

WEIGHT-LOSS MEDICATIONS

Everything you need to know!!



LIVE WEBINAR W/ DR. DAN
WEDNESDAY, MARCH 16, 2022
ONLINE AT 6:00 PM MST

Presenter Disclosures

I have the following relationships with these commercial interests:

- Founder: Healthcare Evolution Inc.
- Consulting/Contracting Fees: SRx Pharmacy – Calgary, AB; Muse Aesthetic Inc., RemedyRx - Didsbury/Carstairs, AB
- Grant Funding: Canadian Foundation for Pharmacy – Innovation Fund Grant
- Advisory Board: CPhA Board Representative on the Pharmacy Examination Board of Canada (PEBC) Board of Directors

I have received no speaker's fee or support for this learning activity.



Learning Objectives

- Review the brain and obesity
- Discuss current and future weight loss medications
- Highlight common questions and my concerns with weight loss medications



Let's Dive In

Obesity

- 70% genetically conferred
 - Genes that are passed down from your mom and dad
- Majority of these are in your brain - Appetite System
 - Weight is determined and regulated here
- Three Parts of the Brain:
 - Homeostatic System - The Gatekeeper
 - Motivation System - The Go Getter
 - Executive Functioning System - The Sleepy Executive

<https://www.youtube.com/watch?v=VEJ6c5emPE8>



A Collision?

Our Appetite System:

- Developed 30,000 years ago when food was scarce
- Provided the motivation to go out and find food; required a great deal of work

Modern Environment:

- Food is not scarce
- Food is engineered to taste as amazing as possible; as quick and as easy as possible
 - Large portions, ultra processed, high fat, salt, and sugar
- We no longer have to work for it
- We are bombarded with societal ideas that 'skinny' = healthy



The Gatekeeper

Homeostatic System

- Defends against fat-loss
- Monitors a hormone called Leptin
 - Leptin is produced by our fat cells
 - Fat-loss = decrease in leptin
- Leptin decreases then the Gatekeeper sounds an alarm
 - 30,000 years ago fat-loss was a bad thing - food was scarce
- Alarm notifies The Go Getter



The Go Getter

Motivational System

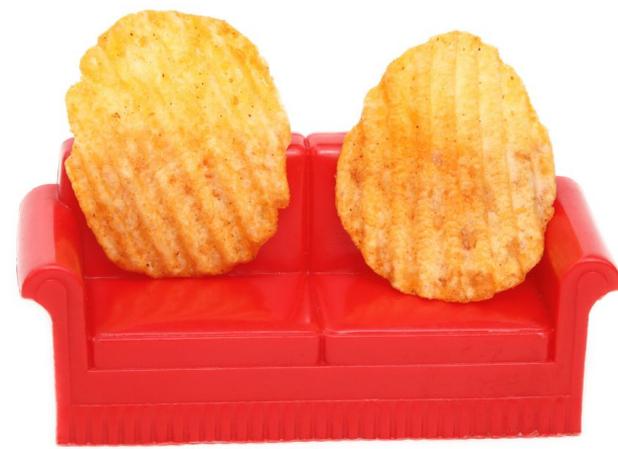
- Our hedonic system
 - Motivates us to seek out food, pleasure, rewards, etc.
- Wanting
 - Cravings, desire, impulses
 - If we did not want to find food/pleasure 30,000 years ago we would not be here today
 - Acts like a wave - it rises, then crests and falls



The Go Getter

Motivational System

- Wanting is created through **Learning**
 - High sugar, salt, fat food + Environment = Associative Learning
 - Ie. Chips + Sitting on the couch, watching TV, at night, after work
 - 'Chunks' things together
 - Then sitting at home, watching TV....The Go Getter, 'Hey, we should be eating chips...'
 - Creates a wave of wanting, or craving for chips
- Note: Greater Pleasure = Faster Learning = Greater Wanting/Cravings



Problem?

- Actions of the Go Getter and Gatekeeper happen without us even knowing it
- Unconscious - Primal Brain?
- No choices are made here...
 - You don't say, 'I choose to want X.'
- Go Getter just sends a wave of Wanting to the next system....



The Sleepy Executive

The Executive System

- All of our decisions and choices are made here
- Conscious - Modern Brain?
- Technically made of 2 parts:
 - Sleepy Executive
 - Autopilot



Wave of Wanting Arrives

Autopilot

- Generates **immediate and automatic** thoughts
- Permission thoughts
 - 'It has been a long day. I deserve to have some chips.'
 - 'We fell off the wagon. So what does it matter?'
 - 'I exercised today so I can eat more.'
- Most of our decisions are made based on these thoughts
 - Especially if our Sleepy Executive is asleep



Not always sleeping...

The Sleepy Executive

- Slows things down and allows you to deliberate and weigh the consequences
- Realizes that the permission thoughts are incorrect
- Can generate Future Thoughts
 - 'I am not actually hungry.'
 - 'I don't need this, I am just bored.'
 - 'Eating this isn't in the direction of what I really want.'
- Our only line of defence against a wave of wanting and our autopilot



Obesity is a Disease?

- Genetic Differences in:
 - Gatekeeper
 - More sensitive to weight loss
 - Go Getter
 - Larger wave of wanting
 - Sleep Executive
 - Sleepier
- Mostly inherited, centered in the brain, influenced by the environment, and gets worse over time



Treatment

1) Behavioural Therapy

- a) Skills to keep the Sleepy Executive awake, and can help with the Gatekeeper and Go Getter

2) Medications

- a) Helps us to manage the Gatekeeper and Go Getter, and ultimately makes the job of the Sleep Executive easier

3) Surgery



Obesity Medications

- Research has had a number of ups and downs
- Many agents have been recalled due to causing adverse effects
- Obesity not being classified as a chronic disease



Obesity Medications

Goals

- Help the Gatekeeper chill out
- Reduce the wave of wanting from the Go Getter
- Reduce Autopilot thoughts
- Keep the Sleep Executive Awake
- Increase metabolic rate?



