

The ABCD of Off-Label Medications for Weight Management

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Learning Objectives

At the conclusion of this presentation, participants should be able to:

Discuss the main principles of management of adiposity-based chronic disease (ABCD).

Identify the efficacy of commonly prescribed medications that may be used off-label for weight reduction.

List major safety considerations for medications prescribed off-label for weight reduction.

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Disclosures

- Speaker for Sanofi.
- All financial interests with ineligible companies have been mitigated.
- This activity may contain discussion of unlabeled/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

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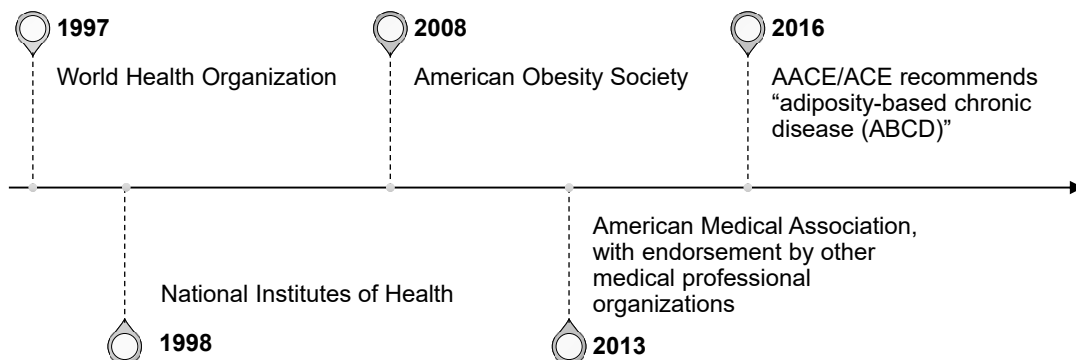
AUDIENCE POLL

What is adiposity-based chronic disease (ABCD)?

- A. diabetes
- B. dyslipidemia
- C. obesity

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Obesity as a Chronic Medical Condition



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ABCD Management Guidelines in the U.S.

AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults – 11/2013

AACE/ACE Comprehensive Clinical Practice Guidelines For Medical Care of Patients with Obesity – 7/2016

AGA Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity – 11/2022

AAP Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity – 2/2023

Others

<https://www.ahajournals.org/doi/10.1161/01.cir.0000437739.71477.ee> [https://www.endocrinepractice.org/article/S1530-891X\(20\)44630-0/fulltext](https://www.endocrinepractice.org/article/S1530-891X(20)44630-0/fulltext)
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[https://www.gastrojournal.org/article/S0016-5085\(22\)01026-5/fulltext](https://www.gastrojournal.org/article/S0016-5085(22)01026-5/fulltext)
<https://publications.aap.org/pediatrics/article/151/2/e2022060640/190443/Clinical-Practice-Guideline-for-the-Evaluation-and>

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Assessment in Adults

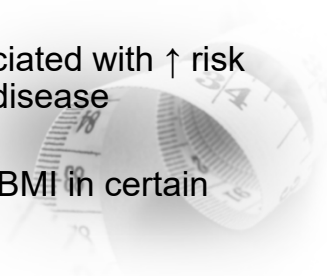
- Body mass index (BMI)
 - Correlated with total body fat, morbidity, and mortality
 - Weight divided by height squared (kg/m^2 or $\text{lbs}/\text{inches}^2 \times 703$)

Normal = BMI 18.5-24.9
Overweight = BMI 25-29.9
Obesity class I = BMI 30-34.9
Obesity class II = BMI 35-39.9
Obesity class III (“severe obesity”) = BMI ≥ 40

- *health risks start at a BMI < 25 in some populations

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Assessment in Adults

- Waist circumference
 - Abdominal/visceral fat associated with greater health risks than peripheral fat
 - **High: > 40 inches in males, > 35 inches in non-pregnant females**
 - Lower in some populations
 - BMI 25-34.9: high waist circumference associated with ↑ risk for type 2 DM, dyslipidemia, HTN, coronary disease
 - Little added predictive value when BMI > 35
 - May be a better predictor of health risk than BMI in certain populations (Asian Americans, elderly)
- 

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Therapeutic Goals in Management of ABCD



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General Management Principles

- Realistic weight loss goals
- Realistic initial target for weight loss
 - Decrease total body weight by 5-10% over 6 months
 - 1-2 lbs per week
- Slow and steady reduction in weight loss
 - To minimize risk of weight regain
 - Very rapid weight loss associated with increased rate of gallstone formation & electrolyte imbalance

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Meta-Analysis of Long-Term Orlistat's RCT (mean placebo-subtracted results for **prescription** dose)*

	Orlistat
Change in weight*	-6.3 lbs (-2.9%)
BMI	-1.1
Waist circumference (cm)	-2.06
SBP, DBP, HR	-1.5, -1.4, NR
LDL-C, HDL-C (mg/dl)	-10, -1.2
Improves glycemic control in patients with diabetes?	Yes (-18.5 mg/dL, -0.38% A1c)
↓ incidence of diabetes?	37% after 4 years
Attrition	7-50%
Longest study duration	4 years

*amount more than placebo

yellow font denotes statistically significant results

Rucker D et al. BMJ 2007;335: 1194 – 1199.

