Obesity 2020:
Wresting Control From Your Hypothalamus

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Standard Teaching

- To lose weight, one should:
  1. Eat Less
  2. Exercise More
- BMR can be increased by exercise; and thin people often have high BMRs.
- You cannot be addicted to something you physiologically need (food).
- No withdrawal = no addiction.
- The overweight enjoy eating.
- Very-low-carb (ketotic) diets change metabolism (i.e., calories don't count, and fat is OK if you are in ketosis).
- Overweight often has a physiological basis.
- After weight loss, you can return to a "reasonable, healthy diet."
- Gastric by-pass makes your stomach smaller, thereby reducing appetite; the operation also reduces caloric absorption.

Overview

- Neurophysiology: What makes us start – and stop – eating?
- Early Visits: Addictions, Education, Tips & Tricks
- Later Visits: Diets, Social Situation, Revisit Additions, Exercise
- Medications to Avoid/Modify
- Medications that Help (Pharmacotherapy reserved for plateaus)
- Overcoming Resistance / Bargaining
- Keeping the Weight Off: Rebound, Hard Truths, The Long Road

We Eat For One Reason Only: *Because Our Brain Tells Us To*

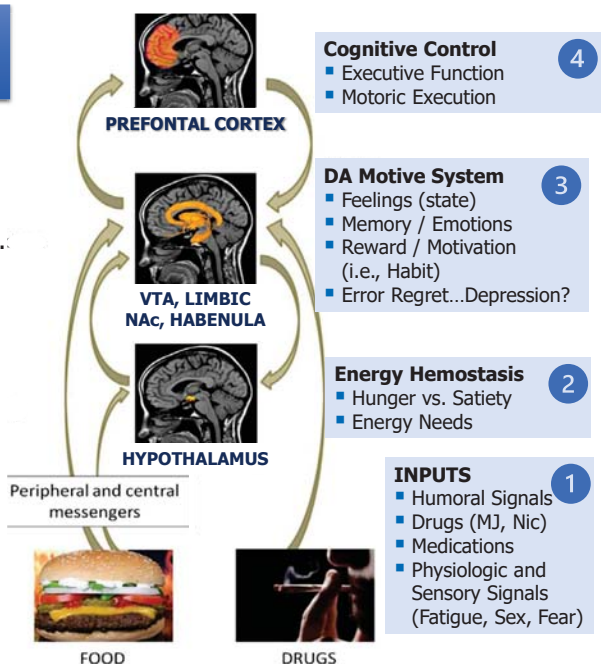
Habit = Trigger → Response → Reward

Everything about eating resembles other programmed behaviors (habits), such as addictions. It all starts with **Inputs** (Trigger).

We *don't* eat because we are "hungry," tired, intoxicated, happy, sad, see something delicious, etc. We eat for **Energy Homeostasis** (Response).

We *do it again* when a complex confluence of forces combine to make our hand reach out and put something in our mouth. The **DA Motive System** and **Cognitive Control** tee-up and execute feeding (Reward).

Thus, the job of treating obesity is to *vary the inputs, responses, and rewards.*



Hypothalamus I: ARC, PVN, LHN The Major Control Centers

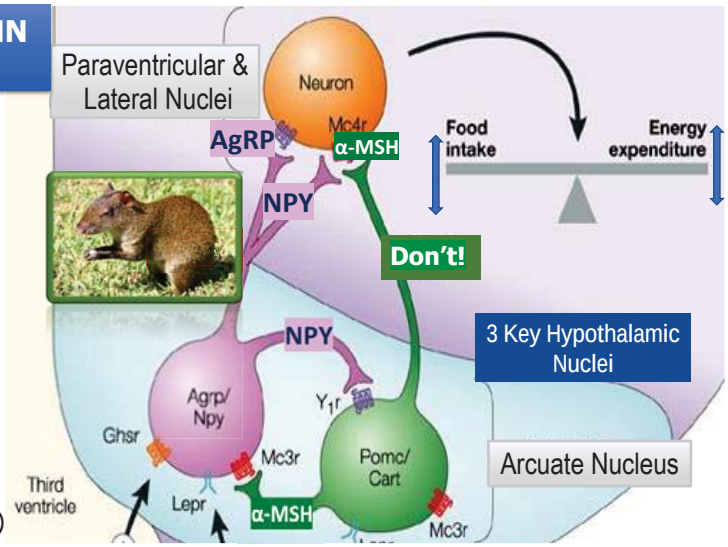
Agouti-Related Protein* / NeuroPeptide Y neurons stimulate PVN and LHN:↓energy expenditure / ↑eating

Proopiomelanocortin /Cocaine and Amphetamine-Related Transcriptase neurons produce α-Melanocyte Stimulating Hormone, which does the opposite.

