

School of COMMUNITY MEDICINE

Medical Obesity Treatment

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Disclosures

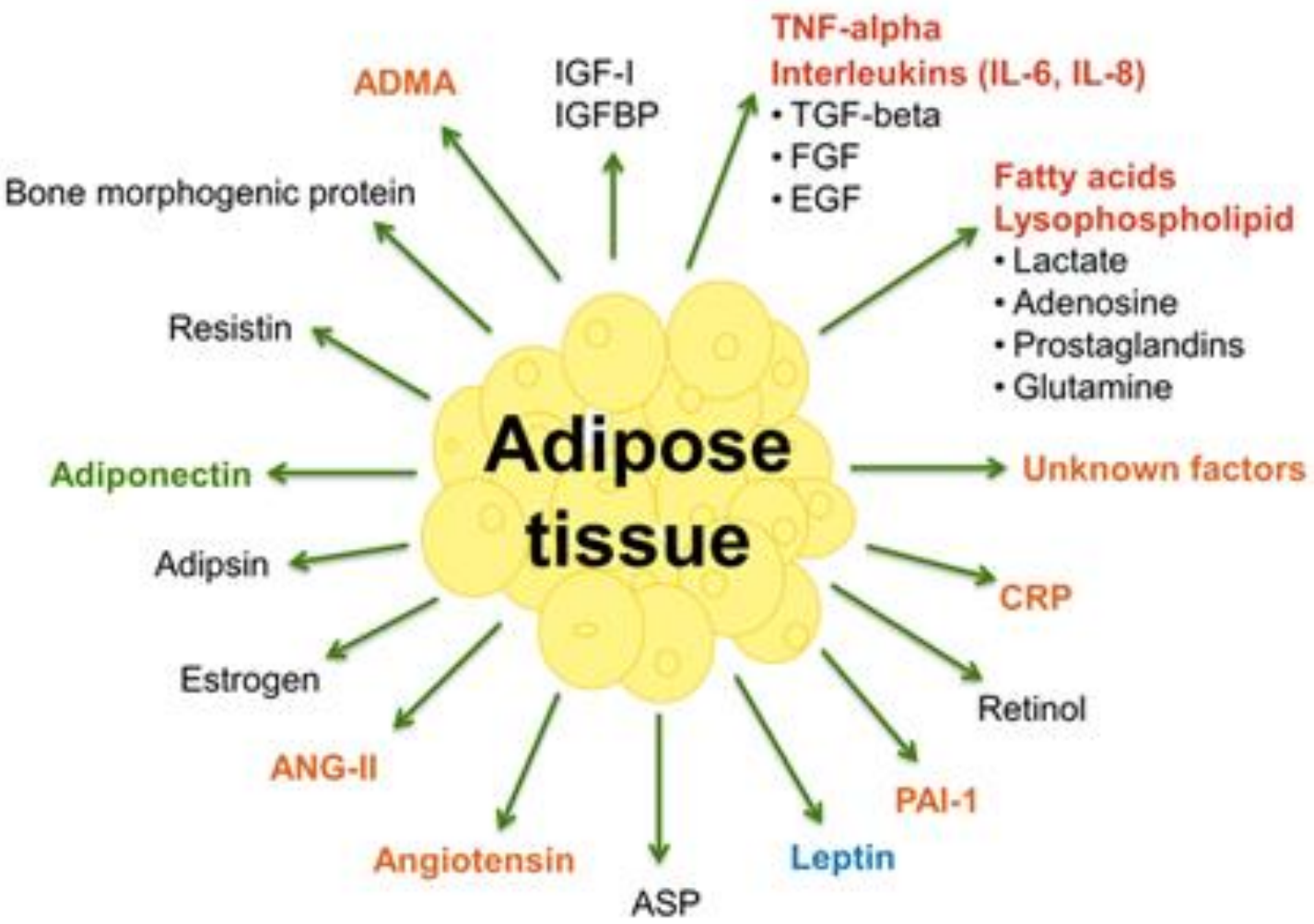
- Speaker's Bureau – Novo Nordisk, Rhythm Pharmaceuticals
- Advisory Board- Rhythm Pharmaceuticals

Objectives

- Define the classifications of obesity
- Lay out the approach to medical weight loss:
  - Screen for comorbid conditions
  - Lifestyle modification
  - Evaluate for obesogenic medications
  - Anti-obesity medications
- Discuss indications for bariatric surgery

Obesity Definition

"Obesity is defined as a **chronic**, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences."


ADMA
IGF-I
IGFBP
TNF-alpha
Interleukins (IL-6, IL-8)
• TGF-beta
• FGF
• EGF
Bone morphogenic protein
Fatty acids
Lysophospholipid
• Lactate
• Adenosine
• Prostaglandins
• Glutamine
Resistin
Adiponectin
Adipose tissue
Unknown factors
Adipsin
CRP
Estrogen
Retinol
ANG-II
PAI-1
Angiotensin
Leptin
ASP

Classification:

- Underweight: <18.5 kg/m2
- Normal weight: 18.5-25 kg/m2
- Overweight: 25-30 kg/m2
- Obesity class 1: 30-35 kg/m2
- Obesity class 2: 35-40 kg/m2
- Obesity class 3: > 40 kg/m2

Approach to Medical Management

1. Screen for comorbid/obesity complications
   - Co-treatments or contraindications to anti-obesity medications
2. Discuss lifestyle modifications
3. Screen for current obesogenic medications
   - Change to weight neutral/negative meds!
4. Discuss anti-obesity medications

1. Screen for comorbid obesity complications

- Type 2 DM
- Cardiovascular disease
- Sleep apnea (STOP-BANG score)
- GERD
- HTN
- Dyslipidemia
- Osteoarthritis/chronic pain (fat mass disease)
- Hypothyroidism
- PCOS
- Urinary Incontinence
- Male Hypogonadism
- Female Infertility
- Depression

Meal Plan (R64, R65, R66)	Physical Activity (R64, R67, R68, R69, R70, R71)	Behavior (R64, R72, R73, R74, R75)
• Reduced-calorie healthy meal plan • ~500–750 kcal daily deficit • Individualize based on personal and cultural preferences • Meal plans can include: Mediterranean, DASH, low-carb, low-fat, volumetric, high protein, vegetarian • Meal replacements • Very low-calorie diet is an option in selected patients and requires medical supervision Team member or expertise: dietitian, health educator	• Voluntary aerobic physical activity progressing to >150 minutes/week performed on 3–5 separate days per week • Resistance exercise: single-set repetitions involving major muscle groups, 2–3 times per week • Reduce sedentary behavior • Individualize program based on preferences and take into account physical limitations Team member or expertise: exercise trainer, physical activity coach, physical/occupational therapist	An interventional package that includes any number of the following: • Self-monitoring (food intake, exercise, weight) • Goal setting • Education (face-to-face meetings, group sessions, remote technologies) • Problem-solving strategies • Stimulus control • Behavioral contracting • Stress reduction • Psychological evaluation, counseling, and treatment when needed • Cognitive restructuring • Motivational interviewing • Mobilization of social support structures Team member or expertise: health educator, behaviorist, clinical psychologist, psychiatrist

2. Lifestyle Modifications

From: **Steps per Day and All-Cause Mortality in Middle-aged Adults in the Coronary Artery Risk Development in Young Adults Study**

JAMA Netw Open. 2021;4(9):e2124516. doi:10.1001/jamanetworkopen.2021.24516

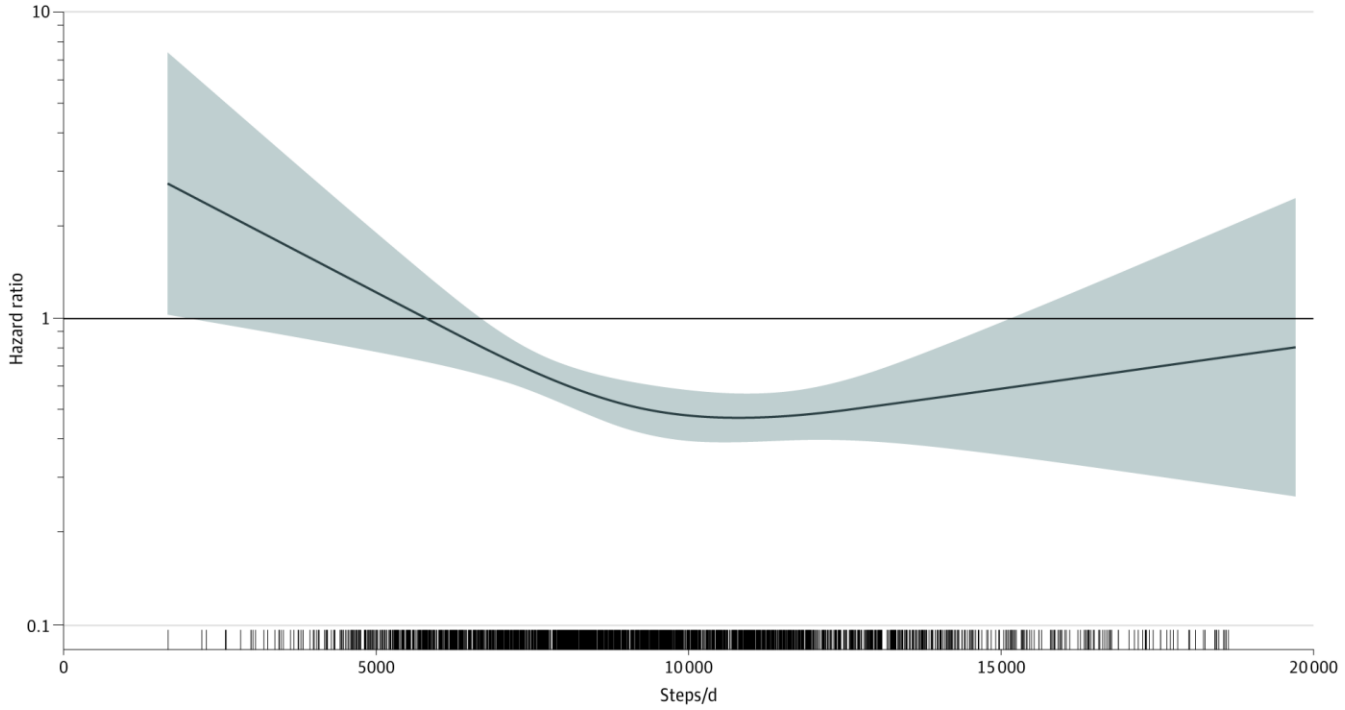


Figure Legend:

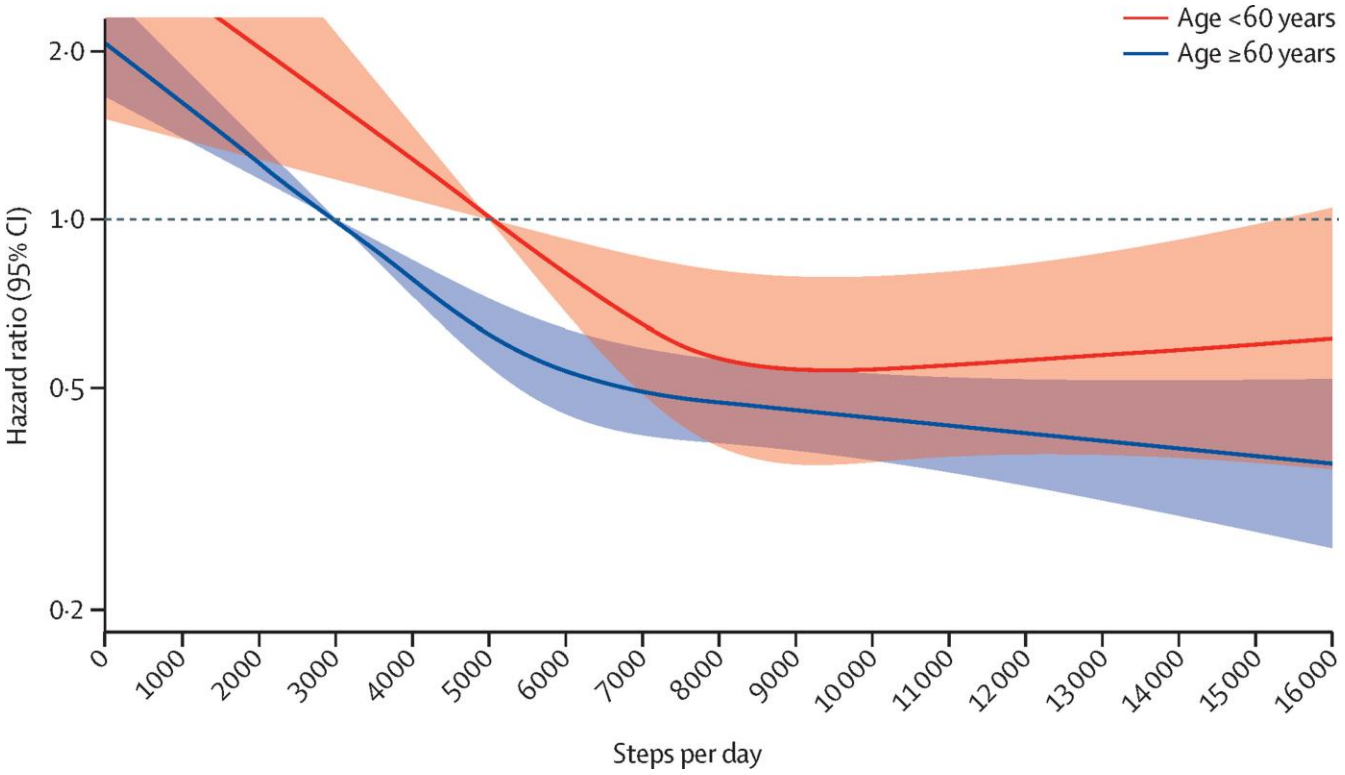
Dose-Response Association of Steps per Day With All-Cause MortalityRestricted cubic splines of hazard ratios of steps/d with all-cause mortality. Knots set at 10th, 50th, and 90th percentile of steps per day. Reference set at 5800 steps/d (the approximate median steps per day of low step group). The model is adjusted for age, accelerometer wear time, race, sex, education, study center, body mass index, smoking, alcohol, systolic blood pressure, hypertension medication use, diabetes, hyperlipidemia, history of cardiovascular disease, and self-rated health. Shading indicates 95% CI.

Daily steps and all-cause mortality: a meta-analysis of 15 international cohorts

Amanda E Paluch, PhD, Shivangi Bajpai, MS, Prof David R Bassett, PhD, Prof Mercedes R Carnethon, PhD, Prof Ulf Ekelund, PhD, Prof Kelly R Evenson, PhD, Deborah A Galuska, PhD, Barbara J Jefferis, PhD, Prof William E Kraus, MD, Prof I-Min Lee, ScD, Charles E Matthews, PhD, John D Omura, MD, Alpa V Patel, PhD, Carl F Pieper, DrPH, Erika Rees-Punia, PhD, Dhayana Dallmeier, PhD, Prof Jochen Klenk, PhD, Prof Peter H Whincup, PhD, Erin E Dooley, PhD, Prof Kelley Pettee Gabriel, PhD, Priya Palta, PhD, Prof Lisa A Pompeii, PhD, Ariel Chernofsky, MS, Martin G Larson, PhD, Prof Ramachandran S Vasan, MD, Nicole Spartano, PhD, Marcel Ballin, MSc, Prof Peter Nordström, PhD, Anna Nordström, PhD, Prof Sigmund A Anderssen, PhD, Prof Bjørge H Hansen, PhD, Jennifer A Cochrane, BA, Prof Terence Dwyer, MD, Jing Wang, PhD, Luigi Ferrucci, PhD, Fangyu Liu, MHS, Jennifer Schrack, PhD, Jacek Urbanek, PhD, Pedro F Saint-Maurice, PhD, Naofumi Yamamoto, PhD, Yutaka Yoshitake, PhD, Robert L Newton, PhD, Shengping Yang, PhD, Eric J Shiroma, ScD, Janet E Fulton, PhD

The Lancet Public Health
Volume 7 Issue 3 Pages e219-e228 (March 2022)
DOI: 10.1016/S2468-2667(21)00302-9

All Cause Mortality



The Lancet Public Health 2022 7e219-e228DOI: (10.1016/S2468-2667(21)00302-9)

Minimum Necessary Exercise Amount
"Exercise Snacks"

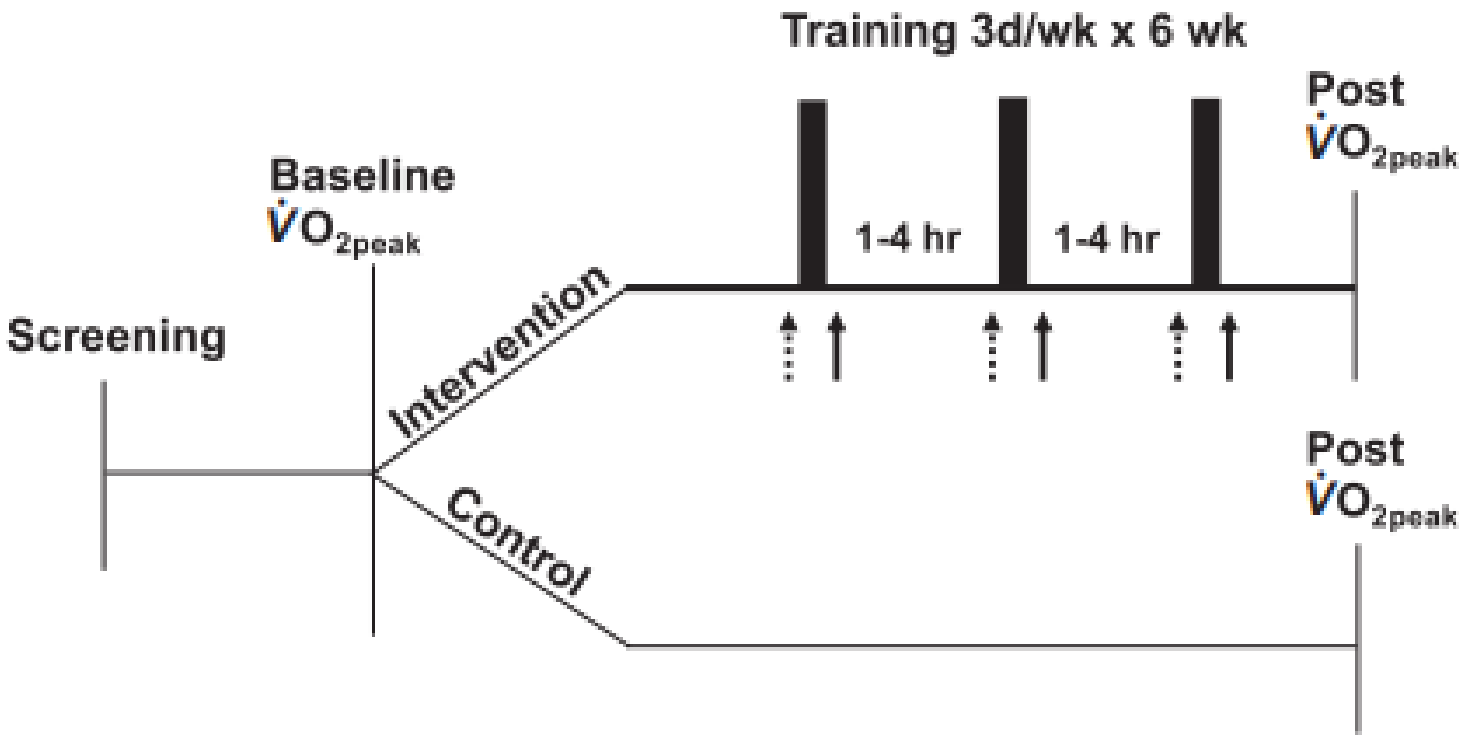


Fig. 1. Study design. Vertical bar represents 1 ascent up a 3-flight stairwell (60 steps). Dashed arrow represent warm-up, solid arrow represent cool-down. $\dot{V}O_{2peak}$, peak oxygen uptake.