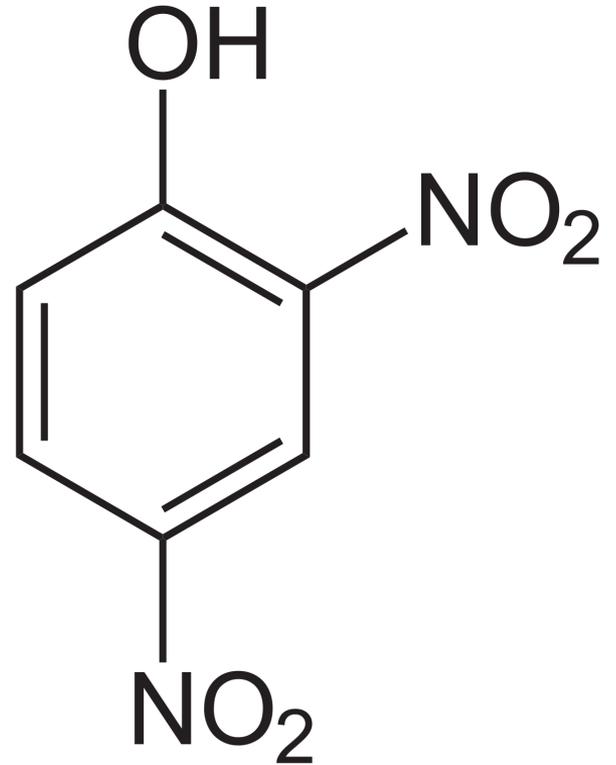
A Brief History

Started in the 1930s

- 2,4 - Dinitrophenol (DNP)
 - Mitochondrial uncoupler?
 - Disrupts how your body stores and uses energy
 - Energy is lost as heat vs. being used efficiently
 - Ex. Driving your car
 - Never approved by health authorities

Problem:

- Uncontrolled increases in body temperature
- 'Cook from the inside out'
- Number of people have died due to this medication



A Brief History

In the 1960s

- All weight-loss drugs approved at the time were amphetamine (stimulant) based
 - Known to suppress appetite
 - Phenetramine was one of these molecules and is still available - more to come

Problem:

- Can be addictive
- Lead to dangerously high blood pressure

Lead to a drought of weight of weight loss medications coming to market.



A Brief History

Until 1996

- Dexfenfluramine was approved by the FDA
 - Stronger version Fenfluramine
 - Appetite suppressant that worked by decreasing serotonin in the brain
- Famous combo of Phenetramine and Fenfluramine called Phen-Fen

Problem:

- Phen-Fen caused damage to heart valves
 - Fenfluramine and Dexfenfluramine were then taken off the market



A Brief History

Things got messy for a few years....

- 1997 - Meridia (Sibutramine) approved by the FDA and pulled in 2010 due to an increased risk of heart attack
- 2006 - Rimonabant approved in Europe. Acted the cannabinoid receptors but in 2008 was removed from the market due to an increase of suicidal ideation
- 2012 - Belviq (Lorcaserin) approved by the FDA but was pulled in 2020 due to an increased risk of cancer

Many issues with medications slowed research and drug development. As well the drugs were not all that effective leading to ~5% weight loss from baseline and quick weight regain once the medications were stopped.



Good News.....

- Strict safety standards and criteria became paramount to bring a weight-loss drug to market
- Shift from acute weight loss treatment to chronic disease management
- Needed effective agents that were safe for long term use



Goals of Therapy

- Health
 - Always #1 priority
- Weight loss of 5-10% from baseline
 - Improvements in heart disease, high blood pressure, fatty liver, cancers, diabetes
- Weight loss >10% from baseline
 - Improvements continue and can lead to things such as remission of diabetes
 - Harder to maintain long term
- Weight Maintenance
 - Long term success is considered weight-loss and maintenance >5 years



Xenical (Orlistat)

- Approved in 1999 by the FDA
- Blocks the absorption of fat in the GI tract
- One of the first medications that can be taken long-term

Effectiveness:

- Over a 24-week placebo controlled trial lead to 5.63% weight-loss from baseline compared to 2.3% in the placebo group



Xenical (Orlistat)

Problem:

- Side effects
 - Flatulence, anal leakage, diarrhea, oily diarrhea, stomach cramps

My Experience?:

- I have yet to prescribe it
- Colleagues have used it and had success - recommend only using it with people who have issues with constipation



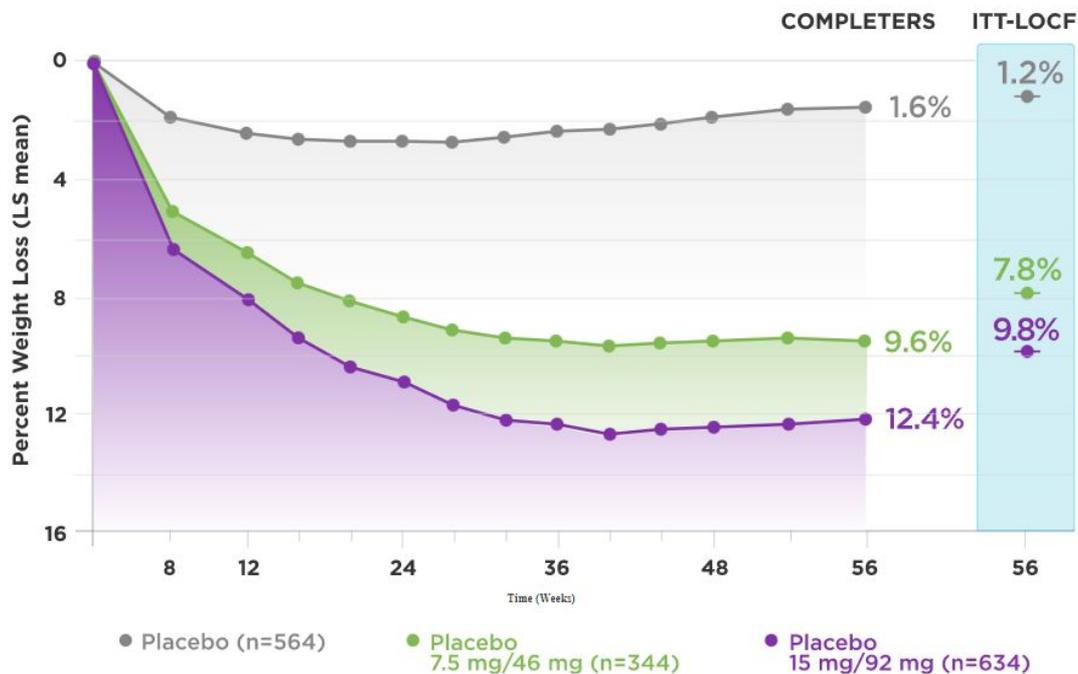
Qsymia (Phentermine/Topiramate ER)

- Two older drugs
- Phentermine (Apidex)
 - Oldest weight-loss medication still on the market (Part of phen-fen, but not the bad part)
 - Used for Obesity (usually short term)
 - CNS stimulant - increases norepinephrine release (Fight or Flight)
- Topiramate (Topamax)
 - Used for seizures, headaches/migraines, alcohol use disorder, obesity, binge eating disorder
 - Called the California Drug
 - Multiple sites of action - GABA receptors, and increases dopamine release?



