Obesity Management for Type 2 Diabetes Population

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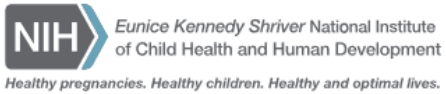
Disclosures



Grants to Tulane University from

- NovoNordisk

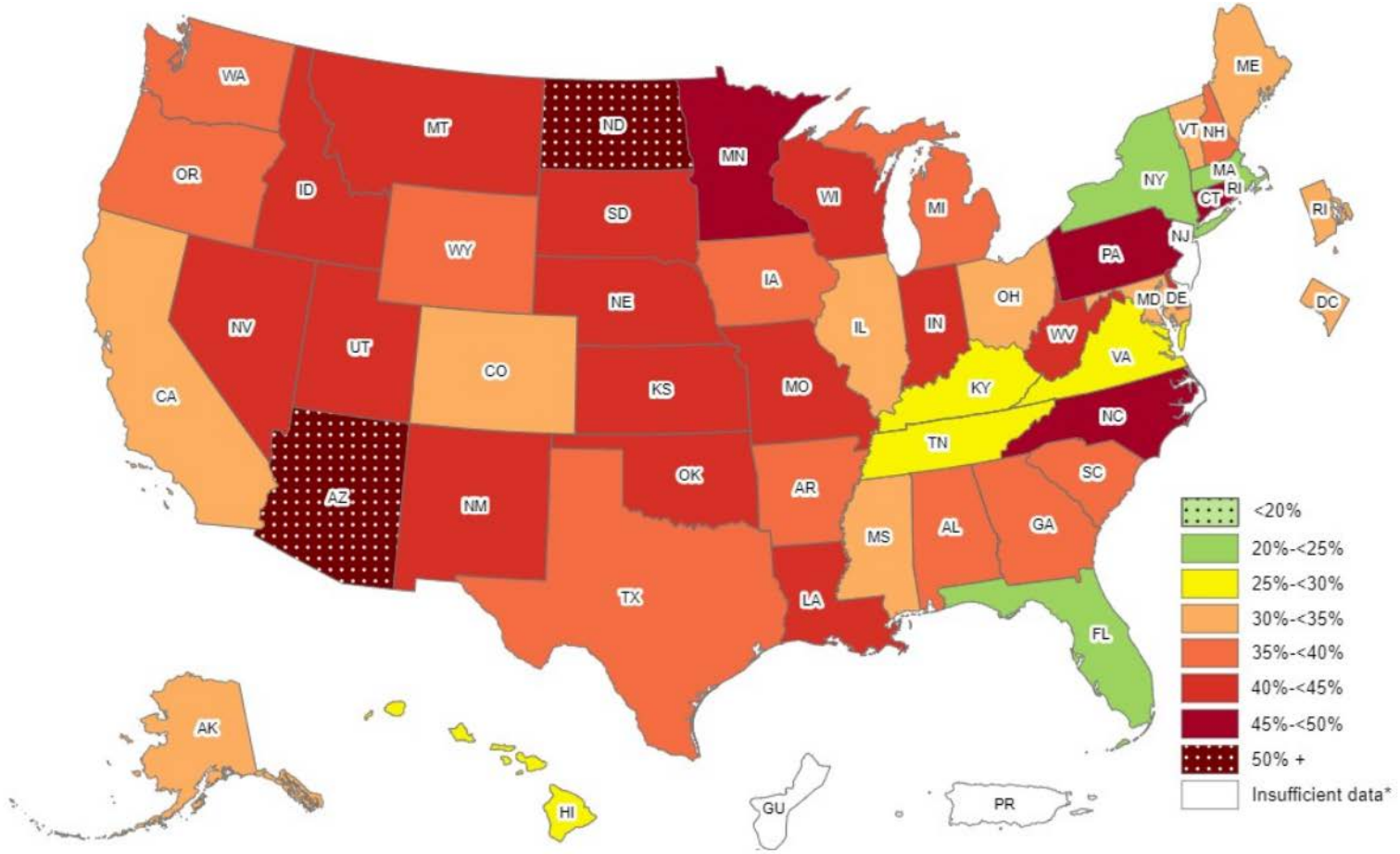
The views expressed are my own and do not necessarily reflect the position or policy of VA or the US government.

Objectives

- To discuss the various pharmacological agents for weight management

- To discuss the risks and contraindications of pharmacological agents for weight management

Prevalence of Self-Reported Obesity Among **Non-Hispanic American Indian or Alaska Native** Adult by State and Territory, BRFSS, 2018-2020



https://www.cdc.gov/obesity/data/prevalence-maps.html#overall

The New York Times

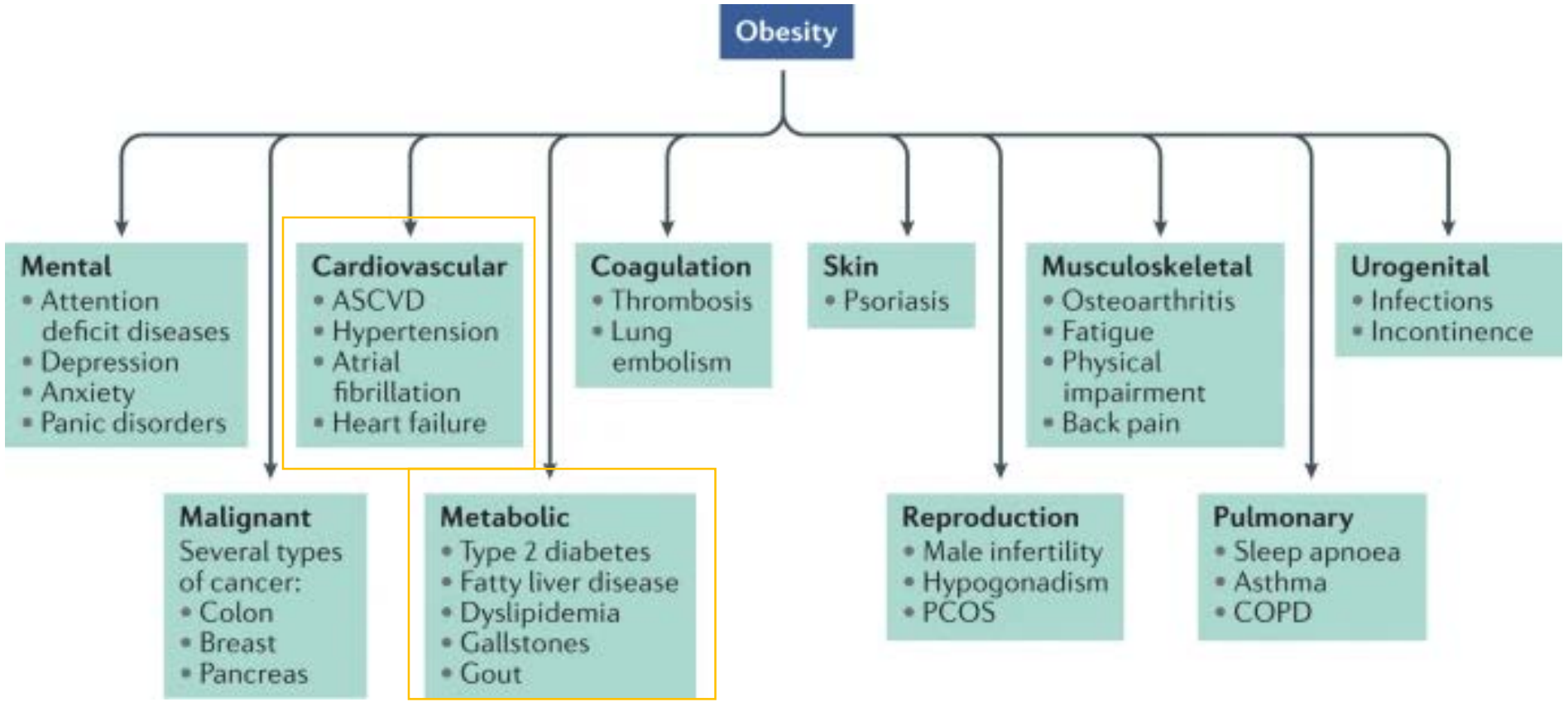
A.M.A. Recognizes Obesity as a Disease

Sugary diets and weight problems remain a central health issue.
Mamta Popat/Arizona Daily Star, via Associated Press

By Andrew Pollack

June 18, 2013

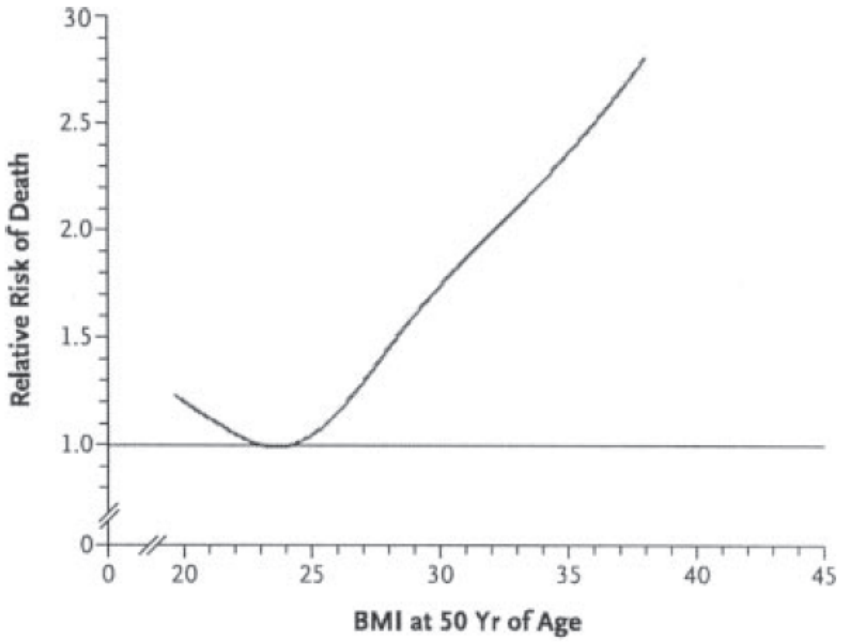
Obesity-associated metabolic disturbances



