criteria for Bardet-Biedl Syndrome
- Started on Setmelanotide, Bromocriptine, and Tirzepatide. Lost 136 lb (32.6%) over 29 months.

Pitfall 4: Worsening Physical Health

Worsening Physical Health

- Dehydration (14% vomiting, 18% diarrhea)[19]
- Malnourished: increasing recs on NuSHs & surveillance
- Constipation, Aspiration, GB
- Loss of lean mass of 1-2%/year (e.g. falls)[20, 21]
- Poor diet
- Retention of visceral fat

5% Weight Loss

Diabetes

Dyslipidemia

Hypertension

MASLD

Infertility (male)

Urinary Incontinence

7% Weight Loss

Sleep Apnea

Asthma/RAD

10% Weight Loss

Infertility (female)

Osteoarthritis

GERD

15% Weight Loss

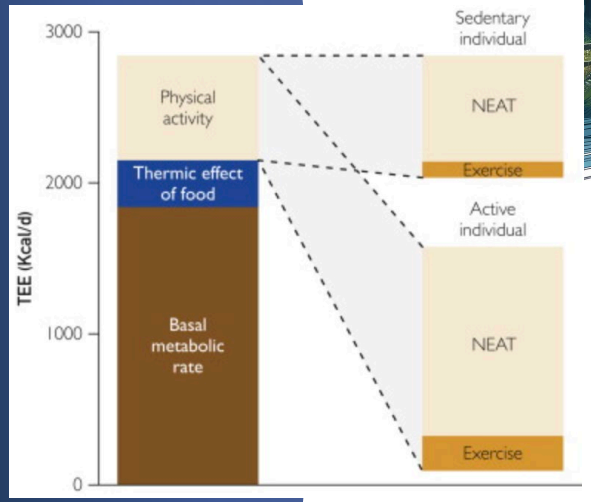
NASH

AACE/ACE Obesity CPG, Endocr Pract. 2016;22(Suppl 3)

Pitfall 5: Ignoring Behavioral and Lifestyle Change

Lifestyle Change

- DPP: 58% reduction in the incidence of type 2 diabetes compared to the placebo group[3]
- Look Ahead: The intensive lifestyle intervention group achieved significantly greater weight loss at year 1 (8.6% of initial body weight) and maintained a greater weight loss than the control group at year 4 (about 5% vs. <1% in the control group) and throughout the study period.[4]
- Surmount 3: ILI + placebo or Tirzepatide; ILI group had improvement in metabolic #s & 6.9% weight loss and kept 4.8% wt off at 72 weeks vs ILI + Tirzepatide group, which kept off 25% weight at 72 weeks.[22]



https://pubmed.ncbi.nlm.nih.gov/25841254/

Exercise

6 studies in a larger Meta-Analysis: Wt-loss maint. 7.47kg LE & 14.99kg EX; Percent Wt-loss maint. 27.20% LE & 53.80% EX; & Wt Red. 6.66% LE & 12.49%.[23]

- 4/4 SR-MAs showed >Wt loss in Ex vs NEx groups. 1 of 2 found >Wt loss in Ex+Diet compared to Diet alone.[24]
- TDEE = BMR + TEF + Exercise + *NEAT* + EPOC[25]

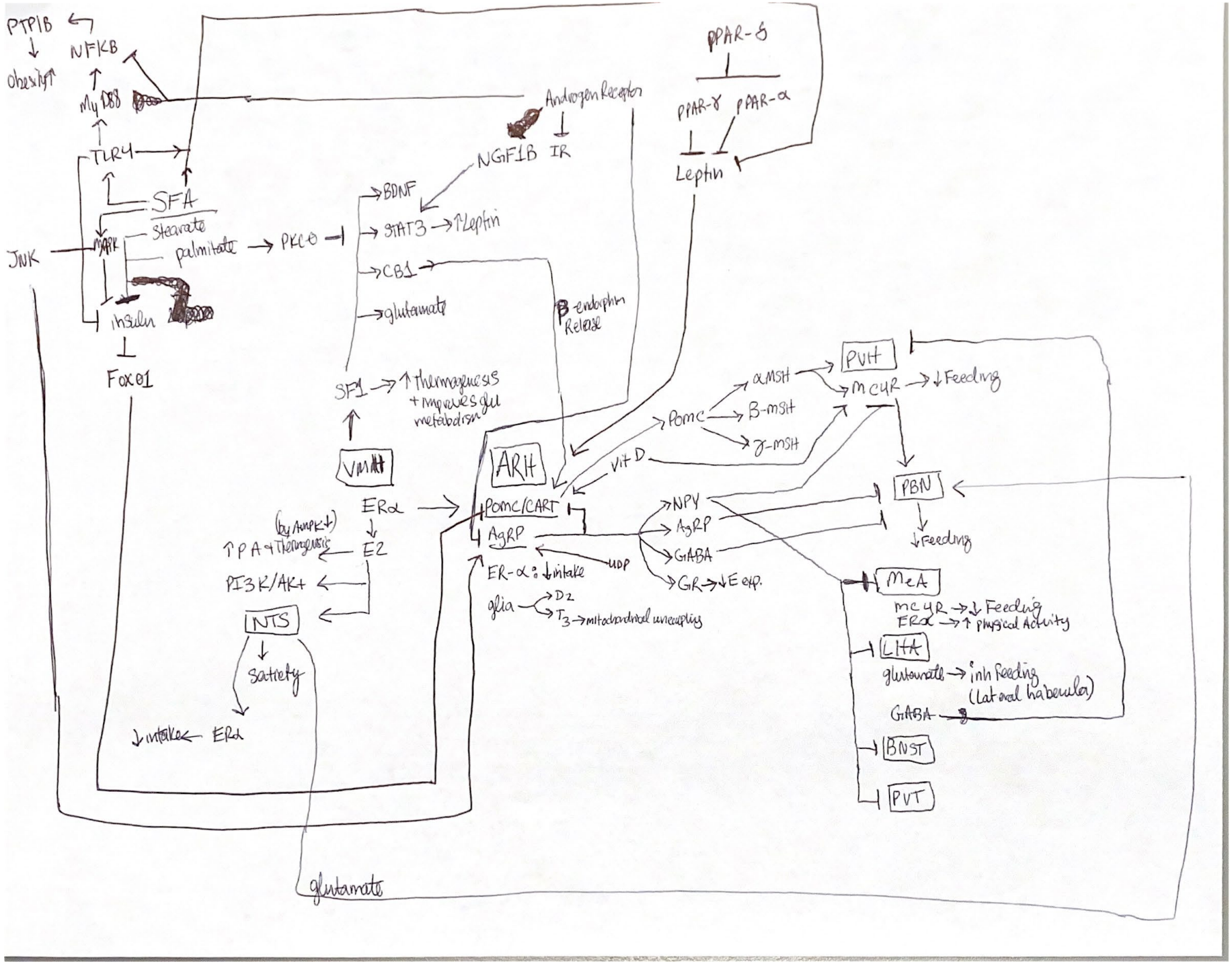
Nutrition

- Energy density, Fiber intake, Fruits & veggies, Meal planning, Nutrition labels, Protein intake, Snacking, Sugary drinks and desserts, Water intake, Whole grains

