Obesity Medicine and Nutritional Psychiatry

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Obesity Medicine

- Obesity measurements, rates, and trends
- Etiologies and effects
- Associations with other diseases
- Assessment
- Treatments
  - Lifestyle
  - Pharmacologic
    - Insurance Treatment Algorithm
      - Prior Authorizations
      - Medication Algorithm
  - Procedures
- Lipedema
- MASLD

Obesity Measurements, Rates, and Trends

"Obesity Is a Disease"

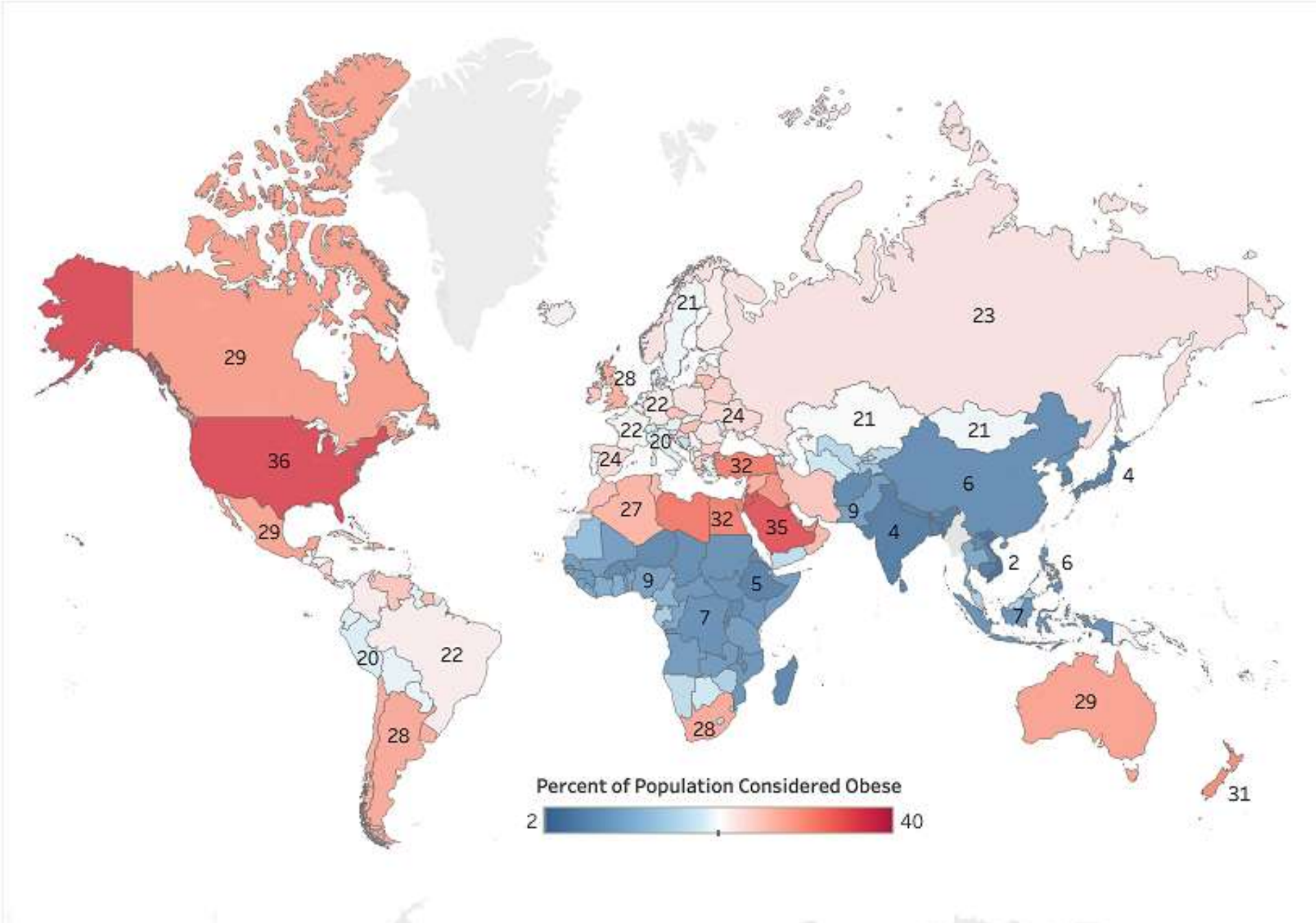
- 1942: World Health Organization
- 1998: National Institutes of Health
- 2008: American Obesity Society
- 2013: American Medical Association
- 2016: Centers for Disease Control
- **Highest prevalence of any disease in the US yet significantly undertreated**

Obesity Measurement

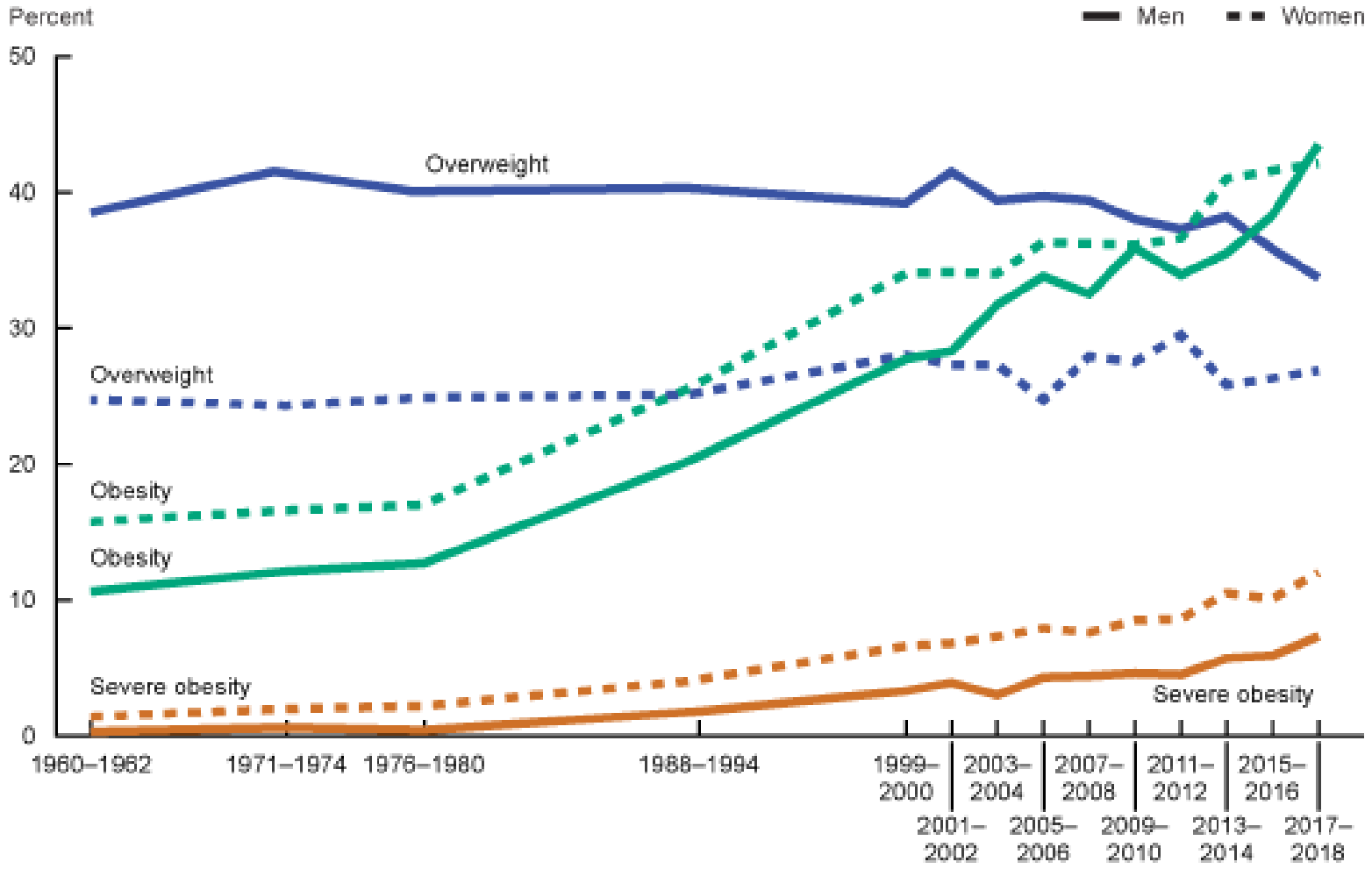
- BMI: Screening tool for metabolic dysfunction
  - <18.5, underweight
  - 18.5 to <25, healthy weight
  - 25 to <30, overweight
    - 73.6% of adults (2018)
  - >=30, obese
    - 41.9% of adults (2020), projected to reach 50% by 2030
    - 19.7% of children (2020)
      - 75% of 17-24 yo not qualified for military service (#1 reason: body weight)
      - 60% of the 25% that ARE qualified could not pass PT test on day 1 of training
    - 27% of sailors, 12% increase from 2020 to 2021
    - Class I: 30 to <35
    - Class II: 35 to <40
    - Class III: >=40
      - 9.2% of adults (2020), projected to reach 25% by 2030
  - For those of Asian descent
    - >23: overweight
    - >27.5: obese

Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2021.
Ward ZJ et al. Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity. N Engl J Med 2019; 381:2440-2450.

Obesity Rate by Country (The World Factbook – Central Intelligence Agency, 2016)

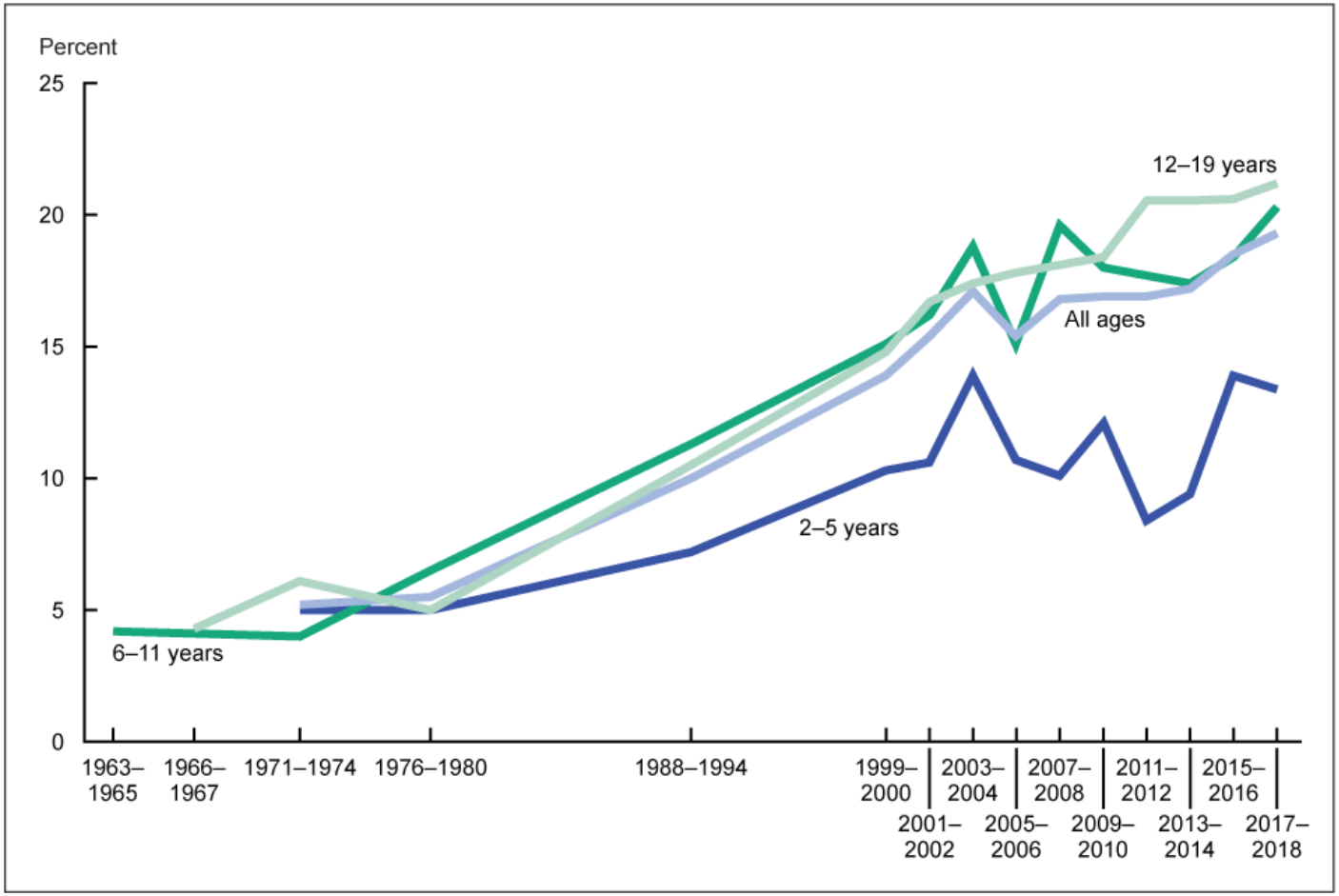


Obesity Rates Over Time



Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among adults aged 20 and over: United States, 1960–1962 through 2017–2018. NCHS Health E-Stats. 2020.