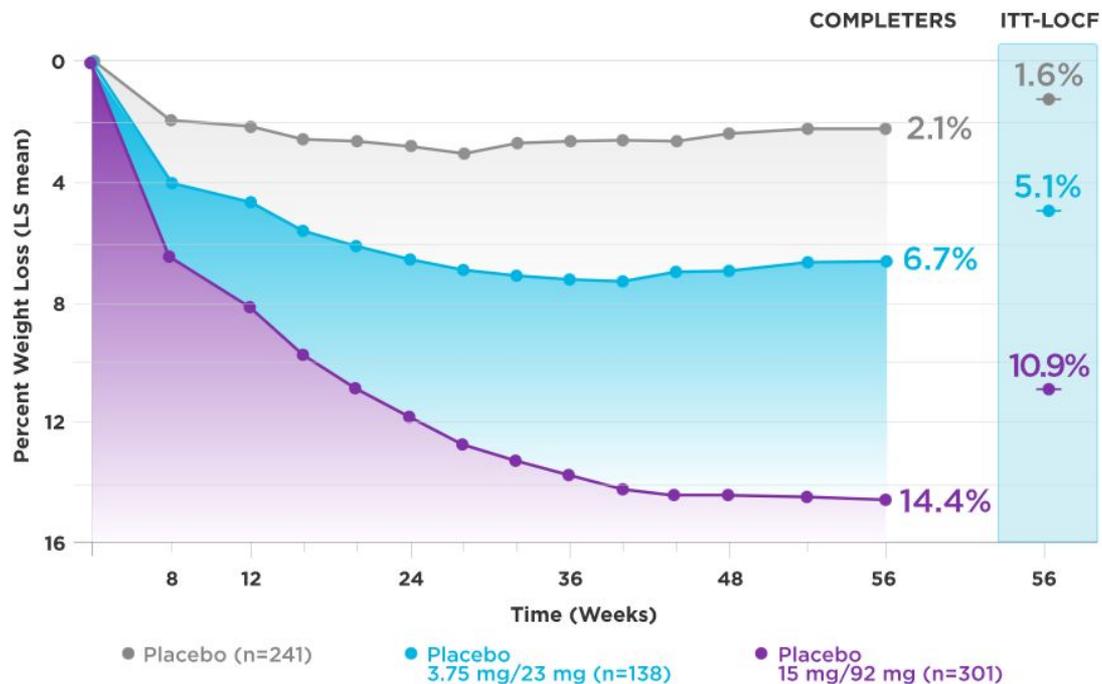
Qsymia (Phentermine/Topiramate ER)

CONQUER Trial - BMI >27 + 2 or more concurrent conditions



Qsymia (Phentermine/Topiramate ER)

EQUIP Trial - BMI >35



Qsymia (Phentermine/Topiramate ER)



Effectiveness:

- Average ~5-10% weight loss from baseline compared to placebo
- Other data shows less impressive results

Problem:

- Side effects - increased blood pressure, cognitive dysfunction, mood changes
- Lots of drug interactions

My Experience?:

- None - Not available in Canada likely never will be

Contrave (Bupropion/Naltrexone)

- Two older drugs
- Bupropion (Zyban/Wellbutrin)
 - Used for depression, ADHD, and smoking cessation
 - NDRI (Norepinephrine and Dopamine Reuptake Inhibitor)
- Naltrexone (Revia)
 - Used for opioid and EtOH dependence
 - Opioid Antagonist (Blocks the Opioid Receptors)

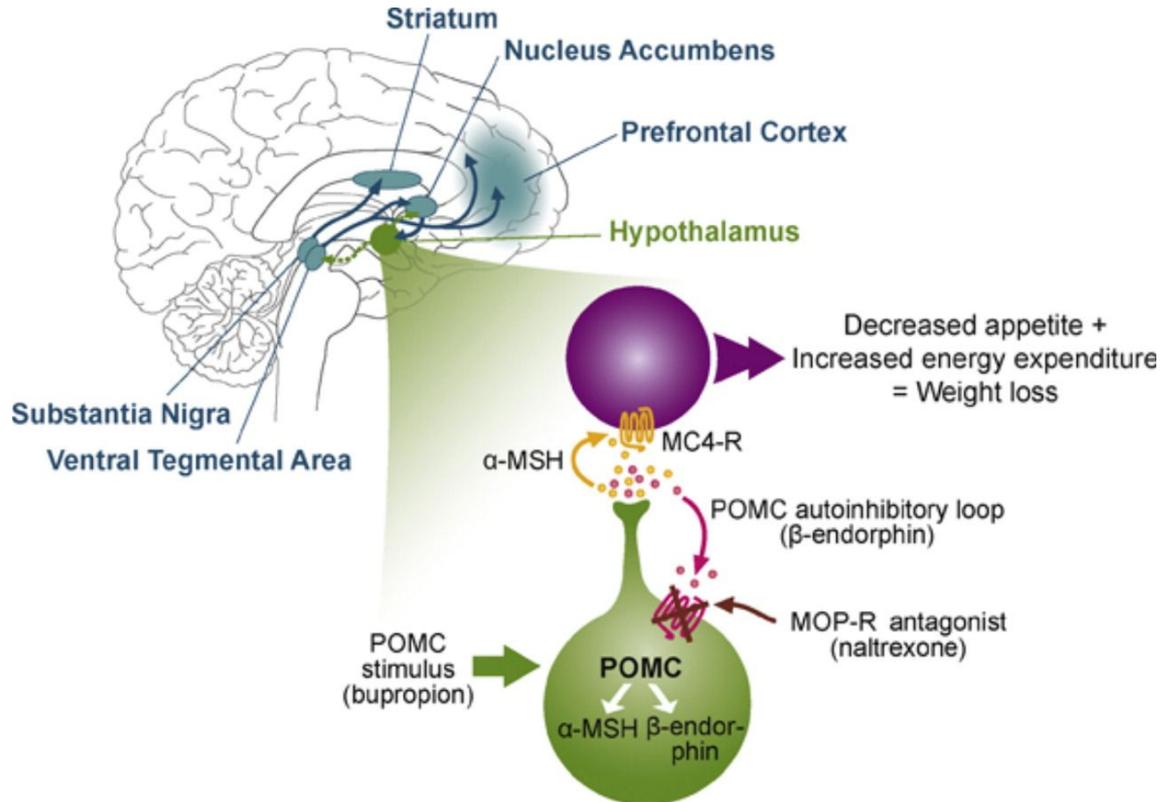


Contrave (Bupropion/Naltrexone)

- Together they seem to have a synergistic effect in weight loss
- Decreases appetite (Gatekeeper sensitivity)
- Decreases cravings (Reduces wave of wanting)
- Decreases liking of food?