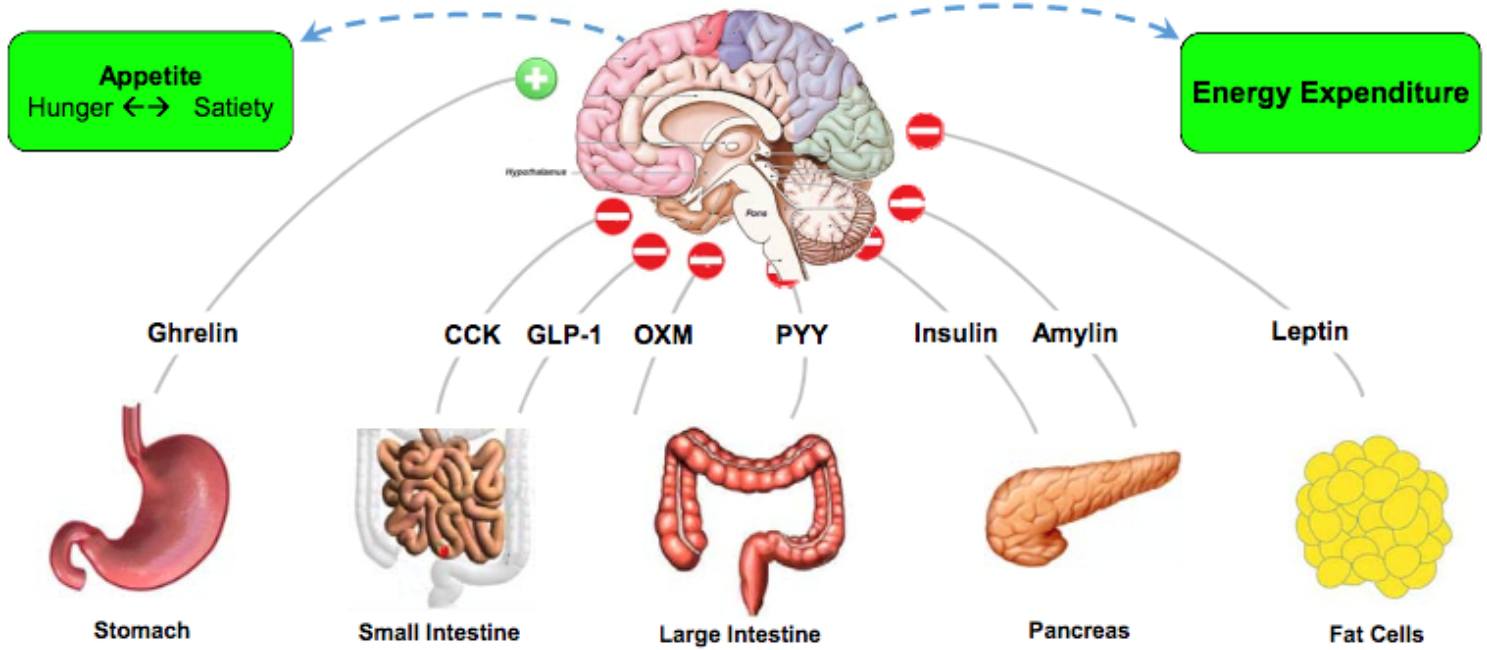
Behavior

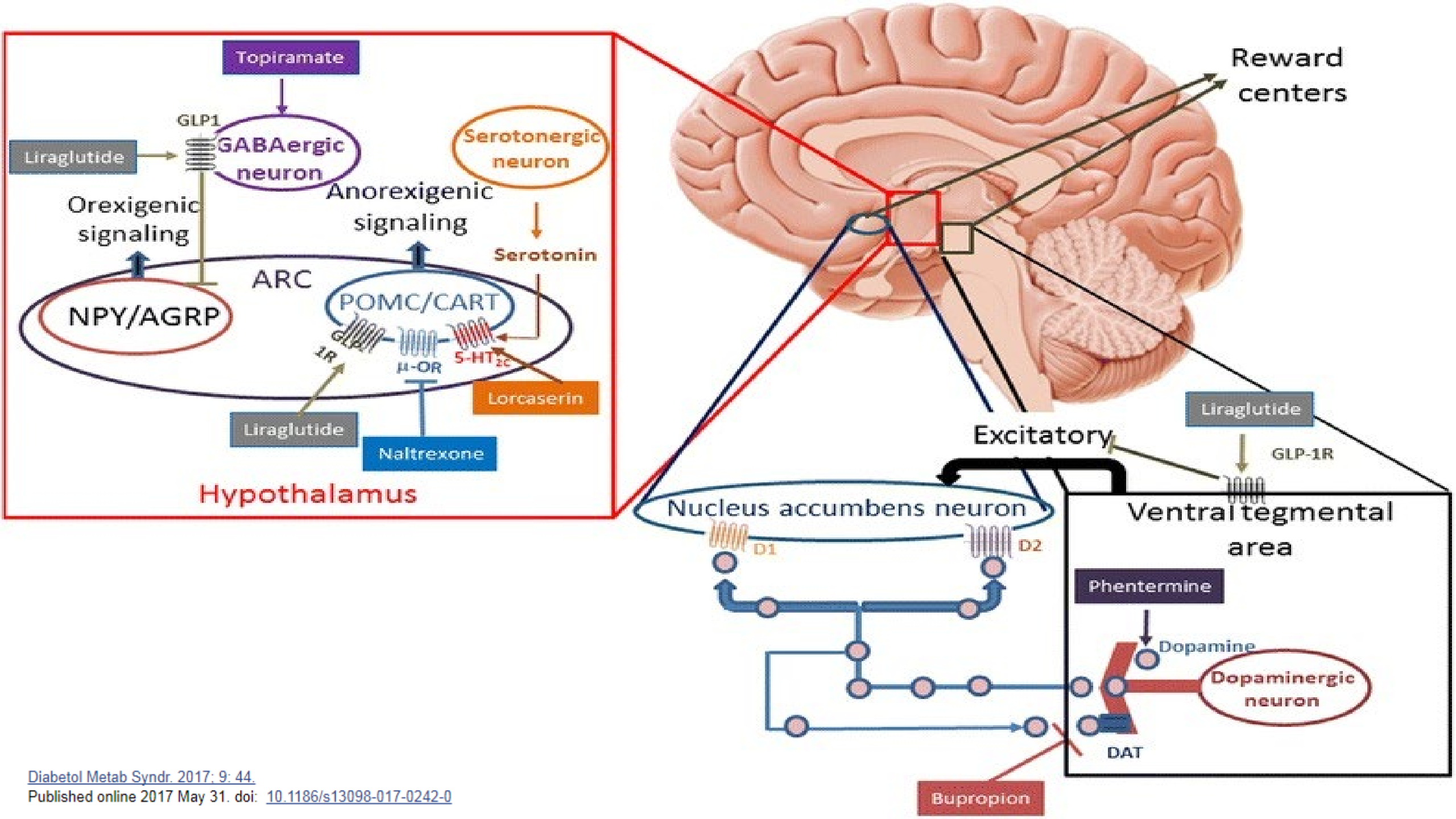
- Distress tolerance, Eating out, Contingencies, Emotional regulation, Goal setting, Habit formation, Medication adherence, Mindfulness, Motivation, Problem solving, Self-monitoring, Sleep hygiene, Social support, Stimulus control, Stress management
- Behavioral interventions >4 months lead to avg Wt loss of 0.45 kg (1 lb/wk). Multiple interventions = more Wt loss. After 9-10 mo of behavioral treatment, ~2/3 achieve & maintain Wt loss. Ex + Diet + IBT achieves a significant weight loss.[26]