Mutual inhibition via NPY and α-MSH.

PVN releases TRH and Oxytocin (and many other metabolic hormones) regulating metabolism, eating; **LH helps regulate orexin** (food seeking, lipolysis)

The job of treating obesity is to ↑stimulation of AgRP/NPY side and ↓stimulation of POMC/CART side.



Hypothalamus II: Key Hormones Ghrelin, Leptin, Insulin, Orexin

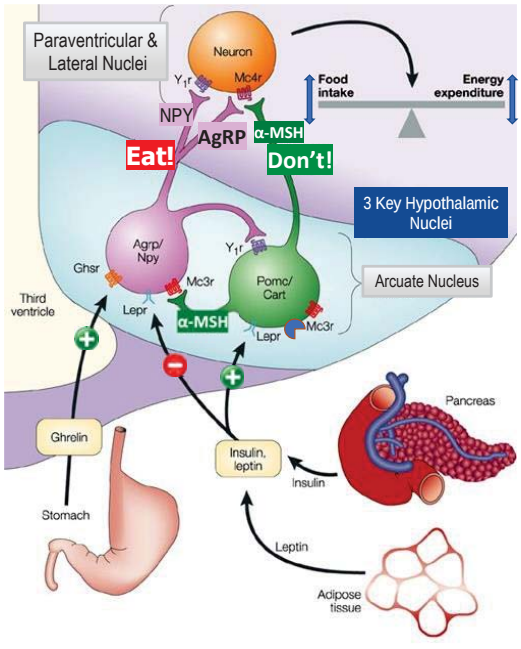
Ghrelin – Short acting – stimulates appetite (and other anabolic functions). Sleeve gastrectomy may work because it removes Ghrelin-producing cells.

Leptin – Long acting – slows eating and signals the body about total fat stores. Resetting the Leptin "adipose-tissue meter" can only be done slowly. *Leptin resistance* in the obese disqualifies it as a treatment.

Insulin – Short acting – decreases appetite but *insulin resistance / metabolic syndrome* similarly limits its therapeutic value.

Orexin – Made in LHN – probably is a progestin antagonist but may only work through arousal.

[Many other hormones, including adipokines (esp. adiponectin), amylin, glucagon, GIP, resistin, and glucose itself, impact peripheral metabolism *and* feeding behaviors throughout CNS.



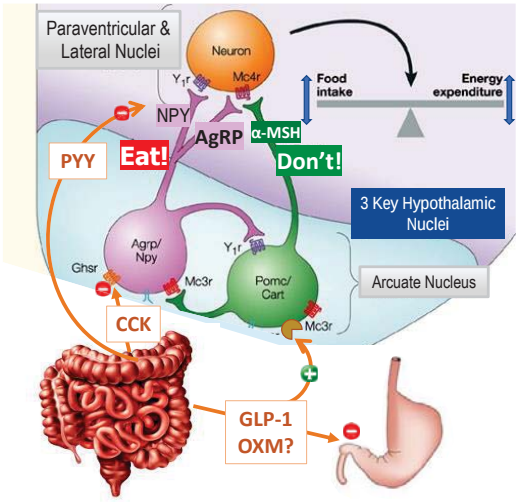
Hypothalamus III: Small intestine Hormones

Cholecystokinin (CCK) – also made in CNS – induces satiety probably by Ghrelin blockade. (Implicated in anxiety.)

Peptide YY (PPY) binds to and so inactivates NPY and AgRP.

Glucagon-like Peptide (GLP-1) – very short acting. It slows gastric emptying and is an agonist of POMC/CART neurons. Longer-acting analogues are the basis for new drugs. (It is also made in the CNS where it has wide functionality in suppressing eating.)

Oxyntomodulin (OXM), a cleavage product of preproglucagon, probably has similar functions to those of GLP-1; may also be glucagon receptor antagonist.