Obesity by Age



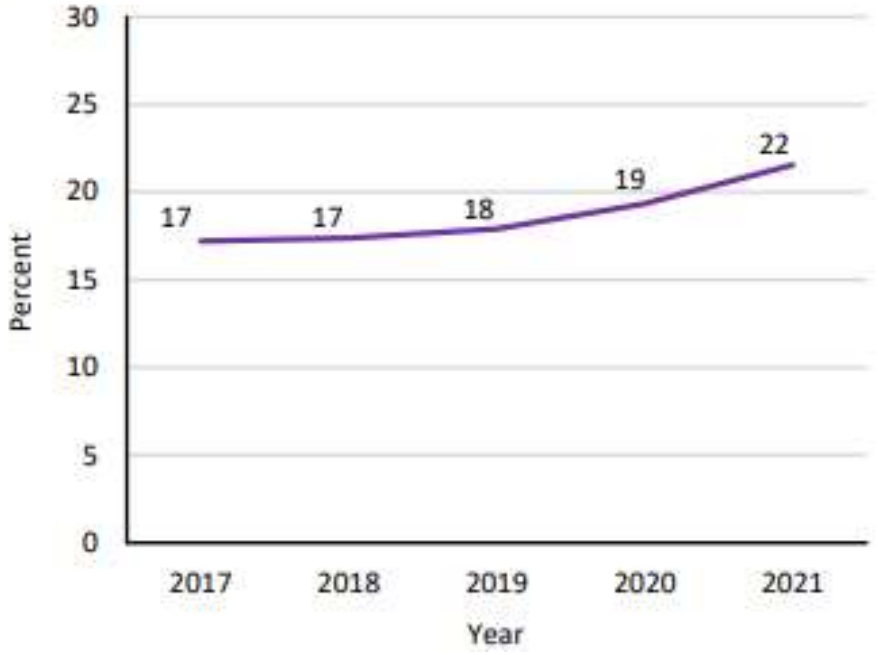
NOTE: Obesity is body mass index (BMI) at or above the 95th percentile from the sex-specific BMI-for-age 2000 CDC Growth Charts.
SOURCES: National Center for Health Statistics, National Health Examination Surveys II (ages 6–11), III (ages 12–17); and National Health and Nutrition Examination Surveys (NHANES) I–III, and NHANES 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018.

Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2–19 years: United States, 1963–1965 through 2017–2018. NCHS Health E-Stats. 2020

Obesity in the US Military

Prevalence of Obesity, AC Service Members, 2017–2021

The prevalence of obesity increased from 17% in 2017 to 22% in 2021.



DOD Health of the Force 2021

Obese Etiologies and Effects

Why Obese Patients Can't Maintain Weight

- Leptin goes down when we lose weight
  - Low leptin leads to decreased satiety
  - Chronic low satiety leads to increased food intake
  - Damage to nerves in the hypothalamus leads to leptin resistance
    - Giving exogenous leptin does not help satiety
  - These nerves can be repaired by use of medications currently only being used in animal models
- Hypothalmic inflammation via ↑ TNF-α
  - Leads to more belly and body fat, and higher insulin resistance
    - This leads to even more inflammation
  - "Bitter" olive oil high in oleocanthal is anti-inflammatory
- Obesity leads to decreased adiponection -> ↓anti-inflammatory

Sumithran P et al. Long-Term Persistence of Hormonal Adaptations to Weight Loss. N Engl J Med 2011; 365:1597-1604.
Fothergill E et al. Persistent metabolic adaptation 6 years after "The Biggest Loser" competition. Obesity. 2016;24(8):1612-1619.

Why Obese Patients Can't Maintain Weight

- Physical
  - Increased stress on joints, immobility, tissue compression, psychosocial
- Increased food intake and/or decreased physical activity
  - Negative energy balance
  - Cascade of metabolic and neurohormonal adaptive mechanisms
    - Decrease in energy expenditure: resting metabolic rate decreases
    - Increase in orexigenic hormones (ie ghrelin)
    - Decrease in anorexigenic hormones (ie PYY, CK, GIP)
    - Patient experiences new "set point" for their weight
      - May take up to 10 years at healthy weight to reset the set point so that they do not regain the weight

Possible Etiologies of Increase in Obesity

- Diet of mother while in utero
  - Increase of 200g of birth weight (all fat) in the last 25 years
- Diet during childhood
- Sedentary lifestyle
  - Exercise does not lead to weight loss
    - Can prevent weight gain
    - Resistance training can prevent muscle loss when losing weight
- Insufficient sleep
- Obesogenic medication use increase
- Obesogens in the environment (ie BPA, parabens, PFAS, DDT)
- Ultra-processed foods (UPFs)

[1]Stunkard et al. An Adoption Study of Human Obesity. NEJM. 1986 Jan, 314(4), 193-198.
[2]Sorensen T et al. Genetics of obesity in adult adoptees and their biological siblings. BJM. 1989 Jan. 298, 87-90.

"A Calorie Is Not A Calorie"

- Calorie numbers on packaging are not 100% accurate
- Not all calories provide the same satiety signal
- Not all calories are absorbed the same
  - 30% of nuts are not absorbed unless in UPF form
  - 30-40% increase in calorie absorption of cooked vs raw starch[1]
  - The more processed/cooked foods are, the easier it is to digest and absorb calories[1]
- Not all calories generate the same insulin response
- Gut microbiota consume some of our nutritional ingestion
  - Affected by diet, medications, antibiotics, fecal transplantation

[1]Wranham R. Catching Fire: How Cooking Made Us Human. New York. Basic Books. 2009.

"A Calorie Is Not A Calorie"

- Speed of metabolism is affected by age, gender, genetics, muscle/fat composition, activity
- Type of fat consumed (ie MUFAs) have different impact on weight gain with same number of calories
- Millions of chemicals (the vast majority of which are unknown) in foods and our bodies affect our metabolism
- Change in mitochondria distribution

Where the Body Stores Fat

- Subcutaneous Fat
  - Mediated by insulin
  - Undesirable but metabolically neutral
  - Healthy fat storage (~22lbs)
- Visceral Fat
  - Mediated by cortisol (stress)
  - Patient could starve themselves but increase visceral fat
  - Healthy fat storage (~3-4lbs)
- Liver Fat
  - Mediated by alcohol and fructose
  - Healthy fat storage (~0.5lb)
  - First case of NAFLD described in 1980

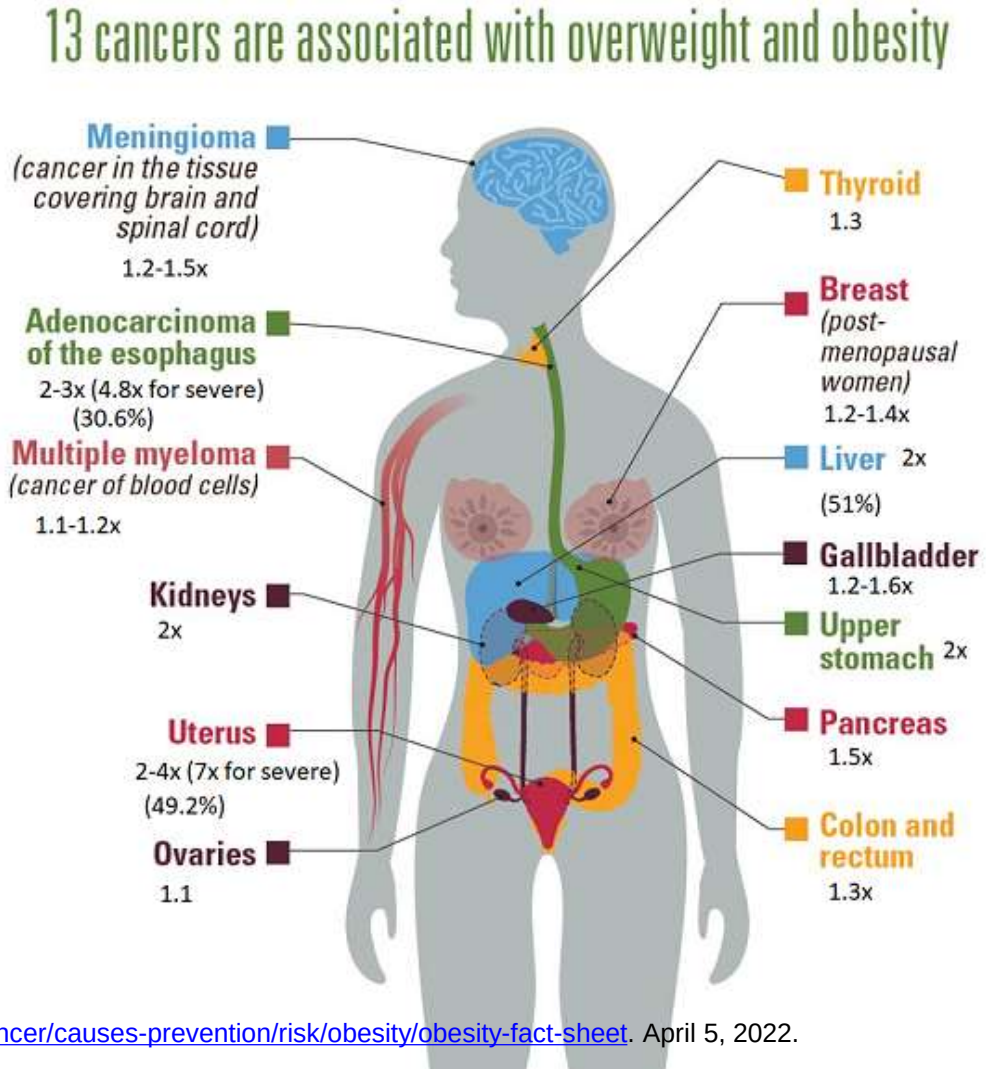
Associations with Other Diseases

Obesity is Associated with Chronic Conditions

- All cause mortality
- Metabolic/Immunologic
  - DMII (dementia, retinopathy, renal failure, heart disease)
  - Inflammation
  - More severe COVID
- Gastrointestinal
  - Metabolic dysfunction-associated steatotic liver disease (MASLD) and MASH (MAS Hepatitis)
  - GERD
  - Cholelithiasis
- Genitourinary
  - Male and female Infertility
  - Polycystic ovarian syndrome
  - Urinary stress incontinence
- Increased risk of 13 types of cancer
- Psychiatric
  - Depression/Anxiety
  - Body image/self-esteem
- Cardiac
  - Dyslipidemia
  - Hypertension
  - Coronary artery disease
  - Heart attacks and strokes
- Pulmonary
  - OSA (pulmonary HTN, falling asleep driving, concentration)
  - Obesity hypoventilation syndrome
- Musculoskeletal
  - Osteoarthritis
  - Chronic Pain
- Obstetric
  - Higher risk neurodevelopmental and psychiatric disorders in children of obese mothers

Obesity and Cancer

- More than 684,000 obesity-associated cancers in the US each year
- Women
  - 470,000 per year
  - #1 is breast cancer
- Men
  - 210,000 per year
  - #1 is colorectal cancer
- Causes
  - Long-lasting inflammation -> oxidative stress -> DNA damage
  - Increased adipokines -> stimulate cell growth
  - Increased insulin
  - Increased IGF-1
  - Increased estrogen
  - Indirect effects on other modulators (ie mTOR, AMP-activated protein kinase)



Obesity and Cancer. National Cancer Institute. www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet. April 5, 2022.