Pitfall 6: Not Explaining the Science to the Patient


PTP1B
obesity
NFKB
MyD88
TLR4
SFA
Stearate
palmitate
PKCθ
JNK
MAPK
insulin
Foxo1
BDNF
STAT3 → ↑Leptin
CB1
glutamate
β-endorphin Release
NGFIB
IR
Androgen Receptor
PPAR-δ
PPAR-γ
PPAR-α
Leptin
SF1 → ↑thermogenesis + improves glu metabolism
VMH
ERα
(by AMPK↓)
↑PA & Thermogenesis
E2
PI3K/AKt
NTS
Satiety
↓intake ← ERα
ARH
Pomc/CART
AgRP
ER-α: ↓intake
glia
D2
T3 → mitochondrial uncoupling
UDP
Pomc
αMSH
β-MSH
γ-MSH
Vit D
NPY
AgRP
GABA
GR → ↓E exp.
PVH
MC4R → ↓Feeding
PBN
↓Feeding
MeA
MC4R → ↓Feeding
ERα → ↑ physical Activity
LHA
glutamate → inh Feeding
(Lateral habenula)
GABA
BNST
PVT
glutamate

Pathophysiology of Eating and Weight Regulation





Diabetol Metab Syndr. 2017; 9: 44.
Published online 2017 May 31. doi: 10.1186/s13098-017-0242-0

Table 2.—Probandwise Concordance Rates for Various Percentages of Overweight* 28

% Overweight	At Induction: % Concordant: Monozygotic Twins	At Induction: % Concordant: Dizygotic Twins	At Induction: χ^2 (1 *df*)	At Follow-up: § Concordant: Monozygotic Twins	At Follow-up: § Concordant: Dizygotic Twins	At Follow-up: χ^2 (1 *df*)
15	61 (8.7)	31 (8.7)	66.05	68 (39.6)	49 (39.1)	113.41
20	57 (4.9)	27 (5.1)	37.78	60 (26.2)	40 (26.9)	80.74
25	46 (2.5)	24 (2.8)	11.68	54 (15.0)	26 (15.2)	103.83
30	51 (1.4)	19 (1.5)	13.30	47 (8.3)	16 (8.3)	76.15
35	44 (0.8)	12 (0.8)	8.18	43 (4.7)	9 (4.3)	55.58
40	44 (0.5)	0 (0.3)	7.66	36 (2.4)	6 (2.2)	24.53

*Each twin whose weight exceeded a given criterion was included as a proband. Percentages in parentheses represent the prevalence of overweight twins at a given criterion level. For 1 *df*, the statistical significance of a χ^2 of 7.88 is <.005.

Changes in energy expenditure, autonomic nervous system function, and neuroendocrine function in subjects maintaining a reduced body weight with or without leptin "replacement" [1, 97, 99] 29

	Effects of 10% Reduced Weight Maintenance	**Effects of Leptin Administration to Weight-Reduced Subjects**
Energy Expenditure		
Twenty-four-hour energy expenditure	Decreased (−15%)	Reversed
Resting energy expenditure	Decreased or unchanged	No significant change
Thermic effect of feeding	Unchanged	Unchanged
Non-resting energy expenditure	Decreased (−30%)	Reversed
Skeletal muscle work efficiency	Increased (20%)	Reversed
Autonomic Function		
Sympathetic Nervous System tone	Decreased (−40%)	Reversed
Parasympathetic Nervous System tone	Increased (80%)	Unchanged
Neuroendocrine Function		
Thyroid stimulating hormone	Decreased (−18%)	Unchanged
Triiodothyronine	Decreased (−7%)	Reversed
Thyroxine	Decreased (−9%)	Reversed
Gonadotropins	Decreased	Reversed
Circulating Leptin	Decreased (proportional to fat mass)	Reversed

"Maintenance of a body weight at a level 10 percent or more below the initial weight was associated with a mean (+/- SD) reduction in total energy expenditure of fat-free mass of […] 8 +/- 5 kcal per kilogram per day in the obese subjects (P < 0.001)." [30]