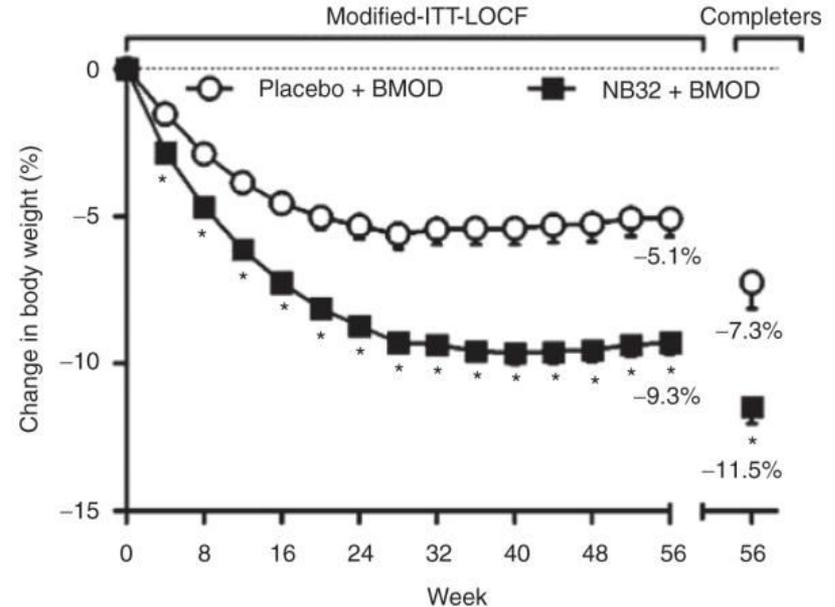
Contrave (Bupropion/Naltrexone)



Contrave (Bupropion/Naltrexone)

Effectiveness:

- In two, 56-week placebo controlled trials Contrave lead to 5.2-8.1% weight-loss from baseline compared to the placebo group
- These results were more pronounced in COR-BMOD trial which included intensive behavioral therapy



Contrave (Bupropion/Naltrexone)

Problem:

- No opioids, previous seizure disorders, kidney issues, or high blood pressure
- Side effects - Constipation, mood changes

My Experience?:

- Most people have some benefit
- ~15% of people it works really well

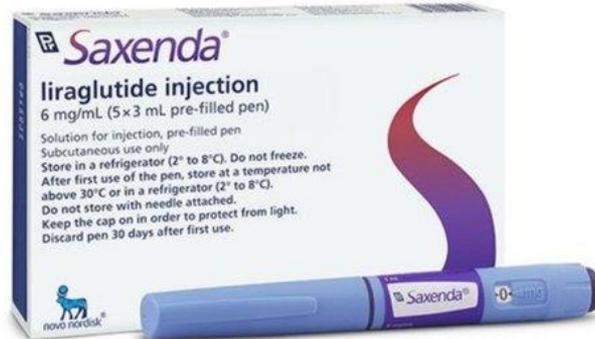


Saxenda (Liraglutide)/Wegovy (Semaglutide)

- Saxenda approved in 2014; Wegovy approved in 2021
- GLP-1 Receptor Agonists
 - Decreases the wave of wanting from the Go Getter; Helps the Gatekeeper chill out
- Once daily vs. Once weekly injections

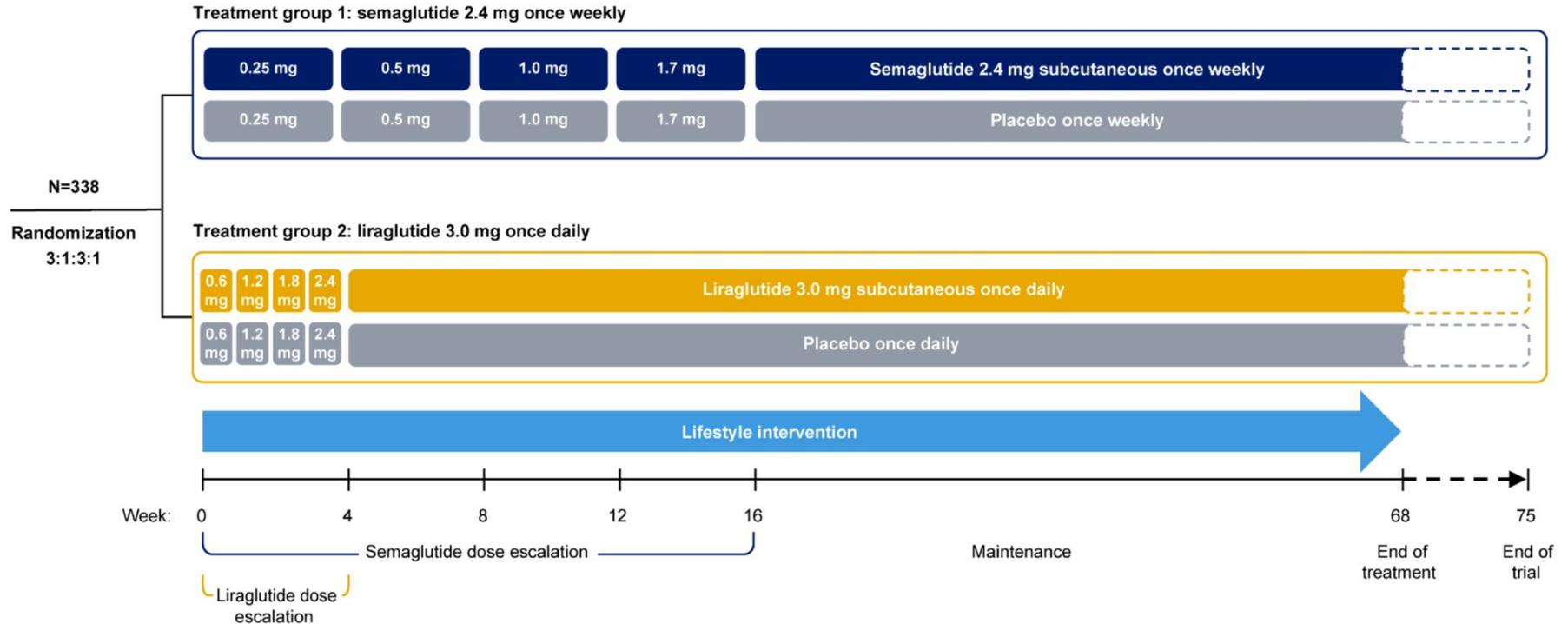
Effectiveness:

- Saxenda vs. Wegovy in the STEP 8 Trial - Published Jan 2022



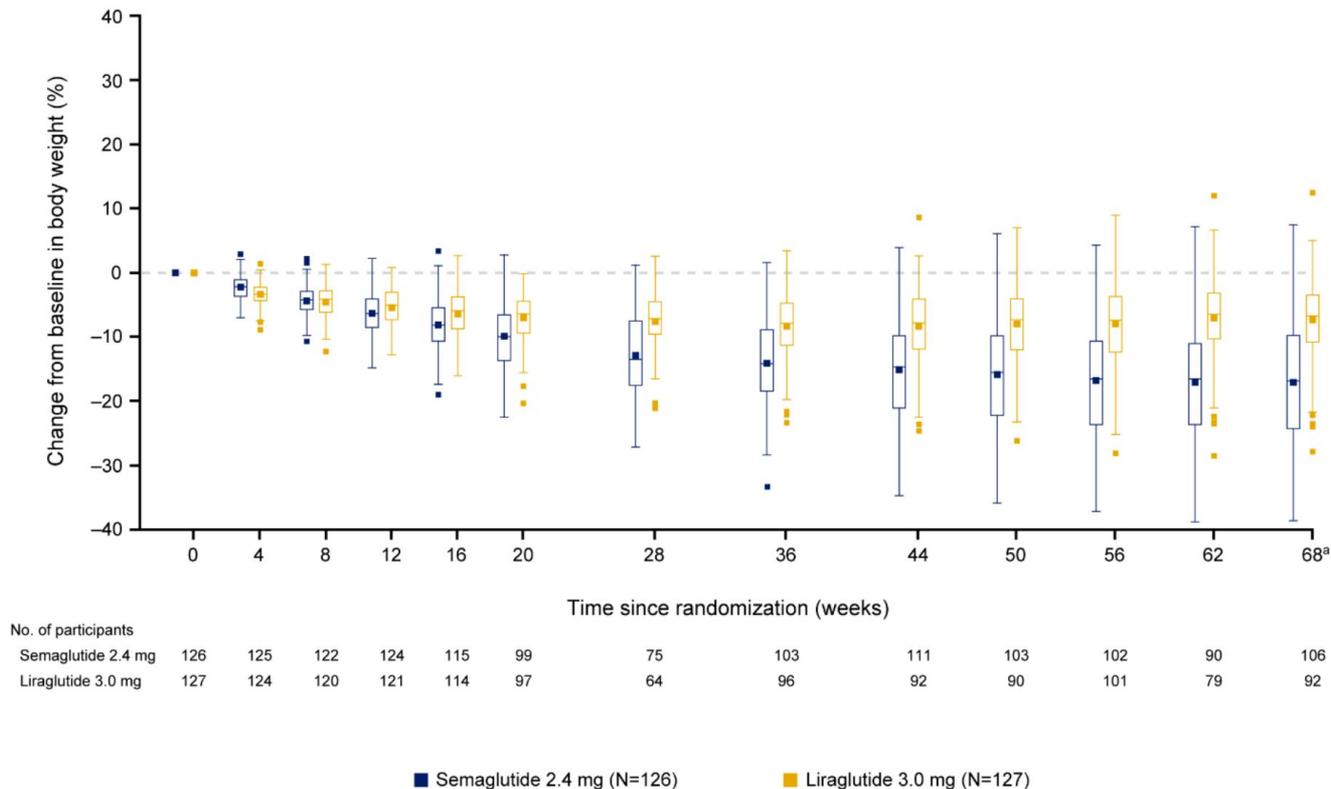
Saxenda (Liraglutide)/Wegovy (Semaglutide)

eFigure 1. Trial Design



Saxenda (Liraglutide)/Wegovy (Semaglutide)

eFigure 5. Percent Change in Body Weight from Baseline to Week 68 (Observed On-Treatment Data; Full Analysis Set)



Saxenda (Liraglutide)/Wegovy (Semaglutide)

Effectiveness:

- Saxenda 3mg daily ~6.4% from baseline
- Wegovy 2.4mg once weekly ~15.8% from baseline
 - In the STEP 1 Trial 1/3 of participants lost >20% of weight from baseline

Problem:

- Side effects - primarily GI in nature (nausea, heartburn, constipation, diarrhea, rarely vomiting)

My Experience?:

- Wegovy is considerably more effective for both weight loss and blood sugars
 - Caveat is more side effects
 - Saxenda ~50% whether someone would have side effects
 - Wegovy ~90% of people experience some kind of side effect
- 

One Piece of Anecdotal Experience

Three types of outcomes depending on the individual:

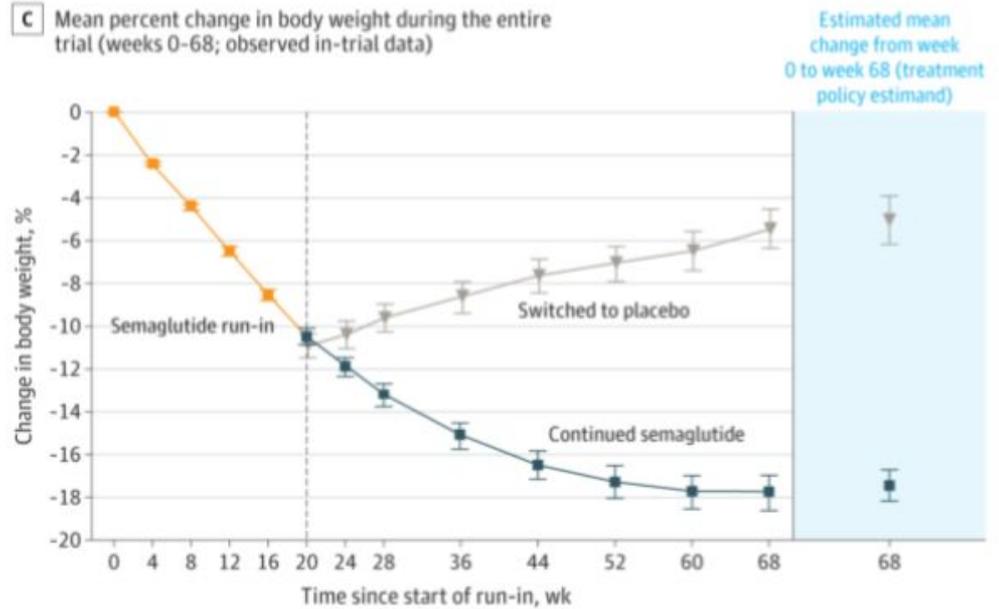
- 1) **Responders** - Variable dietary patterns; Weight has NOT been a lifelong issue; Slow and steady during adult life
 - a) Weight comes off relatively easily; ~1lbs/week and usually sustainable
- 2) **Hyper-Responders** - Consuming large amounts of calories (Emotional/Late Night/Excess processed foods)
 - a) Weight seems to melt off; ~5-10lbs in a month and may or may not be sustainable depending on reasons for large calorie consumption
- 3) **Non-Responders** - Yo-yo dieting for years; Weight has been a lifelong issue; has lost and gained large amounts of weight
 - a) May find minimal or no benefit with medication despite no appetite; Weight loss is an ordeal - **Stay tuned for my Soap Box**

Common Questions?!



Do I have to take these medications for life?

- Most people yes...
 - Obesity is a chronic, relapsing, progressive disease
- Whatever you do to lose the weight you must maintain for the long-term....



No. of participants										
Semaglutide run-in										
	803	803	803	802	801					
Continued semaglutide		535	527	531	525	523	521	516	520	535
Switched to placebo		268	267	265	258	260	254	246	250	268

Are these medications SAFE?!



- Short answer = Yes
- We have a lot of experience/data with many of them
- Many of the side effects are transient in nature - they will go away

Long-term:

- Saxenda/Ozempic/Wegovy
 - Thyroid Cancer Risk is null - specific cancer is Medullary Thyroid Carcinoma (MTC)
 - Pancreatic Cancer/Pancreatitis - Pancreatitis maybe; Pancreatic Cancer - No. New meta-analysis by Zhang et al. shows neutral effect and some data shows protective effect
- Orlistat/Contrave/Qsyima
 - Nothing concerning at present

Are these medications SAFE?!

NOTE:

- Not everyone will tolerate these medications

If you are experiencing side effects that are affecting your quality of life (ie. vomiting every meal) STOP the medication. The potential weight-loss is not worth it!!

REMEMBER: Health is the #1 priority!



Future Therapies?

Tons of agents in the pipeline:

- Tirzepatide - Similar to GLP-1s will likely come to market for diabetes in 2023
 - Better than Ozempic/Wegovy? Maybe but tolerability is showing to be an issue
- Cagrilintide - Semaglutide + Amylin analogue
 - Amylin is another satiety hormone
- Bimagrumab - Muscle wasting prevention drug?
 - Loss fat-mass and gain muscle mass...

Early Stage Research:

- Safe metabolic uncoupling - like DNP but less of a BBQ
- Psilocybin? - Magic Mushrooms for Obesity
 - Neonminds Biosciences Inc.

Hope is to replace bariatric surgery...



My Soap Box



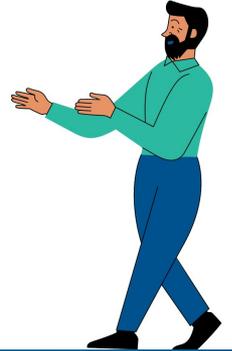
My Soap Box

Eating Disorders (ie. Anorexia, BED, Bulimia):

- Number of individuals with obesity also have an eating disorder
 - 87% of individuals with Binge Eating Disorder also have Obesity
 - 33% of individuals with Bulimia also have Obesity
- Studies that looked these drugs did a terrible or limited job of screening for eating disorders
- Clinicians also do a terrible job of screening for eating disorders

Could this be leading to more harm?

- Worsen their eating disorder?
- Greater failure rate?
- More blame on the individual



My Soap Box

How low can we go?!



- No one is ensuring patients are acquiring adequate nutrition
 - 1200 calories/day is not even enough to sustain a small toddler
 - These drugs make it easy to eat almost nothing
- I am hearing and seeing more patients with symptoms such as hair loss, fatigue, low energy, rebound cravings, binging, and weight gain
 - Many symptoms are similar to those found in patients who have undergone bariatric surgery and those with severe eating disorders leading to malnutrition
- Metabolic Adaptation
 - Limiting weight loss success and sustainability?

Brief Note on Metabolic Adaptation



With every successive cycle of yo-yo dieting, weight rises, while metabolic rate drops.

Brief Note on Metabolic Adaptation

DIETING HISTORY AND CALORIE NEEDS IN THREE WOMEN WITH THE SAME BODY SIZE

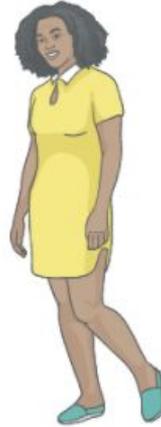
NEVER DIETED



Maintains weight at
-2,475 calories/day



TRIED HER FIRST
DIET RECENTLY



Maintains weight at
-2,225 calories/day



HAS DIETED ON AND
OFF FOR YEARS



Maintains weight at
-1,980 calories/day

Silver Lining?



Reverse dieting helps to maintain weight loss and metabolic rate over time.

Eat More to Lose More?