Müller, Nature. 2022

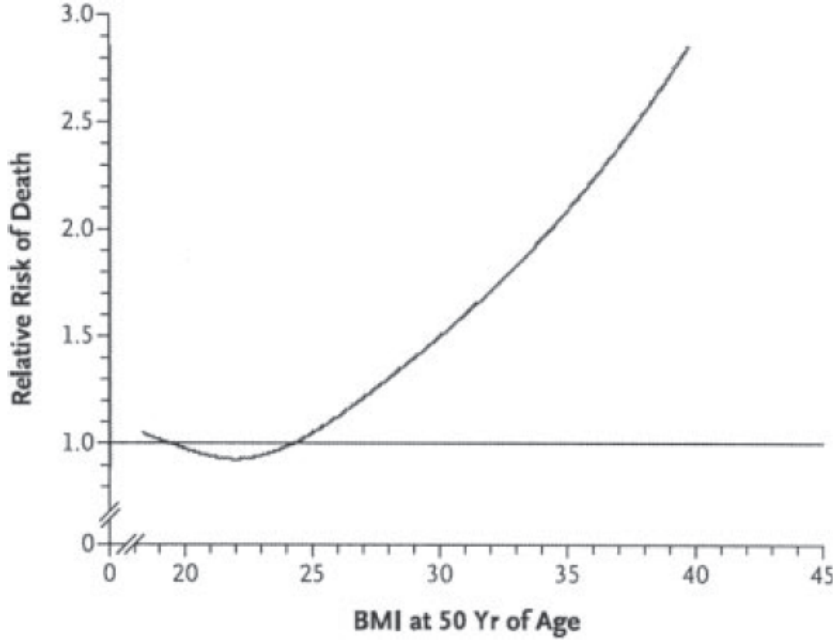
Relative risk of death as a function of BMI at age 50

Men



Men who had never smoked (n=54,925; 18,417 deaths)

Women

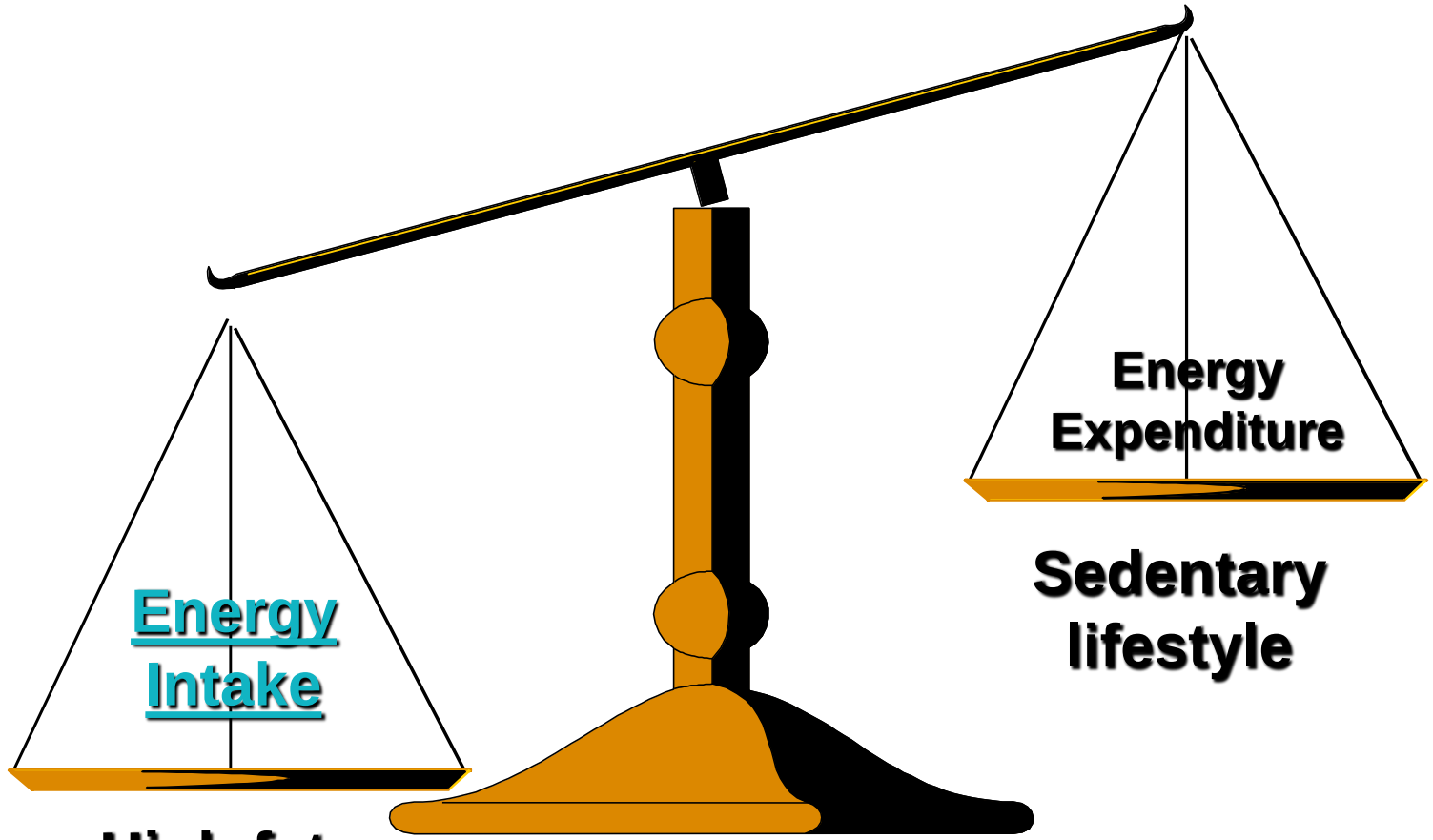


Women who had never smoked (n=56,156; 2867 deaths)

BMI > 35 is associated with a higher risk of death

J Clin Endocrinol Metab, June 2008, 93(6):2027–2034

Etiology of Obesity



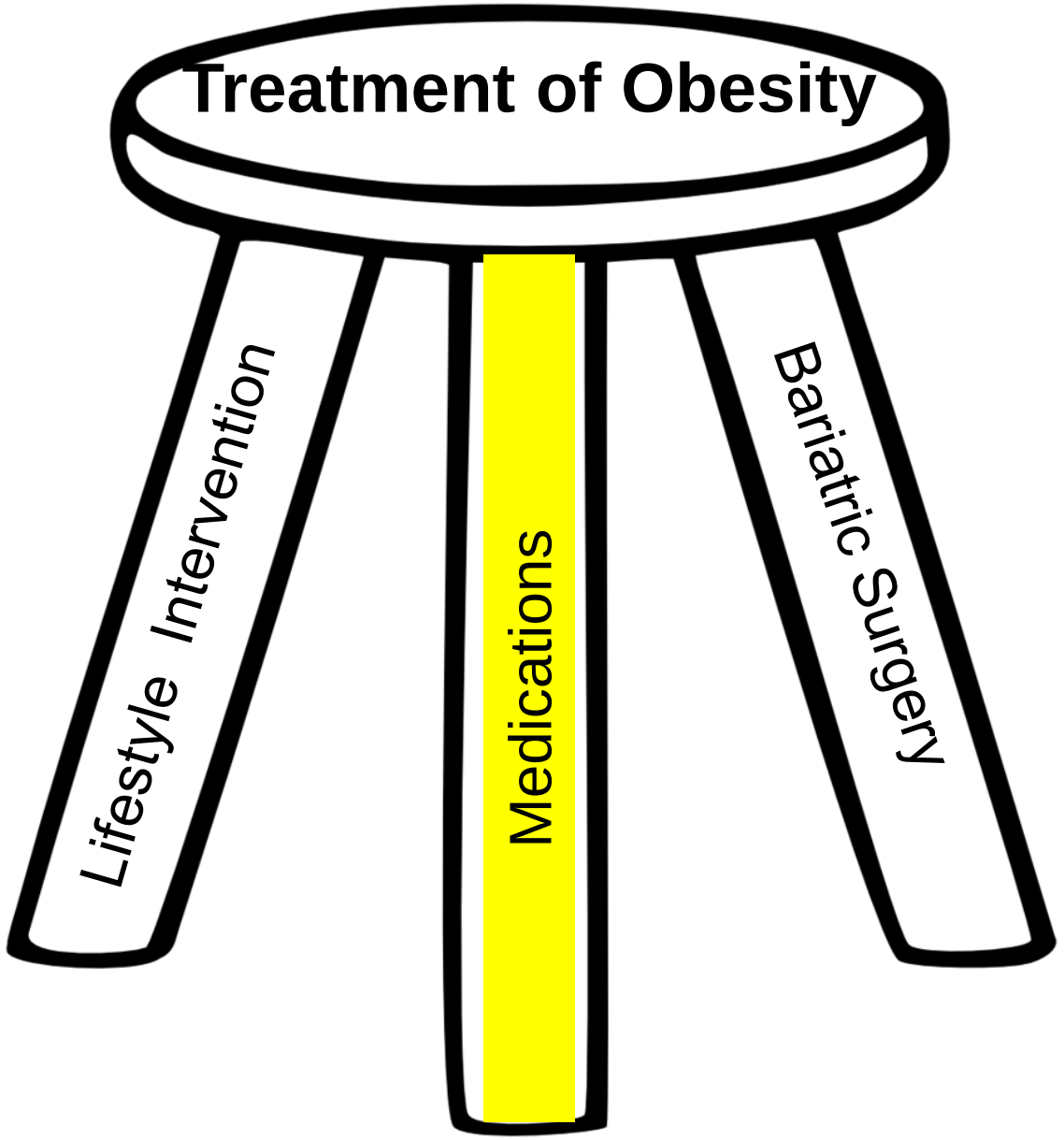

Treatment of Obesity
Lifestyle Intervention
Medications
Bariatric Surgery

Figure 4. Lifestyle Therapy

Evidence-based lifestyle therapy for treatment of obesity should include 3 components
Recommendations: R64 through R75