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Treatment Options

- Dietary therapy
- Physical activity
- Behavioral modifications
- Pharmacologic – used **in conjunction with the above**
- Bariatric surgery
- Devices (eg, intragastric balloon, hydrogels)

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Treatment Selection Guide

Treatment	Body Mass Index Category (kg/m ²)				
	25-26.9	27-29.9	30-34.9	35-39.9	≥ 40
Dietary therapy, physical activity, & behavioral change	With ≥1 co-morbidities, including elevated WC	With ≥1 co-morbidities, including elevated WC	+	+	+



WC = waist circumference

2013
AHA/ACC/
TOS
Guideline
for the
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and Obesity
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Therapeutic Lifestyle Changes

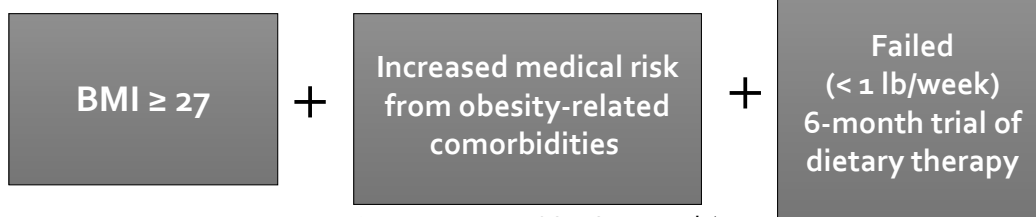
- Meta analysis 31 RCTs – 20,816 participants (70% with cardiometabolic risk factors), duration: ≥1 year
- Excluded RCTs with: specific diets, drug therapy, surgical therapy, RCTs with >5% lost to follow-up
- Interventions: mainly hypocaloric diet, ≥1 face-to-face intervention
- Weight reduction compared to control (usual care)
 - At 1 year: ~8 lbs
 - At 3 year: ~5.4 lbs
 - Greater in RCTs with > 28 compared to ≤ 28 interventions/year (10lbs vs 5.2 lbs)
 - Weight ↓ >5% from baseline achieved only with >28 interventions/year

Singh N et al. BMJ Open. 2019 Aug 18;9(8):e029966.

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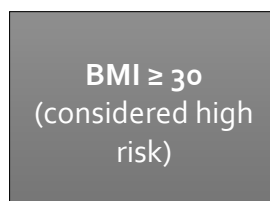
Pharmacologic Therapy

Candidates for Therapy:



(HTN, DM type 2, OSA, CHD, ↑ waist circumference, etc.)

OR



Use as adjunct therapy only!

FDA labeling for approved meds: "...indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management"

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AUDIENCE POLL

Which of the following is the most commonly prescribed medication for the management of ABCD?

- A. phentermine
- B. semaglutide
- C. tirzepatide

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FDA-Approved Medications for Weight Management

- Phentermine (1959), diethylpropion, and similar
- Orlistat (1999 Xenical – prescription, 2007 Alli – OTC)
- Phentermine-topiramate ER (Qsymia) – 2012
- Naltrexone-bupropion ER (Contrave) – 2014
- Liraglutide 3 mg (Saxenda) – 2014
- Setmelanotide (Imcivree) – 2020
- Semaglutide 2.4 mg (Wegovy) – 2021
- Tirzepatide 5, 10, 15 mg (Zepbound) – 2023

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Medications Withdrawn by FDA (for Weight Management)

- Amphetamine
- Levamphetamine
- Methamphetamine (desoxyephedrine)
- Clobenzorex
- Iodinated casein strophanthin
- Pipradrol
- 1997 dexfenfluramine and fenfluramine – valvulopathy, pulmonary arterial hypertension
- 2010 sibutramine – myocardial infarction, CVA
- 2020 lorcaserin – ↑ cancer risk
- 2005 phenylpropanolamine (norpseudoephedrine) – nonprescription ingredient, hemorrhagic stroke

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Main Medications With Off-Label Use for Weight Management

- Phentermine
- Bupropion
- Topiramate
- Zonisamide
- Metformin
- SGLT2 inhibitors
- GLP-1 receptor agonists
- Pramlintide

Combination therapy

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Off-Label Use of Medications for ABCD

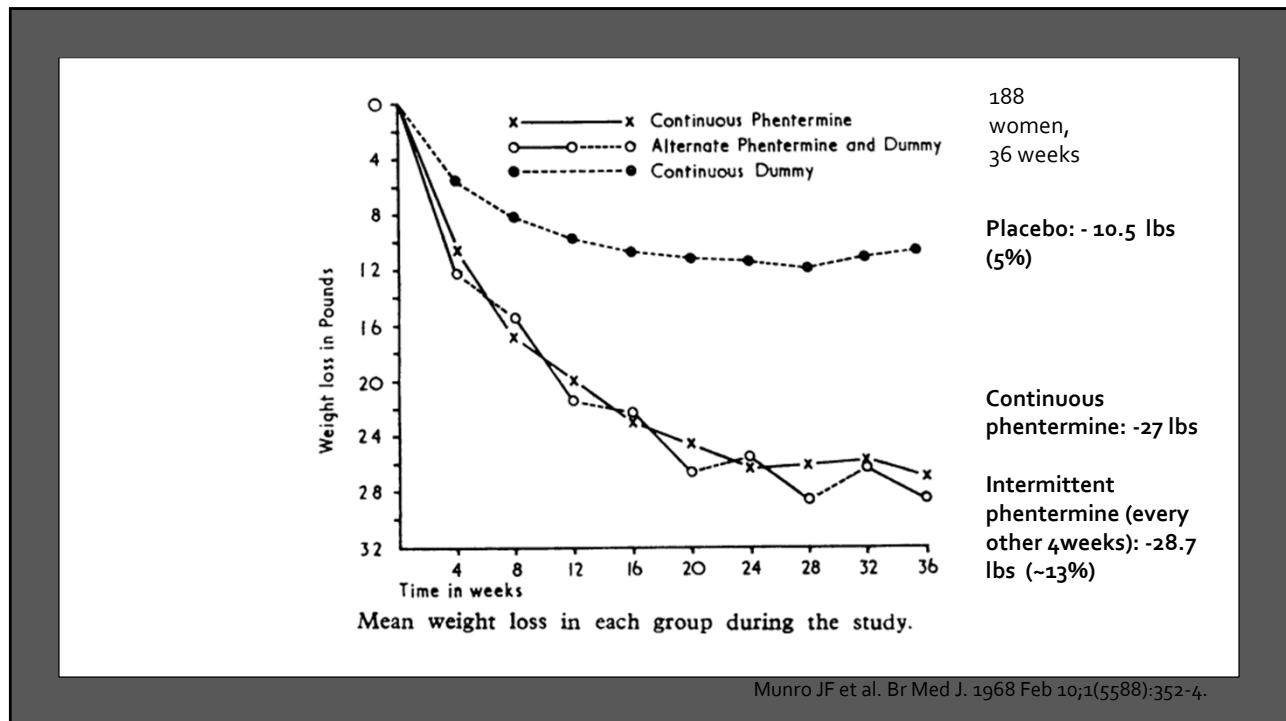
- Medications without FDA-approved indication
- Long-term use
- Higher doses
- Different patient population (eg, lower BMI, pediatric)