- Adequate Nutrition is VITAL
 - Not only for weight loss but to also make sure life does not suck more than it has too
- Quick formulas to get started...
 - Calorie intake (for weight loss) = $12 \times \text{Goal Body Weight (lbs)}$
 - Protein intake = $1 \times \text{Goal Body Weight (lbs)}$
 - Ex. CW = 250lbs; GBW = 200lbs
 - Calorie intake = $12 \times 200\text{lbs} = 2400\text{cals/day}$
 - Protein intake = $1 \times 200\text{lbs} = 200\text{g}$
 - Aim to be within +/-100 calories consistently; More activity = more calories
 - GBW = an estimate or starting point

Go to my Youtube Channel for more details - Dr Dan - Weight-loss via Habit Mastery



Final Notes

- Medications are safe and effective
 - They can change an individual's life
- Used in conjunction with lifestyle interventions
 - I.e. Calorie reduced diets, exercise programs, behavioural interventions/therapy
- Health should always be our #1 priority; Not the number on the scale
- A tool in the tool box
 - Not a miracle
 - Tested in conjunction with lifestyle modifications such as calorie restriction, exercise programs, and behavioral interventions
 - Calorie deficit is still necessary BUT we need to keep in mind adequate nutrition because....



Biology Always Wins



	Orlistat	Liraglutide	Semaglutide	Naltrexone/Bupropion	Phentermine/Topiramate
Drug Class	Gastric and Pancreatic Lipase Inhibitor	GLP-1 Receptor Agonist	GLP-1 Receptor Agonist	Opioid Receptor Antagonist/Norepinephrine-Dopamine Reuptake Inhibitor (NDRI)	CNS Stimulant/Augments appetite and Satiety
Maintenance Dose	120mg PO TID	3mg once daily, SubQ	2.4mg once weekly, SubQ	16/180mg PO BID	15/92mg daily
Indication	≥30kg/m ² or ≥27kg/m ² + Comorbidity	≥30kg/m ² or ≥27kg/m ² + Comorbidity	≥30kg/m ² or ≥27kg/m ² + Comorbidity	≥30kg/m ² or ≥27kg/m ² + Comorbidity	≥30kg/m ² or ≥27kg/m ² + Comorbidity
Contraindication	<ul style="list-style-type: none"> Chronic Malabsorption Syndrome Cholestasis 	<ul style="list-style-type: none"> MEN2; MTC Pregnancy and BreastFeeding 	<ul style="list-style-type: none"> MEN2; MTC Pregnancy and BreastFeeding 	<ul style="list-style-type: none"> High blood pressure, severe kidney or liver disease Seizure disorders or a history of seizure disorders Bulimia and anorexia nervosa Use with opioids or OATs Pregnancy 	<ul style="list-style-type: none"> Glaucoma Pregnancy and Breastfeeding History of Hyperthyroidism Caution with heart disease as can increase heart rate Use with MAOIs and other mental health medications
Most Common Adverse Events	<ul style="list-style-type: none"> Oily spotting, stool, evacuation Flatus with discharge Fecal urgency, increased defecation 	<ul style="list-style-type: none"> Nausea, vomiting, dyspepsia Diarrhea, constipation Abdominal pain 	<ul style="list-style-type: none"> Nausea, vomiting, dyspepsia Diarrhea, constipation Abdominal pain 	<ul style="list-style-type: none"> Nausea, vomiting Diarrhea, constipation Headache, dizziness Insomnia Dry mouth 	<ul style="list-style-type: none"> Dry mouth Constipation Burning sensation in hands and feet Cognitive dysfunction/Lapse in judgement Mood changes



**MEDICAL
DISTILLERY**

medicaldistillery.com

References

- 1) Zhang X, Wang M, Wang X, et al. Comparison of New Glucose-Lowering Drugs on the Risk of Pancreatitis in Type 2 Diabetes: A Network Meta-Analysis. *Endocrine Practice*. 2022;28(3):333-341. doi:10.1016/j.EPRAC.2021.12.007
- 2) Wadden TA, Bailey TS, Billings LK, et al. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. *JAMA*. 2021;325(14):1403-1413. doi:10.1001/JAMA.2021.1831
- 3) Rubino D, Abrahamsson N, Davies M, et al. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. *JAMA*. 2021;325(14):1414-1425. doi:10.1001/JAMA.2021.3224
- 4) Rubino DM, Greenway FL, Khalid U, et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. *JAMA*. 2022;327(2):138-150. doi:10.1001/JAMA.2021.23619
- 5) Jain SS, Ramanand SJ, Ramanand JB, Akat PB, Patwardhan MH, Joshi SR. Evaluation of efficacy and safety of orlistat in obese patients. *Indian Journal of Endocrinology and Metabolism*. 2011;15(2):99. doi:10.4103/2230-8210.81938
- 6) Timothy Garvey W, Mechanick JI, Brett EM, et al. AACE/ACE Guidelines AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR MEDICAL CARE OF PATIENTS WITH OBESITY. *ENDOCRINE PRACTICE*. 2016;22(3). doi:10.4158/EP161365.GL
- 7) Group TLAR. Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes. <http://dx.doi.org/101056/NEJMoa1212914>. 2013;369(2):145-154. doi:10.1056/NEJMoa1212914
- 8) Group TDPP (DPP) R. The Diabetes Prevention Program (DPP): Description of lifestyle intervention. *Diabetes care*. 2002;25(12):2165. doi:10.2337/DIACARE.25.12.2165
- 9) Frias JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *The New England journal of medicine*. 2021;385(6):503-515. doi:10.1056/NEJMoa2107519
- 10) Wharton S, Davies M, Dicker D, et al. Managing the gastrointestinal side effects of GLP-1 receptor agonists in obesity: recommendations for clinical practice. *Postgraduate Medicine*. Published online November 15, 2021. doi:10.1080/00325481.2021.2002616
- 11) Martins C, Dutton GR, Hunter GR, Gower BA. Revisiting the Compensatory Theory as an explanatory model for relapse in obesity management. *The American Journal of Clinical Nutrition*. 2020;112(5):1170-1179. doi:10.1093/AJCN/NQAA243
- 12) NM B, A S, NA K, AP H, RE W. Intermittent energy restriction improves weight loss efficiency in obese men: the MATADOR study. *International journal of obesity (2005)*. 2018;42(2):129-138. doi:10.1038/IJO.2017.2016
- 13) Martins C, Roekenes J, Salamati S, Gower BA, Hunter GR. Metabolic adaptation is an illusion, only present when participants are in negative energy balance. *The American Journal of Clinical Nutrition*. 2020;112(5):1212-1218. doi:10.1093/AJCN/NQAA220
- 14) Fothergill E, Guo J, Howard L, et al. Persistent metabolic adaptation 6 years after The Biggest Loser competition. doi:10.1002/oby.21538
- 15) Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. <http://dx.doi.org/101056/NEJMoa1411892>. 2015;373(1):11-22. doi:10.1056/NEJMoa1411892
- 16) Bethel MA, Patel RA, Merrill P, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *The Lancet Diabetes and Endocrinology*. 2018;6(2):105-113. doi:10.1016/S2213-8587(17)30412-6
- 17) Mali G, Ahuja V, Dubey K. Glucagon-like peptide-1 analogues and thyroid cancer: An analysis of cases reported in the European pharmacovigilance database. *Journal of Clinical Pharmacy and Therapeutics*. 2021;46(1):99-105. doi:10.1111/jcpt.13259
- 18) Kannan S. Q: Should we be concerned about thyroid cancer in patients taking glucagon-like peptide 1 receptor agonists? doi:10.3949/ccjm.81a.13066
- 19) Nauck MA, Friedrich N. Do GLP-1-based therapies increase cancer risk? *Diabetes Care*. 2013;36(SUPPL.2):S245-S252. doi:10.2337/dcS13-2004
- 20) Shaw K, Gennat H, O'Rourke P, del Mar C. Exercise for overweight or obesity. *Cochrane Database of Systematic Reviews*. 2006;(4). doi:10.1002/14651858.CD003817.pub3
- 21) Hall KD, Ayuketah A, Brychta R, Walter PJ, Yang S, Zhou M. Clinical and Translational Report Ultra-Processed Diets Cause Excess Calorie Intake and Weight Gain: An Inpatient Randomized Controlled Trial of Ad Libitum Food Intake. *Cell Metabolism*. 2019;30:67-77.e3. doi:10.1016/j.cmet.2019.05.008
- 22) Rubino D, Abrahamsson N, Davies M, et al. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity. *JAMA*. Published online March 23, 2021. doi:10.1001/jama.2021.3224
- 23) Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metabolism*. 2018;27(6):1212-1221.e3. doi:10.1016/j.cmet.2018.04.010