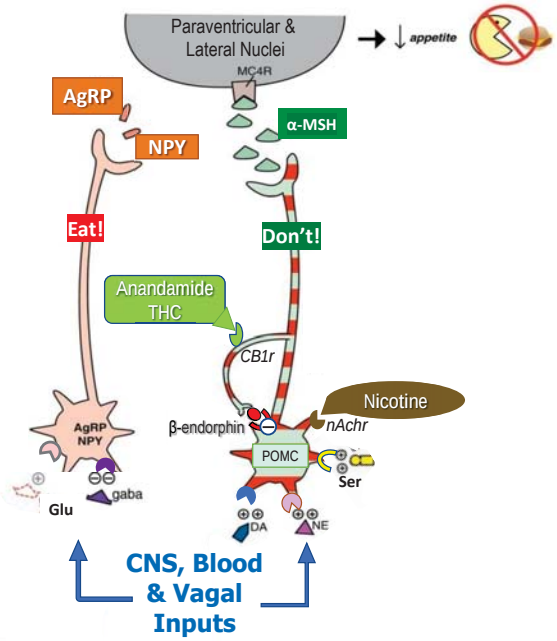


Hypothalamus IV: Neurotransmitters

Several major NTs and drugs act in Arcuate Nucleus via bloodstream and ascending Vagal and descending CNS inputs

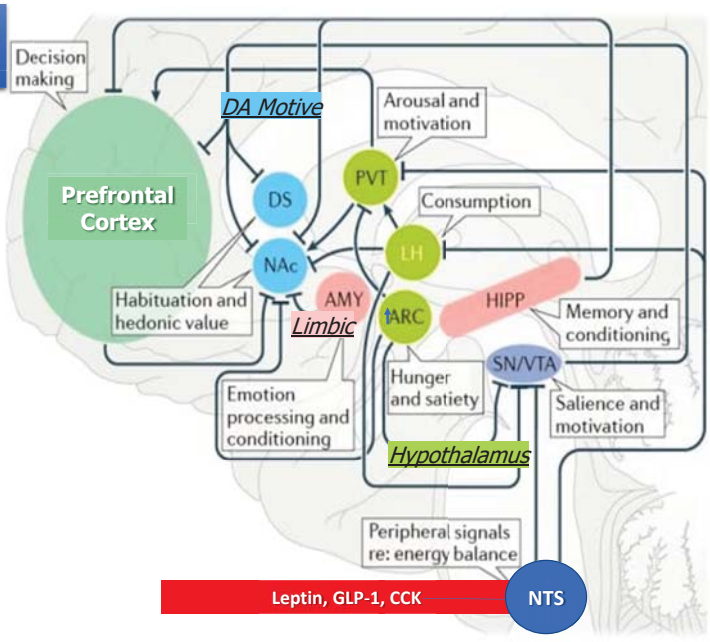
- **DA, NE, Ser, nAch (Nic)** act on POMC/CART to lower appetite
- **β-endorphin** is an agonist of the negative feedback loop in POMC, *increasing* appetite. Rimonabant (CB1r antagonist) failed b/c SE profile.)
- **GABA and Glu** both act on AgRP/NPY system to increase appetite

The actions of many medications that cause obesogenic SEs and that are used to treat obesity are mediated by NTs. (Discussed later.)



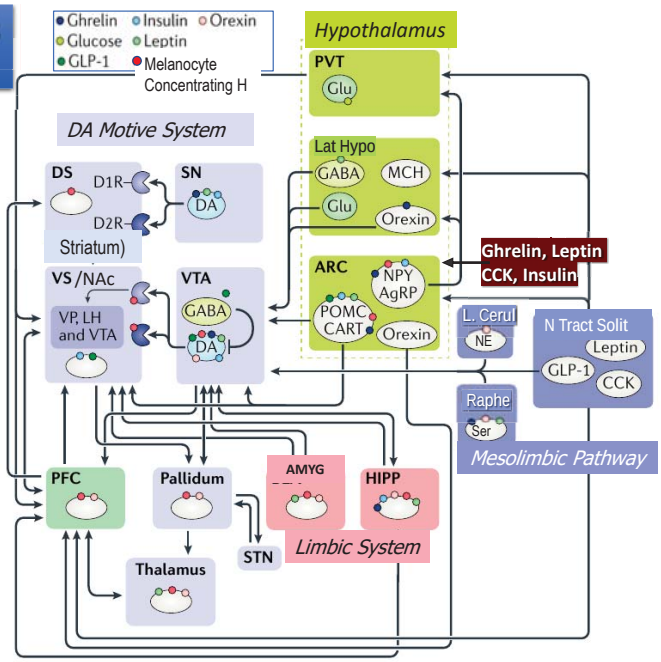
Dopamine Motive System: The Center of the Action