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Phentermine

- Phentermine (Adipex-P, Lomaira, generics) – CIV
 - Previously used in combination with fenfluramine (“phen-fen”)
- FDA-approved dose for weight reduction: 15-37.5 mg qAM (tablets, capsules); Lomaira 8 mg tid 30 min before meals
- Other sympathomimetic amines FDA approved for weight management
 - Diethylpropion – CIV
 - Benzphetamine, phendimetrazine (Bontril PDM, generics) – CIII
- FDA-approved for “short term” use only (12 weeks)
- MOA – enhance catecholamine transmission in CNS, increase sympathetic activity, reduce appetite

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Phentermine – Main ADRs

Adverse effects

- ↑ blood pressure & heart rate
- Nervousness
- Insomnia
- Constipation
- Dry mouth
- Headache
- Euphoria & abuse potential (C-IV) – rare



Use contraindicated in patients with concomitant conditions worsened by these ADRs (e.g. uncontrolled HTN, arrhythmia, hyperthyroidism, narrow-angle glaucoma, etc.)

MAOI within 14 days

- FDA-approved for short-term use (up to 12 weeks) only
- Off-label use: > 12 weeks, higher doses, in combination with other weight loss meds

In addition to hypersensitivity. Not an all-inclusive list.

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Topiramate

- FDA-approved indications
 - Prophylaxis of migraine headache in patients ≥ 12 years of age
 - Seizures: monotherapy or adjunctive therapy in children and adults (seizure type and age vary based on formulation)
- Several off-label uses including antipsychotic-induced weight gain and binge eating disorder
- Proposed MOA of weight reduction – ↓ caloric intake, affects lipogenesis, ↓ leptin, ↓ blood glucose
- 60-week RCT with 854 persons: ↓ 8% (placebo-subtracted) with 256 mg/day

Wilding J et al, OBES-002 Study Group. Int J Obes Relat Metab Disord. 2004 Nov;28(11):1399-410.

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Topiramate – Main ADRs

- Sedation, dizziness, fatigue
- Paresthesia
- Nausea, abdominal pain, dysgeusia
- Gait/balance impairments
- Cognitive impairment (attention, memory, language)
- Psychiatric disturbance
- ↑ seizure frequency – gradual tapering if discontinuing
- Alcohol use within 6 hours before and after administration (Trokendi XR only) → dose dumping
- Teratogenic – very specific birth control recommendations provided in phentermine-topiramate ER (Qsymia)'s approved product labeling

In addition to hypersensitivity. Not an all-inclusive list.

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Topiramate – Warnings and Precautions

- Acute myopia and secondary angle closure glaucoma
- Visual field defects
- Inhibits carbonic anhydrase
 - Metabolic acidosis
 - Nephrolithiasis
 - Decreased BMD, osteoporosis
 - Osteomalacia
 - Hypohydrosis, hyperthermia