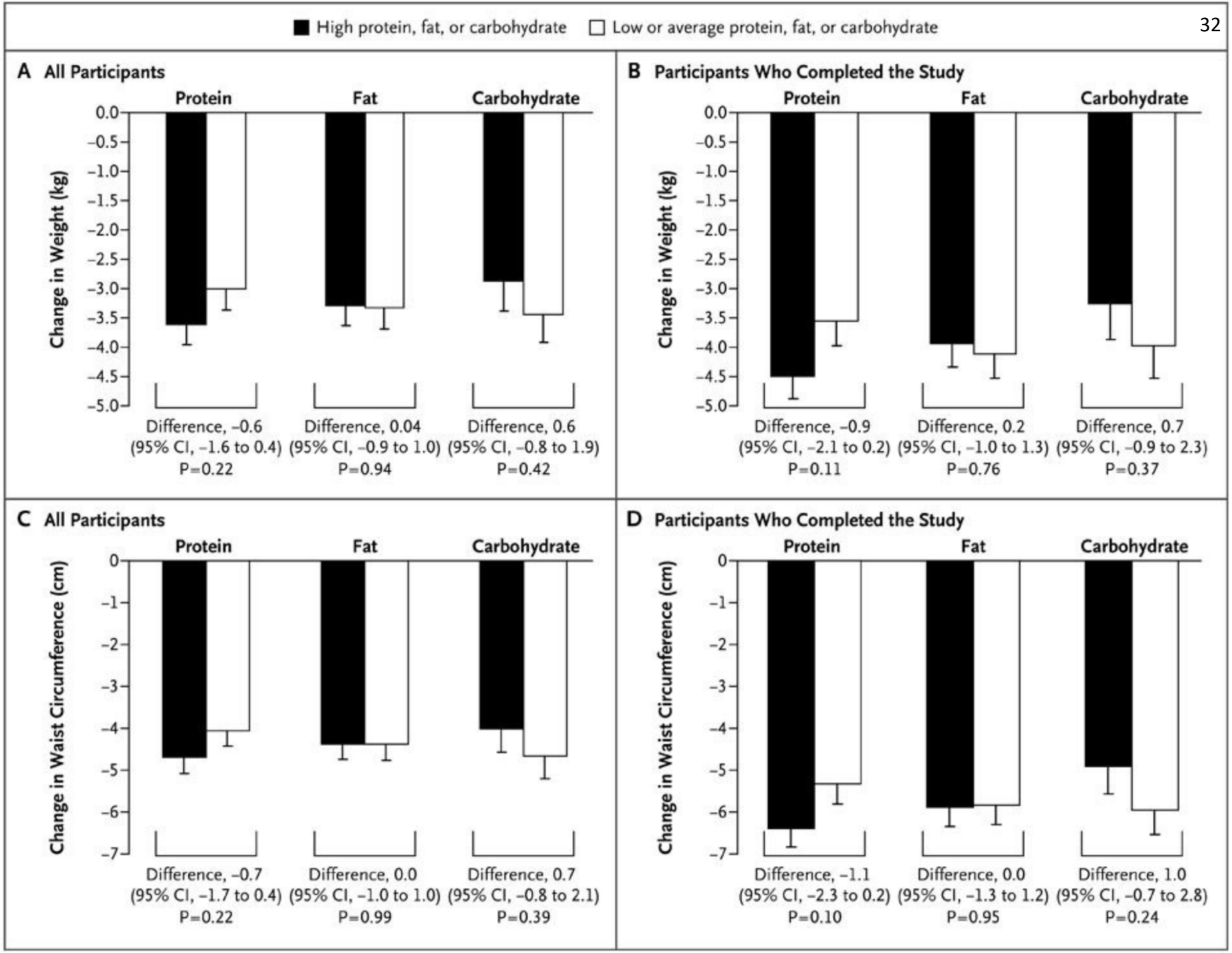
Pitfall 7: Favoring One Diet Over Another

Diet *v* usual diet	Weight loss (kilograms)	Systolic blood pressure reduction (mm Hg)	Diastolic blood pressure reduction (mm Hg)	Low density lipoprotein reduction (mg/dL)	High density lipoprotein reduction (mg/dL)	C-reactive protein reduction (mg/dL)
Atkins	5.46	5.14	3.30	-2.75	3.41	0.64
Zone	4.07	3.46	2.33	-2.89	-0.33	0.27
DASH	3.63	4.68	2.84	3.93	-1.90	NA
Mediterranean	2.87	2.94	1.03	4.59	-0.61	0.25
Paleolithic	5.31	14.56	3.85	7.27	-2.52	0.52
Low fat	4.87	3.95	2.22	1.92	-2.13	0.33
Jenny Craig	7.77	7.86	7.81	0.21	-2.85	0.19
Volumetrics	5.95	2.93	1.95	7.13	-0.13	NA
Weight Watchers	3.90	2.80	1.03	7.13	-0.88	0.87
Rosemary Conley	3.76	2.39	1.44	7.15	-2.04	NA
Ornish	3.64	0.69	0.20	4.71	-4.87	1.11
Portfolio	3.64	5.97	3.98	21.29	-3.26	-0.37
Biggest Loser	2.88	3.17	2.20	3.90	-0.01	NA
Slimming World	2.15	NA	NA	NA	NA	NA
South Beach	9.86	NA	NA	-0.64	0.36	NA
Dietary advice	0.31	0.58	0.40	-2.01	-1.71	-1.15

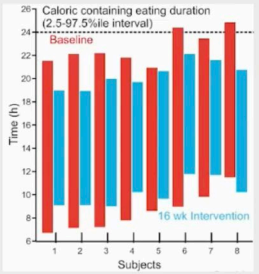
"Among the most effective" with moderate to high certainty
"Inferior to the most effective/superior to the least effective" with moderate to high certainty
"Among the least effective" with moderate to high certainty
"Maybe among the most effective" with very low to low certainty
"Inferior to the most effective/superior to the least effective" with very low to low certainty
"Maybe among the least effective" with very low to low certainty
"Maybe worse than usual diet"

ig 6 | Summary of results of popular named diets network meta-analysis for all outcomes at six months. The number s the point estimates of effect in comparison with usual diet

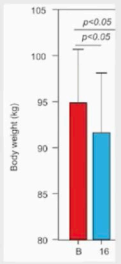
"Differences between diets are, however, generally trivial to small, implying that people can choose the diet they prefer from among many of the available diets (fig 6) without concern about the magnitude of benefits." [31]


High protein, fat, or carbohydrate
Low or average protein, fat, or carbohydrate
A All Participants
Protein
Fat
Carbohydrate
Change in Weight (kg)
0.0
−0.5
−1.0
−1.5
−2.0
−2.5
−3.0
−3.5
−4.0
−4.5
−5.0
Difference, −0.6 (95% CI, −1.6 to 0.4) P=0.22
Difference, 0.04 (95% CI, −0.9 to 1.0) P=0.94
Difference, 0.6 (95% CI, −0.8 to 1.9) P=0.42
B Participants Who Completed the Study
Protein
Fat
Carbohydrate
Change in Weight (kg)
0.0
−0.5
−1.0
−1.5
−2.0
−2.5
−3.0
−3.5
−4.0
−4.5
−5.0
Difference, −0.9 (95% CI, −2.1 to 0.2) P=0.11
Difference, 0.2 (95% CI, −1.0 to 1.3) P=0.76
Difference, 0.7 (95% CI, −0.9 to 2.3) P=0.37
C All Participants
Protein
Fat
Carbohydrate
Change in Waist Circumference (cm)
0
−1
−2
−3
−4
−5
−6
−7
Difference, −0.7 (95% CI, −1.7 to 0.4) P=0.22
Difference, 0.0 (95% CI, −1.0 to 1.0) P=0.99
Difference, 0.7 (95% CI, −0.8 to 2.1) P=0.39
D Participants Who Completed the Study
Protein
Fat
Carbohydrate
Change in Waist Circumference (cm)
0
−1
−2
−3
−4
−5
−6
−7
Difference, −1.1 (95% CI, −2.3 to 0.2) P=0.10
Difference, 0.0 (95% CI, −1.3 to 1.2) P=0.95
Difference, 1.0 (95% CI, −0.7 to 2.8) P=0.24