- DA Motive receives inputs from hypothalamus and periphery (GI, fat)
- Limbic system attaches short/ long-term meaning (emotion)
- Mutual control with prefrontal cortex
- [Hypothalamus and Nucleus Tractus Solitarius are also impacted by blood-born cannabinoids, endorphins, serotonin, NE, GABA, Glu, orexin, hormones]



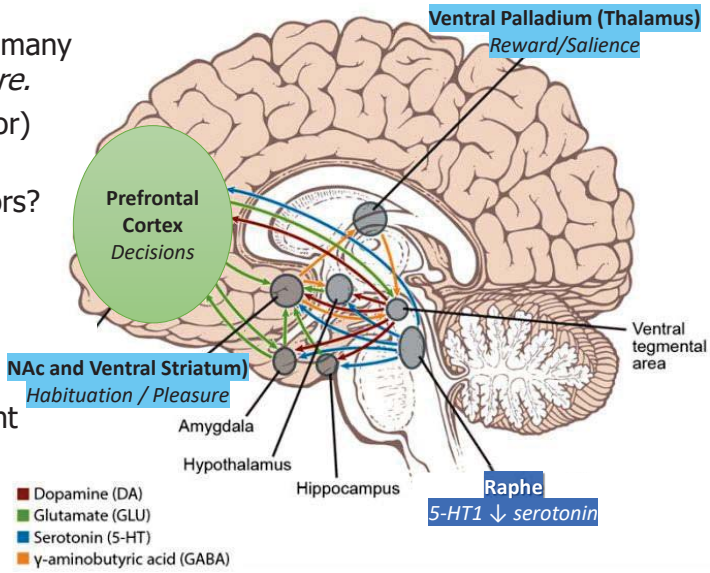
Hormones & Neurotransmitters Act *Everywhere*

- Hormones impact all major control centers.
- Wide diversity of neurotransmitters control:
  - Eating: quantity, amount, choice, "now/later" "Errors Regret" (STN)
  - Energy balance: ATP & Heat *vs.* Glycogen & Fat storage)
- There is no single drug/technique/surgery that can easily override all of this.

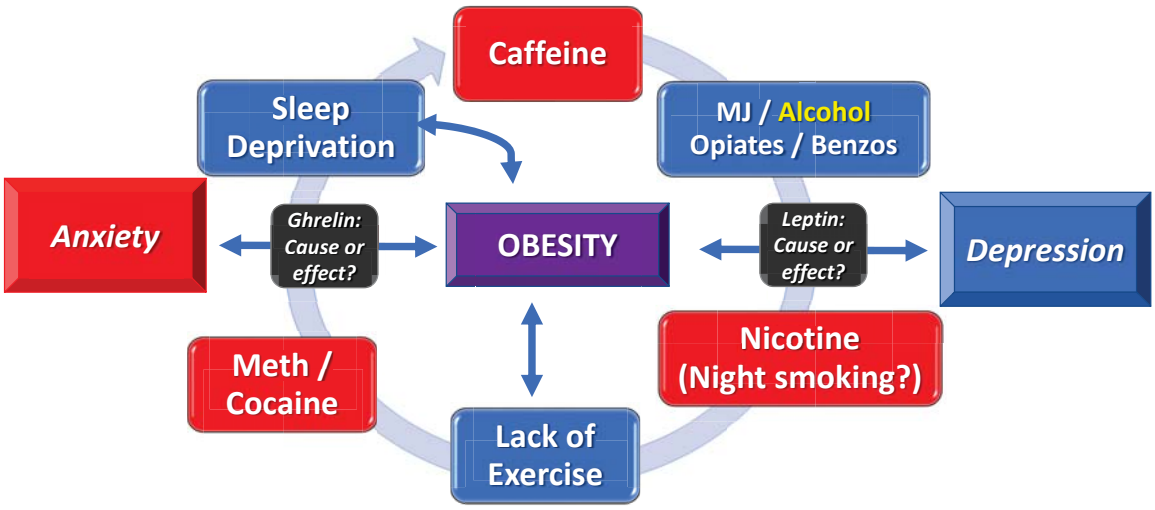


Why Does Regulation Fail?