Lifestyle Takeaways

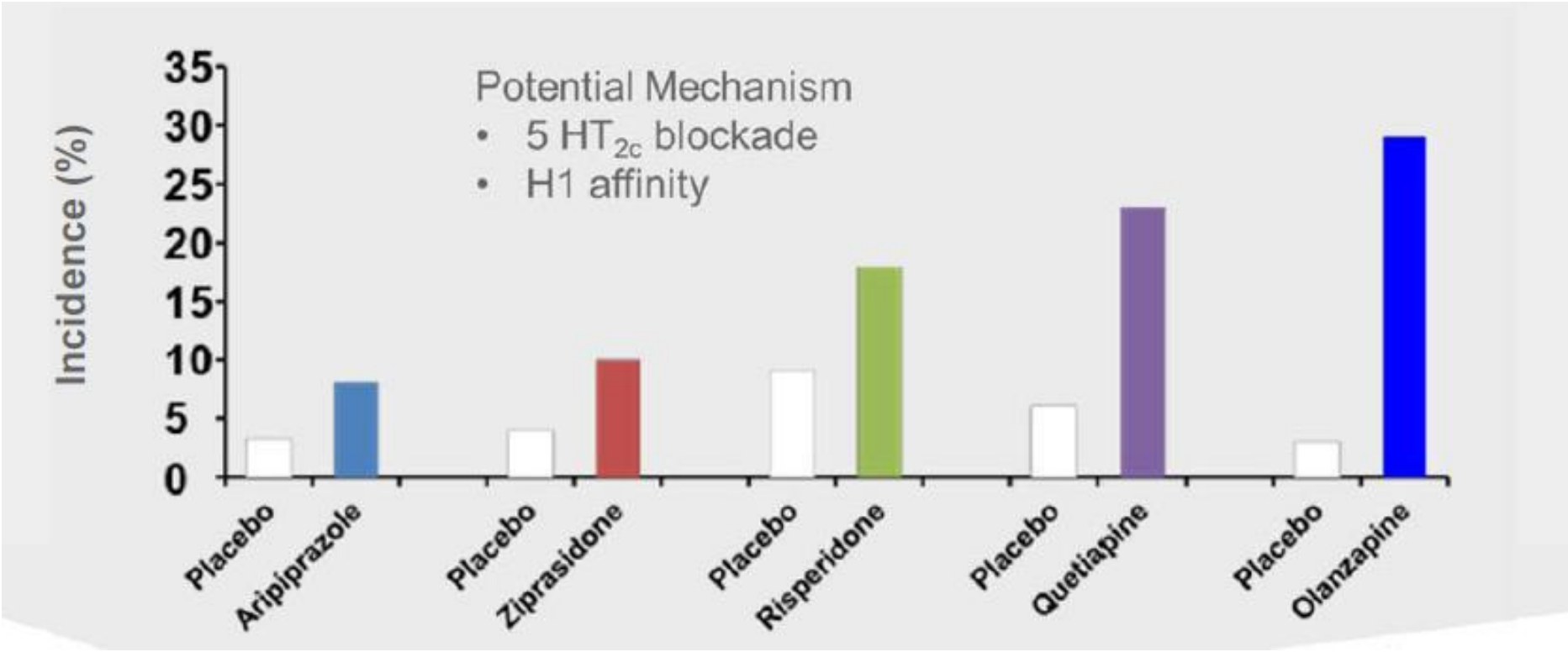
1. Reduce/Eliminate Sugar Sweetened Beverages
2. Increase daily step count
3. Eat some vegetables and protein

3. Obesogenic Medications

- Medications that contribute to weight gain
  - 21% of Adults in the US are on a medication that causes weight gain.

- Common ones:
  - Insulin → add SGLT-2 and GLP-1 to reduce insulin
  - Steroids (PMR pt) → steroid sparing medications
  - SSRI's (Fluoxetine, bupropion most weight neutral)
  - Beta-blockers (Carvedilol preferred: most weight neutral)
  - Depo provera
  - Migraines: Propranolol and amitriptyline are weight +
  - Antipsychotics: Olanzapine and Seroquel most weight +
    - Lybalvi (olanzapine/samidorphan) weight neutral

Anti-psychotic Medications



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The atypical antipsychotic risperidone targets hypothalamic melanocortin 4 receptors to cause weight gain

Li Li[1*], Eun-Seon Yoo[6*], Xiujuan Li[1*], Steven C. Wyler[1], Xiameng Chen[1], Rong Wan[1], Amanda G. Arnold[1], Shari G. Birnbaum[2,3], Lin Jia[5], Jong-Woo Sohn[6], and Chen Liu[1,4]

Atypical antipsychotics such as risperidone cause drug-induced metabolic syndrome. However, the underlying mechanisms remain largely unknown. Here, we report a new mouse model that reliably reproduces risperidone-induced weight gain, adiposity, and glucose intolerance. We found that risperidone treatment acutely altered energy balance in C57BL/6 mice and that hyperphagia accounted for most of the weight gain. Transcriptomic analyses in the hypothalamus of risperidone-fed mice revealed that risperidone treatment reduced the expression of *Mc4r*. Furthermore, *Mc4r* in *Sim1* neurons was necessary for risperidone-induced hyperphagia and weight gain. Moreover, we found that the same pathway underlies the obesogenic effect of olanzapine—another commonly prescribed antipsychotic drug. Remarkably, whole-cell patch-clamp recording demonstrated that risperidone acutely inhibited the activity of hypothalamic *Mc4r* neurons via the opening of a postsynaptic potassium conductance. Finally, we showed that treatment with setmelanotide, an MC4R-specific agonist, mitigated hyperphagia and obesity in both risperidone- and olanzapine-fed mice.

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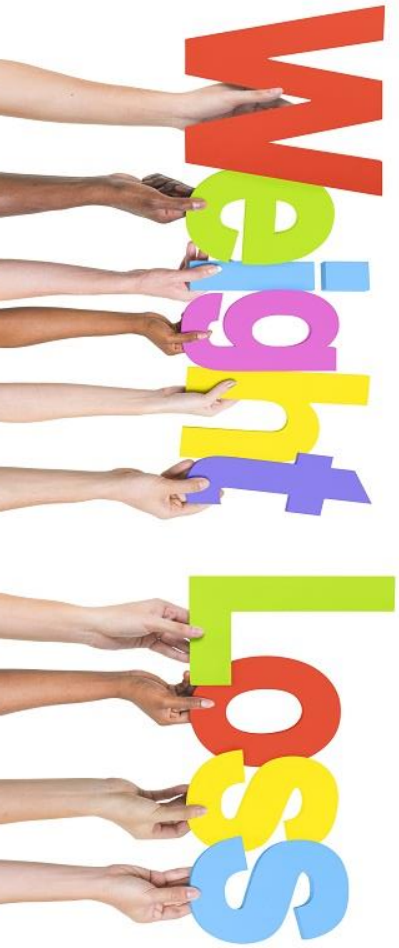
4. Anti-Obesity Medications

Expectations

- Combined with lifestyle changes
- Long term medication use
  - Obesity is a Chronic Disease
- Success: 5-10% weight loss
- Often used off label (more cost effective)
- Closer follow-up

Major goal: at least 5-10% weight loss by 6 months!



Condition	% WL Goals
-Type 2 diabetes -Dyslipidemia -Polycystic Ovarian Syndrome	5% - ≥ 15%
-Metabolic Syndrome -Prediabetes -Female infertility -Osteoarthritis -Gastroesophageal reflux	≥ 10%
Non-alcoholic fatty liver disease -Steatosis -Steatohepatitis	5% or more 10%-40%
Male hypogonadism Urinary stress incontinence	5% - ≥10%
Asthma	7-8%

Indications for Pharmacotherapy

- Patients who failed to benefit from lifestyle modifications/activity alone **AND**
- BMI of 30 (obesity class 1) **OR**
- BMI of 27 (overweight) in presence of at least one weight related comorbidity

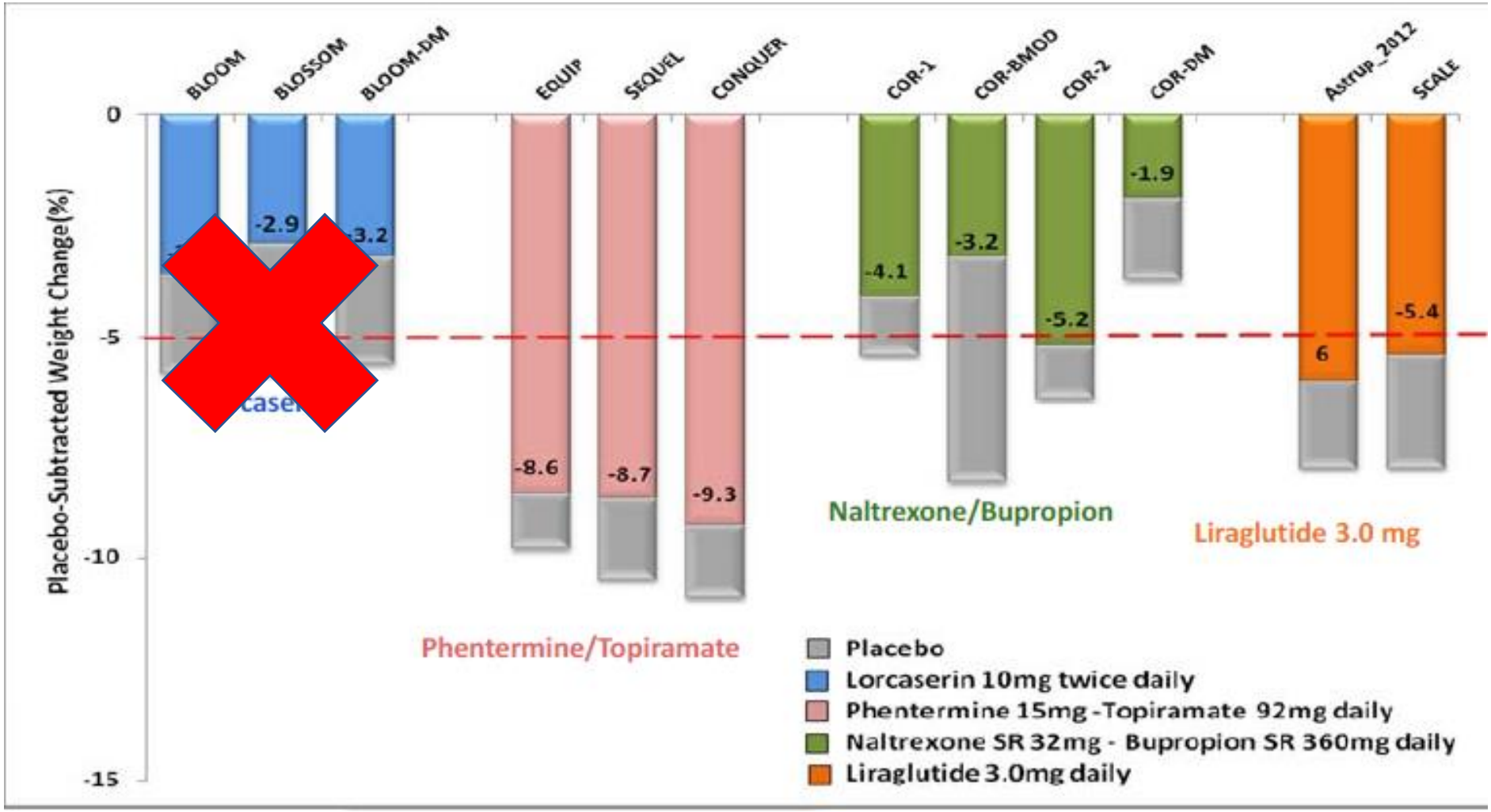
Note: Continue medication if they fall below BMI threshold on medication

HISTORY

Pharm History

- 1947: Amphetamines Approved
- 1959: Phentermine/phendimetrazine/
- Diethylproprion/ benzphetamine
- 1973: Fenfluramine and mazindol
- 1979: Amphetamines: Removed
- 1997: Fenfluramine (part of fen/phen): Removed
- 1999: Orlistat: Approved
- 2012: Lorcaserin (BELVIQ) and Phentermine/topiramate (Qsymia): Approved
- 2014: Buproprion/Naltrexone (CONTRAVE) and liraglutide (Saxend Approved
- 2020: Lorcaserin (BELVIQ) removed and Setmelanotide Approved
- 2021: Semaglutide and Plenity Approved
- 2023: Tirzepatide Approved?

Effective?