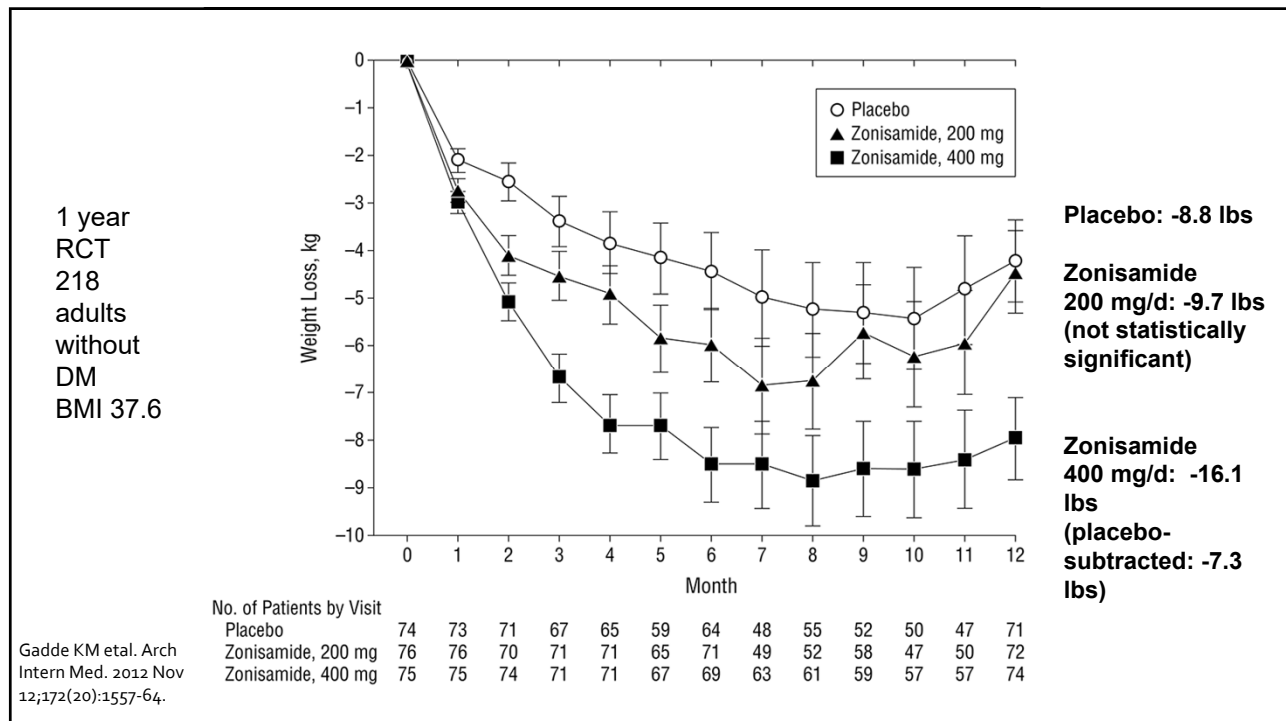
In addition to hypersensitivity. Not an all-inclusive list

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Zonisamide

- FDA-approved indication – adjunctive therapy for the treatment of focal (partial) onset seizures in adolescents ≥ 16 years of age and adults
- MOA of weight reduction – unknown; may be due to 5HT & dopamine activity, taste alteration
 - Typical dosing in RCTs for weight management: 100-400 mg/day (400 mg/day effective)
- Studied in binge eating disorder in adults – small studies, appears to be minimally effective

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Zonisamide – Main ADRs



Somnolence



Anorexia



Dizziness



Ataxia



Agitation/irritability



Difficulty with
memory and/or
concentration

In addition to hypersensitivity. Not an all-inclusive list.

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Zonisamide – Main ADRs

- Serious reactions to sulfonamides
 - Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias
- Serious skin reaction – discontinue at first sign of rash
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity
- Acute myopia and secondary angle closure glaucoma
- Metabolic acidosis – monitor baseline and periodic serum bicarbonate
- Suicidal behavior and ideation
- Teratogenic – use contraception during treatment and for 1 month after discontinuation

Not an all-inclusive list.

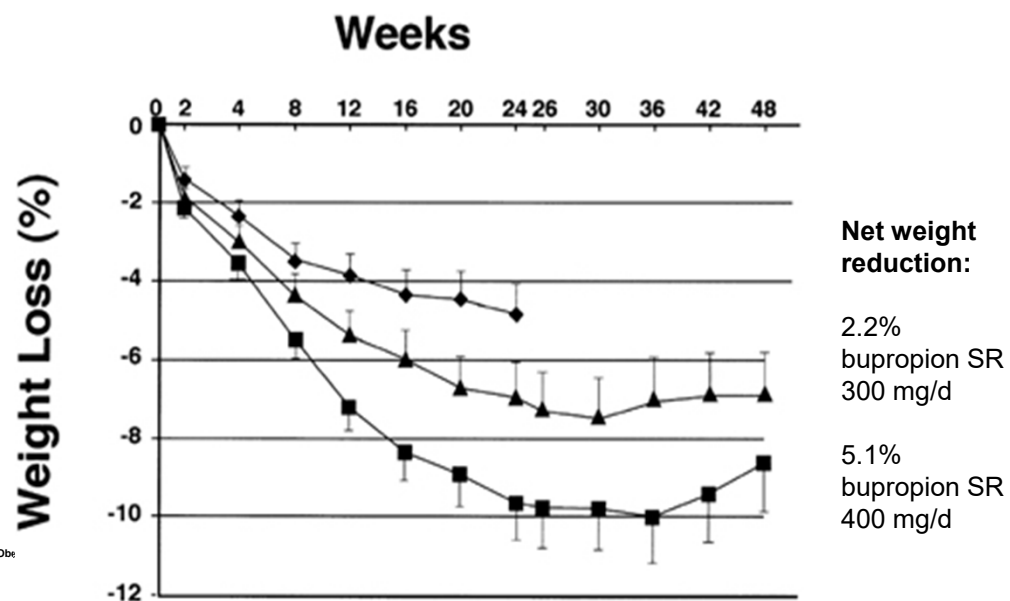
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Bupropion

- FDA-approved indications
 - Major depressive disorder, unipolar
 - Seasonal affective disorder
 - Smoking cessation (SR BID formulation)
- MOA of weight reduction – NDRI
- Studied in binge eating disorder in adults – appears to be minimally effective

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Bupropion SR Enhances Weight Loss: A 48-Week Double-Blind, Placebo- Controlled Trial