References

- 24) Zhang X, Wang M, Wang X, et al. Comparison of New Glucose-Lowering Drugs on the Risk of Pancreatitis in Type 2 Diabetes: A Network Meta-Analysis. *Endocrine Practice*. 2022;28(3):333-341. doi:10.1016/j.eprac.2021.12.007
- 25) Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring, Md)*. 2011;19(1):110-120. doi:10.1038/OBY.2010.147
- 26) Apovian CM, Aronne L, Rubino D, et al. A Randomized, Phase 3 Trial of Naltrexone SR/Bupropion SR on Weight and Obesity-related Risk Factors (COR-II). *Obesity (Silver Spring, Md)*. 2013;21(5):935. doi:10.1002/OBY.20309
- 27) Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*. 2010;376(9741):595-605. doi:10.1016/S0140-6736(10)60888-4
- 28) Yeo GSH, Heisler LK. Unraveling the brain regulation of appetite: lessons from genetics. *Nature Neuroscience* 2012 15:10. 2012;15(10):1343-1349. doi:10.1038/nn.3211
- 29) Wadden TA. Eight-year weight losses with an intensive lifestyle intervention: The look AHEAD study. *Obesity*. 2014;22(1):5-13. doi:10.1002/OBY.20662
- 30) Rosenbaum M, Sy M, Pavlovich K, Leibel RL, Hirsch J. Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. *The Journal of Clinical Investigation*. 2008;118(7):2583-2591. doi:10.1172/JCI35055
- 31) Leibel RL, Rosenbaum M, Hirsch J. Changes in Energy Expenditure Resulting from Altered Body Weight. <http://dx.doi.org/101056/NEJM199503093321001>. 2009;332(10):621-628. doi:10.1056/NEJM199503093321001
- 32) Higgs S. Cognitive processing of food rewards. *Appetite*. 2016;104:10-17. doi:10.1016/j.appet.2015.10.003
- 33) Hall KD, Kahan S. Maintenance of Lost Weight and Long-Term Management of Obesity. *Medical Clinics*. 2018;102(1):183-197. doi:10.1016/j.mcna.2017.08.012
- 34) Hall KD, Hammond RA, Rahmandad H. Dynamic interplay among homeostatic, hedonic, and cognitive feedback circuits regulating body weight. *American Journal of Public Health*. 2014;104(7):1169-1175. doi:10.2105/AJPH.2014.301931
- 35) Gettens KM, Gorin AA. Executive function in weight loss and weight loss maintenance: a conceptual review and novel neuropsychological model of weight control. *Journal of Behavioral Medicine* 2017 40:5. 2017;40(5):687-701. doi:10.1007/S10865-017-9831-5
- 36) Elks CE, Hoed M den, Zhao JH, et al. Variability in the heritability of body mass index: A systematic review and meta-regression. *Frontiers in Endocrinology*. 2012;3(FEB):29. doi:10.3389/FENDO.2012.00029/BIBTEX
- 37) Diamond A. Executive Functions. <http://dx.doi.org/101146/annurev-psych-113011-143750>. 2013;64:135-168. doi:10.1146/ANNUREV-PSYCH-113011-143750
- 38) Cui H, López M, Rahmouni K. The cellular and molecular bases of leptin and ghrelin resistance in obesity. *Nature Reviews Endocrinology* 2017 13:6. 2017;13(6):338-351. doi:10.1038/nrendo.2016.222
- 39) Berthoud HR, Münzberg H, Morrison CD. Blaming the Brain for Obesity: Integration of Hedonic and Homeostatic Mechanisms. *Gastroenterology*. 2017;152(7):1728-1738. doi:10.1053/J.GASTRO.2016.12.050
- 40) Appelhans BM, Woolf K, Pagoto SL, Schneider KL, Whited MC, Liebman R. Inhibiting Food Reward: Delay Discounting, Food Reward Sensitivity, and Palatable Food Intake in Overweight and Obese Women. *Obesity*. 2011;19(11):2175-2182. doi:10.1038/OBY.2011.57
- 41) Behavior and Psychology Overview. doi:10.1038/oby.2008.638
- 42) Billes SK, Sinnayah P, Cowley MA. Naltrexone/bupropion for obesity: An investigational combination pharmacotherapy for weight loss. *Pharmacological Research*. 2014;84:1-11. doi:10.1016/j.phrs.2014.04.004

Questions?!



MORE WAYS TO CONNECT



theofficialdrdan



Dr. Dan - Weight-loss
via Habit Mastery



theofficialdrdan



officialdrdan



dan.burton@healthcareevolve.ca

**Subscribe to my
newsletter @**



healthcareevolve.ca