BLOOM
BLOSSOM
BLOOM-DM
EQUIP
SEQUEL
CONQUER
COR-1
COR-BMOD
COR-2
COR-DM
Astrup_2012
SCALE
0
-5
-10
-15
Placebo-Subtracted Weight Change(%)
-2.9
-3.2
-8.6
-8.7
-9.3
-4.1
-3.2
-5.2
-1.9
6
-5.4
Phentermine/Topiramate
Naltrexone/Bupropion
Liraglutide 3.0 mg
Placebo
Lorcaserin 10mg twice daily
Phentermine 15mg -Topiramate 92mg daily
Naltrexone SR 32mg - Bupropion SR 360mg daily
Liraglutide 3.0mg daily

Cardiovascular Benefit

Medication	LDL	TG	HDL	A1c	SBP
Phentermine/Topiramate CR	↓	↓	↑	↓	↓
Lorcaserin	↓	↓	—	↓	↓/--
Naltexone SR/Bupropion SR	—	↓	↑	↓	↑
Liraglutide 3.0mg	↓	↓	↑	↓	↓

Journal of the American College of Cardiology, Volume 68, Issue 8, August 2016

Cardiovascular Effects of the New Weight Loss Agents

General Contraindications

- Pregnancy: Women who are pregnant or trying to become pregnant

PEDIATRICS:

- < Age of 12 years old:
- Saxenda Approved 2020
- Setmelanotide Approved 2020

Exceptions:

FDA approved AOD use in Adolescents:

Metformin for DM2, PCOS, IR ≥ 10 yo

(Off label for weight)

Phentermine for ≥ 16 yo (Short term use)

Orlistat for ≥ 12 yo (Long term use)

Orlistat

- Dose (TID w/ Fatty meal):
  - 60 mg (OTC Alli)
  - 120mg (Rx Xenical)

- Mechanism of Action
  - Pancreatic lipase inhibitor
  - Prevents absorption of 30% of ingested fat

- Contraindications
  - Pregnancy, Chronic malabsorption, Cholestasis

Orlistat

- Common Adverse Effects
  - Diarrhea
  - Oily stool (stains)
  - Fecal incontinences
  - Urinary oxalate
  - Fat soluble vitamin deficiency
  - Hepatotoxicity

- Weight Lose: 3.9%; 2 year 2.3%
- ≥ 5% wt loss: 21%
- ≥ 10% wt loss: 12%

Phentermine/ Topiramate ER (Qsymia)

- Mechanism: Sympathomimetic- likely due to release of catecholamines in hypothalamus = decreased appetite and food intake, Topiramate decreases food cravings

- ≥ 5% wt loss: 67% (full dose)
- ≥ 10% wt loss: 47% (full dose)

Phentermine/ Topiramate ER (Qsymia)

- Risk Evaluation and Mitigation Safety (REMS)

- Contraindications:
  - Pregnancy
  - Glaucoma
  - Hyperthyroidism
  - Uncontrolled hypertension
  - Kidney Stones
- Common adverse effects: Paresthesia, dizziness, dysgeusia, carbonated beverages taste weird.

Naltrexone/Buproprion HCL ER (Contrave)

- ≥ 5% wt loss: 42-57%
- ≥ 10% wt loss: 21-35%

Contraindications:

- Uncontrolled HTN
- Seizure disorder (anorexia)
- Chronic opioid use

Common adverse reactions: Nonspecific (Nausea)

Plenity

- Dose: 3 pills before 2 largest meals of the day with 16 oz of water, 20 minutes before meals

- Indications: BMI 25-40.

- Mechanism: Capsules absorb water, enlarging to 100x their size to increase satiety, resulting in less calorie consumption

Plenity

- ≥ 5% wt loss: 59%
- ≥ 10% wt loss: 25%

- Contraindications: Pregnancy, allergic to cellulose, gelatin, citric acid, sodiu, steraryl fumarate. Avoid in those with esophageal or GI transit/motility disorders.

- Adverse drug reaction: Diarrhea, distended abdomen, constipation, flatulence (similar to placebo).

Liraglutide (Saxenda)

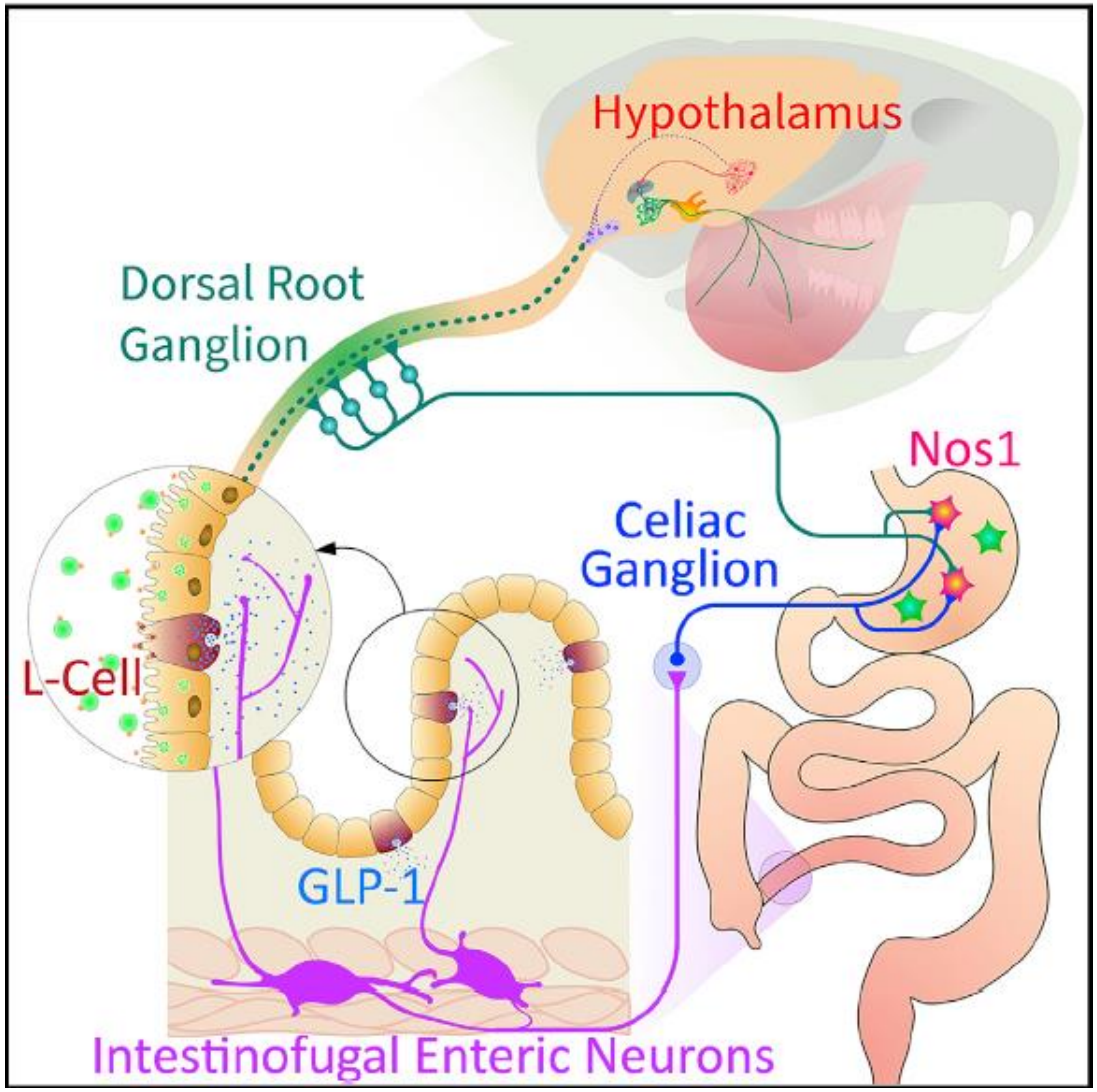
- Dose:
  - 0.6mg SC x 7 days
  - Increase Q Week by 0.6 mg until…
  - 3.0 mg daily maintenance dose

- If < 4% weight loss after 16 weeks = stop

- Mechanism: GLP-1 agonist. Works in hypothalamus reducing food intake, increased satiety, and decreased caloric intake, while improving glucose metabolism

GLP1 Appetite Reduction

- GLP1 is produced by the intestinal cells, acts locally, then the satiety signal is conducted to the brain
- GLP1 is the mechanism for the “Ileal Brake”



Zhang et al., 2022, Cell 185, 1–17
July 7, 2022 ª 2022 Elsevier Inc.
https://doi.org/10.1016/j.cell.2022.05.007

Liraglutide (Saxenda)

- ≥ 5% wt loss: 62%
- ≥ 10% wt loss: 34%

Saxenda®

- Contraindications: FH of medullary thyroid cancer or MEN type II, Pregnancy

- Adverse drug reaction: NAUSEA! Abdominal pain, headache, decreased appetite, hypoglycemia (if on insulin)

Semaglutide

- Newest GLP-1 Approved for Obesity (6/2021)
- Once weekly (autoinjector)
  - Increase dose monthly until at 2.4 mg/week
  - 0.25 → 0.5 → 1.0 → 1.7 → 2.4

- Same mechanism/side effects of liraglutide

wegovy™

Semaglutide

- STEP trials (Semaglutide Tretment Effect in Patients with Obesity)
- Step 1 (Weight management 68 weeks)
  - **14.9% weight loss at 68 weeks**
- Step 8 (Semaglutide vs Liraglutide)
  - Average of 9% greater bodyweight than liraglutide 3.0mg

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Off-label use Medication

Why off-Label?

- Mostly cost and insurance coverage
- Safety has been studied
- Target comorbidities
  - I.e. Topiramate for migraines, and Wellbutrin for depression.
- Contraindication to one medication in combo med
  - I.e. If history of kidney stones, can not use Qsymia, but phentermine monotherapy may be effective.