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Bupropion – Main ADRs

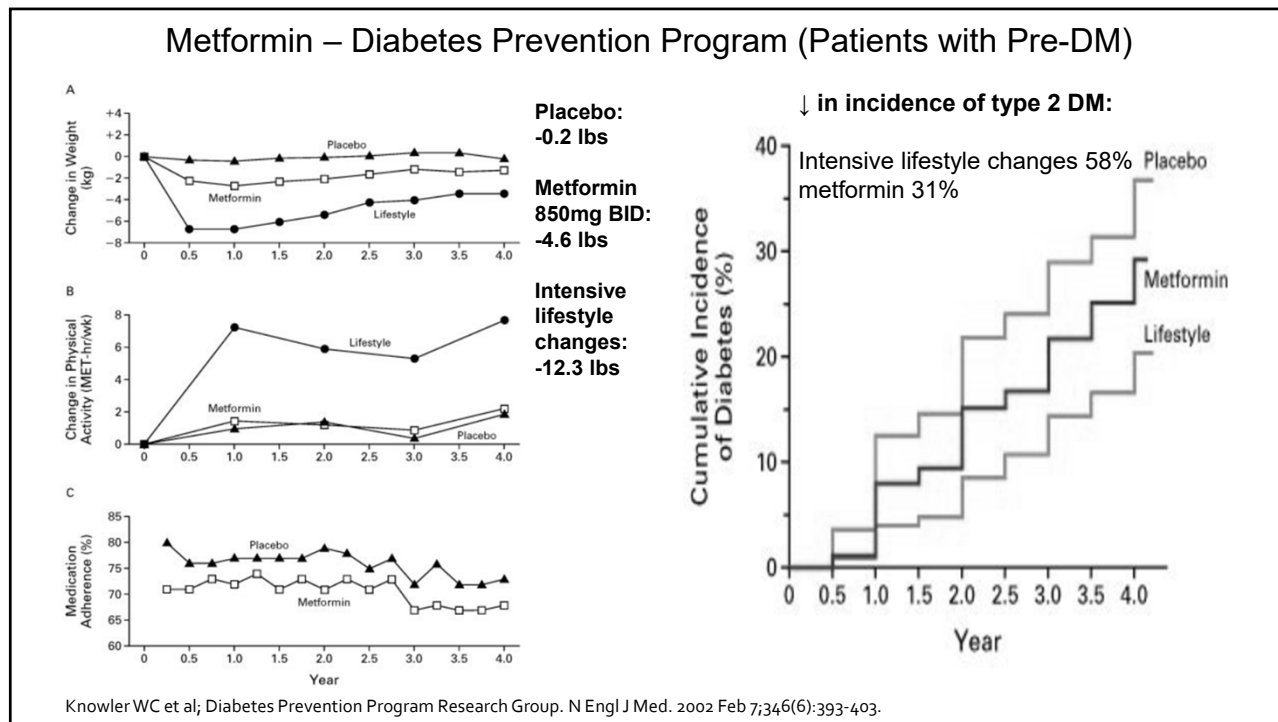
- Dry mouth
- Nausea
- Headache
- Insomnia
- Tachycardia
- Agitation, anxiety
- ↑ bp
- Dose-dependent increase in seizure risk
- Activation of mania/hypomania
- Psychosis and other neuropsychiatric reactions

In addition to hypersensitivity. Not an all-inclusive list.

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Medications with FDA Indication for Diabetes Management (off-label for weight reduction)

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Metformin

- Diabetes Prevention Program
- 2020 meta-analysis of 21 RCTs, cohort, and case-control trials – monotherapy
 - 21 studies, published 2000-2018, mean age 7-56 years, mean baseline BMI 26-41 kg/m², length of treatment with metformin 3-32 months
 - 7 studies in children/teens age 18 years or younger
 - Most of the adult studies had a younger mean age (30's-40's)
 - **Mean reduction in BMI of ~ 1**
 - **Best weight reduction at 6 months, higher dose (>1,500 mg/day), and higher BMI (BMI > 35 kg/m²)**
 - **Weight reduction plateaus after 6 months, weight regain by 12 months**

Pu R et al. Ther Adv Endocrinol Metab. 2020 May 21;11:2042018820926000

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Metformin

- Proposed MOA of weight reduction
 - ↑ **insulin sensitivity**
 - ↓ **intestinal glucose absorption**
 - ↓ lipid synthesis and deposition in liver and muscle
 - ↑ GLP-1
 - ↓ ghrelin
 - restores leptin sensitivity
 - microbiome changes

Igel LI et al. Curr Atheroscler Rep. 2016 Apr;18(4):16.

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Metformin – Main ADRs

- **Diarrhea**
- **Nausea**
- Abdominal bloating
- Metallic taste
- Vitamin B12 deficiency
- Lactic acidosis – rare

In addition to hypersensitivity. Not an all-inclusive list.

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SGLT2 Inhibitors

- Bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin with FDA approval
- FDA-approved indications – hyperglycemia in type 2 diabetes, ↓ CV death in type 2 DM*, ↓ CV death and hospitalization in HF**, ↓ progression of renal impairment in CKD***
 - *canagliflozin, empagliflozin
 - **dapagliflozin, empagliflozin
 - ***canagliflozin, dapagliflozin, empagliflozin

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SGLT2 Inhibitors

- MOA
 - Reduce renal reabsorption of filtered glucose → increased urinary glucose excretion
- Weight loss – ~2-3% baseline body weight, ~5-8 lbs
- ↓ waist circumference, visceral fat area, subcutaneous fat area, percentage body fat
- ↓ lean muscle mass

Pan R et al. PLoS One. 2022 Dec 30;17(12):e0279889.