First TRF weight loss study
10 h window, overweight, 16 weeks



Eating Duration ↓ 4 h



BW -3 kg
Kcal -20%

Gill & Panda, 2015, Cell Metabolism

Unintentional calorie restriction – 8h TRF

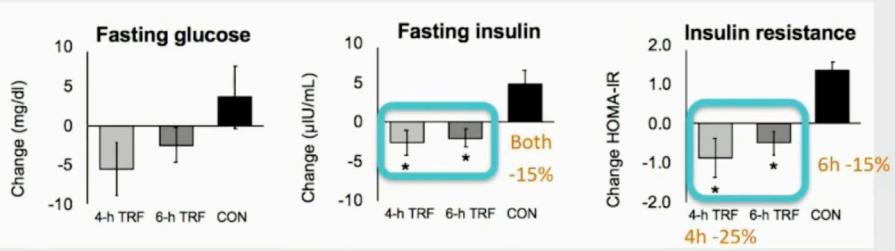
8h reduced energy intake by ~350 kcal/d

	Time restricted feeding (n = 23)		Control (n = 23)		P-value Time × group
	Baseline	Week 12	Baseline	Week 12	
Energy (kcal)	1676 ± 114	1335 ± 162	1645 ± 113	1654 ± 191	0.04
Protein (%)	16 ± 1	17 ± 1	17 ± 1	17 ± 1	0.40
Carbohydrates (%)	47 ± 2	46 ± 2	46 ± 2	45 ± 2	0.61
Fat (%)	37 ± 1	37 ± 2	37 ± 1	38 ± 2	0.74
Cholesterol (mg)	279 ± 24	214 ± 27	275 ± 27	265 ± 37	0.32
Fiber (g)	16 ± 2	13 ± 1	14 ± 1	15 ± 2	0.17

All values reported as mean ± SEM. Data were included for 46 participants; means were estimated using an intention-to-treat analysis using last observation carried forward.

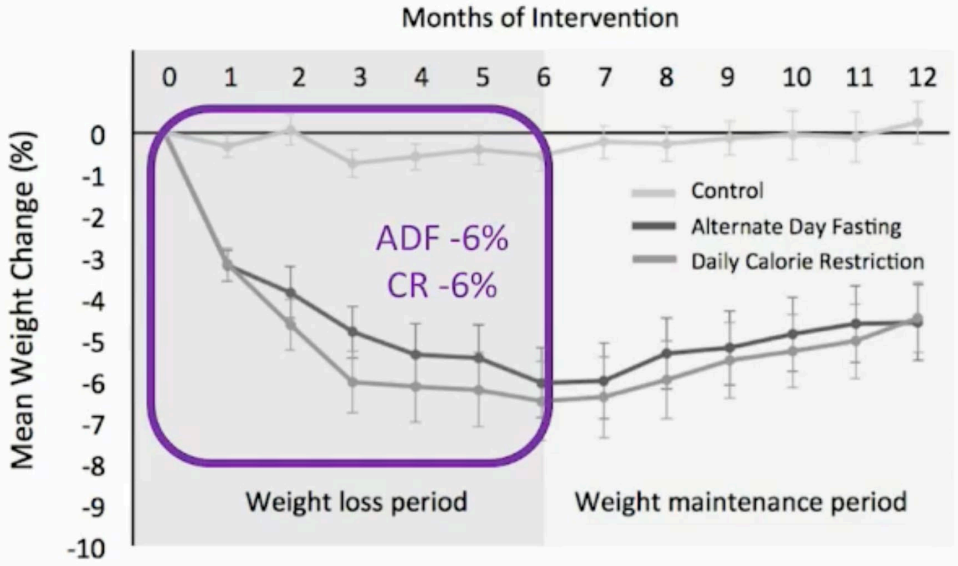
Gabel et al. 2018. Nutr Healthy Aging

4h and 6h produced similar reductions in insulin and insulin resistance



All values reported as mean ± SEM. Fasting glucose was not affected by either 4-h or 6-h TRF. Fasting insulin and insulin resistance decreased similarly by 4-h TRF and 6-h TRF. *P < 0.05 relative to controls.

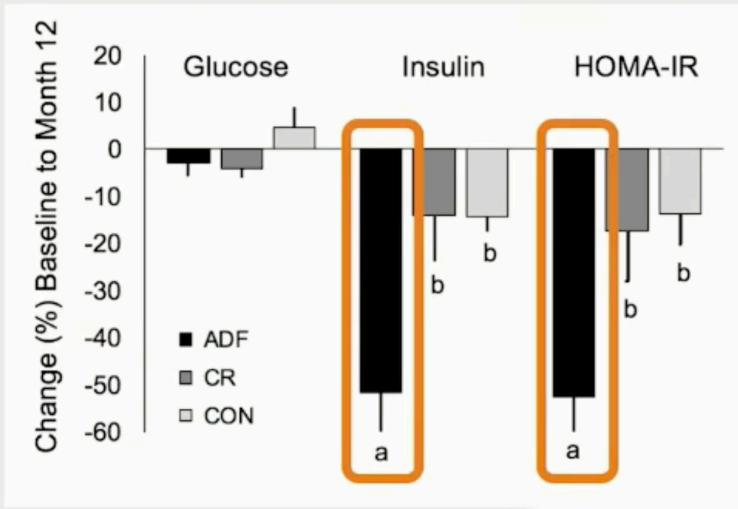
Cienfuegos S et al. 2020. Under Review



Data were included for 100 participants; means were estimated using an intention-to-treat analysis using a linear mixed model.

Trepanowski JF, 2017. JAMA IM.