Cost (good rx- Walmart)

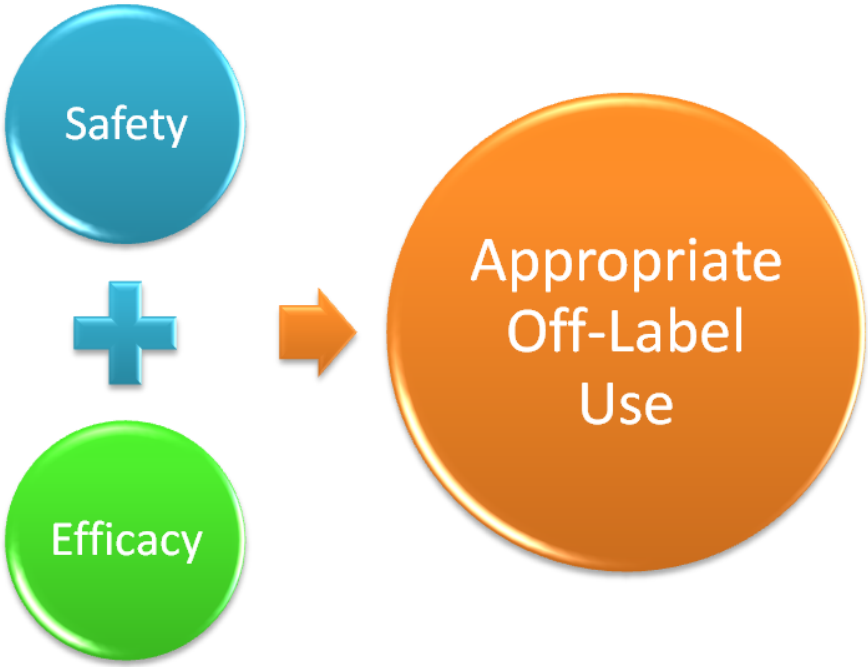
- Phentermine (37.5 mg Tablet) x 30: $12.77
- Topamax (50 mg tablet) x 60: $9.00
- Qsymia (7.5/46 mg) x 30 capsules: $193.70

- Naltrexone: (50 mg) 50 tablets: $21.63
- Buproprion: (75 mg) 60 tablets: $13.94
- Contrave (8/90 mg) x 120 tablets: $272.10

- Saxenda/Wegovy (one month box) $1462

Off Label Use

- Sympathomimetics (phentermine) > 12 wks
- Naltrexone/Buproprion
- Phentermine/Topiramate
- Metformin
- Topiramate
- Tirzepatide



Phentermine

- FDA approved for short term use only

- NOT amphetamine
- No evidence of addiction or withdrawal
- However, FDA approved in 1959 during U.S. epidemic of amphetamine addiction
  - Therefore approved for short term to prevent addiction.

- Prescribe longer than 3 months? Off label!

Phentermine

- 8 mg tablet (1/2 to 1 tablet daily – TID)
- 15 mg capsule
- 30 mg capsule
- **37.5 mg scored tablet (Qd);**
  - Capsule (Qd)

- DEA Schedule IV

Phentermine

Most Common

- Dry mouth – weak anticholinergic agent; usually tolerable
- Insomnia – early, usually fades; if not melatonin may help
- Constipation

Less Common

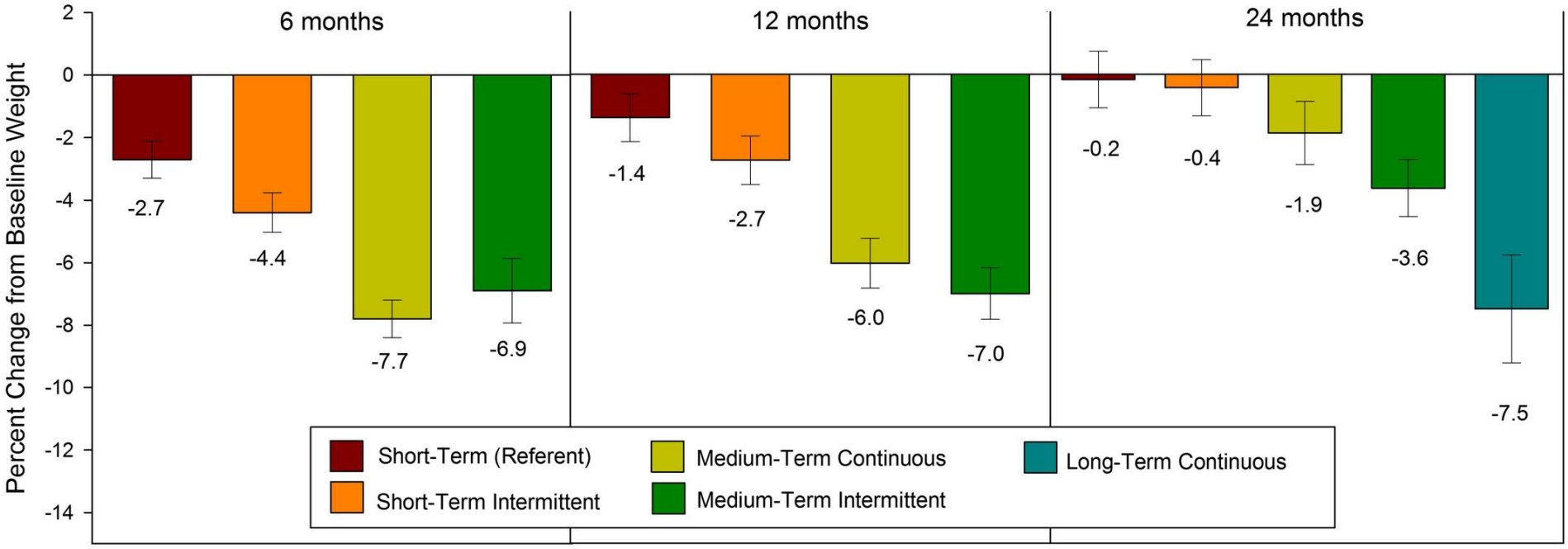
- Bruxism
- Palpitations
- Difficulty with urination in males with prostatic hyperplasia
- Headache

Uncommon

- Impotence, changes in libido
- Dysphoria
- Irritability

Safety and Effectiveness of Longer-Term Phentermine Use:

Clinical Outcomes from an Electronic Health Record Cohort



Obesity, Volume: 27, Issue: 4, Pages: 591-602, First published: 21 March 2019, DOI: (10.1002/oby.22430)

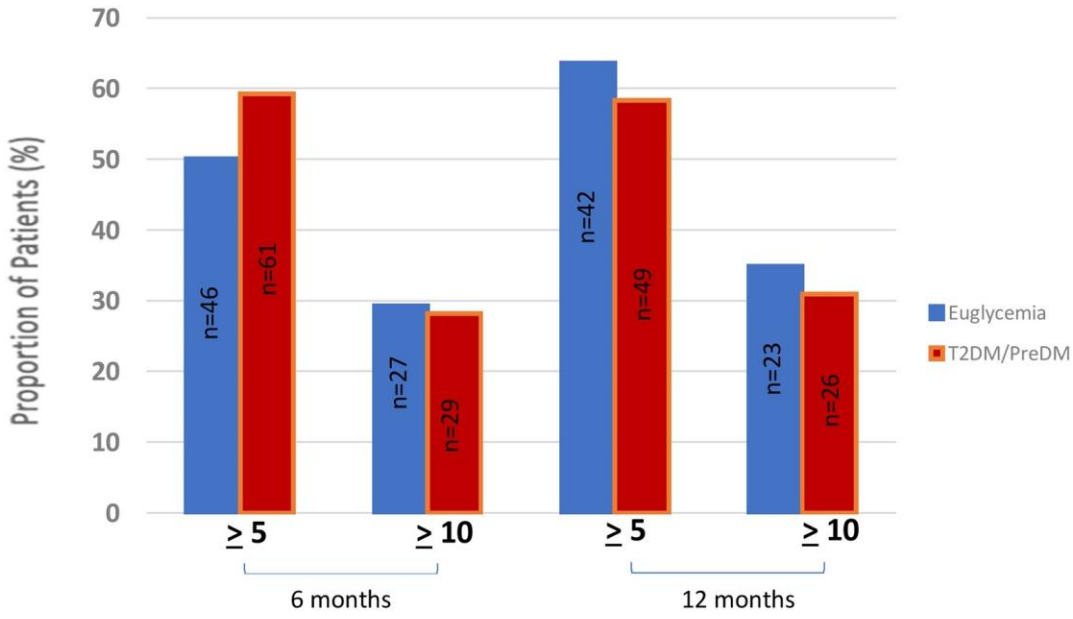
Metformin

- Weight Loss: 2% in T2DM and insulin resistance (including PCOS)
- ANTIPSYCHOTIC-RELATED WEIGHT GAIN!
- Dose 500-2,000 mg/day

- Mechanism: Decreases hepatic glucose production, increased muscle glucose uptake

- Side effects: GI! Use ER
  - If s/p RYGB use IR

Metformin Weight Loss



Metformin-induced weight loss in patients with or without type 2 diabetes/prediabetes: A retrospective cohort study, Obesity Research & Clinical Practice, Volume 15, Issue 1, 2021

Diabetes Meds

- SGLT2 have a modest weight benefit (5-10 pounds) as well as cardiovascular benefits
  - Empagliflozin 10/25mg or Dapagliflozin 5/10mg
  - Very helpful for fluid retention weight

- GLP1 medications for Diabetes
  - Dulaglutide, Liraglutide, Semaglutide, Tirzepatide while a different brand definitely have weight benefits
- Pramlinitide
  - Currently available Amylin analog (mealtime dosing is difficult) soon available in combination with mealtime insulin

Topiramate

- Approved for seizures and migraines
- Except for Qsymia, not approved for weight loss

- Typical dosing:
  - Epilepsy: 400 mg/day
  - Migraines: 100-200 mg/d
  - Obesity: 25 – 100 mg/day

- Start at 25 qHS.
  - Increase every 2 weeks by 25 mg (BID)

**If not tolerating, consider zonisamide

Binge Eating Disorder

- The key diagnostic features of BED are:
- Recurrent and persistent episodes of binge eating
- Binge eating episodes are associated with three (or more) of the following:
  - Eating much more rapidly than normal
  - Eating until feeling uncomfortably full
  - Eating large amounts of food when not feeling physically hungry
  - Eating alone because of being embarrassed by how much one is eating
  - Feeling disgusted with oneself, depressed, or very guilty after overeating
- Marked distress regarding binge eating
- Absence of regular compensatory behaviors (such as purging).
- Frequency is 1 episode per week for 3 months.

Binge Eating Disorder

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- Vyvanse FDA Approved but sometimes difficulty with insurance coverage and cost
- Topiramate: efficacious and cheap

TABLE 3. Response to Treatment Among Patients With Binge Eating Disorder Randomly Assigned to 14 Weeks of Double-Blind Treatment With Topiramate or Placebo

	Intent-to-Treat Group[b]				Patients Who Completed 14 Weeks of Treatment[c]			
	Placebo (N=30)		Topiramate (N=28)		Placebo (N=19)		Topiramate (N=16)	
Response[a]	N	%	N	%	N	%	N	%
None	11	37	5	18	5	26	1	6
Moderate	7	23	2	7	6	32	0	0
Marked	3	10	3	11	3	16	2	13
Remission	9	30	18	64	5	26	13	81

[a] Categories defined by the percentage decrease in binge frequency from baseline: remission=cessation of binges; marked=75%–99% reduction; moderate=50%–74% reduction; none=less than a 50% reduction.