- Many overlapping systems means many points of balance, but also of *failure.*
- Control over any single (even major) NT will have constrained impact.
- Endogenous deficiency D2 receptors?
- Leptin resistance.
- Insulin resistance.
- PFC override: Anxiety/Depression.
- Drugs (licit and illicit).
- Cheap and plentiful food – constant stimulation and opportunity.
- But: *these are our only entry points for treatment.*

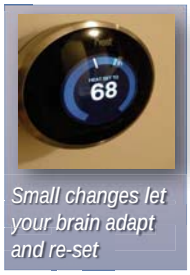


The First Visit: Assess for *the Cycle of Addictions*

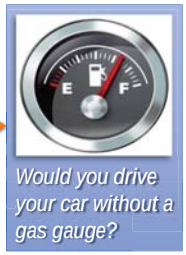


Early Visits: The Conversation (Education)

- We eat because our brain tells us to *and for no other reason*.
- Obesity is a neuropsychiatric disease, and not a moral failing.
- "Will power"? *No*. Give you control over your choices? *Yes*.
- Slow change is best because it is more robust (and easier!). Thus, we will aim for 3-4/*month.* (Sigh of relief.)
- Changing habits, social environment, medications help the most.
- Our pancreas is stupid → Built for 50,000 BC (no Little Debbie) → It always overreacts to **all** carbs → So carbs make you hungry.
- Anyone can lose weight: keeping it off is the challenge.
- **Written** daily weighing is key first step. Then sleep (↓TV), moderate exercise. (100% of my successful patients do this.)
- The amphetamine phentermine (Adipex®) is what many patients want; it is not a robust treatment. Urine screen!



Small changes let your brain adapt and re-set



Would you drive your car without a gas gauge?

Early Visits: Tips and Tricks

- 2 cups liquid 30 min before each meal: stomach stretches, GLP-1, ↓ appetite (probably why most meals last ~25 min).
- Bouillon and homemade soup.
- Leave one bite on your plate (tells you brain you are OK). (Thin people always do this.)
- Smaller plates, esp smaller bowls.
- Give up 1 food [snails (adverse conditioning)]
- Are you hungry… or thirsty?
- ✗ Sugared soda (Gatorade, Mountain Dew)
- ✗ Commercial salad dressing (2300 calories in 8 oz bottle)!
- Dieting is done at the grocery store.
- Separate shelves for children (or put foods elsewhere).

Later Visits: There is No Magic (Myth of Ketosis)

Diet	Mechanism	Pros	Cons
Very Low Carb (a.k.a. Keto)	Ketosis (7%) ↓Appetite (93%) → ↓ Calories	Rapid weight loss ↑Energy	Almost no one can stick to it for very long
Low/V Low Cal	↓ Calories	Rapid weight loss	Hunger, rebound → yo-yo → muscle loss
Mediterranean	↑ Satiety→ ↓ Calories	Easy to stick to ✓ CV benefits	Easy to cheat, esp. on fats portion creep
Low Fat	↓ Calories	Tolerable ✓ CV benefits	Requires vigilance Appetite can go up fast
Low carb	↓ Hypoglycemia → ↓ Appetite → ↓ Calories	~ Easy to stick to ✓ Metabolic Syndrome	Boring (a good thing: single-chow-fed rats eat less)

Diets 2: Miracle Diets and Cures (if only they worked)

Packaged	They work if you can afford them. Long term solution? For some.
Fasting	Reduced time frame for eating. Ketosis reduces hunger. May be hard to stick to. Muscle wasting. Goal of dieting ≠ weight loss. ***It's fat loss.***
Paleo	High fat diet and everything bad that goes with it. Coconut oil is poison (supersaturated). ***Plants are the best food there is.***
Vegetarian/ Vegan	Good for planet, certainly. Muscle wasting unless you are diligent. Weight loss effects very variable. True amount of protein humans need is uncertain.
Pritkin	Low Fat. Great if you can stick to it. (Fats → Taste, Satiety)
Atkins	Very Low carb. (He used amphetamines.)
Supplements	Vit B, Zinc, HCG, Testosterone, plants: useless, some dangerous

Later Visits: Specific Foods for Lower Carb Diet

Go

- **Soup** (esp. Knorr bouillon)
- **Green Plants**: kale, spinach, lettuce, broccoli, cabbage, cauliflower, Brussel sprouts, celery
- **Berries** (frozen)
- **Non-starchy nightshades:** eggplant, yellow/spaghetti squash, zucchini, peppers, tomato
- **Low fat protein**:meat/fish cottage/yoghurt 0%,egg
- **Liquids**: almond milk, V8, Splenda-sweetened tea