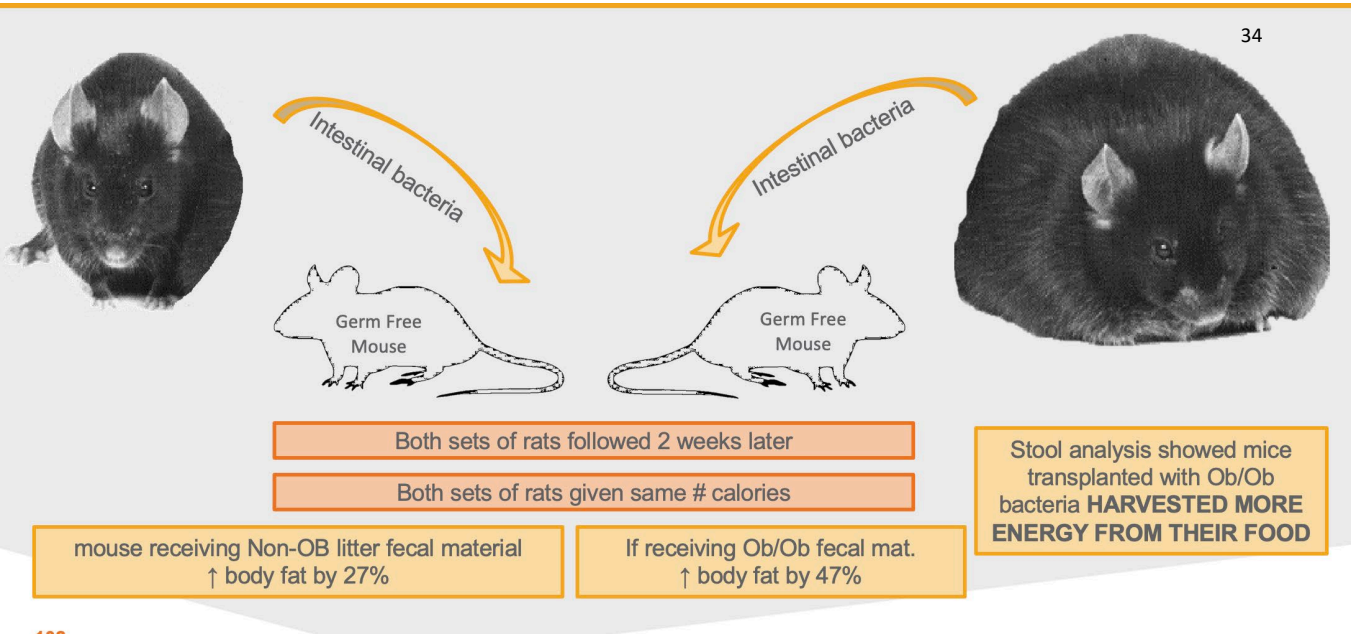
ADF produced greater reductions in insulin resistance versus CR in subjects with insulin resistance

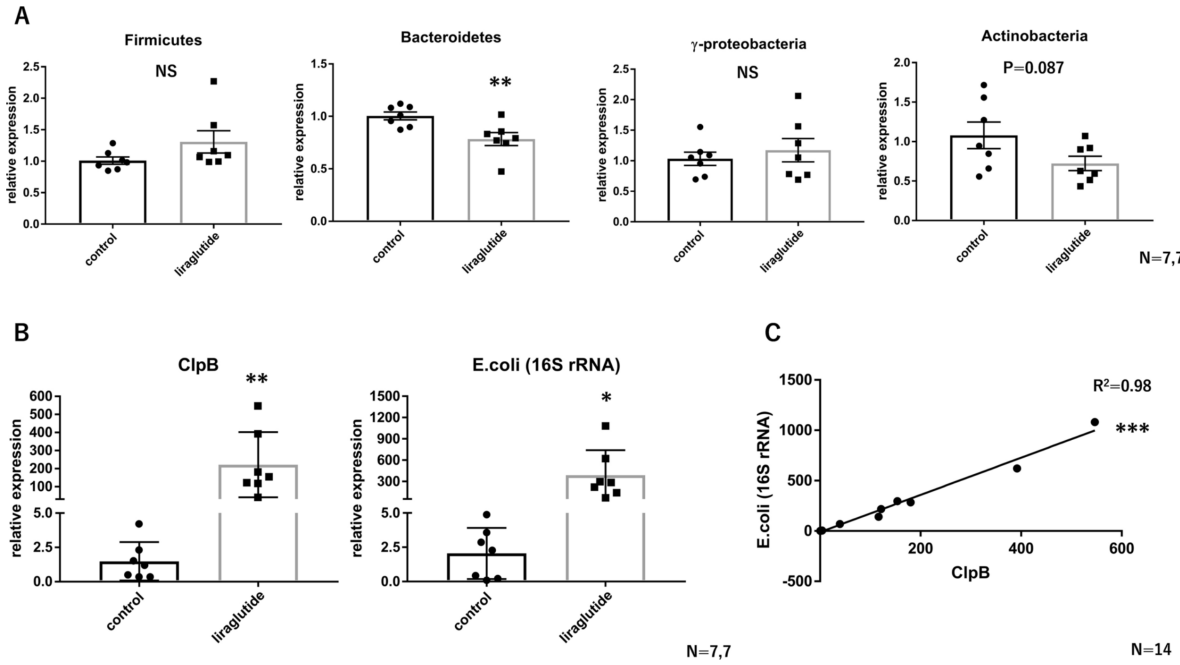


Gabel K, 2019. Obesity.

IF (TRF or ADF) vs RCT [33]

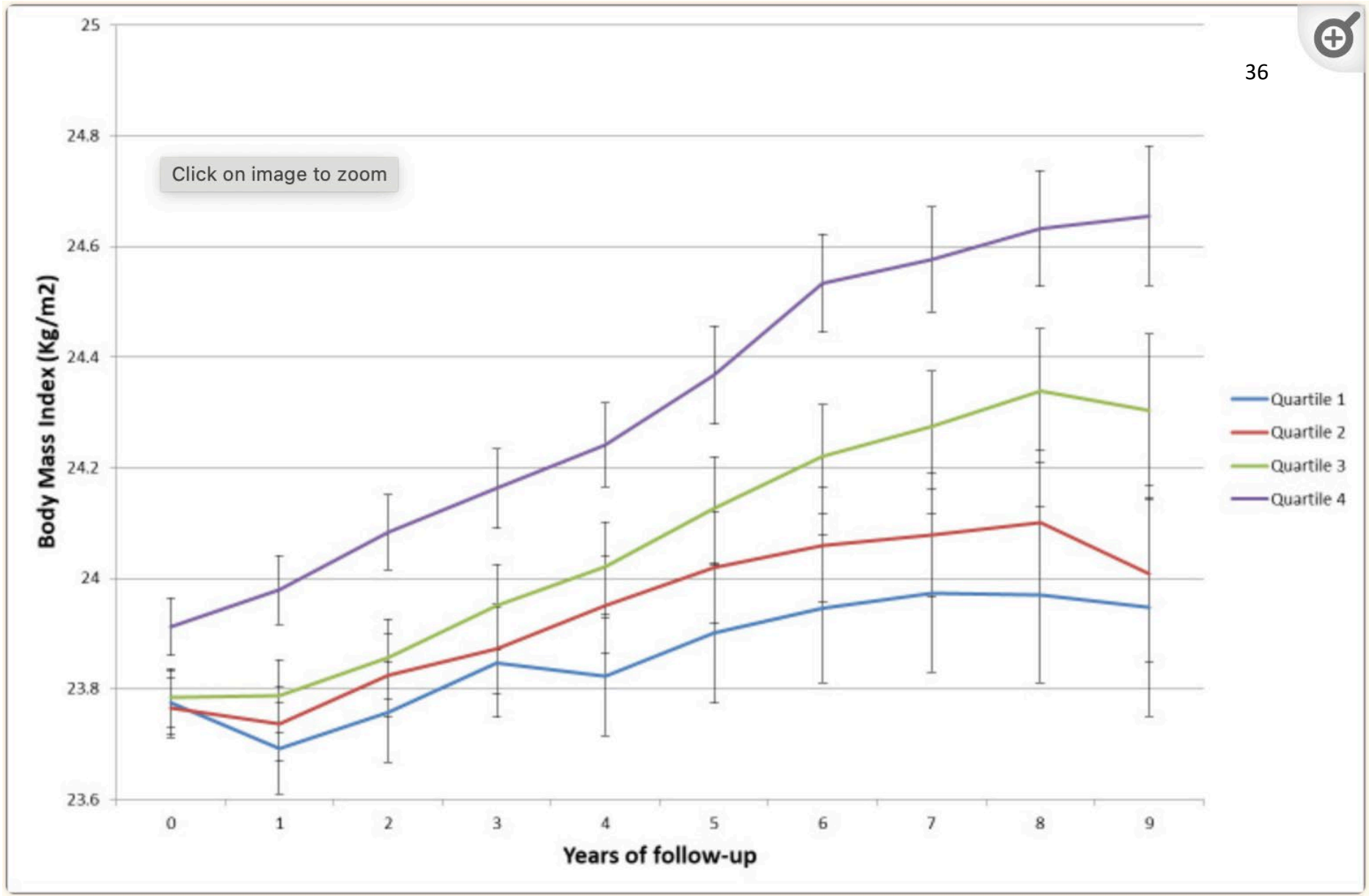
- 14 hours is average eating window (14F:10E); by changing to 10F:14E able to reduce 3kg and decrease calorie intake by 20%.
- Another studied showed that buy going to 16:8 they were able to reduce calorie intake by 350 kcal a day