Meal Plan (R64, R65, R66)	Physical Activity (R64, R67, R68, R69, R70, R71)	Behavior (R64, R72, R73, R74, R75)
• Reduced-calorie healthy meal plan	• Voluntary aerobic physical activity progressing to >150 minutes/week	An interventional package that includes any number of the following:

Indications For Pharmacotherapy of Obesity

- **Chronic** weight management
- As an adjunct to a lifestyle therapy
- In patients with initial BMI of ≥30 kg/m^2 **or**
- An initial BMI of ≥27 kg/m^2 and at least

  one weight-related comorbid condition
  - **hypertension,**
  - **dyslipidemia,**
  - **type 2 diabetes**

https://www.nhlbi.nih.gov/health-topics/managing-overweight-obesity-in-adults

Who is a Candidate for Bariatric Surgery?

- BMI ≥ 40, or more than 100 pounds overweight.
- BMI ≥ 35 and at least one or more obesity-related co-morbidities
  - Type 2 diabetes
  - sleep apnea and other respiratory disorders
  - non-alcoholic fatty liver disease
  - Osteoarthritis
  - hypertension
  - heart disease
- Inability to achieve a healthy weight loss sustained for a period of time with prior weight loss efforts.

Work up of obesity

- Thyroid function tests (TSH)
- Medication list review
- 1mg dexamethasone suppression test *

(Cushing's syndrome in 0.8% of pts referred for bariatric surgery)

Fierabracci, Obes Surg. 2011

Medications associated with weight gain and alternatives

Category	Drug class	Weight gain	Alternatives
Psychiatric agents	Antipsychotic	Clozapine, risperidone, olanzapine, quetiapine, haloperidol, perphenazine	Ziprasidone, aripiprazole
	Antidepressants/mood stabilizers: tricyclic antidepressants	Amytriptyline, doxepin, imipramine, nortriptyline, trimipramine, mirtazapine	Bupropion*, nefazodone, fluoxetine (short term), sertraline (<1 year)
	Antidepressants/mood stabilizers: SSRIs	Fluoxetine¶, sertraline¶, paroxetine, fluvoxamine	
	Antidepressants/mood stabilizers: MAOIs	Phenylzine, tranylcypromine	
	Lithium	–	
Neurologic agents	Antiseizure medications	Carbamazepine, gabapentin, valproate	Lamotrigine¶, topiramate*, zonisamide*
Endocrinologic agents	Diabetes drugs	Insulin (weight gain differs with type and regimen used), sulfonylureas, thiazolidinediones, sitagliptin¶, metiglinide	Metformin*, acarbose*, miglitol*, pramlintide*, edenatide*, liraglutide*
Gynecologic agents	Oral contraceptives	Progestational steroids, hormonal contraceptives containing progestational steroids	Barrier methods, IUDs
	Endometriosis treatment	Depot leuprolide acetate	Surgical methods
Cardiologic agents	Antihypertensives	alpha-blocker¶, beta-blocker¶	ACE inhibitors¶, calcium channel blockers¶, angiotensin-2 receptor antagonists
Infectious disease agents	Antiretroviral therapy	Protease inhibitors	–
General	Steroid hormones	Corticosteroids, progestational steroids	NSAIDs
	Antihistamines/anticholinergics	Diphenhydramine¶, doxepin¶, cyproheptadine¶	Decongestants, steroid inhalers

* Weight-neutral or promotes weight loss.

¶ The data supporting the effects of these medications on weight gain are low quality or conflicting.

Information from: Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015; 100:342.

UpToDate®

Effects of Antidiabetic Agents on Weight

Weight neutral or slight weight loss

- Meglitinides (repaglinide, nateglinide),
- α-glucosidase inhibitors (acarbose, miglitol), and
- Metformin
- DDP-4 inhibitors

Weight loss

- SGLT-2 inhibitors
- GLP-1RA
- GLP-1RA +GIP

Weight gain

- Insulin
- Sulfonylureas
- Thiazolidinediones (pioglitazone)

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Aronne LJ et al. *Practical Guide to Drug-Induced Weight Gain*. Minneapolis, Minn: McGraw-Hill Companies; 2002.

Project ECHO

Pharmacotherapy of Obesity

*Adult and pediatrics

JOURNAL ARTICLE

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, Donna H. Ryan, Christopher D. Still

The Journal of Clinical Endocrinology & Metabolism, Volume 100, Issue 2, 1 February 2015, Pages 342–362,
Published: 01 F

AACE. Disease State Resources Education and Events Publications Careers About

Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity © 2016

These AACE/ACE evidence-based clinical practice guidelines address key aspects of obesity care: screening, diagnosis, clinical evaluation, treatment options, therapy selection, and treatment goals. Implementing these CPGs should facilitate high-quality care and will be useful for all health care professionals involved in the care of patients with, or at risk for, obesity and adiposity-related complications.

READ THE FULL GUIDELINE

Get Credentialed in Obesity Medicine

Get recognized for your obesity medicine expertise by sitting for the next American Board of Obesity Medicine (ABOM) Exam, November 7-19, 2022. To qualify, you must submit 60 CME credits in obesity medicine along with your application, due July 15, 2022 (regular deadline) or August 8, 2022 (late deadline).

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Seven ~~Six~~ FDA approved antiobesity meds

Table 1
Summary of the most commonly prescribed FDA-approved antiobesity medications*

Category	Orlistat	Phentermine	Phentermine-topiramate	Naltrexone-bupropion	Liraglutide	Semaglutide
Class	Lipase inhibitor	Sympathomimetic amine	Sympathomimetic amine-antiepilieptic	Antidepressant-opioid receptor antagonist	Glucagon-like peptide 1 analogue	Glucagon-like peptide 1 analogue
Administration	PO	PO	PO	PO	SQ	SQ
Renal adjustment	No	Maximum daily dose (MDD) of 15 mg. Avoid in dialysis or ESRD	MDD of 7.5–46 mg. Avoid use with severe impairment.	MDD of 1 tablet bid. Avoid use in ESRD.	Use with caution. Postmarketing report of acute kidney injury.	Use with caution. Postmarketing report of acute kidney injury.
Hepatic adjustment	No	No	MDD of 7.5–46 mg. Avoid use with severe impairment.	MDD of 1 tablet bid.	Use with caution.	Use with caution.
Contraindications	Chronic malabsorption syndrome, cholestasis	Cardiovascular disease, hyperthyroidism, glaucoma, agitated states, history of drug abuse, within 14 d of MAOI	Glaucoma, hyperthyroidism, or within 14 d of MAOI	Uncontrolled hypertension, seizure disorders, eating disorders (anorexia nervosa or bulimia), chronic opioid therapy, within 14 d of MAOI, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 3
Drug interactions	Cyclosporine, fat-soluble vitamins, levothyroxine, warfarin	MAOI, alcohol, adrenergic neuron blockers	Oral contraceptives, CNS depressants (i.e., alcohol), non-potassium-sparing diuretics	CYP2D6 metabolizer (i.e., antidepressants, antipsychotics, beta-blockers, and type 1C antiarrhythmics), CYP2B6 inhibitors, CYP2B6 inducers, drugs that lower seizure threshold, dopaminergic drugs	May slow down absorption of oral medications	May slow down absorption of oral medications

FDA = U.S. Food and Drug Administration; PO = oral; SQ = subcutaneous; MDD = maximum daily dose; ESRD = end-stage renal disease; MAOI = monoamine oxidase inhibitor; MTC = medullary thyroid cancer; MEN2 = multiple endocrine neoplasia type 2.

* All AOMs are contraindicated during pregnancy and lactation.

FDA approved Obesity Pharmacotherapy

Agents	Action	Approval
Orlistat (Alli)	• Pancreatic lipase inhibitor	• Approved, 1999
Phentermine/ Topiramate ER (**Qsymia**)	• Sympathomimetic • Anticonvulsant (GABA receptor modulation)	• Approved, 2012
Bupropion/ Naltrexone (**Contrave**)	• Dopamine/noradrenaline reuptake inhibitor • Opioid receptor antagonist	• Approved, 2014
Liraglutide 3mg (**Saxenda**)	• GLP-1 receptor agonist	• Approved, 2014
Semaglutide 2.4mg **(Wegovy)**	• GLP-1 RA	• Approved, 2021

*Setmelanotide (IMCIVREE) for children ages 6 years and older who have genetic disorders causing obesity.