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SGLT2 Inhibitors – Main ADRs

- **Genital mycotic infections**
- **Urinary tract infections**
- **Increased urination**
- Volume depletion (hypotension, AKI)
- Hypoglycemia – with concomitant use with insulin and insulin secretagogues
- Urosepsis and pyelonephritis
- Lower limb amputation
- (Euglycemic) DKA
- Fournier's gangrene

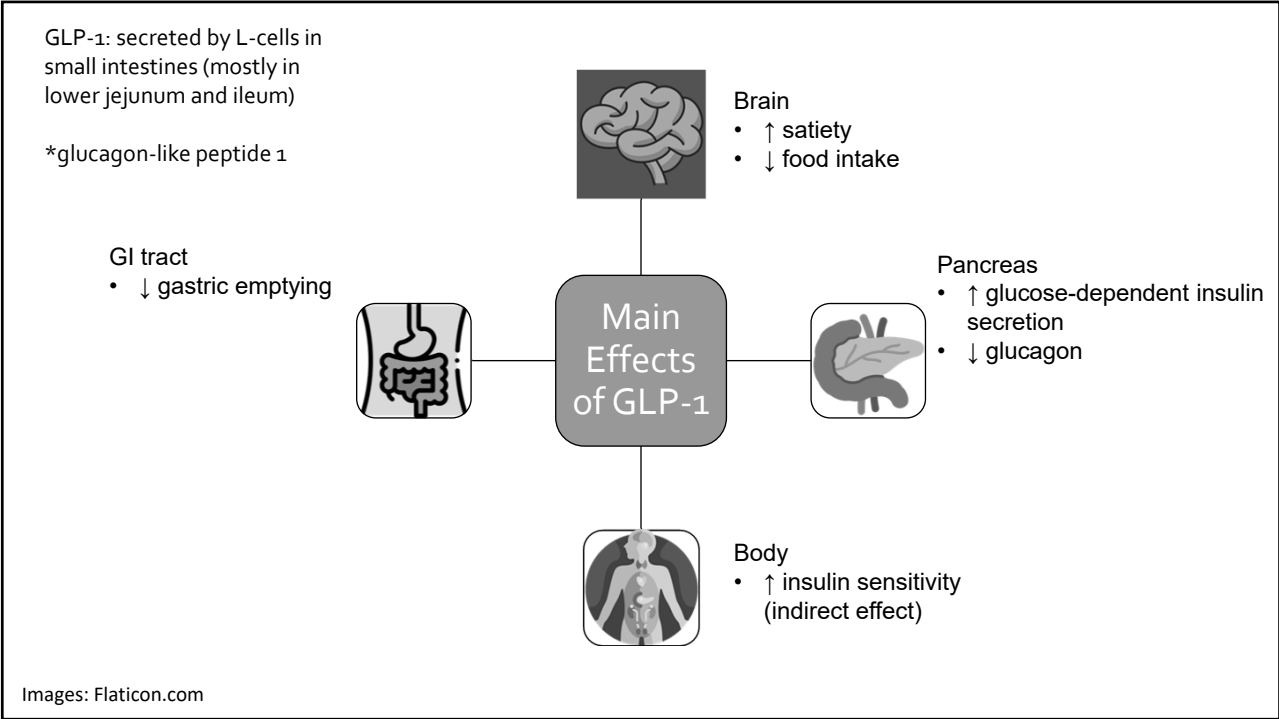
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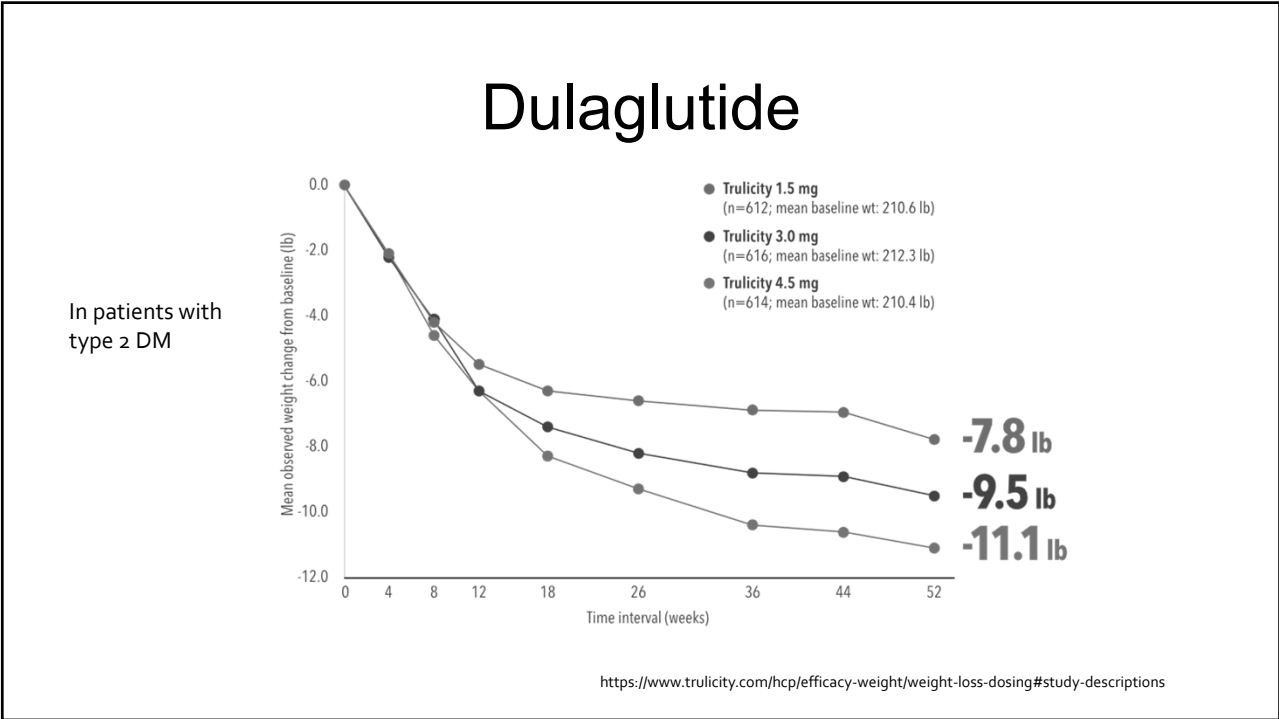
GLP-1 Receptor Agonists