Assessment

Assessment

- Weight
  - BMI (not perfect but ok for tracking)
  - Waist circumference
    - >=35in. for women, >=40in. for men
  - Waist-to-height ratio
  - Body Fat %
    - Calipers: Peri-umbilical, chest, thigh
    - Bioelectrical Impedance (BIA)
  - Weight Hx
- Social History
  - Family history
  - Lifestyle factors

Assessment

- Screen for co-morbid conditions
  - CVD, DM2, HLD, hypertriglyceridemia, HTN, OSA, MASLD, GERD, depression, anxiety, insomnia, chronic pain
    - 12.2% of Americans are metabolically healthy (0/5 metabolic syndrome symptoms)
- Screen for secondary causes
  - Lipedema, Cushing's syndrome, secondary hypogonadism, hypothyroidism, PCOS
- Screen for conditions affecting med choice
  - Migraines, constipation, diarrhea, MEN2, medullary thyroid cancer, seizures, glaucoma, kidney stones, bulimia, pregnancy
- Motivation/expectations for weight loss
- Labs: A1C, FPG, CMP, TSH, Lipids

Assessment: Labs

- CMP with elevated AST and ALT
  - Obese patients and those with DMII typically have NAFLD/MASLD
    - 20% will get NASH, which is hepatitis and can progress into cirrhosis
    - Rule out alcohol as cause with hx and PEth
    - FIB4 score to evaluate fibrosis
    - Rule out other causes
      - Hep B, Hep C: Hep C Antibody, Hep B Core, Hep B Surface
      - Alpha-1 antitrypsin
      - Autoimmune hepatiis: levels >5x's normal -> check
        - ANA, ASmA, IgG-1 kidney/liver
    - Medication causes: tamoxifen, amiodarone, corticosteroids; exhaustive list at livertox.gov
    - Other rare causes to check later: Wilsons Disease, Celiac Disease
      - Consider ferritin/transferrin saturation (hemochromatosis)
        - Check in caucasian males for sure; perhaps females

Medications Associated with Weight Gain

Class	Examples
Antipsychotics	Clozapine>>Olanzapine>Quetiapine>>Risperidone> (possible with all SGAs)
Antidepressants	Mirtazapine>TCAs>>SSRIs (paroxetine worst), MAOIs
Antiepileptics/Mood Stabilizers	Divalproex>>Carbamazepine>Lithium>Gabapentin, Pregabalin
Glucocorticoids	Prednisone, Methylprednisolone, Hydrocortisone
Antihistamines	Diphenhydramine, Cyproheptadine
Hormonal agents	Progestins (controversial), medroxyprogesterone
Diabetes agents	Insulin, Sulfonylureas (-ide)>>Meglitinides (-glinide), Thiazolidinediones (TZD) (-glitazone)
Alpha/Beta-blockers	(due to exercise intolerance, fatigue)

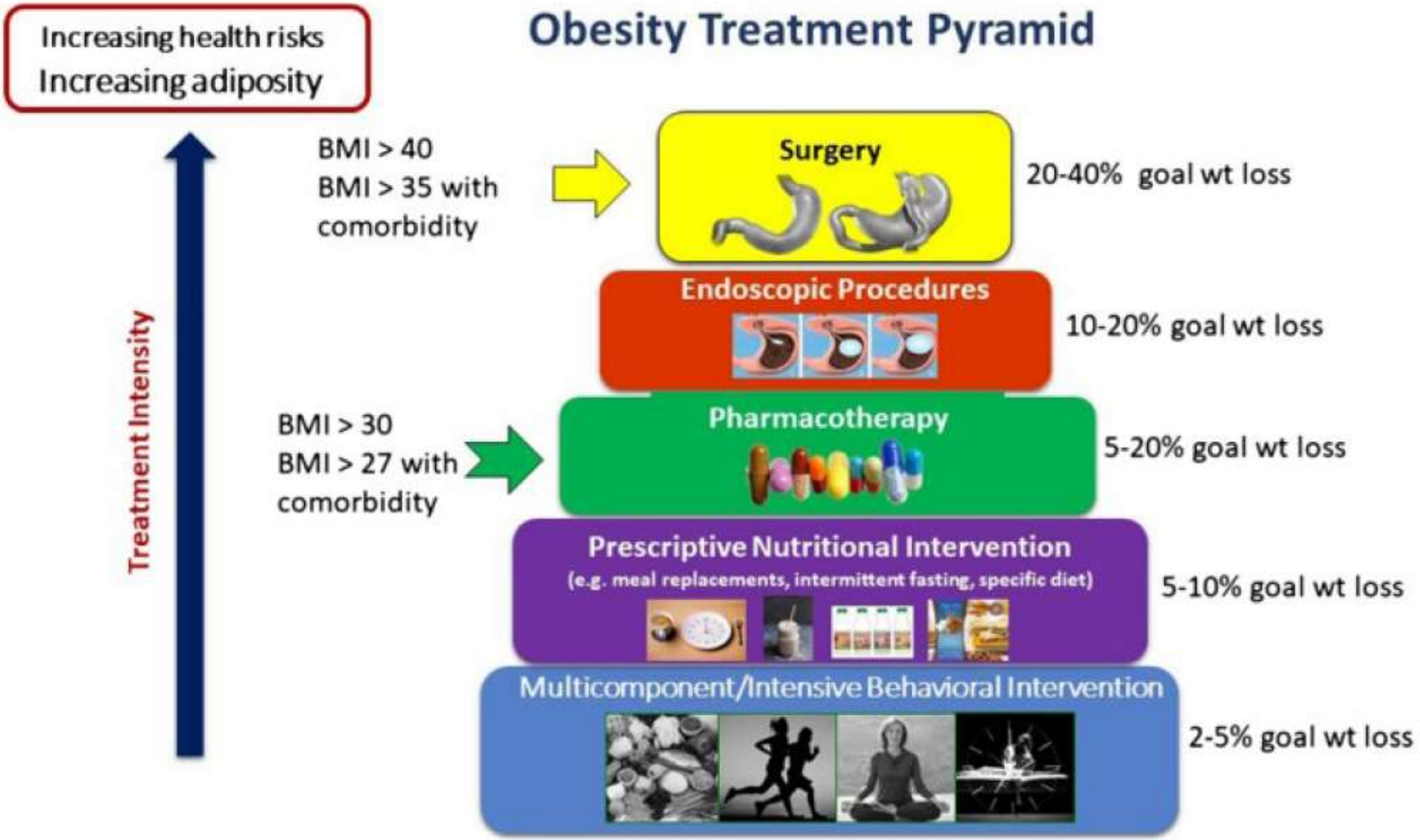
Medications Associated with Weight Gain

- Antidepressants/Antipsychotics
  - H_1 antagonism: Decreased metabolic rate
  - $5HT_{2c}$ antagonism: Decreased satiety signal, carb craving
  - Increase in prolactin
  - Anticholinergic activity: likely affects glucose and insulin
  - Potentially some effect on GLP-1 receptors
- Glucocorticoids
  - Increase appetite, lower metabolism, drive storage of adiposity in the abdomen

Medications Associated with Weight Gain

- Diabetes agents
  - Insulin
    - Leads to storage of glucose which can cause weight gain
    - Eating to avoid hypoglycemia can lead to weight gain
  - Sulfonylureas
    - Forces pancreas to produce more insulin which can lead to weight gain
  - Thiazolidinediones (TZDs) (ie pioglitazone)
    - Helps healthy fat cells store fat
    - Water retention
    - Weight gained is relatively healthy weight

Treatments



Tucket et al. Curr Obes Rep. 2021 Sep;10(3):396-408.

Lifestyle Medicine

Integrative Psychiatry

- Psychotherapy
- Pharmaceuticals
- Non-pharmaceutical supplements
  - Herbals
  - Vitamins and minerals
  - Others
- Diet changes
- Meditation
- Yoga
- Art therapy
- Massage
- Aromatherapy
- Acupuncture

Nutritional and Lifestyle Psychiatry

- Nutritional psychiatry
  - Integrates nutrition into the standard treatment plan
  - Dietary changes
  - Supplements
- Lifestyle psychiatry/medicine
  - Nutrition
  - Movement
  - Adequate Sleep
  - Decreased/elimination of toxins
    - Tobacco, alcohol, drugs
    - Trans fats, (fructose)
  - Stress management (ie mindfulness)
  - Being in Nature
  - Continual Education (including hobbies)
  - Social Connection and Healthy Relationships

Nutrition

Nutrition

- Please remember….
- This is simplified, but NOTHING about nutrition is simple
- An isolated nutrient may act nothing like it does as a constituent in **whole food**
- When reading the nutrition literature, remember mice are not rats are not pigs are not cows are not primates are not healthy humans are **not humans with disease**

Intake Recommendation for Weight Loss

- Calorie Restriction (800-1200 kcal/day or 500 kcal deficit)
  - Extremely difficult unless using one of these techniques
  - Intermittent fasting, alternate-day fasting, time-restricted feeding
    - Limit eating to 10-12 hours per day
      - Less is not healthy or helpful, but may help with weight loss short-term
      - Weight loss will take at least a month
    - Has health benefits far beyond weight loss
      - Fasting induces "clean up" in our bodies that maintains healthy functioning
      - Reduced inflammation (especially in the gut)
      - Improvements: immunity, mood, anxiety, energy, decreased appetite
      - Leads to healthier gut microbiome
    - If inconsistent in fasting, may worsen weight and health
    - Most adjust after a few days of intermittent fasting
    - A little better to have an earlier eating window than later, but later is easier
    - Fasting time: water, coffee, plain tea only
  - Free apps like "Lose It" can help patients track
  - Medications

Intake Recommendation for Longevity

- Fasting Mimicking Diet (FMD): "The Longevity Diet"
  - Studied by Dr. Valter Longo
  - Helps to trigger cellular and metabolic changes that are similar to fasting
    - Increased autophagy (cellular clean up)
    - Improved insulin sensitivity
  - Can help to reduce biological age
  - Improvements in metabolic health
  - Improved immune system
  - Primarily plant-based with omega-3 rich fish no more than 2-3 times/week
  - 12 hour eating window
  - 5 days of "fasting"
    - 40-50% of calorie intake on first day (~1100)
    - 10-20% on subsequent days (~800)
    - Macronutrient ratio of 10% protein, 45% fat, 45% carbs
    - 2-4 times a year for healthy weight individuals
    - Up to 12 times per year for overweight individuals

Nutrition Recommendations

- Eat a whole foods diet such as the Mediterranean diet
  - Reduce/eliminate ultra-processed foods
    - Reduce sugars, omega-6 FAs?, trans fats, processed meats, additives, etc
  - Fermented foods
    - Kefir, sauerkraut, kimchi, yogurt, kombucha
    - Homemade fermented vegetables
  - Complete adequate proteins
    - Lean meats, eggs, legumes, whole grains
    - Is filling
    - Helps with muscle growth in concert with resistance training
    - If eaten in excess will be stored as fat
  - Fiber
    - Increase varieties of plants
  - Significantly reduce snacking (especially unhealthy snacking)
    - Healthy options: Nuts, seeds, dark chocolate, whole fruit in moderation, salsa, yogurt or smoothies without added sugar

Nutrition Recommendations

- Eat healthy fats
  - Dietary cholesterol not a concern unless in extreme excess
  - Health of fats in order
    - Omega-3: anti-inflammatory, healthy for neuronal structure and fx
      - Wild fish or wild fish oil; farmed?
      - Omega-3 is found in algae that fish eat
      - Many farmed fish eat feed that is high in omega-6
    - MUFAs
      - Oleic acid: anti-inflammatory, ligand for PPAR: helps liver
    - Omega-6
      - Seed oils: corn, soy, cottonseed, sunflower, safflower
      - Pro-inflammatory, but are they?
    - Saturated fat is controversial: sdLDL vs lbLDL
      - Cardiovascularly neutral? Probably not
    - Medium chain triglycerides (MCTs)
      - Found in coconut oil
      - Can overwhelm the liver but likely fine is smaller quantities
    - Trans fats: no amount is ok!

Nutrition Recommendations

- Eat more plants than meat
- Nutrient dense foods
- Leafy greens
  - Darker the better
- Rainbow fruits, veggies, mushrooms
  - Berries are some of the best
  - Avoid products with added sugar or fiber removed
- Nuts
  - Almonds, cashews, pumpkin seeds
  - Protein, healthy fats, slow-burning carbohydrates, minerals
- Omega-3 fatty acids
  - Long-chain: DHA/EPA (Seafood high in omega-3 twice a week)
    - **S**almon, **M**ackerel, **A**nchovies, **S**ardines, **H**erring, Oysters
  - Short-chain: ALA (nuts and seeds)
    - Flaxseed, Chia seeds, Walnuts

Ramsey D. Eat to Beat Depression and Anxiety: Nourish Your Way to Better Mental Health in Six Weeks. 2021.