Lake, NJ: Eisai Inc.; 2012. Clinicaltrials.gov. Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects With Cardiovascular Risk Factors (The Light Study). 2012. Clinicaltrials.gov. Effect of Liraglutide on Body Weight in Non-diabetic Obese Subjects or Overweight Subjects With Co-morbidities: SCALE™ - Obesity and Pre-diabetes. 2011.

AACE/ACE Obesity CPG, *Endocr Pract.* 2016;

WEIGHT-LOSS MEDICATIONS APPROVED BY THE FDA FOR LONG-TERM TREATMENT OF OBESITY

Anti-obesity Medication (Trade Name) Year of FDA Approval	Mechanism of Action, Study Name, Study Duration: % TBWL Greater Than Placebo	Dose	Common Side Effects	Contraindications, Cautions, and Safety Concerns ✓ Contraindication • Warning, Safety Concern	Monitoring and Comments

Orlistat
 	
(Xenical™)
(Alli™) – OTC
 	
1999
	Lipase inhibitor
	
	XENDOS
	
	1 yr: 4.0%
	4 yr: 2.6%
		120 mg PO TID (before meals)
		
		OTC: 60 mg PO TID (before meals)
			• Steatorrhea
			• Fecal urgency
			• Incontinence
			• Flatulence
			• Oily spotting
			• Frequent bowel movements
			• Abdominal pain
			• Headache
				✓ Pregnancy and breastfeeding
				✓ Chronic malabsorption syndrome
				✓ Cholestasis
				✓ Oxalate nephrolithiasis
				• Rare severe liver injury
				• Cholelithiasis
				• Malabsorption of fat-soluble vitamins
				• Effects on other medications:
				  • Warfarin (enhance)
				  • Antiepileptics (decrease)
				  • Levothyroxine (decrease)
				  • Cyclosporine (decrease)
					Monitor for:
					• Cholelithiasis
					• Nephrolithiasis
					
					- Recommend standard multivitamin (to include vitamins A, D, E, and K) at bedtime or 2 hours after orlistat dose
					- Eating >30% kcal from fat results in greater GI side effects
					- FDA-approved for children ≥12 years old
					- Administer levothyroxine and orlistat 4 hours apart

Lorcaserin (Belviq®) 2012	Serotonin (5HT2c) receptor agonist BLOSSOM BLOOM **1 yr: 3.0%-3.6%** **2 yr: 3.1%**	10 mg PO BID	• Headache • Nausea • Dizziness • Fatigue • Xerostomia • Dry eye • Constipation • Diarrhea • Back pain • Nasopharyngitis • Hyperprolactinemia	✓ Pregnancy and breastfeeding ✓ Serotonin syndrome or neuroleptic malignant syndrome • Safety data lacking in patients who have depression • Concomitant use of SSRI, SNRI, MAOI, bupropion, St. John's wort as may increase risk of developing serotonin syndrome • Uncontrolled mood disorder • Cognitive impairment • Avoid in patients with severe liver injury or renal insufficiency • Caution with patients with bradycardia, heart block, or heart failure • Unproven concern for potential cardiac valvulopathy • Leukopenia	**Monitor for:** • Symptoms of cardiac valve disease • Bradycardia • Serotonin syndrome • Neuroleptic malignant syndrome • Depression • Severe mood alteration, euphoria, dissociative state • Confusion/somnolence • Priapism • Leukopenia • Euphoria at high doses could predispose to abuse • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas
Phentermine/ Topiramate ER (Qsymia®) 2012	NE-releasing agent (phentermine) GABA receptor modulation (topiramate) EQUIP CONQUER SEQUEL **1 yr: 8.6%-9.3% on high dose; 6.6% on treatment dose** **2 yr: 8.7% on high dose; 7.5% on treatment dose**	**Starting dose:** 3.75/23 mg PO QD for 2 weeks **Recommended dose:** 7.5/46 mg PO QD **Escalation dose:** 11.25/69 mg PO QD **Maximum dose:** 15/92 mg PO QD	• Headache • Paresthesia • Insomnia • Decreased bicarbonate • Xerostomia • Constipation • Nasopharyngitis • Anxiety • Depression • Cognitive impairment (concentration and memory) • Dizziness • Nausea • Dysgeusia	✓ Pregnancy and breastfeeding (topiramate teratogenicity) ✓ Hyperthyroidism ✓ Acute angle-closure glaucoma ✓ Concomitant MAOI use (within 14 days) • Tachyarrhythmias • Decreased cognition • Seizure disorder • Anxiety and panic attacks • Nephrolithiasis • Hyperchloremic metabolic acidosis • Dose adjustment with hepatic and renal impairment • Concern for abuse potential • Combined use with alcohol or depressant drugs can worsen cognitive impairment	**Monitor for:** • Increased heart rate • Depressive symptomatology or worsening depression especially on maximum dose • Hypokalemia (especially with HCTZ or furosemide) • Acute myopia and/or ocular pain • Acute kidney stone formation • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas - Potential for lactic acidosis (hyperchloremic non-anion gap) in combination with metformin - MAOI (allow ≥14 days between discontinuation) - 15 mg/92 mg dose should not be discontinued abruptly (increased risk of seizure); taper over at least 1 week - Health care professional should check ßHCG before initiating, followed by monthly self-testing at home - Monitor electrolytes and creatinine before and during treatment - Can cause menstrual spotting in women taking birth control pills due to altered metabolism of estrogen and progestins

Anti-obesity Medication (Trade Name) Year of FDA Approval	Mechanism of Action, Study Name, Study Duration: % TBWL Greater Than Placebo	Dose	Common Side Effects	Contraindications, Cautions, and Safety Concerns ✓ Contraindication • Warning, Safety Concern	Monitoring and Comments
Naltrexone ER/ Bupropion ER (Contrave®) 2014	Opiate antagonist (naltrexone) Reuptake inhibitor of DA and NE (bupropion) COR-I COR-II COR-BMOD **1 yr: 4.2%-5.2%**	**Titrate dose:** **Week 1:** 1 tab (8/90 mg) PO QAM **Week 2:** 1 tab (8/90 mg) PO BID **Week 3:** 2 tabs (total 16/180 mg) PO QAM and 1 tab (8/90 mg) PO QHS **Week 4:** 2 tabs (total 16/180 mg) PO QHS	• Nausea • Headache • Insomnia • Vomiting • Constipation • Diarrhea • Dizziness • Anxiety • Xerostomia	✓ Pregnancy and breastfeeding ✓ Uncontrolled hypertension ✓ Seizure disorder ✓ Anorexia nervosa ✓ Bulimia nervosa ✓ Severe depression ✓ Drug or alcohol withdrawal ✓ Concomitant MAOI (within 14 days) ✓ Chronic opioid use • Cardiac arrhythmia • Dose adjustment for liver and kidney impairment • Narrow-angle glaucoma • Uncontrolled migraine disorder • Generalized anxiety disorder • Bipolar disorder • Safety data lacking in patients who have depression • Seizures (bupropion lowers seizure threshold)	**Monitor for:** • Increased heart rate and blood pressure • Worsening depression and suicidal ideation • Worsening of migraines • Liver injury (naltrexone) • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas • Seizures (bupropion lowers seizure threshold) - MAOI (allow ≥14 days between discontinuation) - Dose adjustment for patients with renal and hepatic impairment - Avoid taking medication with a high-fat meal - Can cause false positive urine test for amphetamine - Bupropion inhibits CYP2D6
Liraglutide 3 mg (Saxenda®) 2014	GLP-1 analog SCALE Obesity & Prediabetes **1 yr: 5.6%**	**Titrate dose weekly by 0.6 mg as tolerated by patient (side effects):** 0.6 mg SC QD→ 1.2 mg SC QD→ 1.8 mg SC QD→ 2.4 mg SC QD→ 3.0 mg SC QD	• Nausea • Vomiting • Diarrhea • Constipation • Headache • Dyspepsia • Increased heart rate	✓ Pregnancy and breastfeeding ✓ Personal or family history of medullary thyroid cancer or MEN2 ✓ Pancreatitis ✓ Acute gallbladder disease • Gastroparesis • Severe renal impairment can result from vomiting and dehydration • Use caution in patients with history of pancreatitis • Use caution in patients with cholelithiasis • Suicidal ideation and behavior • Injection site reactions	**Monitor for:** • Pancreatitis • Cholelithiasis and Cholecystitis • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas • Increased heart rate • Dehydration from nausea/vomiting • Injection site reactions - Titrate dose based on tolerability (nausea and GI side effects)

Abbreviations: BID = twice daily; DA = dopamine; FDA = US Food and Drug Administration; GI = gastrointestinal; HCTZ = hydrochlorothiazide; MAOI = monoxidase inhibitor; MEN2 = multiple endocrine neoplasia type 2; NE = norepinephrine; OTC = over-the-counter medication; % TBWL = percent total body weight loss from baseline over that observed in the placebo group; PO = oral; QAM = every morning; QD = daily; QHS = every bedtime; SC = subcutaneous; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TID = 3 times a day; T2DM = type 2 diabetes mellitus.

FDA indication for all medications: BMI >30 kg/m² or BMI ≥27kg/m² with significant comorbidity.

After 3 to 4 months of treatment with antiobesity medication:

- **For naltrexone ER/bupropion ER and lorcaserin:**
  If the patient has not lost at least 5% of their baseline body weight at 12 weeks on the maintenance dose, the medication should be discontinued.
- **For phentermine/topiramate ER:**
  Continue medication if the patient has lost >5% body weight after 12 weeks on recommended dose (7.5 mg/42 mg); if the patient has not lost at least 3% of body weight after being on the recommended dose for 12 weeks then the medication should be discontinued, or the patient can be transitioned to maximum dose (15 mg/92 mg); if patient has not lost at least 5% after 12 additional weeks on the maximum dose, the medication should be discontinued.
- **For liraglutide 3 mg:**
  If the patient has not lost at least 4% of body weight 16 weeks after initiation, the medication should be discontinued.