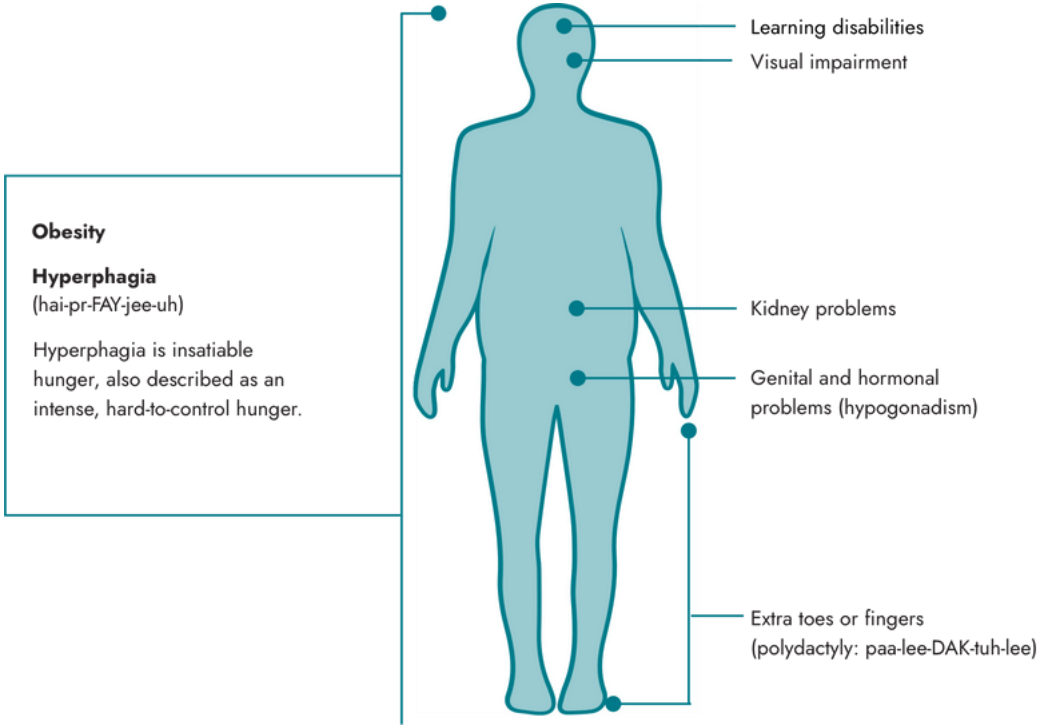
[b] Last observation carried forward, patients had at least one postrandomization efficacy measure; significant difference between groups ($p<0.02$, exact trend test).

[c] Significant difference between groups ($p=0.002$, exact trend test).

Genetic Obesity

- First Targeted Medication Setmelanotide Approved in December 2020
- Initially studied in Homozygous PCSK1, Leptin Receptor, and POMC deficiency.
- 2022 indication approval expanded to including Bardet Biedl Syndromic Obesity
- Efficacy: 80% of patients lost >10% TBW, average weight loss in responders of 28% TBW
- Efficacy: approximately 10% TBW in BBS
- Long Term Case Series for POMC: two patients on medicine for 6 years maintained bodyweight loss of 37 and 46%.

Syndromic Obesity



Dietary Supplements?

- No legal supplement has demonstrated long-term efficacy for weight loss

- Supplements usually contain stimulants
  - Not pure
  - May contain stimulants previously taken off the market (sibutramine, fenfluramine) thyroxine, diuretics, laxatives
  - **Common cause for hepatotoxicity! (20% of cases in US due to dietary supplements)**

Indications for Bariatric Surgery

- BMI of 40 (obesity class 3) **OR**
- BMI of 35 (obesity class 2) in presence of at least one weight related comorbidity

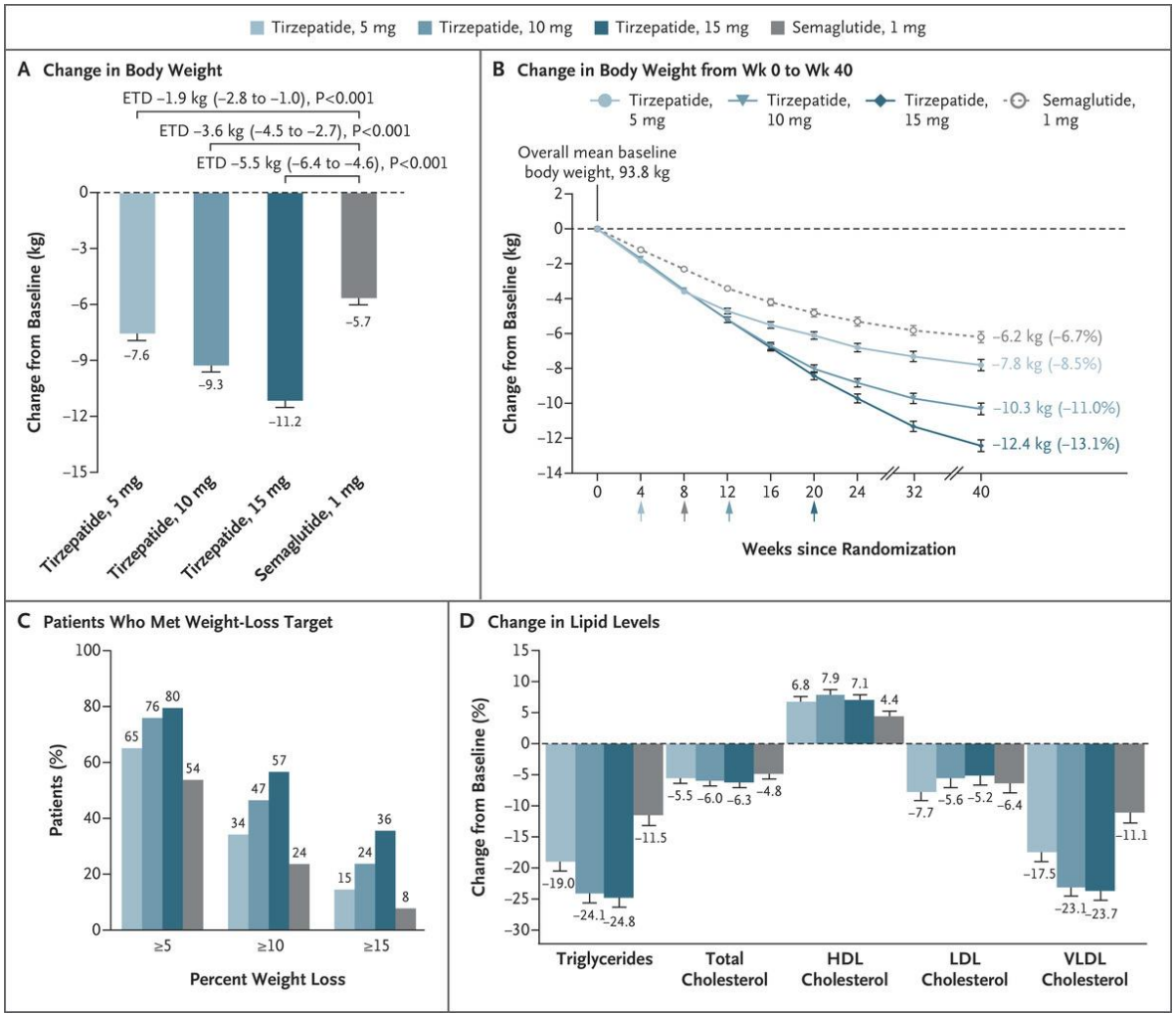
Effects of Bariatric Surgery

- Large Cardiovascular mortality benefit in DM2, CAD, CHF, CKD/ESRD (NNT for mortality of 7-15)
- Long term weight loss on average around 25% Total Bodyweight
- Risk of nutritional deficiencies

The Future is Bright!

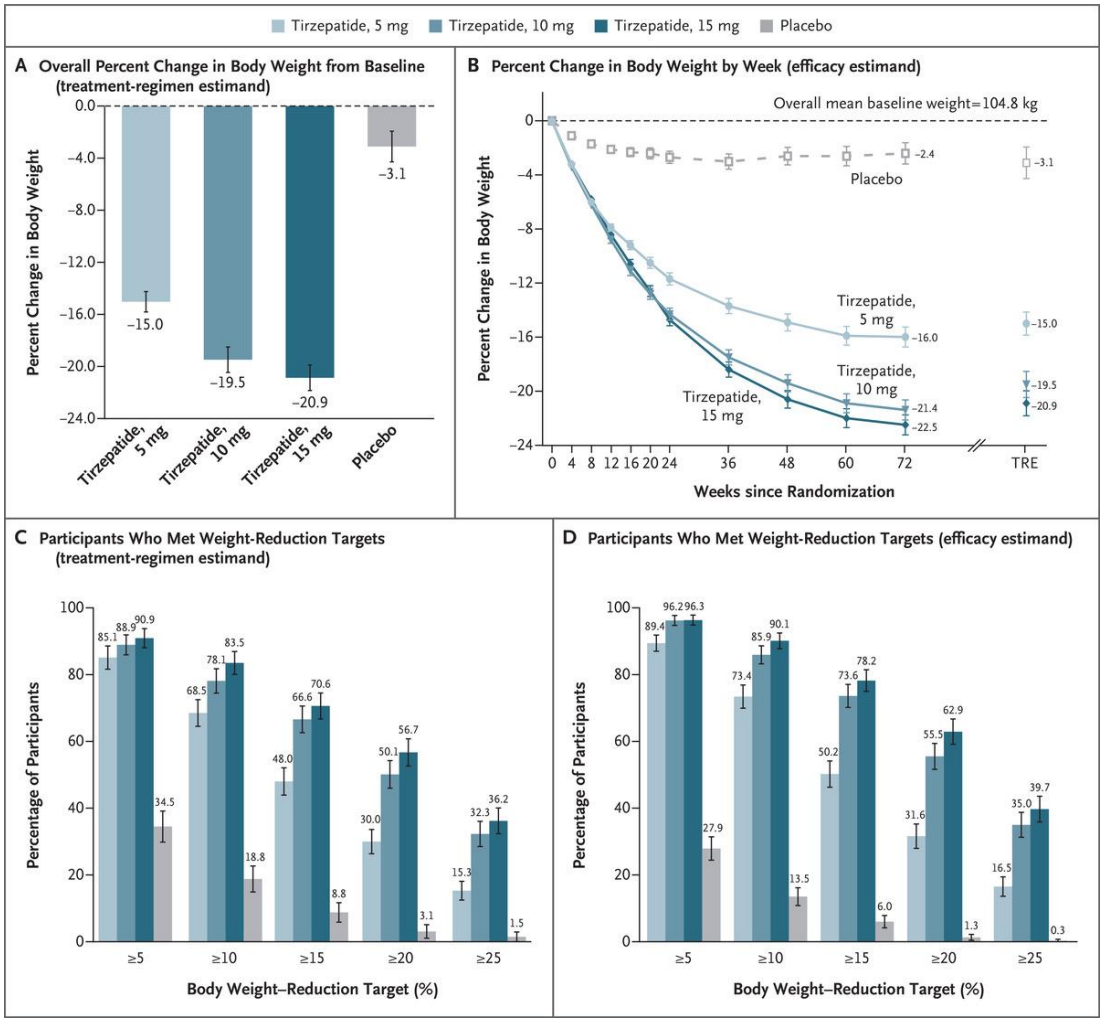
- Clinical Efficacy of Wegovy compared to previous medications is a large step forward.
- Next Generations therapies:
  - Combination GLP-1 & GIP analogues (Tirzepatide)
  - Long Acting amylin Analogues
  - Dual GRA/GLP therapies
  - Triple Incretin Therapy
  - Monoclonal Antibodies

Effect of Once-Weekly Tirzepatide, as Compared with Semaglutide, on Body Weight, the Percentage of Patients Who Met Weight-Loss Goals, and the Lipid Profile.