- FDA-approved for weight management – liraglutide 3 mg, semaglutide 2.4 mg
- FDA-approved for diabetes management – dulaglutide, exenatide, exenatide LAR, liraglutide 1.8 mg, lixisenatide, semaglutide 2 mg
- MOA for weight reduction – next slide

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Semaglutide 1 mg, 2 mg/week SC

- SUSTAIN FORTE RCT
- Compared semaglutide 2 mg/week to 1 mg/week SC in adults with inadequately controlled type 2 DM on metformin +/- sulfonylurea
- 40 weeks, n = 961
- Main goal of RCT is to assess efficacy and safety of 2 mg dose in management of type 2 DM
- Weight change from baseline to week 40:
 - **-14.1 lbs with semaglutide 2 mg/week**
 - **-12.3 lbs with semaglutide 1 mg/week**

Friás JP et al. Lancet Diabetes Endocrinol. 2021 Sep;9(9):563-574.

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GIP/GLP-1 Receptor Agonist

- Tirzepatide (Mounjaro) approved for type 2 diabetes
- Tirzepatide (Zepbound) approved for weight management
- Same doses for both versions

GLP-1: secreted by L-cells in small intestines (mostly in lower jejunum and ileum)

*glucagon-like peptide 1

GI tract

- ↓ gastric emptying



Adipocytes

- ↑ fatty acid and glucose uptake



Brain

- ↑ Satiety
- ↓ food intake
- ↓ food intake

GIP: secreted by K-cells in upper small intestines (mostly in duodenum and jejunum)

*glucose-dependent insulinotropic polypeptide



Pancreas

- ↑ glucose-dependent insulin secretion
- ↓ glucagon
- ↑ glucose-dependent insulin secretion
- ↑ glucagon



Body

- ↑ insulin sensitivity (indirect effect)

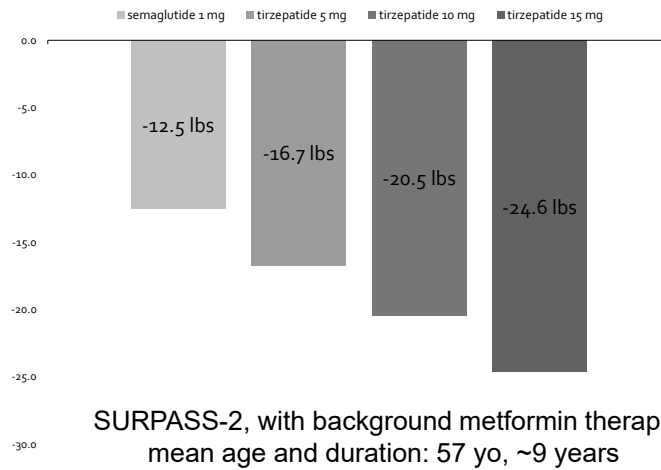
Main Effects of GIP & GLP-1

Images: Flaticon.com

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Tirzepatide in Type 2 Diabetes Comparison with Semaglutide 1 mg

Weight Change



Frias JP et al. N Engl J Med. 2021;385(6):503-515.

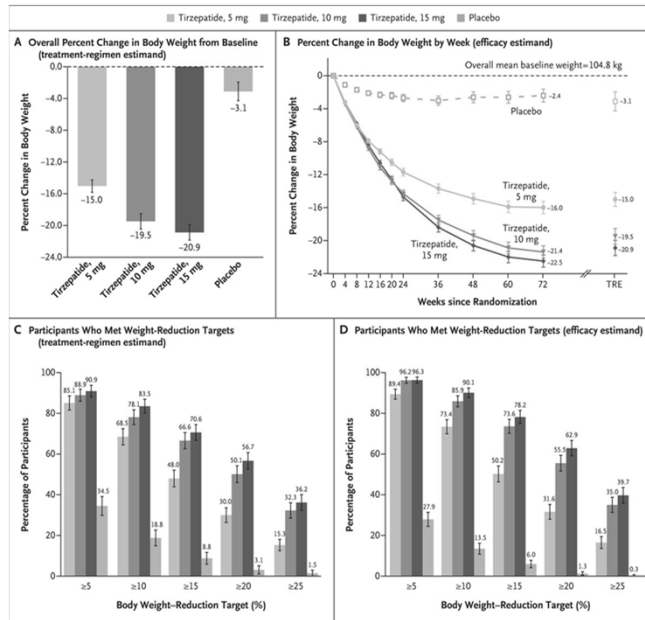
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Efficacy of FDA-Approved Semaglutide and Tirzepatide for Management of Overweight and Obesity

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

SURMOUNT-1
RCT



AM Jastreboff et al. N Engl J Med 2022;387:205-216.