"liraglutide administration significantly decreased Bacteroidetes and tended to increase Actinobacteria (Fig. 1A). However, Firmicutes and Proteobacteria were not changed (Fig. 1A). At the genus level, liraglutide administration significantly reduced Ruminococcus and did not increase Akkermansia (Supplementary Fig. 1A)." [35]

ULTRA-PROCESSED FOOD



“Forty-one trials were included in the review: 31 isocaloric trials […] and 10 hypercaloric trials.” Furthermore, “Twelve isocaloric trials and four hypercaloric trials were judged as high quality.”

“There was no overall significant effect on body weight between the fructose and non-fructose carbohydrate groups in isocaloric trials.”

“High dosages of fructose in hypercaloric trials (104 to 250g/day, 18% to 97% of total daily energy intake) were associated with a significant increase in body weight (WMD 0.53 kg, 95% CI 0.26 to 0.79; 10 trials).” [37]

So Basically…

IT’S COMPLICATED!!!

Pitfall 8: Recommending “Compounded” Medication Without Evidence to Support It

Compounded NuSHs

- FDA issued warnings and a letter advising against salt formulations (acetate or sodium) instead of free-base form
- Compounded drugs use “FDA-approved” bulk products from an FDA-inspected/approved facility (i.e. not from another country selling bulk alternative form product saying for research purposes only).
- Compounded pharmacies test for LPS, sterility, potency, and use sterile equipment
- If adverse event, the prescribers are liable, and the AE cannot be reported to the FDA

There are currently no FDA-approved products containing a semaglutide salt (e.g., semaglutide acetate or semaglutide sodium) as an active ingredient. Although FDA has carefully evaluated the chemical and pharmacologic properties of semaglutide in the context of the approved drug products, FDA is not aware of information regarding the chemical and pharmacologic properties of the semaglutide salts (e.g., semaglutide sodium or semaglutide acetate) or whether the semaglutide salts have the same safety or efficacy profile as semaglutide.

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Silver Spring, MD 20993
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U.S. FOOD & DRUG ADMINISTRATION

Compounded Drug Products Containing Semaglutide Salts

FDA is not aware of any basis in the FD&C Act for compounding a drug using semaglutide salts such as semaglutide sodium and semaglutide acetate.

Sections 503A and 503B of the FD&C Act describe the conditions that must be satisfied for compounded human drug products to be exempt from certain sections of the FD&C Act, including the requirements of premarket approval and labeling with adequate directions for use. Among the conditions of sections 503A and 503B are restrictions on the bulk drug substances (active pharmaceutical ingredients or APIs) that may be used to compound human drug products.

Specifically, under section 503A (which applies to drugs products compounded outside an outsourcing facility registered by FDA, e.g., by licensed pharmacists in a State licensed pharmacy or a Federal facility, or by licensed physicians), the drug product must be compounded using bulk drug substances that (1) comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are components of drugs approved by FDA; or (3) if such a monograph does not exist and the bulk drug substances are not components of a drug approved by FDA, appear on a list developed by FDA through regulations (the 503A Bulks List). Semaglutide salts are not the subject of an applicable USP or NF monograph, are not components of an FDA-approved drug product, and do not appear on the 503A Bulks List.

For compounded drug products to qualify for the exemptions under section 503B, they must be compounded in an outsourcing facility that does not compound drugs using bulk drug substances unless the bulk drug substance (1) appears on a list established by FDA identifying bulk drug substances for which there is a clinical need (the 503B Bulks List), or (2) the drug compounded from such bulk drug substances appears on FDA’s drug shortage list at the time of compounding, distribution and dispensing. Semaglutide salts do not appear on the 503B Bulks List, nor do products containing semaglutide salts appear on FDA’s drug shortage list.

Compounded Drug Products Containing Semaglutide

Semaglutide is a component of an FDA-approved drug product and appears on FDA’s drug shortage list. Therefore, compounded drug products containing this API are potentially eligible for the exemptions under sections 503A or 503B of the FD&C Act, provided they meet all of the conditions in those sections. These sections describe the conditions that must be satisfied for compounded human drug products to be exempt from certain sections of the FD&C Act, including the requirements of premarket approval and labeling with adequate directions for use.