Foods Good for Mental Health

- Shellfish
  - High protein, B12, Fe, Zn, Mg, Cu, omega-3s
  - A few times a month
- Legumes
  - Beans, Chickpeas, Lentils, Peas
  - Protein, Fiber, Complex carbohydrates
- Extra virgin olive oil: MUFA
- Dark Chocolate
  - Fermented, Flavanols, Fe, Mg, Zn, Cu, Ph, fiber
  - Darker means less sugar and more nutrients
    - 85% dark chocolate may improve mood[1]

[1]Shin J. Consumption of 85% cocoa dark chocolate improves mood in association with gut microbial changes in healthy adults: a randomized controlled trial. The Journal of Nutritional Biochemistry. 2022:99.

Foods Good for Mental Health

- Liquids
  - Water, Unsweetened tea and coffee
  - Don't drink your calories
- In moderation
  - Eggs (limit 6 per week?)
  - Dairy
    - Milk
    - Unprocessed healthy cheeses
      - Feta, Mozzarella, Ricotta, Cottage cheese, Parmesan, Swiss, Goat, Blue, Cheddar
    - Unsweetened yogurt
  - Lean meat (1 serving a day, mix red and white)

Carbohydrates

- There are essential amino acids, fatty acids, vitamins, and minerals
  - Our bodies cannot produce these, they must be consumed
- There are NO essential carbohydrates
- It is NOT recommended to eliminate carbs
  - Except in some situations
  - Ketogenic diet to be discussed later
- Healthiest ways to consume carbohydrates
  - Fruits and vegetables
  - Legumes
  - Whole grains
    - Grains where you can see the grain with its coating or ground from them
    - Excludes most breads except "100% Whole Grain"
    - Do not be fooled by the words "Made from Whole Grain" or "Multigrain"
    - Sprouted breads, oatmeal without added sugars, home-popped popcorn, quinoa, freekeh, bulgur wheat, kasha, barley, spelt, brown rice, corn, whole-grain pasta, amaranth, farro, millet

Nutrients Good for Mental Health

- Nutrients involved in relieving depression
  - Iron: builds hemoglobin involved in carrying oxygen to the brain
  - Mg: regulates neurotransmitters involved in mood
  - K: necessary for electric impulses in neurons
  - Se: assists in creating antioxidants in the brain; helps thyroid
  - Zn: regulates brain signals and neuroplasticity
  - Vitamin A: neuroplasticity
  - Thiamine: role in energy production
  - B6: brain development and function
  - Folate: creation of new cells
  - B12: involved in production of serotonin, norepinephrine, and dopamine
  - Vitamin C: antioxidant
- Supplements lack phytonutrients from whole foods
- Supplements do not contain all of the naturally occurring compounds
  - For example, vitamin E supplement contains 1/8 tocopherols/tocotrienols

Foods Good for Mental Health

- Organic foods
  - Some foods contain more pesticides than others
    - "The Dirty Dozen"
      - Strawberries, spinach, kale, greens, nectarines, apples, grapes, peppers, cherries, peaches, pears, celery, tomatoes
    - "The Clean 15"
      - Avocados, Corn, pineapple, onions, papaya, sweet peas, asparagus, melons, kiwi, cabbage, mushrooms, mangoes, sweet potatoes
      - Generally foods with thick covering that is not eaten are "clean"
    - If not able to buy organic, clean thoroughly

Foods Good for Mental Health

- Avoid
  - Simple carbs
    - Fried and fast foods
    - Refined flour
    - Ultra-processed foods
    - Sodas
    - Sweets
    - Pastries
    - Most condiments
      - Exceptions: mustard, olive oil, smashed avocado, pesto, tahini, hot sauce, vinegar, spices
  - Cured and Processed meats
    - Bacon and sausage
    - Deli meats

Ultra-Processed Foods

- Ultra-processed foods (UPFs)
  - Wrapped in plastic and contains at least one ingredient that you will not typically find in a domestic kitchen
  - Highly palatable food, readily available, inexpensive
  - Soft (baby food-like), take less time to chew and eat
    - Every 10 years our jaws are getting smaller
  - Much of it is designed to not make us full so we will eat more
  - 73% of food in the grocery store
  - 60% of American diet (70% for children)
  - Fat and sugar do not exist together in the natural environment
  - Fructose/starch always exists with fiber in the natural environment
    - Sugar causes 4 diseases
      - DMII, MASLD, CVD, Tooth decay
  - Highly processed oils are new in our diets

Ultra-Processed Foods

- Examples of processed vs ultra-processed foods
  - Camembert vs Velveeta
  - Butter vs Margarine
  - Sourdough and rye bread vs White bread
  - Non-instant oatmeal vs Breakfast cereals
  - Plain yogurt with only milk vs Plain yogurt with thickeners and sugar
  - Dates and honey vs Artificial sweeteners
    - Artificial sweeteners can disrupt the gut microbiome
  - Simple ingredient energy bar vs most protein/energy/granola bars
  - Whole fruit vs fruit juice
  - Fresh popcorn vs microwave popcorn
  - Fresh chicken breast vs bacon, most salamis and sausages
- Common additives and alterations
  - Thickeners, stabilizers, emulsifiers (glues), sweeteners, dyes, starch, chemicals
  - Foods stripped of fiber, fat, protein, and vitamins
  - Nutrients removed from food then added back lacks the same properties
    - Something is important about how it naturally existed

Ultra-Processed Foods

- Hall et al. Cell Metabolism. 2019.
  - Two groups, one given a healthy diet, the other an UPF diet
  - Equal macronutrients and calories
  - UPF group frequently went back for seconds and gained weight
- Arlet et al. Annals of Internal Medicine. 2011.
  - Same calorie restricted diet
  - One group adequate sleep vs one group sleep deprived
  - Adequate sleep group lost more body fat (55%) vs muscle mass (60%)
- Barr et al. Food and Nutrition Research. 2010.
  - Compared whole bread and cheese sandwich with ultra processed version
  - Same calories for each sandwich
  - Satiety was the same between the groups
  - Energy expenditure was 50% greater with the whole food group

Ultra-Processed Foods

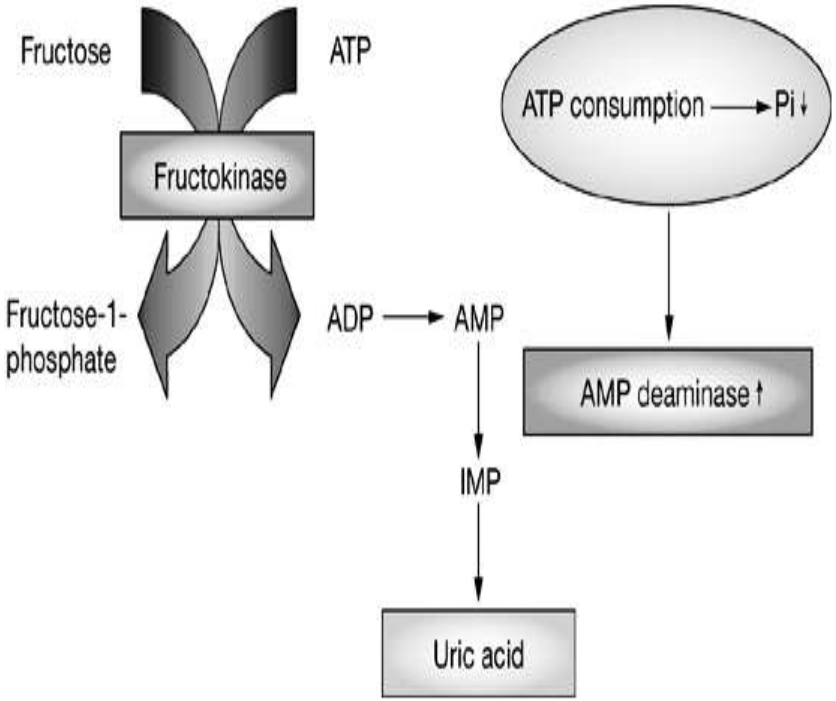
- UPFs are designed to make people overeat and override our natural satiety signals in the brain
- These periods of calorie excess cause damage to neurons in the hypothalamus which disregulates the weight set point
  - Not all are susceptible (~25%)
- Potential fix
  - Don't allow false claims on packaging
  - Insist on warnings of the dangers of the product be listed on the packaging
  - Label as a toxin: fructose, UPFs, cured meats with known cancer risk
  - Change the subsidy system to reward healthy options

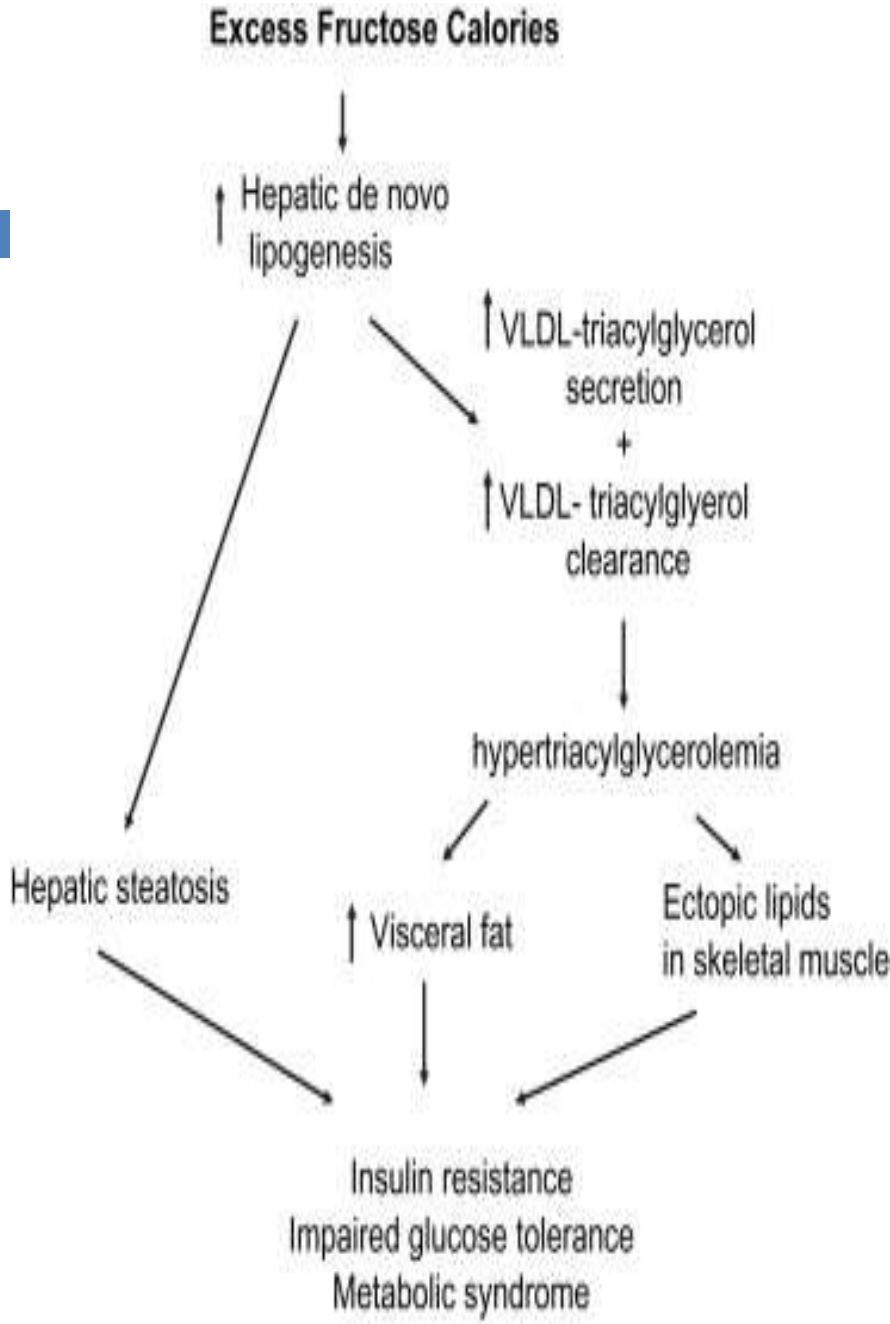
Fructose

- Fructose has minimal influence on serum insulin concentrations and plasma glucose levels
- Is sweeter per molecule than glucose
- Is 50% of table sugar
- Initially thought to be great sweetener alternative for patient's with diabetes
- Doesn't stimulate insulin from pancreas
  - Ghrelin (the "hunger hormone") is not suppressed
  - Leptin (the "satiety hormone") is not stimulated
  - You eat more → energy excess→ insulin resistance
  - Reduces dopamine signaling in the NA → decreasing the pleasure derived from food → Eat more
  - Metabolized **only** in liver: no storage form

Fructose

- Metabolism favors lipogenesis
- VLDL/TG accumulation
- Uric Acid →lowers nitric oxide
  - Link to HD, HTN, gout?