References:
1–4 and package inserts for each medication

1. Wyatt HR. Update on treatment strategies for obesity. *J Clin Endocrinol Metab*. 2013;98(4):1299-1306.
2. Garvey WT, Garber AJ, Mechanick JI, Bray GA, Dagogo-Jack S, Einhorn D, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the 2014 advanced framework for a new diagnosis of obesity as a chronic disease. *Endocr Pract*. 2014;20(9):977-989.
3. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA*. 2014;311(1):74-86.
4. Fujioka K. Current and emerging medications for overweight and obesity in people with comorbidities. *Diabetes Obes Metab*. 2015;17(11):1021-1032.

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Drug	Orlistat (XenicalTM) (AlliTM) – OTC 1999 Oral BID/TID 1 yr: 4.0% 4 yr: 2.6%
Dose	120 mg PO TID (before meals) /60 mg PO TID (before meals)
Common Side Effects	• Steatorrhea • Fecal urgency • Incontinence • Flatulence • Frequent bowel movements
Caution	**Pregnancy and breastfeeding • Chronic malabsorption syndrome •** Cholestasis • Oxalate nephrolithiasis • Rare severe liver injury • Malabsorption of fat-soluble vitamins • Effects on other medications: • Anti-epileptics (decrease) • Levothyroxine (decrease)
Monitoring	Cholelithiasis • Nephrolithiasis Recommend standard multivitamin at bedtime or 2 hours after orlistat dose, Administer levothyroxine and orlistat 4 hours apart

WELL-AHEAD

Project ECHO

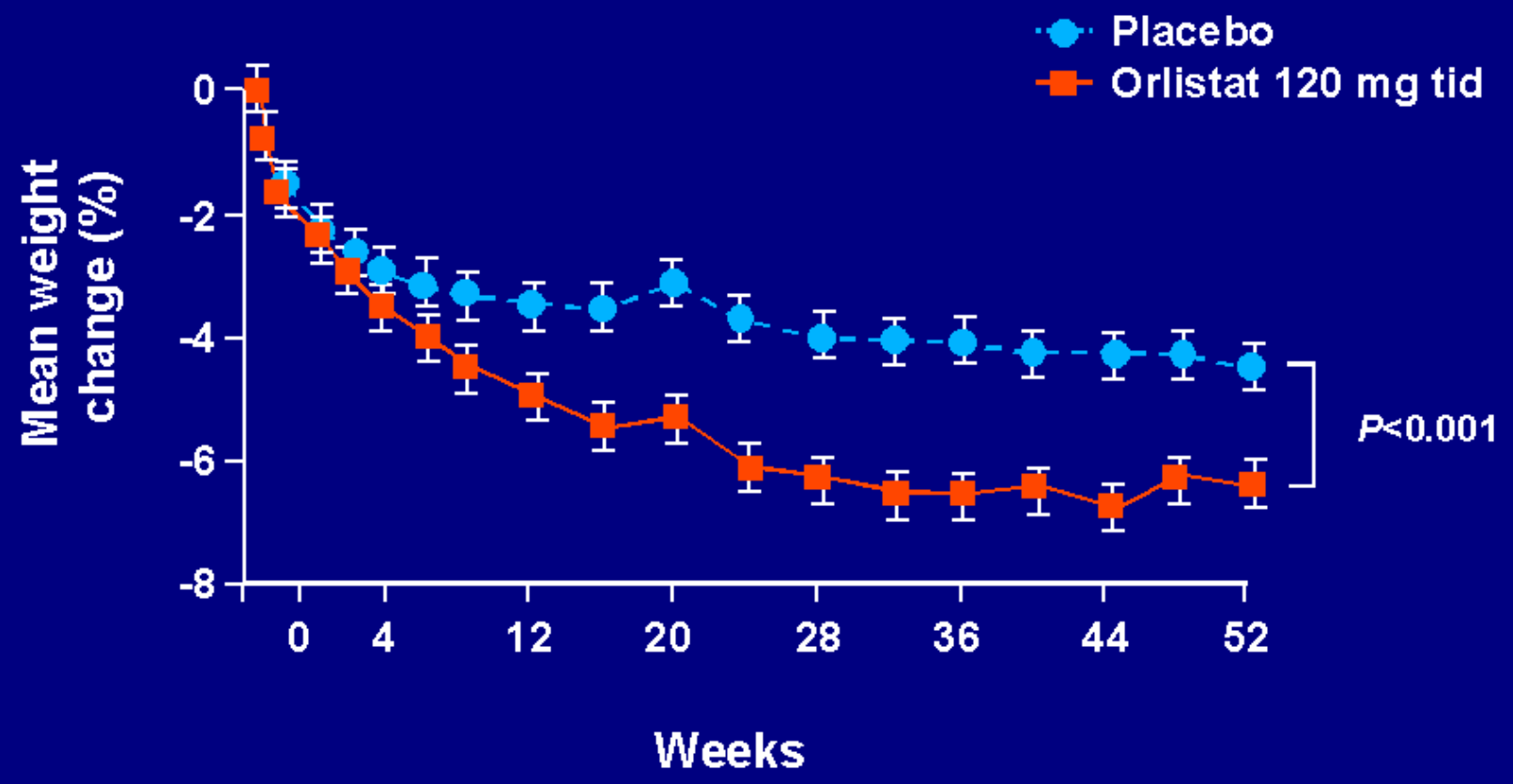
Drug	Phentermine/ Topiramate ER (Qsymia®) 2012 Oral Daily 1 yr: 8.6%-9.3% HD; 6.6% TD 2 yr: 8.7% HD; 7.5% on TD
MAO Dose	Starting dose: 3.75/23 mg PO QD for 2 weeks Recommended dose: 7.5/46 mg PO QD Escalation dose: 11.25/69 mg PO QD Maximum dose: 15/92 mg PO QD
Common Side Effects	Headache • Paresthesia • Insomnia • Xerostomia • Constipation • Nasopharyngitis • Anxiety • Depression • Cognitive impairment (concentration and memory) • Dizziness • Nausea • Dysgeusia
Caution	P and B (topiramate teratogenicity) • Hyperthyroidism • Acute angle-closure glaucoma • Concomitant MAOI use (within 14 days) • Tachyarrhythmia • Seizure disorder • Anxiety and panic attacks • Nephrolithiasis • Dose adjustment hepatic/renal impairment
Monitoring	Increased HR• Worsening Depression • ↓K • Acute myopia/ocular pain • Acute kidney stone formation • MAOI (allow ≥14 days b/w discontinuation) • Abrupt discontinuation (increased risk of seizure); taper over wks • check ßHCG before initiating, followed by monthly self-testing at home

Drug	Naltrexone ER/ Bupropion ER (Contrave®) 2014 Oral BID 1 yr: 4.2%-5.2%
MAO Dose	**Titrate dose:** Week 1: 1 tab (8/90 mg) PO QAM Week 2: 1 tab (8/90 mg) PO BID Week 3: 2 tabs (total 16/180 mg) PO QAM and 1 tab (8/90 mg) PO QHS Week 4: 2 tabs (total 16/180 mg) PO QHS
Common Side Effects	Nausea • Headache • Insomnia • Vomiting • Constipation • Diarrhea • Dizziness • Anxiety • Xerostomia
Caution	• P and B • Uncontrolled hypertension • Seizure disorder • Anorexia/ Bulimia nervosa • Severe depression • Drug or alcohol withdrawal • Concomitant MAOI (within 14 days) • Chronic opioid use • Cardiac arrhythmia • Dose adjustment for liver or kidney impairment
Monitoring	Increased HR and BP• Worsening depression and migraines • Liver injury (naltrexone) • Seizures (bupropion lowers seizure threshold) - MAOI (allow ≥14 days between d/c) - Dose adjustment for patients with renal and hepatic impairment - Can cause false positive urine test for amphetamine

Drug	Liraglutide 3 mg (Saxenda®) 2015 Subcutanous daily 1 yr: 5.6%
MAO Dose	Titrate dose weekly by 0.6 mg as tolerated by patient (side effects): WEEK 1- 0.6 mg SC QD WEEK 2- 1.2 mg SC QD WEEK 3- 1.8 mg SC QD WEEK 4-2.4 mg SC QD WEEK 5 and on 3.0 mg SC QD
Common Side Effects	• Nausea • Vomiting • Diarrhea • Constipation • Headache • Dyspepsia • Increased heart rate
Caution	P and B • Personal or family history of MTC or MEN2 • Pancreatitis • Acute gallbladder disease • Gastroparesis • Severe renal impairment can result from vomiting and dehydration • Use caution in patients with cholelithiasis • Suicidal ideation and behavior • Injection site reactions
Monitoring	• Pancreatitis • Cholelithiasis and cholecystitis • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas • Increased heart rate • Dehydration from nausea/vomiting • Injection site reactions - Titrate dose based on tolerability (nausea and GI side effects)