While compounded drug products containing semaglutide may be lawfully marketed under federal law, please be advised that FDA does not evaluate the safety, effectiveness, or quality of compounded drug products before such drugs are marketed. As stated, FDA has received an increased number of adverse event reports and complaints concerning these compounded drug

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Conclusions

the interest of “primum non nocere” (i.e., first do no harm), the Obesity Medicine ssociation recommends:

Anti-obesity medications and their formulations should undergo clinical trial testing for efficacy and safety as overseen by the FDA

The components of compounded peptides should be legally produced by source companies whose identities are readily disclosed, and who have documented manufacturing processes compliant with oversight by applicable regulatory agencies (i.e., the FDA for example, if the source component is a prescription drug) (https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process#:~:text=Drugs%20are%20tested%20on%20people,they%20are%20safe%20and%20effective.&text%20=%20FDA%20review%20teams%20thoroughly%20examine,or%20not%20to%20approve%20it.&text%20=%20FDA%20monitors%20all%20drug%20and,for%20use%20by%20the%20public↗

Prescribers and patients should avoid use of compounded polypeptides from undisclosed sources

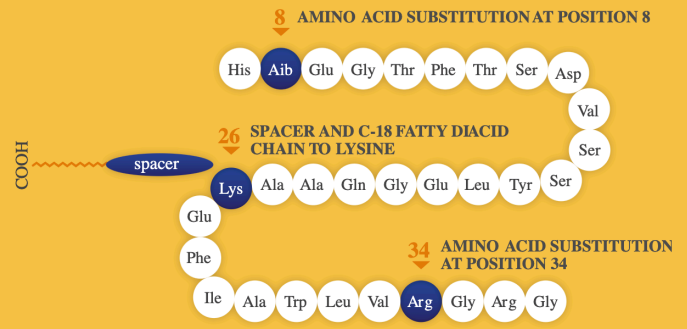
Prescribers should be cautious of compounded peptides where the safety, efficacy, quality, and purity of the source molecule, and their combination with other molecules, cannot be assured. At minimum, patients should be informed of potential limitation of compounded peptides.

OMA Position Statement:
https://www.sciencedirect.com/science/article/pii/S2667368123000074#sec6

Compounded Oral Semaglutide?

- Moisture exposure
- SNAC tech
- pH, gastric absorption
- Sublingual never studied
- Placebo is powerful
- Financial risks
- If negative news comes out later, the sinking ship will destroy faith in other excellent options.
- Weight loss does not ALWAYS equal improved HEALTH

Structural modifications of the RYBELSUS® molecule prevent degradation by DPP-4 and prolong incretin activity.



DPP-4=dipeptidyl peptidase-4.

Innovative coformulation with an absorption enhancer[a] enables once-daily oral administration

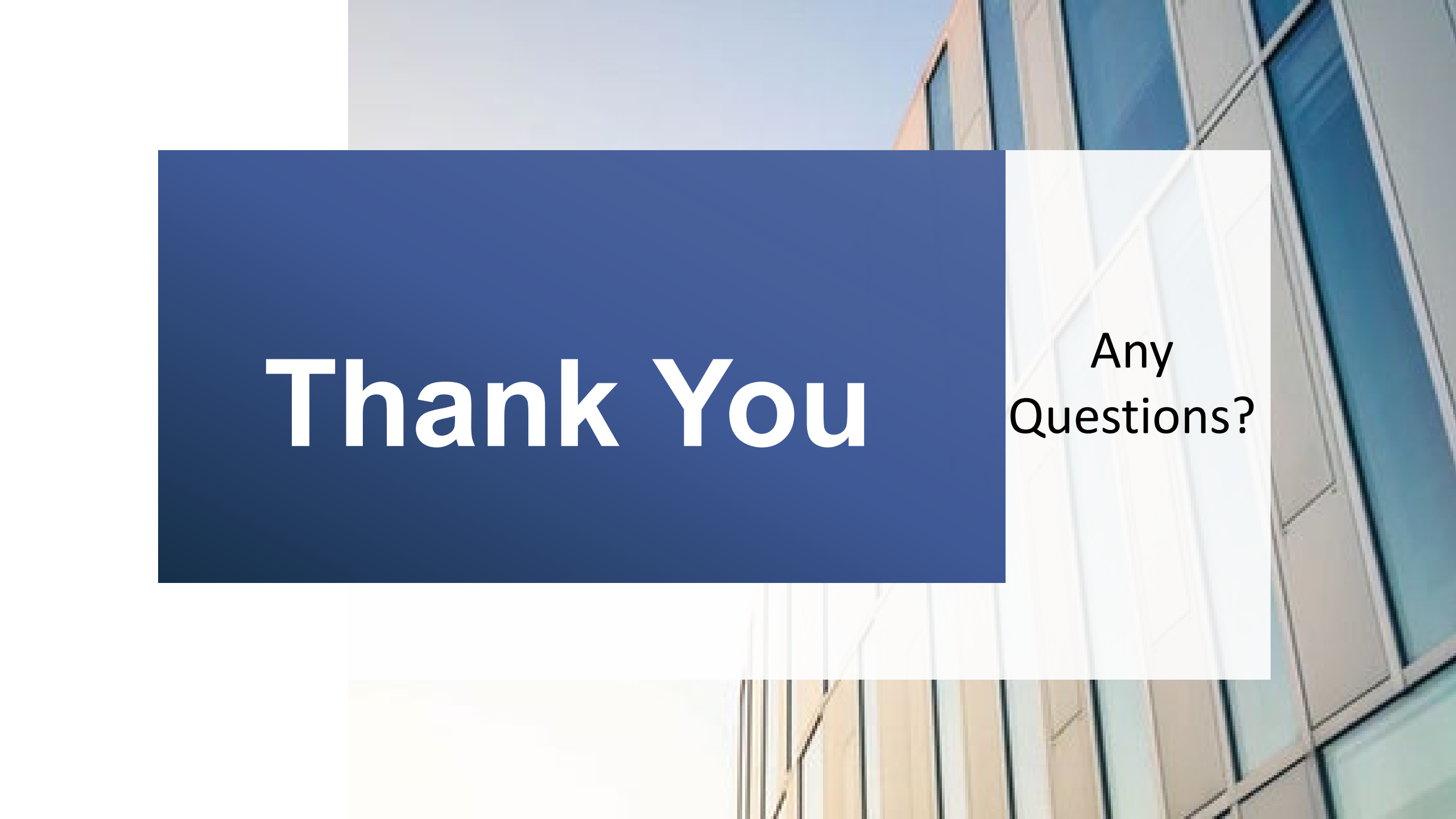
[a]SNAC: Sodium-N-[8-(2-hydroxybenzoyl) amino] caprylate: a small fatty-acid derivative.

4 to 5 weeks

- Steady-state exposure is achieved following 4 to 5 weeks of administration
- Following oral administration, maximum concentration of RYBELSUS® is reached after 1 hour

SUMMARY

- This is life-long and it's a disease. Diet, exercise, and behaviour will improve total weight loss and longevity but may not guarantee sustaining the weight loss.
- Just like how exercise, diet, stress, sleep, etc. affect blood pressure, so too can these things affect our weight.
- Bone on bone arthritis doesn't self-correct, why would obesity be different?
- Your family and friends aren't trying to stop their loved ones from stopping their blood pressure medications. There is bias and stigma and shame when it comes to weight.
- If BP, BS, or lipids were controlled, does your doctor stop you when you're finally normal?
- Not all blood pressure, cholesterol, and diabetes medications are the same for every patient, so your approach for anti-obesity medication will need to be tailored as well.



Thank You

Any Questions?

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