2539 adults BMI ≥ 30 or more, or ≥ 27 and at least one weight-related complication, *excluding DM* (1896 tirzepatide 5, 10, 15 mg; 643 placebo)

72 weeks with 20-week dose titration

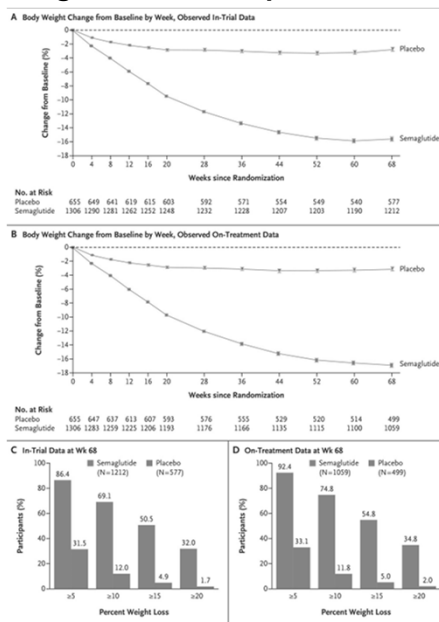
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Effect of Once-Weekly Semaglutide, as Compared with Placebo, on Body Weight.

STEP 1 RCT
semaglutide 2.4
mg

adults BMI ≥ 30
or more, or ≥ 27
and at least one
weight-related
comorbidity,
excluding DM
(1306 semaglutide,
655 placebo)

68 weeks



JP Wilding et al. N Engl J Med 2021;384:989-1002.

Change in weight from
baseline:
semaglutide -14.9%
placebo: -2.4%

**Treatment difference:
-12.4%**

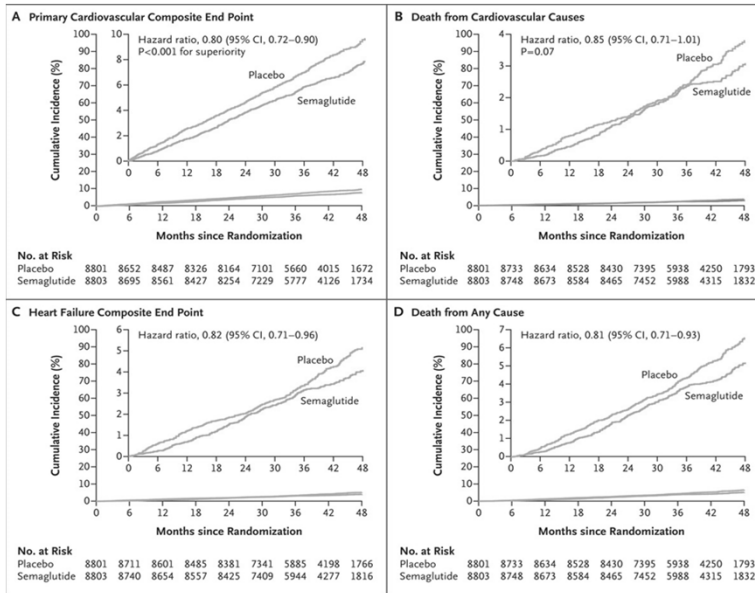
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Time-to-First-Event Analysis for Primary and Confirmatory Secondary Efficacy End Points.

Semaglutide 2.4 mg SELECT RCT

45 years of age or older with preexisting CVD (but without DM) and BMI ≥ 27

8803 semaglutide, 8801 placebo ~ 3 years



Change in weight from baseline semaglutide: -9.39%
placebo: -0.88%

Treatment difference: -8.5%

↓ CV composite endpoint, heart failure composite endpoint, and death from any causes

AM Lincoff et al. N Engl J Med 2023. DOI: 10.1056/NEJMoa2307563

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GLP-1RA-Based Therapies – BBW

Black Box Warning of risk of thyroid C-cell tumors

“...contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors.”

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GLP-1RA-Based Therapies – Warnings and Precautions

-  Severe GI disease
-  Acute pancreatitis
-  AKI
-  Diabetic retinopathy complications in patients with h/o diabetic retinopathy
-  Acute gallbladder disease
-  ↑ heart rate
-  Suicidal behavior and ideation

Images: Flaticon.com

In addition to hypersensitivity. Not an all-inclusive list.

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GLP-1RA-Based Therapies – Common ADRs



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GLP-1RA-Based Therapies – Drug Interactions

- Hypoglycemia with concomitant insulin or insulin secretagogue
- Delay gastric emptying → may affect absorption of concomitant oral medications, consider monitoring with narrow therapeutic index medications
 - Tirzepatide and oral hormonal contraceptives – FDA's labeling recommends:
 - Switch to non-oral contraceptive, OR
 - Add a barrier method of contraception, for 4 weeks after initiation with tirzepatide and for 4 weeks after each dose escalation

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Example Case

- Ms. A: 40 year-old female with newly-diagnosed HTN.
- Concerned about this new diagnosis and her future CV health in general and is interested in the “medication that the FDA just approved for weight loss”.
- **PMH:** type 2 DM, HTN, migraines. BMI 33 kg/m², A1c 7.5%, bp today (average of 2) 140/90 mmHg, HR 72.
- **Current meds:** metformin 1,000 mg bid, amlodipine 5 mg qday (added today by PCP), rizatriptan 5-10mg ODT prn migraine (max 30 mg/day); NKDA

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AUDIENCE POLL

Which of the following would be the best recommendation for Ms. A?

- A. attempt lifestyle modifications first
- B. a GLP-1-based medication
- C. phentermine or phentermine-topiramate

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Session Code

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