JP Frías et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2107519

Effect of Once-Weekly Tirzepatide, as Compared with Placebo, on Body Weight.



Over 20% average weight loss on full dose

38% of patients on full dose lost over 25% of Total bodyweight!

Currently only approved for T2DM (estimated 2024)

AM Jastreboff et al. N Engl J Med 2022. DOI: 10.1056/NEJMoa2206038

Diabetes. 2022;71(Supplement_1). doi:10.2337/db22-334-OR

334-OR: Pemvidutide (ALT-801) , a Balanced (1:1) GLP-1/Glucagon Dual Receptor Agonist, Induces Rapid and Marked Weight Loss without the Need for Dose Titration in People with Overweight/Obesity

10% TBW loss in 12 weeks with no dose titration

Table 1: Changes (Δ) in body weight and cardiometabolic risk factors

Outcome		Pemvidutide			Placebo (n=7)
		1.2 mg (n=7)	1.8 mg (n=9)	2.4 mg (n=11)	
Weight loss	% Δ, mean (SE)	-4.9 (1.2)	-10.3 (1.1) ***	-9.0 (1.1)**	-1.6 (1.3)
Total cholesterol	% Δ, mean (SE)	-21.2 (2.8)*	-27.2 (3.4)***	-25.3 (4.6)***	-5.3 (3.7)
LDL cholesterol		-19.3 (3.6)*	-24.3 (3.7)***	-21.2 (6.4)***	2.1 (6.1)
Triglycerides		-40.0 (1.7)	-30.2 (7.7)	-23.9 (6.7)	-16.6 (7.0)
Systolic blood pressure†	Δ mmHg, mean (SE)	-8.7 (4.2)	-14.0 (3.9)	-13.0 (3.2)	-9.3 (7.9)
Diastolic blood pressure†		-5.3 (4.0)	-7.1 (1.0)	-6.5 (3.5)	-2.7 (5.5)
HOMA-IR, Baseline	mean (SE)	2.5 (0.5)	2.4 (0.8)	3.1 (0.5)	2.4 (0.6)
HOMA-IR, Week 12		2.0 (0.6)	2.2 (0.9)	2.4 (0.4)	2.4 (0.5)

HOMA-IR= Homeostatic Model Assessment of Insulin Resistance
Value different from placebo, *p <0.05, **p < 0.01, ***p<0.005; † per protocol, all subjects were normotensive at baseline

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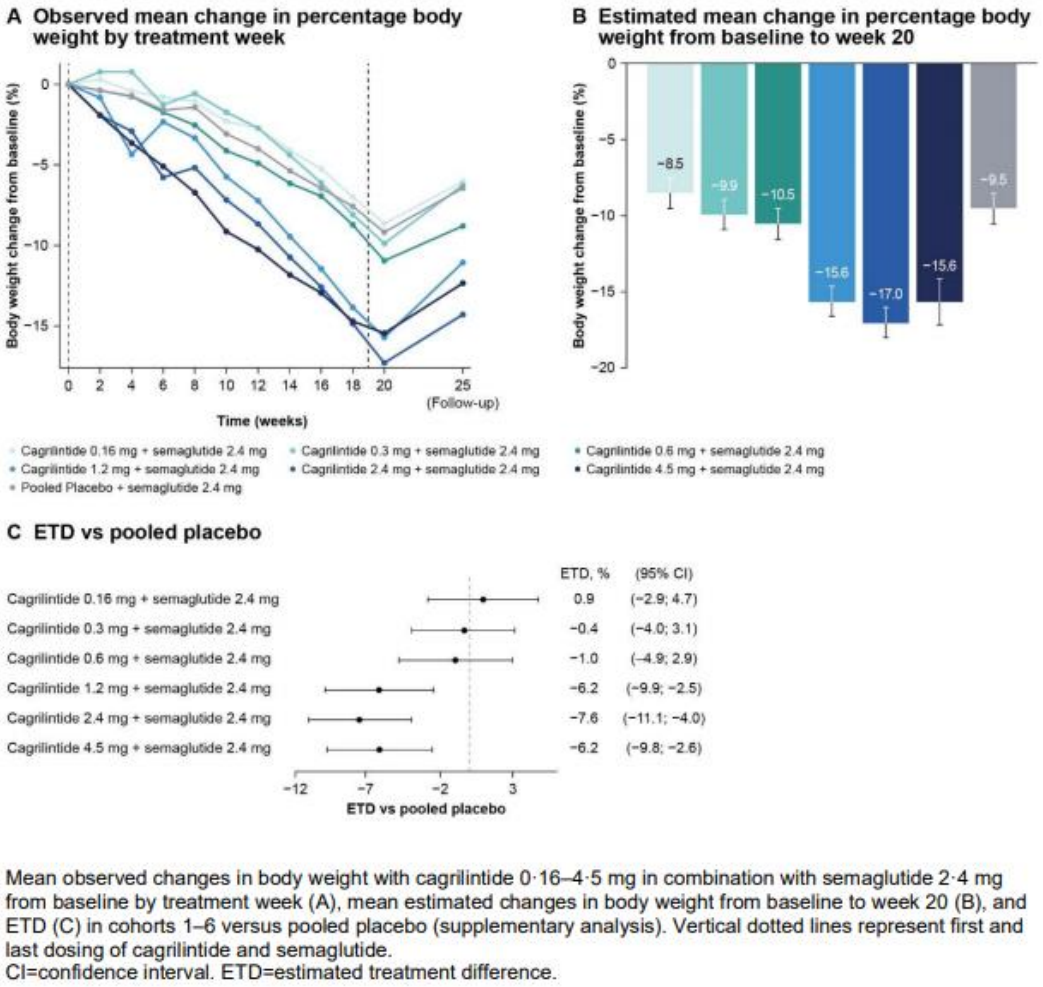
MOMENTUM Week 24 Interim Analysis—Summary of Efficacy Findings

Primary Endpoint: Body weight		Placebo (n=39)	1.2 mg (n=40)	1.8 mg (n=40)	2.4 mg (n=41)
Δ Body weight, all subjects	%, LSM (SE)[1]	-1.0 (0.8)	-7.3 (0.8)***	-9.4 (0.8)***	-10.7 (0.9)***
Impact of Baseline Body Weight on Efficacy		**Placebo (n=28)**	**1.2 mg (n=30)**	**1.8 mg (n=31)**	**2.4 mg (n=31)**
Δ Body weight, subjects with baseline weight ≤ 115 kg	%, LSM (SE)[1]	-0.8 (1.0)	-8.2 (1.1)***	-10.6 (1.1)***	-11.9 (1.1)***

Cagrilinitide + Semaglutide

Recent Phase 1 trial in Lancet in combination with Semaglutide 2.4mg demonstrated weight loss of 16-17% TBW at 20 weeks.

Figure S3: Changes in body weight from baseline (secondary analysis)



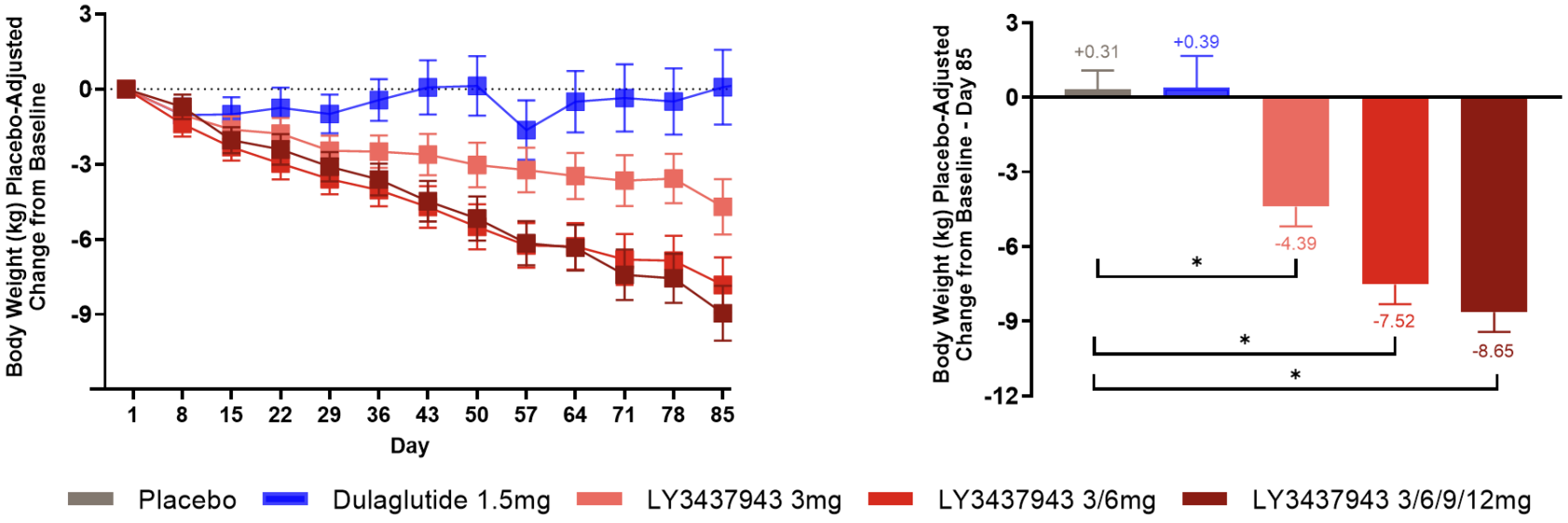
Mean observed changes in body weight with cagrilintide 0·16–4·5 mg in combination with semaglutide 2·4 mg from baseline by treatment week (A), mean estimated changes in body weight from baseline to week 20 (B), and ETD (C) in cohorts 1–6 versus pooled placebo (supplementary analysis). Vertical dotted lines represent first and last dosing of cagrilintide and semaglutide.
CI=confidence interval. ETD=estimated treatment difference.

CagriSema Phase 2

According to top line trial results, following **32 weeks** of treatment, subjects who received CagriSema attained a 2.18%-points numerically greater decline in HbA1c versus 1.79%-points and 0.93%-points for semaglutide and cagrilintide alone, respectively.
Subjects in the CagriSema arm had a 15.6% numerically greater decline in body weight versus 5.1% and 8.1% with semaglutide and cagrilintide, respectively.