Fructose

- Poorly absorbed from GI tract; requires more energy
  - Depletes energy needed to maintain integrity of gut lining
    - Leads to food and bacteria "leaking" across gut wall causing inflammation
- 1/3 of the Western European population has fructose malabsorption
  - Intolerance and problematic absorption
  - Fructose (and lactose) can react chemically and degrade tryptophan
    - Tryptophan is used by gut bacteria
      - Fructose malabsorbers have lower levels of tryptophan in thier serum than normal controls
  - Lower serum zinc and folic acid

Chronic Fructose Exposure

- Hypertension (uric acid)
- Myocardial infarction (dyslipidemia, insulin resistance)
- Dyslipidemia (*de novo* lipogenesis)
- Pancreatitis (hypertriglyceridemia) and pancreatic cancer
- Obesity (insulin resistance)
- Malnutrition (obesity)
- Hepatic dysfunction (non-alcoholic steatohepatitis)
- Habituation, if not addiction

Fruit vs Table Sugar vs HFCS

- Fruit
  - Low energy density, high water content, phytonutrients, fiber
  - Yearly fructose consumption increased from 20 teaspoons 10,000 years ago to 140 lbs today
- Table sugar (sucrose)
  - Glucose bound to fructose
- High fructose corn syrup (HFCS)
  - Pure fructose? (Not really!)
    - May contain contaminants such as mercury as well as other unknown substances that are neither glucose nor fructose
  - Rats with access to HFCS gained significantly more weight than those with access to table sugar with equal caloric intake
    - The critical differences in appetite, metabolism, and gene expression that underlies this phenomenon is unclear
  - Presence of HFCS is a sign of poor quality food!

Fatty Acids

- Saturated: no double bonds
  - Short-chain
    - Butyric Acid - 4C
  - Medium-chain
    - Lauric Acid – 12 C
      - Coconut oil, palm kernel oil, breast milk
  - Long-chain
    - Myristic Acid – 14 C's
      - Cow's milk and dairy products
    - Palmitic Acid
      - Palm oil and meats
    - Stearic Acid – 18 C
      - Meat and cocoa butter
- Solid at room temperature
- Not oxidized

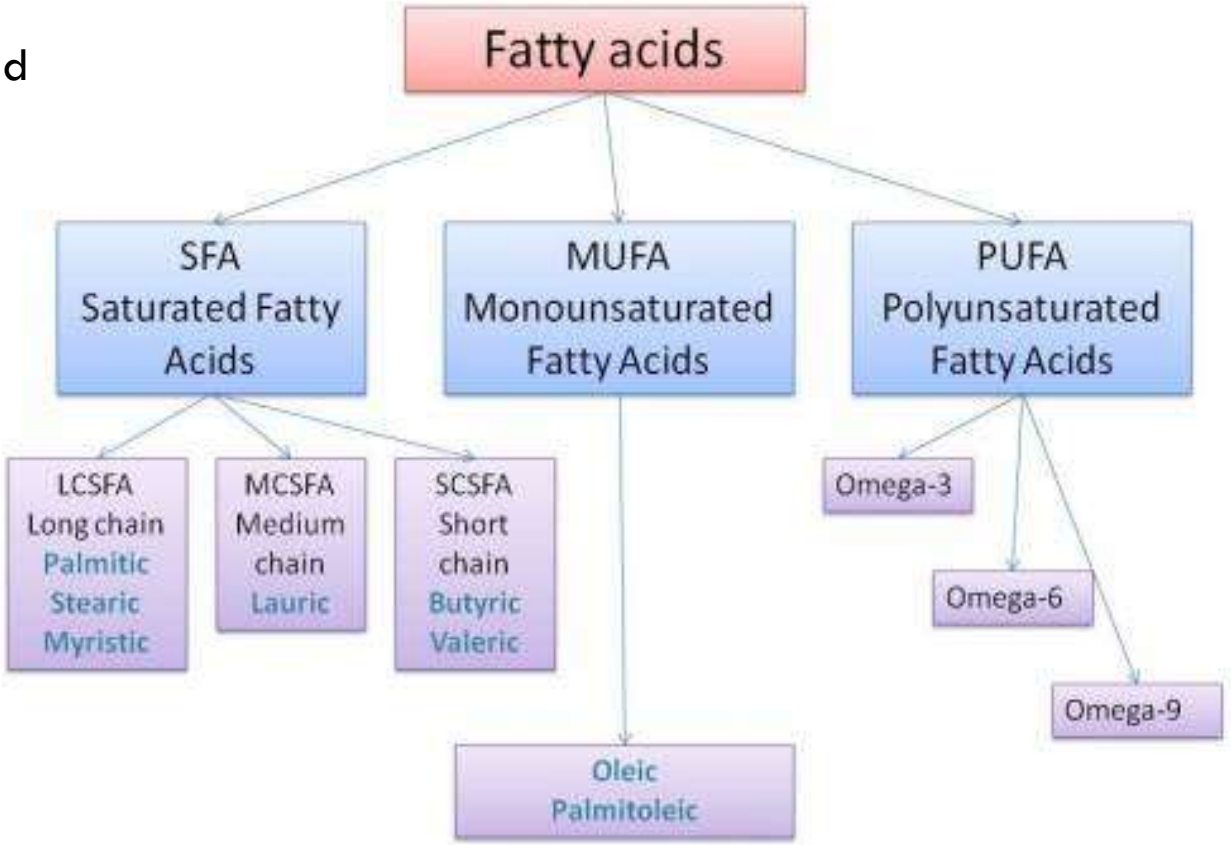
- Unsaturated
  - Mono (MUFAs)
    - Oleic Acid
    - Palmitoleic Acid
  - Poly (PUFAs)
    - One or more double bonds
    - Named by bond location
    - Omega-3 (ALA, DHA, EPA)
      - Nuts, Seeds, Fish, Algae, Krill
      - Grass-fed livestock
    - Omega-6 (AA, LA)
      - Vegetable oils (corn, soy, cottonseed, sunflower)
      - Processed foods
  - Trans
    - Heated to a point to create a trans double bond

Vitamin F

- Essential fatty acids used to be known as vitamin F until they were reclassified as fats
- There are only two essential fatty acids
  - ALA: can be converted in limited quantities to EPA and DHA
  - LA: can be converted into AA
- Saturated fatty acids
  - Can be made in the liver from excess carbohydrates
- Monounsaturated FAs
  - Oleic acid can be made from stearic acid
  - Palmitoleic acid can be made from palmitic acid

The Free Fatty acids

- Omega-3's
  - DHA: Docosahexaenoic acid
    - Seafood
  - EPA: Eicosapentaenoic acid
    - Seafood
  - ALA: Alpha-linolenic acid
    - Nuts and seeds



Saturated Fat and CVD

- Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease[1]
  - There is no significant evidence for concluding that dietary saturated fat is associated with an increased risk of CHD or CVD. More data are needed to elucidate whether CVD risks are likely to be influenced by the specific nutrients used to replace saturated fat.
- The association between dietary fats and the incidence risk of cardiovascular outcomes: Tehran Lipid and Glucose Study[2]
  - Saturated fat intake was not associated with a higher risk of heart disease. Researchers didn't find any benefit to consuming other macronutrients instead of saturated fats.
- Dietary fatty acids, macronutrient substitutions, food sources and incidence of coronary heart disease: Findings from the EPIC-CVD case-cohort study across nine European countries[3]
  - Though total saturated fat intake has no effect on the risk of heart disease, certain foods high in saturated fat may impact heart health differently

[1]Am J Clin Nutr. 2010 Mar;91(3):535-46. Epub 2010 Jan 13.
[2]Nutr Metab. 2021 Oct; 18(1):96.
[3]J Am Heart Assoc. 2021 Dec; 10(23):e019814.

Saturated Fat and CVD

- Mounting evidence that saturated fat does not contribute to CVD disease risk
  - Does increase total LDL which is linked to CVD risk
    - However saturated fat likely only increases large boyant LDL (lbLDL) which is not linked to CVD risk
      - lbLDL may actually improve CVD risk
    - Most concern is with small dense LDL (sdLDL) which is mostly increased due to diet of sugars and simple carbohydrates
    - Several articles published on this in the Journal of the American Heart Association
      - Despite this, the AMA continues to demonize saturated fats for contributing to heart disease
- However meat heavy diets, which contain saturated fats may have other risk
  - Processed meats are linked to cancer/DM likely due to sodium nitrite
  - Red meat is linked to colorectal cancer
- Fermented dairy such as cheese, yogurt, and kefir that may be higher in saturated fats confer benefits to the microbiome
- Eggs are not high in saturated fat

Cholesterol and the Brain

- 1/4 of the body's free cholesterol is found in the central nervous system
- Cholesterol is also needed for forming a nerve synapses and making myelin
- Cholesterol may be involved in GABA and NMDA receptor signaling, opioid signaling, and the transport of excitatory amino acids

Cholesterol

- Low serum cholesterol has been linked in numerous scientific papers to suicide, accidents, and violence
- Depleting cholesterol impairs the function of the serotonin 1A receptor and the serotonin 7 receptor, and reduces the ability of the membrane serotonin transporter to do its thing
- Low serotonin is associated with violent suicide, impulsive acts, hostility, and aggression
- Dr. James Lake recommends that depressed patients with elevated cholesterol aim not to go lower than a total cholesterol of 160

Cholesterol

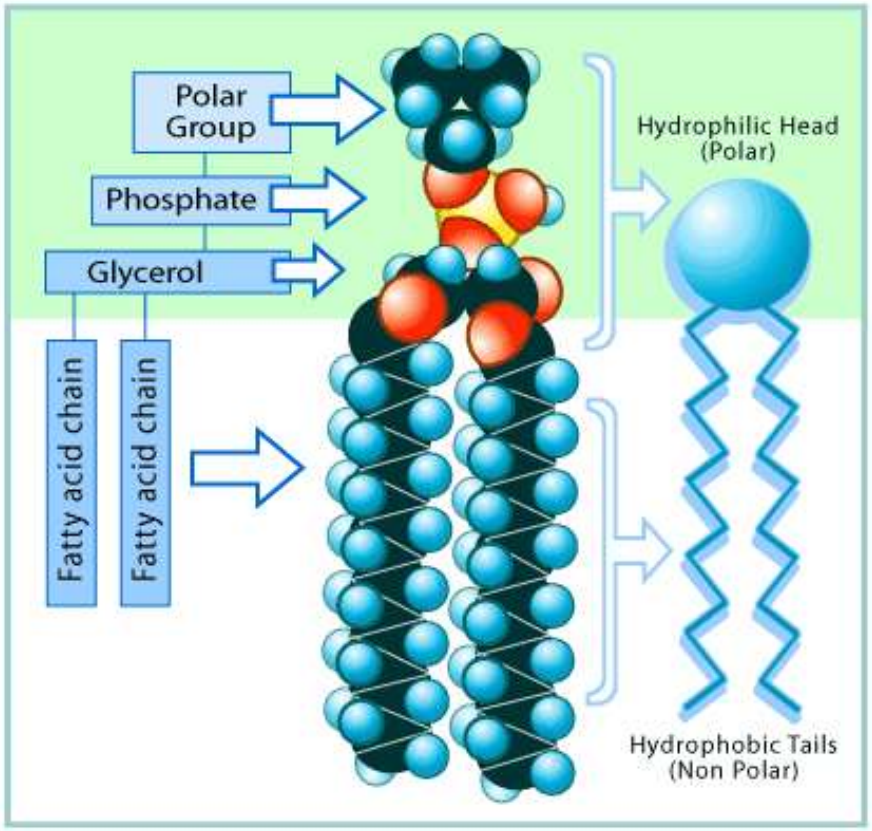
- Dietary cholesterol is very unlikely to affect serum cholesterol
  - Rarely some patients may be affected
- Almost all cholesterol in the body is produced by the liver
  - Most concerning is sdLDL which increases in response to diet of sugar and highly processed grains
  - sdLDL is the most atherosclerotic cholesterol
  - sdLDL can be calculated
    - lbLDL = 1.43x(LDL-C)-(0.14x(ln(triglycerides)x(LDL-C)))-8.99
    - sdLDL = (LDL-C)-lbLDL
    - This meaurement is less correlated with measured sdLDL in patients with diabetes, patients with low sdLDL, and nonfasting patients
  - Saturated fat intake is associated with increases in lbLDL which is not thought to be atherosclerotic and may be protective