Slow

- **Nuts/Seeds**: almonds (unsalted), walnuts, sunflower, pumpkin (roast!) (crunch relief)
- **Apples** (*small only*)
- **Root Veg**: carrots, turnip, rutabaga,
- **Legumes**: beans, peas, chickpeas, soy beans (sparingly)
- **Mod. fat proteins**: *hard* cheese, tofu, 2-4% dairy

No

- **Dense Carbs** (albeit w/some protein): pasta, rice, corn, sweet potato
- **Slave Foods**: potato, banana
- **Protein-free Foods**: plantain, cassava (=manioc, yuca), yam
- **Sugar Bombs**: soda (pH~3), juice (pH~3.5), watermelon, grapes, pineapple, oranges, yoghurt cups, ice cream (with salt now!)
- **Baked Goods:** Goodbye…
- "**In-hand" fat bombs:** chips, peanuts, hummus, avocado

Later Visits: Social Situations, Don't Deprive: Plan

Restaurants / Work meals / Break room: Battle Plan

- You are *not* on holiday (no Heroin on Xmas)
- Review menu in advance (it's a military campaign)
- "*What can I bring you folks to drink*?"
- No bread, no appetizer! (Do you have them at home?)
- Sharing is *good*; ask for ½ portion or take-home box (immediately)
- Why do restaurants disallow separate checks?
- Dessert: Yes… coffee and cream
- **Fast Food**: Danger! (Fat, salt, sugar, and maybe something else.)

Dining with Friends and Family/Holidays/Parties

- Ask them to support you, not tempt you (children can have stuff later)
- Make the analogy with an allergy: No shame! No "try a little"!
- "Defensive eating" before and after (never arrive hungry)
- Beware sabotage! (Unconscious, of course…)

Later Visits: Alcohol, MJ / CBD oil (most has THC) , Sex *

Alcohol
- Not *that* caloric (~125 / 5oz) nor high in carbs
- The *real* problem is loss of inhibition
- Feeds the cycle of addictions (depression, lethargy, low-quality sleep, ↓ sex)

Marijuana / CBD Oil
- Orexigenic (accentuates ϴfeedback in POMC/CART)
- Loss of inhibition
- Feeds the cycle of addictions (depression, lethargy, ↓sleep, ↓↓sex)

Sex
- It may be *the* reason they are concerned about their weight
- Obesity causes low testosterone (↓ libido, anorgasmia, ED)
- Discussing it is important for gaining rapport
- Can be key motivational tool

** 4-day course at Harvard didn't mention sex or alcohol or MJ once!*

Later Visits: Exercise is Not a Panacea

- Does not contribute to new weight loss (compensatory hunger)
- Does help maintain weight loss (retrospective evidence)
- BUT: Best treatment for anxiety and depression
- How to get them to start?* 5 min maximum; buddy system
- You *must* get your heart rate up (intervals are best)
- You must be breathless (but you can do anything for a minute!)
- Walking, water aerobics, gentle hiking, yoga, tai chi: *don't count*
- Swimming and sitting on bike rest body's largest muscles
- Speed walking with hand / leg weights or vest (great with kids)
- 25 intensive minutes every day (=5x/week) (more time = resting)
- Weight training for *everyone* – try 3 personal trainers
- Get cardio by not resting in-between sets (look at the old guys)
- Bluetooth headphones / TV. No time? *Tell it to Bush / Obama.*

Obesogenic Meds I: Psychiatry

	Offenders	Mechanism (some ?)	Alternatives
SSRIs, Mirtazapine (-His, -Ser, -α-blocker)	Paroxetine/Mirtazapine > Fluoxetine > Sertraline: early weight loss, then *very variable*); [Es-] citalopram: weak.	↓ His, ↓α_2 (esp. Mirtazapine) ↓ mAch (esp. Paroxetine) → sedation / ↓ BMR	SNRI: [Des-] Venlafaxine Atypicals: Bupropion (DAT, NET) Serotonin Modulators: Vortioxetine, Trazo/Nafazo/Vilazodone (~no mAch, His, α-adrenergic effects)
SGAs	1st< 2nd metabolic synd. Worst: Olanzapine/Quetiapine, Risperidone, [Clozapine]	↓ DA_2 [Ari/Brex: dual effect] Cariprazine ↓DA_3, ↓$5HT2_c$ and/or ↓mAch, ↓His, ↓α_2-adrenergic ↑ Appetite (probably) ↓BMR Insulin resistance: separate effect?	Ari/Brexipiprazole (DA modulation? Or less adrenergic?) Consider as adjunct Lurasidone (no His, no mAch) Ziprasidone (no insulin resistance?) Pimavanserin (no DA, His effects) Add: Metformin (some effect)
Anti-convulsants GABA drugs	Valproic acid Carbamazepine? Gabapentin/pregabalin [Levetiracetam/Phen OK]	Hard to understand given that topiramate/zonisamide have opposite effect Insulin resistance?	Zonisamide Lamotrigine Topiramate
Misc	$Li^{+?}$	Activity reduction? Only in previously obese?	Per above