Triple Agonists

Recent Phase 1 trial of “GGG” produced 10% total bodyweight loss at 12 weeks in patients with diabetes (Double Tirzepatide)



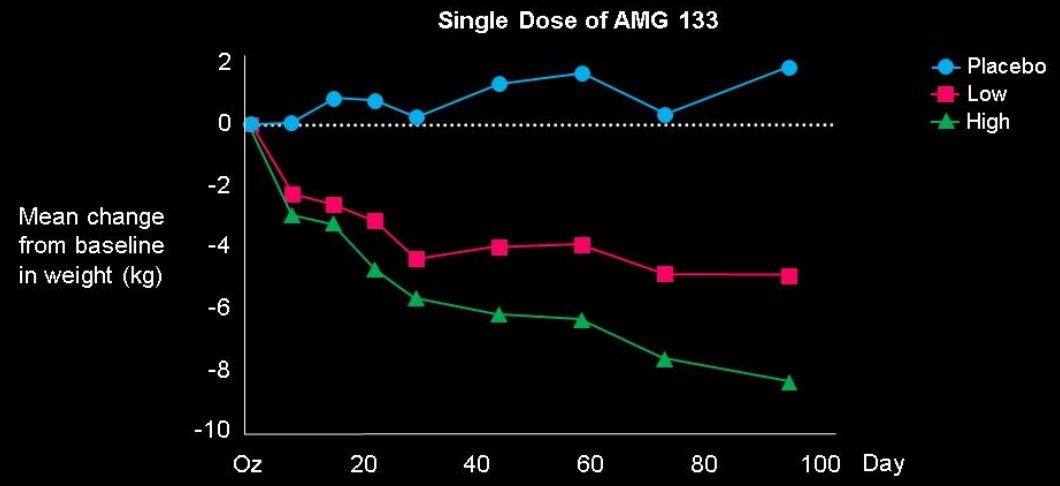
Retatrutide (Triple G)

Preliminary analysis from phase 2 trials indicated people taking retatrutide with obesity (a body mass index of 30 or higher), but not diabetes, could lose up to 24% of their body weight in 48 weeks.

That's more weight loss at a faster rate than trial results for tirzepatide, which led to 20% reduction in body weight in 72 weeks

A New Challenger Enters the Arena?

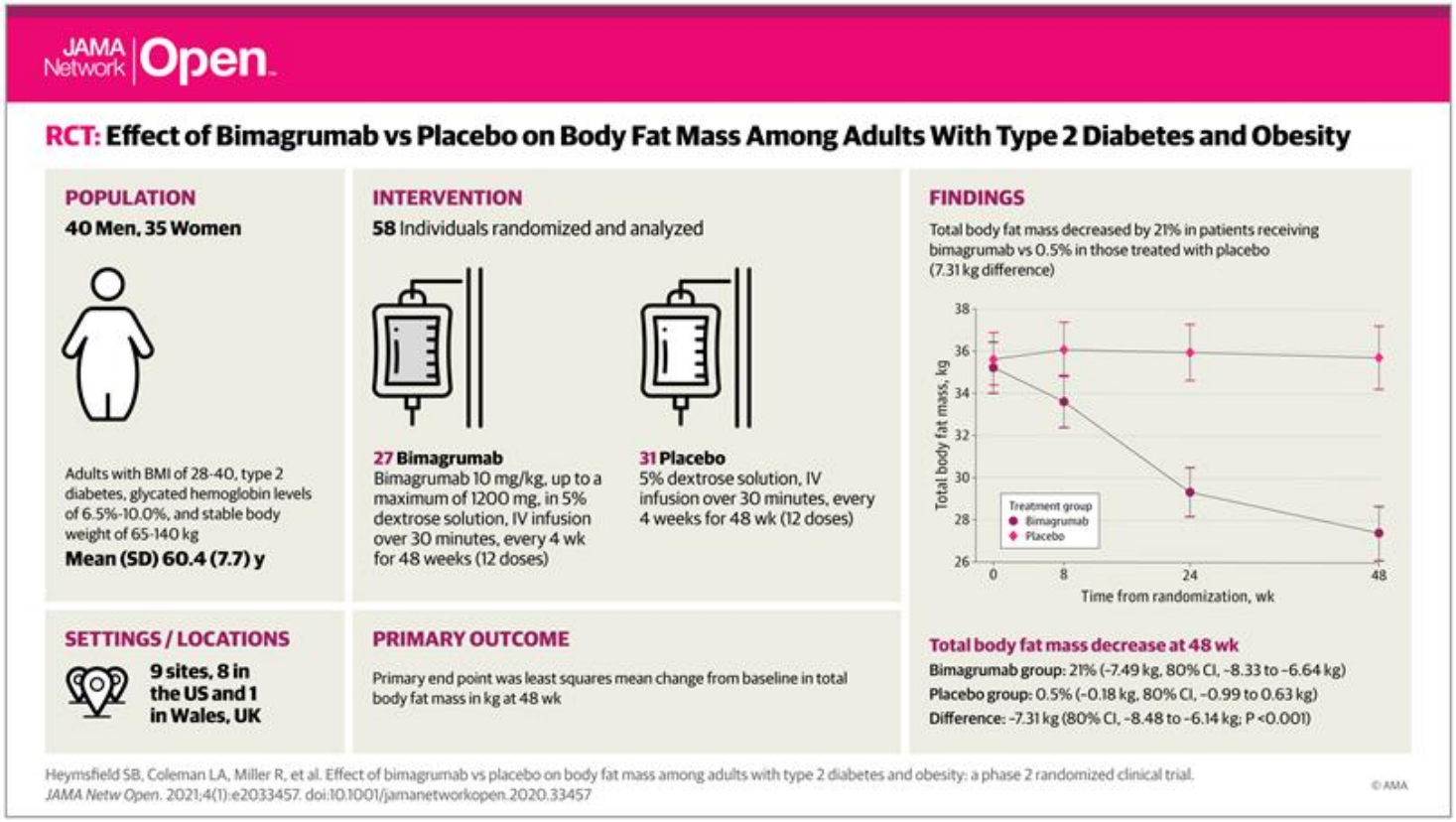
The GIPR Antagonist-GLP-1R Agonist AMG 133
Single Dose efficacy in people with obesity



Multi-dose mean percent change in BW by day 85: -7.19% (low dose) to -14.52% (high dose) in AMG 133-treated vs 1.49% in placebo.–Total of three doses, each 4 weeks apart.
–Plateau on weight reduction not observed- Nov 7 2022 AHA 2022

Kg = kilogram
Data source: Amgen internal data
https://investors.amgen.com/static-files/6d823d7d-2fd1-405a-8c0e-22aa91bee682

Bimagrumab: the next frontier?



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Questions?

References

1) AACE/TOS/ASMBS/OMA/ASA 2019 Guidelines

CLINICAL PRACTICE GUIDELINES FOR THE PERIOPERATIVE NUTRITION, METABOLIC, AND NONSURGICAL SUPPORT OF PATIENTS UNDERGOING BARIATRIC PROCEDURES – 2019 UPDATE: COSPONSORED BY AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/AMERICAN COLLEGE OF ENDOCRINOLOGY, THE OBESITY SOCIETY, AMERICAN SOCIETY FOR METABOLIC & BARIATRIC SURGERY, OBESITY MEDICINE ASSOCIATION, AND AMERICAN SOCIETY OF ANESTHESIOLOGISTS*

2) AACE/ACE Guidelines 2016 Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR MEDICAL CARE OF PATIENTS WITH OBESITY

References

3) 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society

4) Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline

Caroline M. Apovian, Louis J. Aronne, Daniel H. Bessesen, Marie E. McDonnell, M. Hassan Murad, Uberto Pagotto,

5) Obesity medical association: 2021 Obesity Algorithm

Appendix 1

Medication Category	Weight positive	Weight neutral/ variable effect	Weight negative

Antidepressants	• TCA's (Tertiary amines)
	  ○ Amitriptyline
	  ○ Doxepin
	  ○ Imipramine
	• SSRIs
	  ○ Paroxetine
	  ○ Citaprolam
	  ○ Escitaprolam
	  ○ Sertraline
	  ○ Duloxetine
	• MAOIs
	  ○ Isocarboxazid
	  ○ Phenelzine
	  ○ Mirtazapine
	  ○ Brexiprazole
		• TCA's (Secondary amines)
		  ○ Desipramine
		  ○ Nortriptyline
		  ○ Protriptyline
		• SSRIs
		  ○ Escitalopram
		  ○ Fluoxetine
		  ○ Sertraline
		• SNRIs
		  ○ Desvenlafaxine
		• Some irreversible monoamine oxidase inhibitors (i.e., tranylcypromine)
		• Some other serotonergic agents (Vortioxetine)
			• Bupropion

Anti Seizure	• Carbamazepine • Gabapentin • Valproate • Pregabalin		• Lamotrigine • Topiramate • Zonisamide

 Reference/s: [133] [141] [142] [143]

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Medication Category	Weight positive	Weight neutral/ variable effect	Weight negative
GYN	• Depo provera	• IUDs or other LARC	• Barrier methods
Hormones	• Glucocorticoids • Estrogens	• Progestins ○ Injectable or implantable progestins may have greatest risk for weight gain • Testosterone	• Testosterone: May reduce percent body fat and increase lean body mass
Migraine	• Amitriptyline • Gabapentin • Paroxetine • Valproic acid • Some beta-blockers		• Topiramate

Reference/s: [133] [141] [142] [143]

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Medication Category	Weight positive	Weight neutral/ variable effect	Weight negative
Mood Stabilizer	• Gabapentin • Divalproex • Lithium • Valproate • Vigabatrin • Cariprizane • Carbamazepine	• Lamotrigine (sometimes reported to decrease body weight) • Carbamazepine (sometimes reported to increase body weight) • Oxcarbazepine	• Lamotrigine
Antipsychotics	• Olanzapine • Quetiapine • Clozapine • Risperidone • Zotepine • Asenapine • Chlorpromazine • Iloperidone • Paliperidone • Sertindole • Lithium • Bexipiprazole	• Amisulpride • Aripiprazole • Haloperidol • Lurasidone • Ziprasidone • Cariprazine	

Medication Category	Weight positive	Weight neutral/ variable effect	Weight negative
Hypnotics	• Diphenhydramine	• Benzodiazepines • Melatonergic hypnotics • Trazodone	

Medication Category	Weight positive	Weight neutral/ variable effect	Weight negative

Cardiovascular	• Beta Blockers:
	  ○ Propranolol
	  ○ Atenolol
	  ○ Metoprolol
	• Older and/or less lipophilic dihydropyridine ("dipine") calcium channel blockers may increase body weight gain due to edema, compared to non-dihydropyridines and lipophilic dihydropyridines. The increased edema may exacerbate obesity-related edema (and sleep apnea related peripheral edema), and also confound body weight as a measure of body fat
	- Nifedipine
	- Amlodipine
	- Felodipine
		Carvedilol	

Diabetes	• **Most insulins** • Sulfonylureas • Thiazolidinediones • Meglitinides		• Metformin • GLP1-agonists • SGL 2 inhibitors • Alpha glucosidase inhibitors • Pramlintide