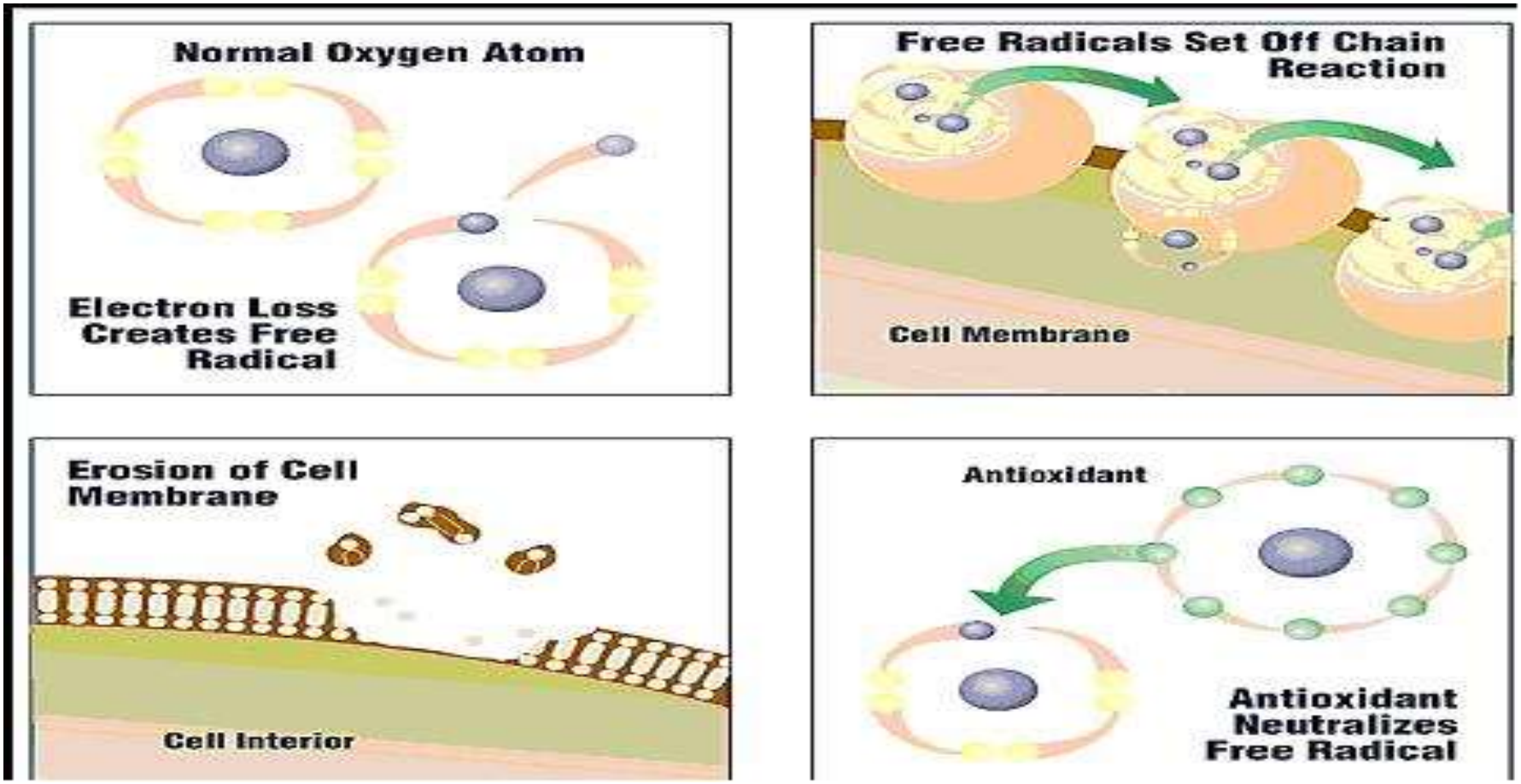
Statins

- Statins improve mortality for middle-aged men who have known heart disease, have had a stroke, or have high levels of inflammatory markers.
  - If you don't meet those particular criteria, statins will give you no mortality benefit
- Simvastatin
  - Some evidence that statins that cross the blood brain barrier inhibit serotonin production
- Most statin studies exclude patient's with psychiatric disease and women

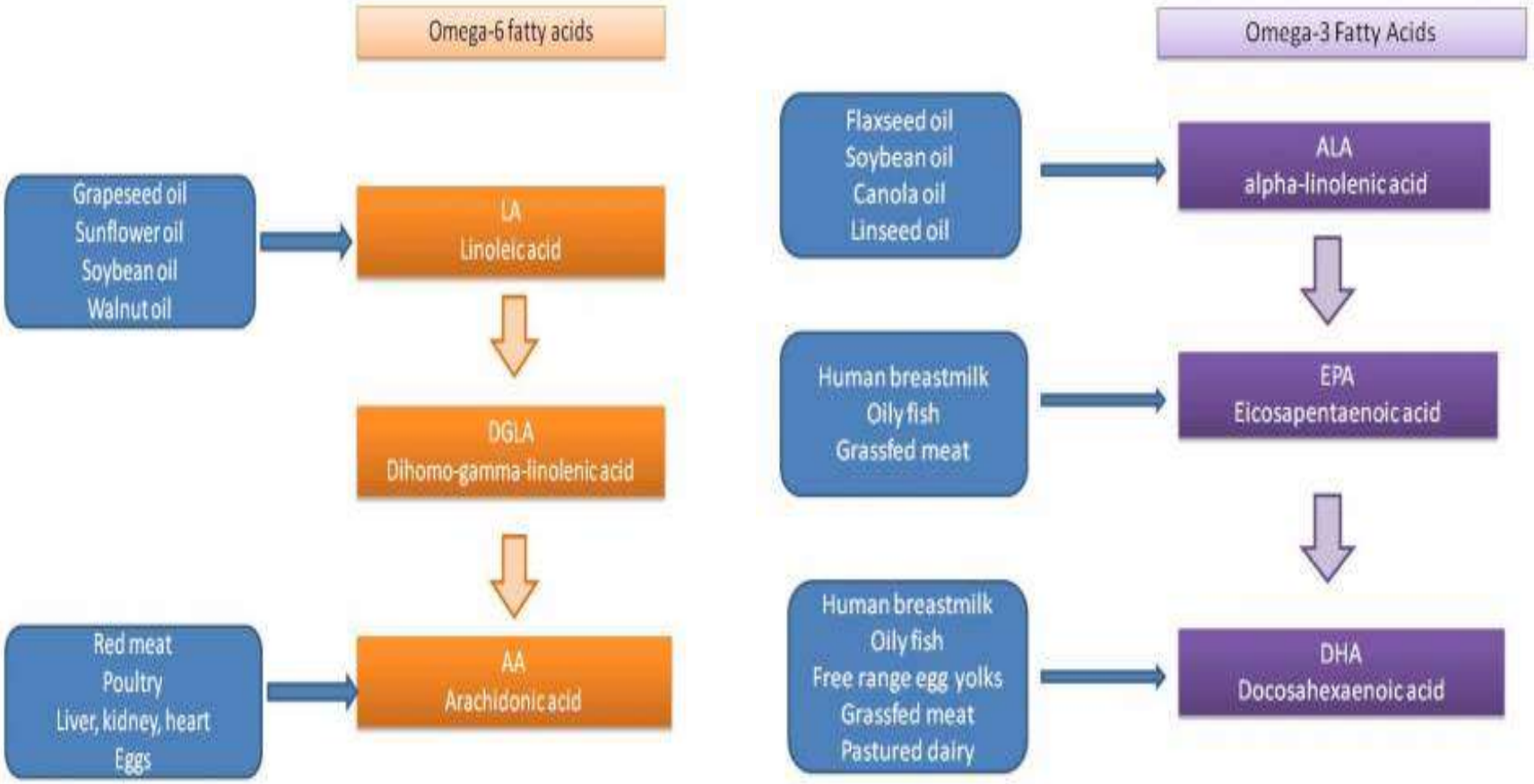
PUFA's and the Brain

- Critical for membrane structure and neuronal function and signal transduction
- Usually either DHA (Omega-3) or Arachidonic Acid (Omega-6)
- DHA and AA act as second messengers
- Effect alters ion channels, cyclic nucleotides and gene function

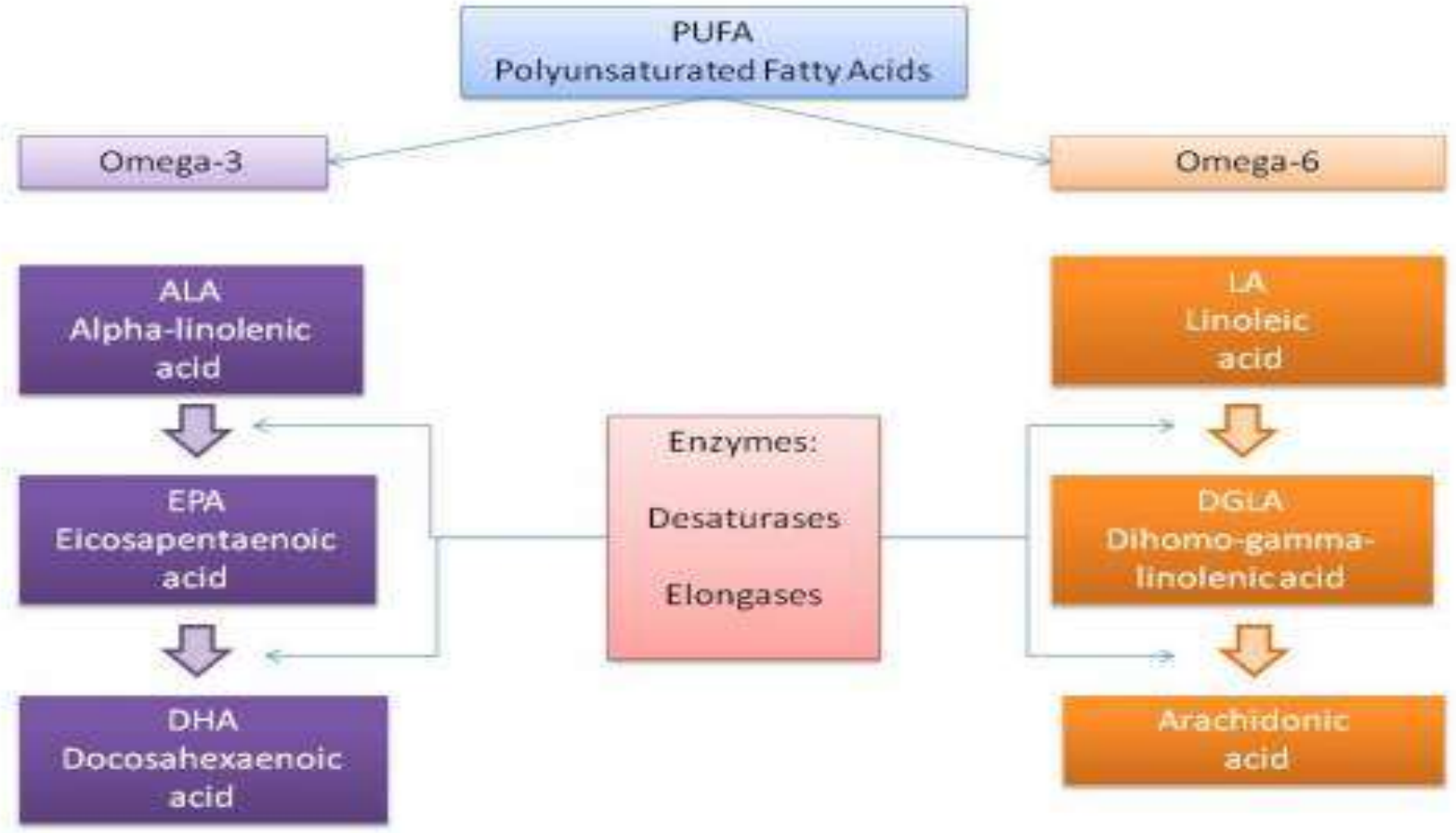




- PUFAs may cause health problems due to becoming oxidized or rancid when subjected to heat, oxygen and moisture
- This happens during processing → free radicals are created
- A triglyceride is a storage for fatty acids as processing and heating may damage polyunsaturated fats
- Excessive energy is stored as saturated fat



- **Omega-6 FA's become pro-inflammatory mediators**
  - **Inflammation is bad for health, however the impact Omega-6 has on this process is debatable**
- **Omega-3 FA's become anti-inflammatory**



Omega-3 and Omega-6 use the same enzymes and therefore they are in competition for them

Inflammation and Mood

- Inflammation: Depression Fans the Flames and Feasts on the Heat (2015)
  - Inflammation and depression have a bi-directional relationship
  - Stressors, pathogens, childhood adversity and obesity, pain, disturbed sleep, poor diet, sedentary lifestyle can contribute to inflammation and ultimately mood
  - Depression, childhood adversity, stressors, and diet can influence the gut microbiome and promote intestinal permeability leading to inflammation
  - Inflammation can lead to negative mental and physical health consequences

Kiecolt-Glaser JK. Inflammation: Depression Fans the Flames and Feasts on the Heat. The American Journal of Psychiatry. 2015:172(11), 1075-1081.