Drug	Semaglutide 2.4 mg (Wegovy®) 2021 Subcutanous Weekly 1 yr: 15%
MAO Dose	Titrate dose Q4weekly by 0.25 mg as tolerated by patient (side effects): Start with 0.25mg SC QW x 4 wks→ increase to 0.5 mg SC QW x 4 wks Until reaching→2.4 mg SC QW as final dose
Common Side Effects	• Nausea • Vomiting • Diarrhea • Constipation • Headache • Dyspepsia • Increased heart rate
Caution	P and B • Personal or family history of MTC or MEN2 • Pancreatitis • Acute gallbladder disease • Gastroparesis • Severe renal impairment can result from vomiting and dehydration • Use caution in patients with cholelithiasis • Suicidal ideation and behavior • Injection site reactions
Monitoring	• Pancreatitis • Cholelithiasis and cholecystitis • Hypoglycemia in patients having T2DM treated with insulin and/or sulfonylureas • Increased heart rate • Dehydration from nausea/vomiting • Injection site reactions - Titrate dose based on tolerability (nausea and GI side effects)

Effect of Orlistat on Weight Loss in Patients With Type 2 Diabetes

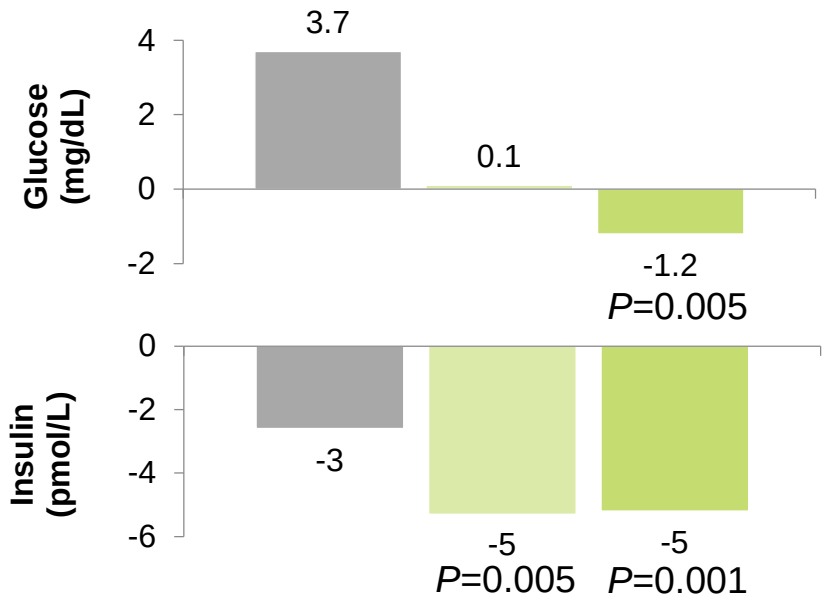


Hollander PA et al. *Diabetes Care.* 1998;21:1288-1294.

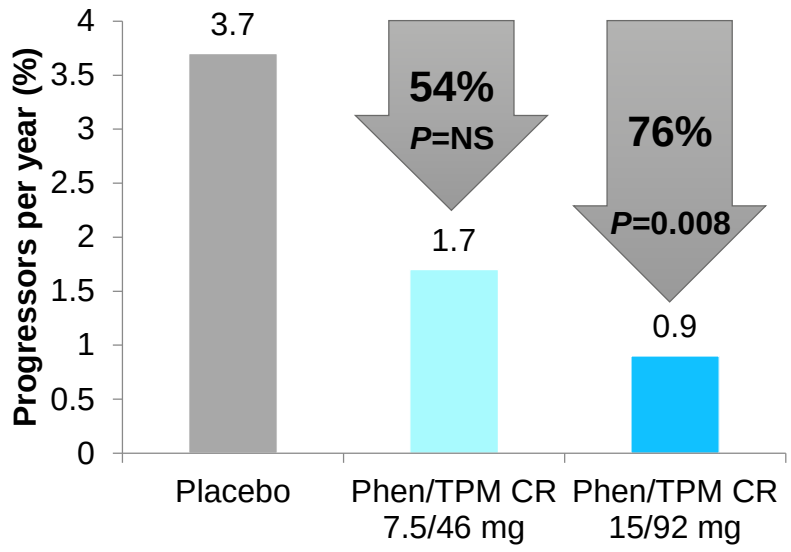
Effects of Phentermine/Topiramate ER on Glucose, Insulin, and Progression to T2D

SEQUEL Study (N=675)

Fasting Glucose and Insulin



Annualized Incidence of T2D



Placebo* Phen/TPM ER 7.5/46 mg* Phen/TPM ER 15/92 mg*

*All groups had lifestyle intervention.

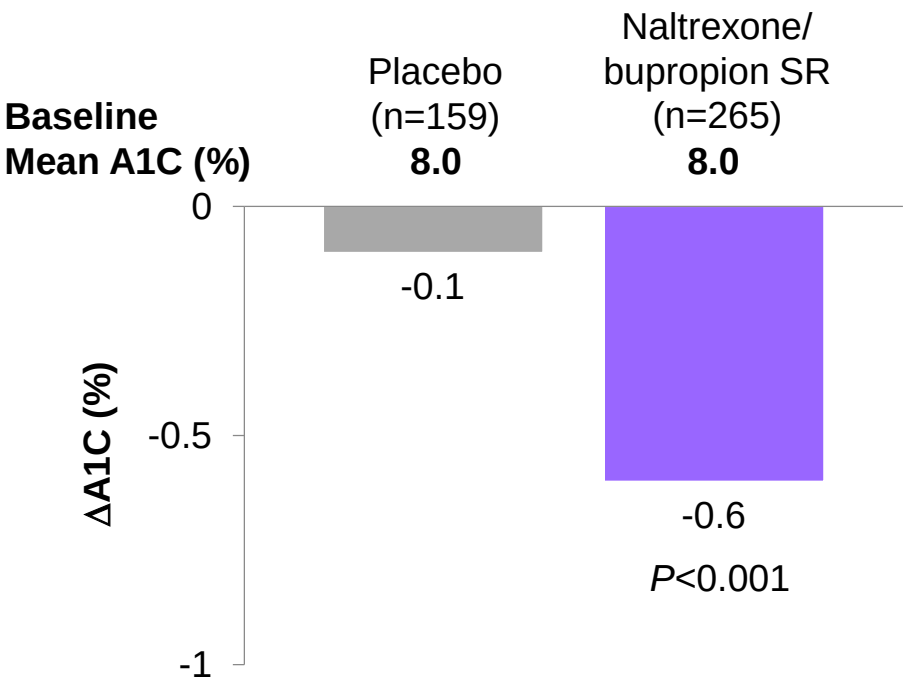
NS = not significant; Phen/TPM ER = phentermine/topiramate extended release; T2D = type 2 diabetes.

Garvey WT, et al. *Am J Clin Nutr*. 2012;95:297-308.

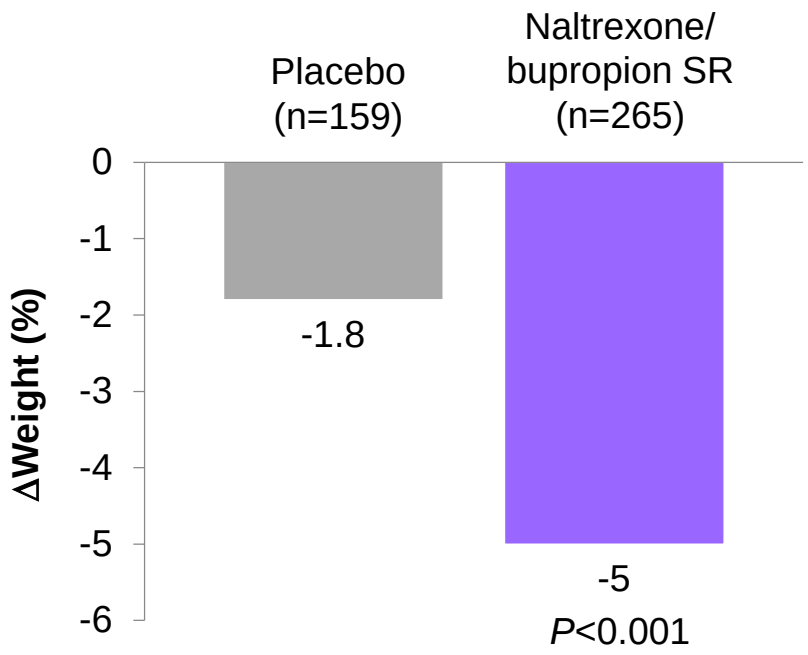
Effect of Naltrexone/Bupropion SR on Glycemia in Type 2 Diabetes