Obesogenic Meds 2: General Practice (often refilled w/o need)

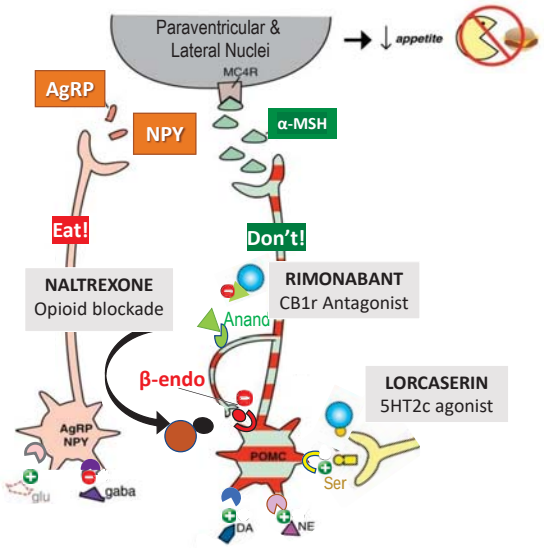
	Offenders	Mechanism	Alternatives
α_1-agonist	[Phenylephrine]	↑ NE	[NA] Drug Screen!
antagonist	Terazosin, Tamsulosin	↓NE ↓BMR	Doxazocin; 5α-reductase inhibitors (↓DHT) Finasteride…BUT ↓androgen
α_2–agonist	Clonidine (HTN, ADHD), Guanfacine (ADHD)	*BS, PFC:* ↓NE ↓BMR	ACE, ARBs, CCBs; Atomoxetine
antagonist	Mirtazapine	↓ His	Fluoxetine
Steroids	Prednisone	Insulin resistance	Ketorolac cream, CBT, yoga?
	Depo-MPA (likely) Low dose BCP? HRT?		UIDs (underutilized) Barrier methods (good luck)
β-blocker	Metoprolol Propranolol	↓BMR 10% (!)	ACE, ARB, CCB (esp. in obesity) Carvedilol/Nebivolol (↑β-selective)
Anti-histamines	Diphenhydramine Hydrox; Cyproheptadine	↓Central His → ↑ sedation → ↓BMR	Fexofenadine or Loratadine: Peripheral only (or at least largely)
Diabetes meds	Insulin, Sulfonylureas Thiazolidinediones TZDs	Hyperinsulinemia	GLP-1: Liraglutide < Semaglutide SGLT-2; Metform;DDP-4;Pramlindtide

Medications for Weight Loss: ~5% Weight Loss

Medication	Class	Mechanism	Pros	Cons
Bupropion + Naltrexone	Bup: ↓DAT/NET NTX: ↓β-endorphin – feedback	+POMC/CART – feedback: ↓Appetite	Well tolerated Antidepressant ADD, AUD (~Nic)	Bup: Anxiety, insomnia NTX: Nausea (Ondansetron)
Phentermine	↓ NE/DA transport	+POMC/CART ↓ Appetite	Patients love it Works fast	Patients love it (families hate it). Rebound.
Topiramate Phentermine	T: –GLU/+GABA	–AgRP/NPY: ↓Appetite	Fairly well tolerated	Headache Topiramate "fog"
Orlistat	Binds to gastric / pancreatic lipase	↓Fat absorption	Easy to stick to CV benefits	Oily stool / diarrhea, flatus → Fat aversion
Liraglutide	Glucagon-Like Peptide (GLP-1) agonist	↓Gastric emptying ↑Insulin ↓DA in NAc, ST	Works even w/T2DM Rx Metabolic synd ? Rx Coc, AUD	Injectable Expensive
Metformin*	Multiple effects in liver and CNS	↑Insulin, ↓Gluconeo ↑GLP-1, ↓Ghrelin: ↓Appetite ↑Lep/Ins S	Rx Metabolic synd. of SGA, clozapine	~ Effective

Weight Loss Medications: Central Action

- Phentermine (blocks DAT, NET) is the prototypal weight loss drug.
- Bupropion (DAT, NET) plus NTX (opioid blockade) is my "go-to" with good safety/efficacy profile, often with "2-fer" benefit.
- Topiramate (-Glu, +GABA) has a weak effect alone.
- *Lorcaserin has been temporarily withdrawn: cancer concerns.
- *Rimonabant (never approved in US): unacceptable SE profile.