The Greenland Eskimo Research: Fatty acid composition in thrombocyte phospholipids

- **A Acid:** 26%US, 21% Japan, 8% GE
- **EPA:** 0.5% US, 1.6% Japan, 8% GE
- **Omega 6/3 ratio:** 50 US, 12 Japan, 1 GE
- **Cardiovascular Mortality:** 45%, 12%, 7%

- Most of the Western world is between 14-25:1
- Goal for reduction in chronic/inflammatory disease 4:1
- The conclusions of this old study have been called into question

FAs and Mental Illness

- Mounting evidence 'links' Omega-3 deficiency or unbalanced omega 6/3 ratio in humans to
  - Depression
  - Aggression and violence
  - Bipolar disorder
  - ADHD
    - Severity of illness often proportionate to deficiency
  - Cognitive decline

Omega-3 FAs

- The amount and ratios of Omega-3/6's in our brain are dependent upon what we consume in our diet
- Omega-3 is made by photosynthetic algae eaten by krill or fish or oysters, etc which we eventually consume
  - Farmed seafood is unlikely to contain much omega-3
- Dampens inflammatory cascades that are required for necessary cellular function
  - Helps dampen excessive cascade that occur in depression and cognitive disorders
  - Contributes to neuronal membrane stability and longevity

Omega-3 FAs

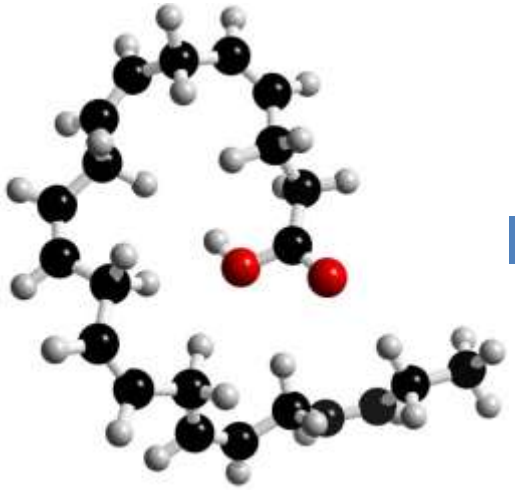
- Chronic disease risk reduction
  - Cardioprotective
    - Lowers BP, decreases TG and LDL, increases HDL, decreased risk of arrhythmias and thrombosis, improve endothelial function
  - Colorectal Cancer
- Neuroprotective in Alzheimer's and Parkinson's neurodegenerative diseases
  - Decreased risk for preterm birth / low birth weight
  - Head trauma / cerebral edema

TARGET OF HEALTH IMPROVEMENT	DOSAGE USED IN HUMAN CLINICAL STUDIES
Cardiovascular Health	600- 4000mg per day of combined EPA and DHA. Low doses (600- 900mg per day) deliver highly significant benefit. Larger dosages (2000- 4000mg per day) provide some further benefit. See discussion below.
Improved Mood	No less than 1000mg of **EPA** per day. The oil should contain significantly more EPA than DHA.
Childhood Attention Mood Concentration	In children ages 5 and up, 500- 1000mg of EPA per day. The oil should contain significantly more EPA than DHA.
Joint Health	2000- 4000mg of combined EPA and DHA.
Pregnancy and Breastfeeding	No less than 300mg of DHA per day. The oil should contain more DHA than EPA, unless otherwise recommended by a healthcare practitioner.
Bowel Health	2000- 4000mg of combined EPA and DHA per day.
Respiratory Health	2000- 4000mg of combined EPA and DHA per day.

Omega-3 and Recommendations

- Meta-Analysis of effects of EPA 2011
  - "EPA identified as effective treatment component in depression"
  - Recommendation: Supplement of at least 60% EPA
  - Best results 1000mg-2000mg of EPA in excess of DHA
  - Not pure EPA
    - 2:1 EPA:DHA is most often recommended
- Many discrepancies between studies
  - Use of fish oil, EPA/DHA ratio, dose
  - What was placebo? (Olive Oil?)
  - Method of detection (food questionnaire?)
  - Studying depression in non-depressed people
  - Huge individual variation and response to supplementation

PUFAs and Inflammation

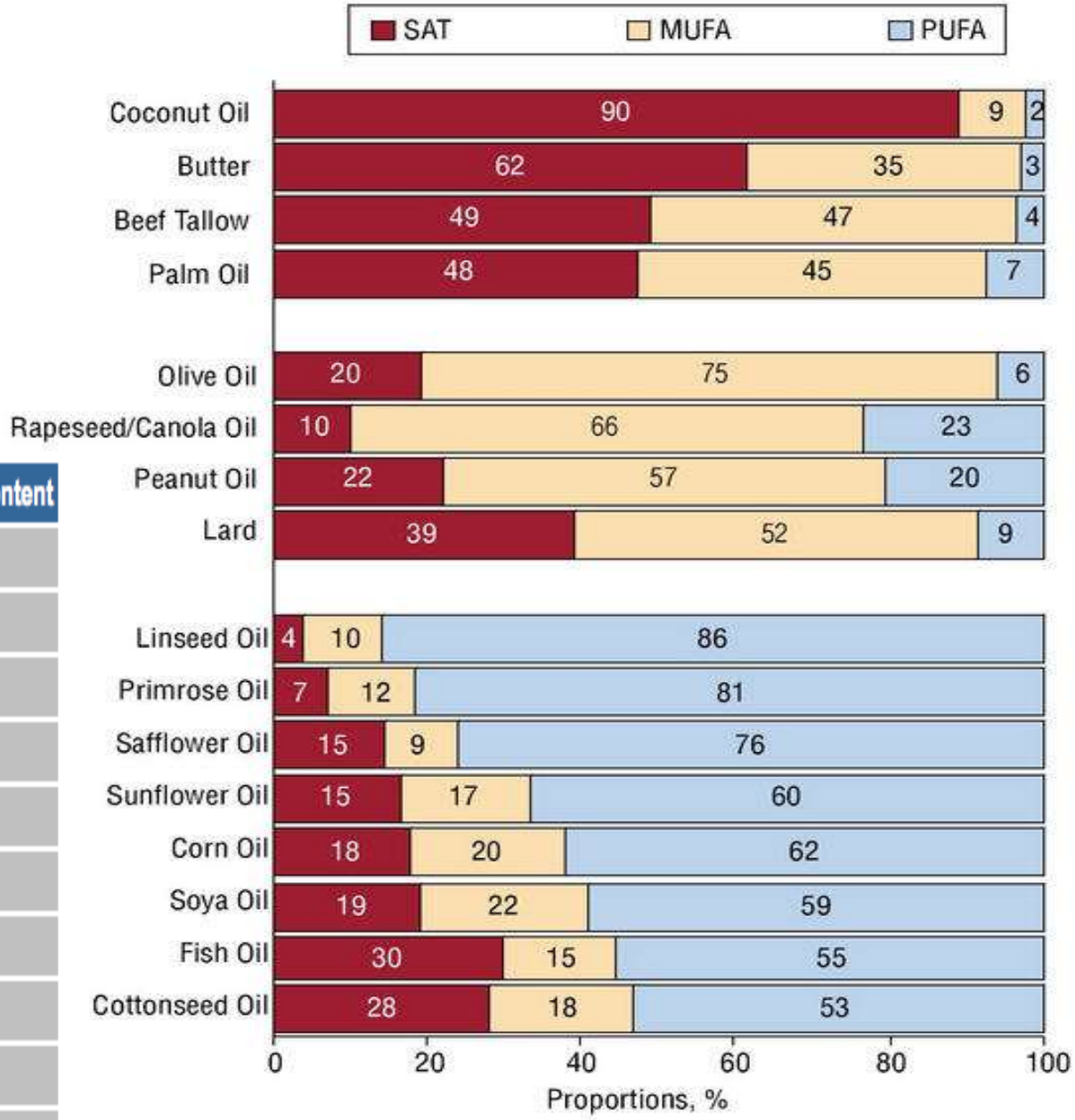


- Inflammatory stimuli
  - Air pollution
  - Smoking, second-hand smoke
  - Hydrogenated vegetable oils
    - Margarine, vegetable shortening
    - Many processed foods: fried foods, coffee creamer, dough, baked foods, snacks
  - Other toxins
  - Pro-inflammatory FAs (Omega-6)
    - Vegetable oils (soy, corn, cottonseed, sunflower)
    - Processed foods
- Omega-3 FAs decrease omega-6 FAs
  - ALA displaces linoleic acid from enzymes that produce AA
  - EPA inhibits phospholipase A2's release of AA from cell membranes
  - Either neutral on inflammation or anti-inflammatory

Seed Oils

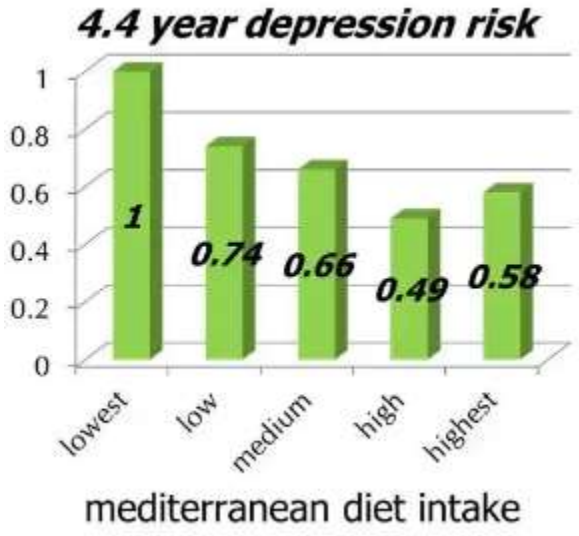
- Many are high in Omega-6
- Highly processed with heat, results in increased oxidation and trans fats not listed on label
- Biggest problems when combined with high sugar and CHO diets
- Despite the hype that seed oils are dangerous, the vast majority of studies suggest the opposite
  - Diets with seed oils vs saturated fats have better outcomes
  - Seed oil, if problematic, is the last processed food you should consider eliminating and is almost certainly better than saturated fats
    - Butter and lard in small quantities for cooking are less problematic than as toppings and ingredients
  - Not everyone can afford olive, avocado, and nut oils which are the best options

Oil	Omega-6 Content	Omega-3 Content
Safflower	75%	0%
Sunflower	65%	0%
Corn	54%	0%
Cottonseed	50%	0%
Sesame	42%	0%
Peanut	32%	0%
Soybean	51%	7%
Canola	20%	9%
Walnut	52%	10%
Flaxseed	14%	57%
Fish*	0%	100%



Diet and Mood: The SUN Study 2009

- Test hypothesis that Mediterranean diet improves inflammatory, vascular, and metabolic pathways linked to development of depression
- 10,094 university graduates who were not initially depressed mailed a 136-item food frequency questionnaire
- Incidence of depression (diagnosed or prescribed an antidepressant) assessed 4.4 years later
- Results
  - Respondents separated into 5 groups based on adherence
  - Hazard ratios for 4 highest quintiles: 0.74, 0.66, 0.49, 0.58 (P <0.001)
  - Largest improvements seen with increased fruits, nuts, high MUFA foods, and fish in moderation



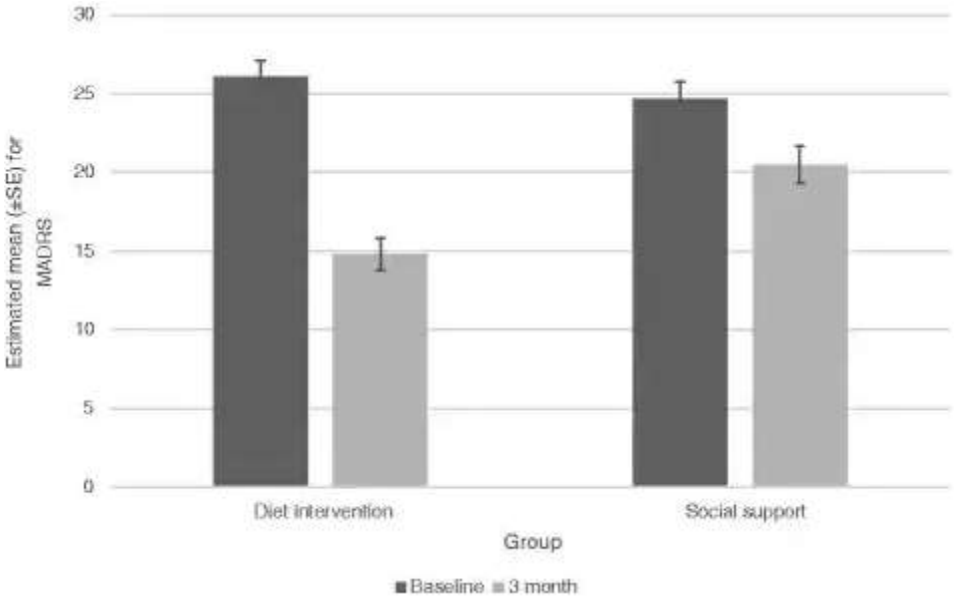
Sanchez-Villegas A et al. Association of the Mediterranean dietary pattern with the incidence of depression: the Seguimiento Universidad de Navarra/University of Navarra follow-up (SUN) cohort. Archives of general psychiatry. 2009. 66(10), 1090-1098.