COR-Diabetes Study

Change in A1C



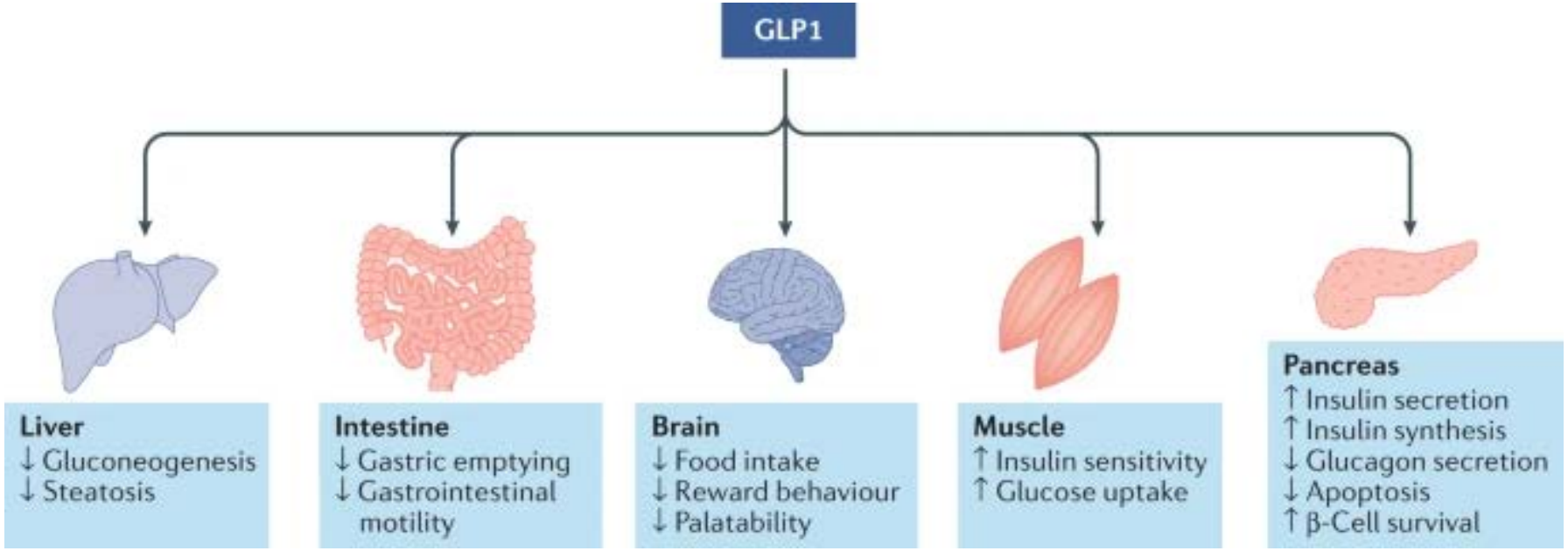
Change in Weight



COR = CONTRAVE Obesity Research; LOCF = last observation carried forward; MITT = modified intent to treat; SR, sustained release.

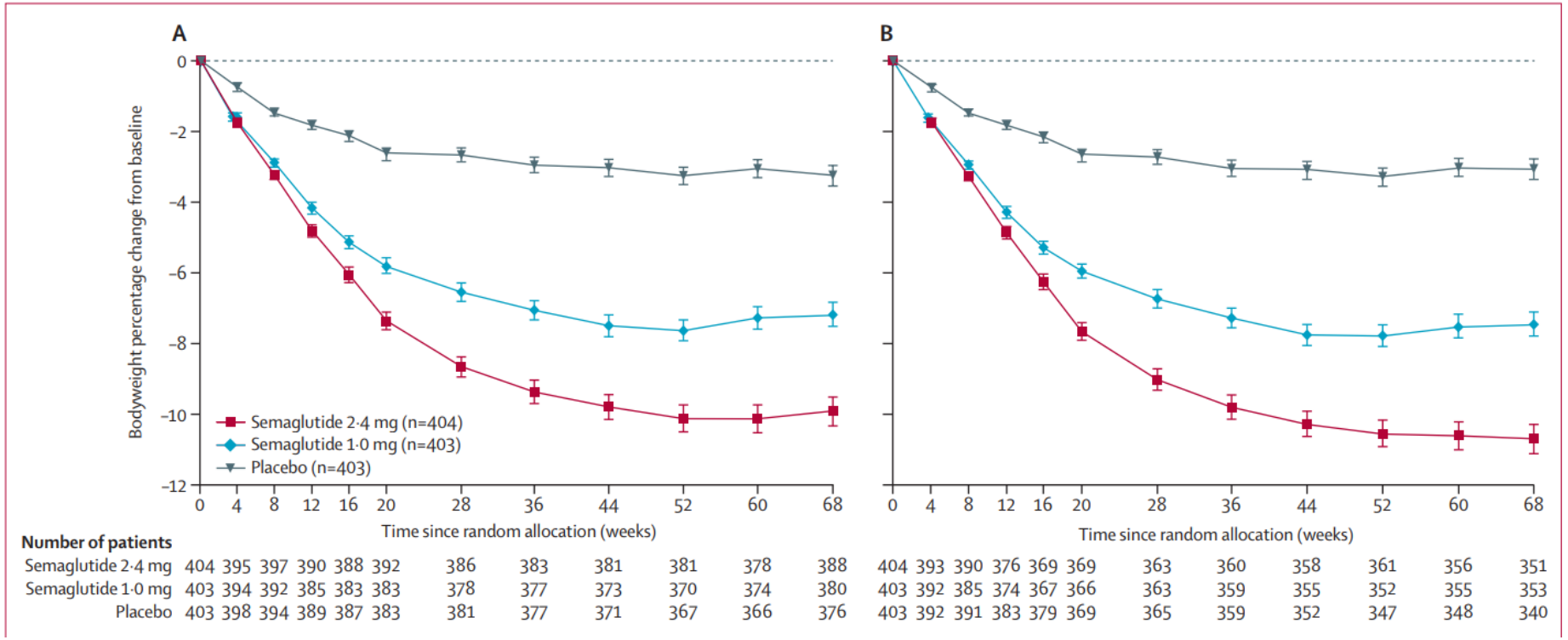
Hollander P, et al. *Diabetes Care*. 2013;36:4022-4029.

Regulation of body weight and glucose metabolism by GLP1R agonism



Müller, Nature. 2022

Trial population: Overweight or obese people with type 2 diabetes



Davis, Lancet. 2021

STEP trials

Cardiometabolic Disease Staging, designed by Garvey and fellow UAB colleagues, to predict the participants' risk of developing T2D in the next 10 years.

"Transformational" semaglutide can cut Type 2 diabetes risk by more than half

by Adam Pope

October 05, 2022 | Print | Em

New research presented by University of Alabama at Birmingham researchers shows that a 2.4mg dose of the obesity drug semaglutide can reduce the risk of Type 2 diabetes, or T2D, by 60 percent.

"Semaglutide appears to be the most effective medication to date for treating obesity and is beginning to close the gap with the amount of weight loss following bariatric surgery," said W. Timothy Garvey, M.D., Butterworth Professor of Medicine in the Department of Nutrition Sciences and lead researcher. "Its approval was based on

JAMA Network

QUESTION What effect does continued treatment with subcutaneous semaglutide, 2.4 mg once weekly, have on the maintenance of body weight loss in adults with overweight or obesity without diabetes?

CONCLUSION Among adults with overweight or obesity who completed a 20-week run-in of semaglutide treatment, maintaining treatment with semaglutide vs switching to placebo resulted in continued weight loss over the following 48 weeks.

POPULATION

634 Women
169 Men

Adults with body mass index of at least 30 (or ≥27 with ≥1 weight-related comorbidity) and without diabetes

Mean age: 46 years

LOCATIONS

73 Sites in 10 countries

INTERVENTION

803 Participants randomized

535
Continued semaglutide
Continued to receive semaglutide, 2.4 mg once weekly, for 48 weeks (after 20-week run-in period with semiglutide)

268
Placebo
Switched to once-weekly placebo for 48 weeks (after 20-week run-in period with semaglutide)

PRIMARY OUTCOME

Percent change in body weight from week 20 to week 68

FINDINGS

Mean body weight change from week 20 to week 68

Continued semaglutide	Weight change: −7.9%
Placebo	Weight change: +6.9%

Between-group difference in percent change in body weight was statistically significant:

−14.8 percentage points

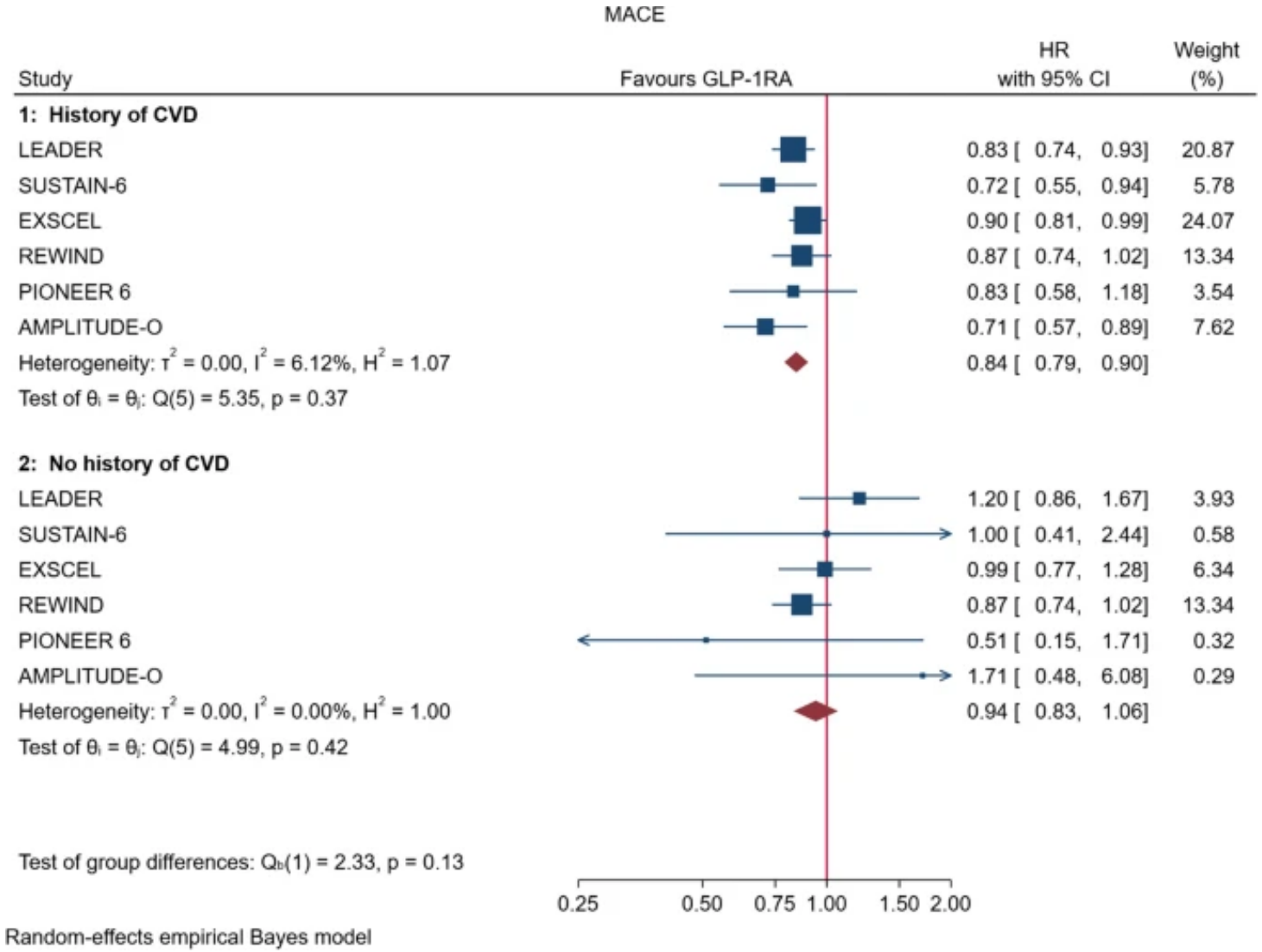
(95% CI, −16.0 to −13.5); $P < .001$

© AMA

Rubino D, Abrahamsson N, Davies M, et al; STEP 4 Investigators. 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*. Published online March 23, 2021. doi:10.1001/jama.2021.3224

WELL-AHEAD

Project ECHO



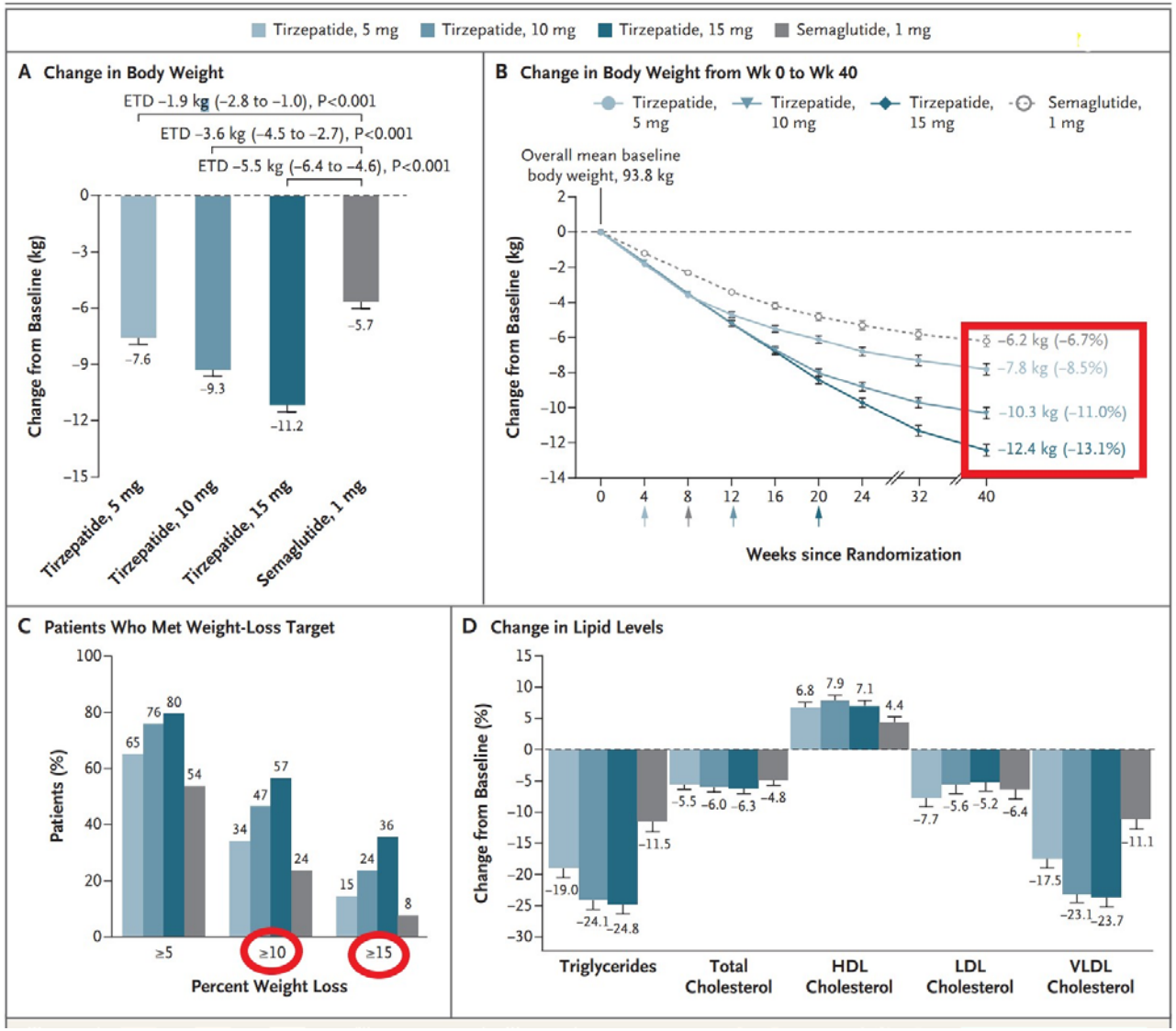
Giugliano, D., Scappaticcio, L., Longo, M. *et al.* GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs. *Cardiovasc Diabetol* **20**, 189 (2021)

The FDA granted fast track designation to the combination GIP/GLP-1 receptor agonist tirzepatide for overweight and obesity based on the SURMOUNT clinical

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist

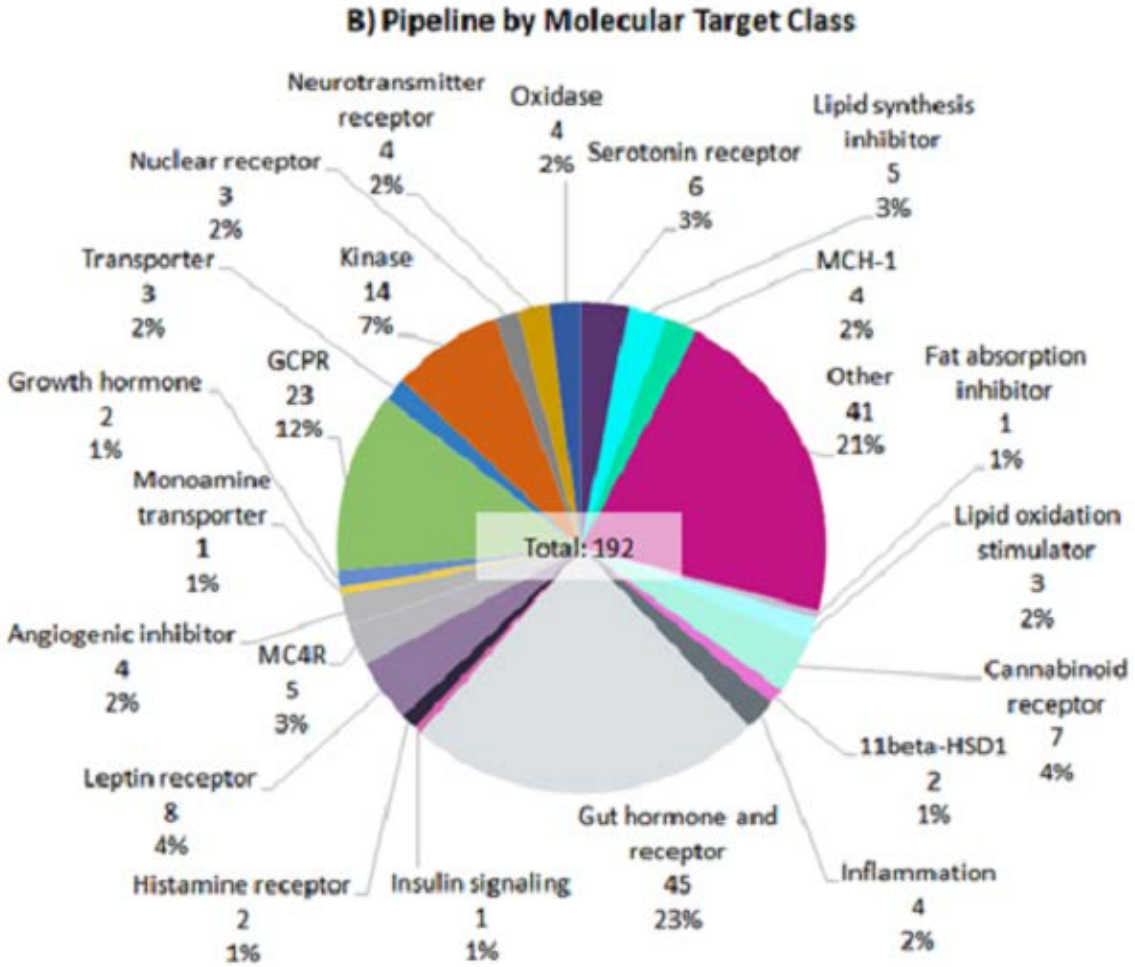
SURMOUNT-1- Obesity Trial (Tirzepatide)

SURPASS trials- Diabetes Trials



Jastreboff, NEJM 2022

What about the future of Obesity Treatments?



Source: GlobalData, Pharma Intelligence Center (Accessed February 25, 2019)

Thank you!

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