F/u Visits: Overcoming Resistance; Bargaining

Issue	Response
I must have my "special food" at least sometimes!	"Should I allow my Heroin patients to have 'a taste' on special occasions?"
I'm bored with food/meals.	"Congratulations!" (Duller diets → ↓ interest, ↓ eating)
My spouse/child complains.	"Let them eat brioche."
Vegetables are too expensive!	"Compared to eating out? Really?" (Try frozen)
I feel sad when I think about what I'm missing.	"Nothing tastes as good as being slender!" "Find something more interesting than food."
I feel helpless when I see sugar… fried foods… etc.	"What is your "special power"? Prepared snacks
I'm hardly eating anything and still not losing!	Do a 24 hr. recall. Check liquids, snacks, new meds. Don't want breakfast? → Evening/night eating

F/u Visits 2: Painful Truths

- There is no such thing as a "good carb"; and fats *are* fattening (cal-for-cal>carbs)
- Aging is not for wimps: your metabolism slows, esp. as you lose weight!
- You cannot exercise your way thin.
- No days off.
- You will never eat ice cream again. Say goodbye.
- You can't go out for lunch anymore (bring it!).
- Some people *are* cursed with an inefficient metabolism.
- Most slender people don't each much.
- "Spot reduction" is impossible (liposuction → rebound).

Goodbye, old friend

Hello new friend!

Summary

- We eat because our brain tells us to *and for no other reason.*
- Obesity is an addiction: a neuropsychiatric disease. Thus, its treatment is life-long, and aimed at eating less, esp. fat and carbs.
- Our pancreas is stupid, which is why carbs make you hungry/tired (insulin hypersecretion → hypoglycemia → hunger).
- Changing habits/nudges and medications help; weird diets don't.
- Slow change is more robust (and easier).
- Anyone can lose weight: keeping it off is the challenge.
- The more you lose, the harder it gets, because ↓ BMR
- Obesity is a hard problem (simplifying hard problems → failure).
- Amphetamine (phentermine) is a quick-fix, not a durable treatment.
- It is very unlikely we will have a very good anti-obesity medication any time soon.
- These techniques are applicable across broad spectrum of patients because *Persuasion and Healing* (Frank) are still your most powerful tools.

Suggested Reading

- Apovian CM, Aronne L, Powell AG. *Clinical Management of Obesity.* West Islip, NY: Professional Communications, Inc., 2015. [Compact, detailed, data-packed. Probably the best place to start. Endocrinologic orientation. The picture on Amazon is incorrect but the listing is correct.]
- Volkow N, Wise RA, Baler R. The dopamine motive system: implications for food and drug addiction. *Nat Rev Neurosci* 2017;18:471-752. doi:10.1038/nrn.2017.130. [Great review by a great psychiatrically-oriented neuroscientist.]
- Astbury, et al. A systematic review and meta-analysis of the effectiveness of meal replacements for weight loss. *Obesity Reviews* 2019;20:569–587. [Makes a good case for meal replacements.]
- Hall KD, Kahan S. Maintenance of lost weight and the long-term management of obesity. *Med Clin N Am* 2018; 102:183-187. [Hall runs a physiology lab at NIH; Kahan is in public health, so they cover the waterfront of points-of-view. Excellent review.]
- Hall KD, et al. Ultra-processed diets cause excess calorie intake and weight gain. *Cell Metab 2019;* 30:226. [However bad you thought junk food was, it's worse. Much worse.]
- Hall KD, Chung ST. Low-carbohydrate diets for the treatment of obesity and type 2 diabetes. *Curr Opin Clin Nutr Metab Care* 2018;21:308-312. [Good review. But no magic here: you must restrict calories, *especially* fats.]
- Kumar RB, Aronne LJ. Iatrogenic obesity. *Endocrinol Metab Clin N Am 2020;* 49:265–273. [Good information but incomplete on mechanisms. Read with Stahl at hand.]
- Ponzer H. The exercise paradox. *Sci Am (Feb) 2017*; 2:26-31. [Sedentary humans do not actually burn more calories than hunter-gatherers, although we do use those calories differently (and less healthfully)].