Diet and Mood: SMILES Trial 2017

- Conducted to find what effects food has on moderate to severe depression
- 12-week trial (n=67) randomized to the control
- Control group: 7 sessions of "befriending protocol"
- Intervention group: 7 sessions of nutritional counseling and mindful eating
  - Mediterranean-style diet
    - Whole grains, vegetables, fruit, legumes, low-fat/unsweetened dairy, raw and unsalted nuts, lean red meat, chicken, eggs, olive oil, reduced sugar and processed foods
- Both groups started with a poor diet identified using a dietary screening tool
- MADRS was the depression scale used

Diet and Mood: SMILES Trial 2017

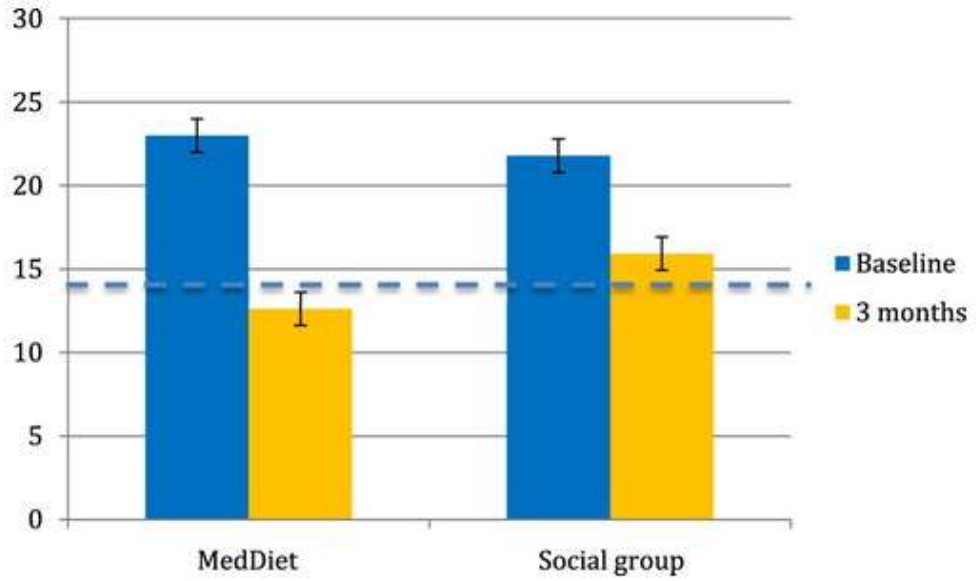
- Results
  - 32.3% vs 8% remission for intervention group
  - MADRS decreased 7.1 points in diet group compared to control
  - Cohen's d = **-1.16,** NNT 4.1
  - Weight loss not seen at all
- Actual changes made by participants
  - Increase in whole grains 1.2 serv/day
  - Increase in fruit 0.46 serv/day
  - Increase in dairy 0.56 serv/day
  - Increase in olive oil 0.42 serv/day
    Increase in legumes 0.2 serv/day
  - Increase in fish 0.16 serv/day
  - Decrease in unhealthy foods **3.11** serv/day



Jacka, FN et al. A randomized controlled trial of dietary improvement for adults with major depression. BMC Medicine. 2017, 15(1), 1-13.

Diet and Mood: HELFIMED Trial 2019

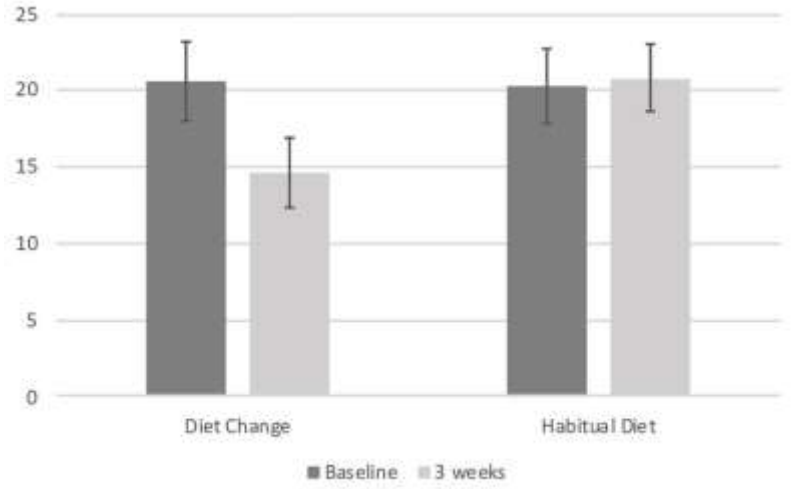
- Mediterranean diet supplemented with fish oil
- Depression improved by 45% vs 26.8% in the Social group (1.68x)
- Sustained at 6 months
- Improvement correlated to increased MedDiet score, nuts, and vegetable diversity
- ↑ EPA: ↓ anxiety and stress
- ↑ DHA: ↓ stress and negative emotions
- ↓ AA: overall ↑ QoL



Parletta N et al. A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: A randomized controlled trial (HELFIMED). Nutr Neurosci. 2019; 22(7):474-487.

Diet and Mood

- 2022 AMMEND study: 12-week parallel-group, open-label, randomized controlled trial assessing effect of Mediterranean diet of moderate to severe depression in young males
  - Difference in Beck Depression Inventory from placebo (14.4 points)
  - QoL score difference (12.7 points)
- 2019 young adult study on Mediterranean-like diet showed effect size of recommended diet vs habitual diet on depression between 0.65-0.75



[1]Bayes J et al. The effect of a Mediterranean diet on the symptoms of depression in young males (the "AMMEND: A Mediterranean Diet in MEN with Depression" study): a randomized controlled trial. Am J Clin Nutr. 2022: 116(2): 572-580.
[2]Francis HM et al. A brief diet intervention can reduce symptoms of depression in young adults – A randomized controlled trial. PLoS One. 2019: 14(1):30222768.

Diet and Mood

- 2011 PREDIMED-NAVARRA Study: Mediterranean diet with nuts increased BDNF in depressed patients[1]
- 2013 meta-analysis of 22 studies showed high adherence to the Mediterranean diet was consistently associated with reduced risk for stroke (RR 0.71), depression (0.68), and cognitive impairment (0.60)[2]

[1]Sanchez-Vellegas A et al. The effect of the Mediterranean diet on plasma brain-derived neurotrophic factor (BDNF) levels: the PREDIMED-NAVARRA randomized trial. Nutritional Neuroscience. 2011: 14(5), 195-201.
[2]Psaltopoulou T et al. Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. Annals of Neurology. 2013:74(4), 580-591.

Borderline PD and Omega-3 FAs

- Karaszewska D et al. **Marine Omega-3 Fatty Acid Supplementation for Borderline Personality Disorder: A Meta-Analysis.** *Journal of Clinical Psychiatry*. 2021:81(3):20r13613.
  - Meta-analysis of 5 RCTs comparing omega-3 fatty acids to placebo or active comparator
  - Effect size
    - Overall BPD symptom severity: 0.54
    - Affect dysregulation: 0.74
    - Impulsive behavior: 0.45
    - Cognitive-perceptual symptoms (no significant effect)
  - These effect sizes are higher than for antidepressants and antipsychotics

ADHD and Diet

- 2011 meta-analysis of omega-3 FAs[1]
  - Effect sizes ranging 0.3-0.5 with high EPA
- 2021 meta-analysis of 9 studies on Iron-Zinc supplementation[2]
  - May be less helpful in the US as there is less zinc deficiency
- 2021 DASH (Dietary Approaches to Stop Hypertension) diet[3]
  - Fruits, vegetables, fish, whole grains, nuts, beans
  - Avoiding sugar, salt, saturated fats, cholesterol, refined grains
  - Compared to controls those on the DASH diet had significant improvements on multiple parent-, teacher-, and child-rated measures of ADHD after 3 months
  - Also more prosocial behaviors and few conduct problems

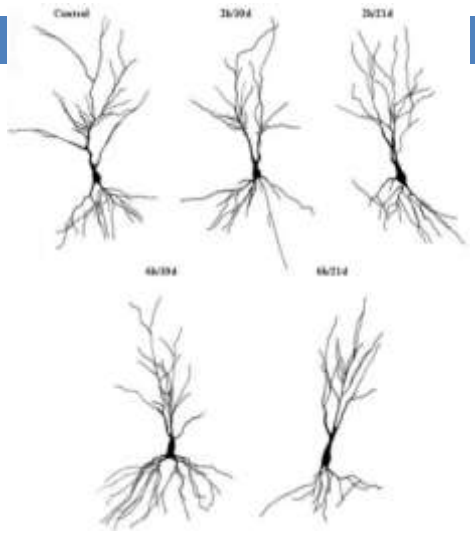
[1]Bloch MH and Qawasmi A. Omega-3 fatty acid supplementation for the treatment of children with attention-deficit/hyperactivity disorder symptomatology: systematic review and meta-analysis. J Am Acad Child Adolesc Psychiatry 2011;50(10):991–1000.
[2]Granero R et al. The Role of Iron and Zinc in the Treatment of ADHD among Children and Adolescents: A Systematic Review of Randomized Clinical Trials. Nutrients 2021;13(11):4059.
[3]Khoshbakht Y et al. The effect of dietary approaches to stop hypertension (DASH) diet on attention-deficit hyperactivity

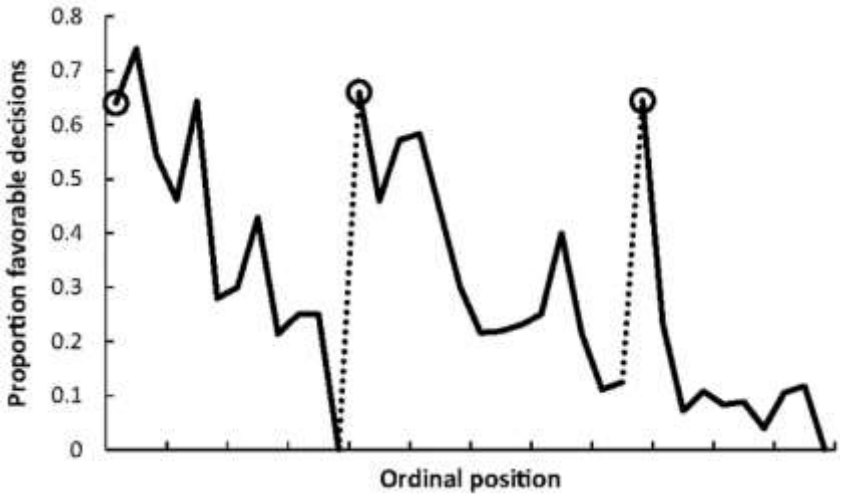
ADHD and Diet

- 2025 Danish registry study of 60000 mother-child pairs assessed at age 10
  - A western dietary pattern during pregnancy is associated with neurodevelopmental disorder in childhood and adolescence
    - Significant association with ADHD and autism diagnoses
      - Moderate shifts along this dietary spectrum associated with 66% increased risk of ADHD and 122% increased risk of autism
    - Diet high in fat, sugar, and refined products
    - Diet low in fish, vegetables, and fruit
    - Association strongest in early pregnancy

Stress and Cognitive Functioning

- 2007 study on rats: Chronic psychological stress caused hippocampal-dependent cognitive deficits; decreased dendrites after 21 days in rats restrained in metal wire 6 hours per day for 21 days[1]
- 2011 study of court rulings and snack hour: Judges were found to be more lenient when well fed[2]



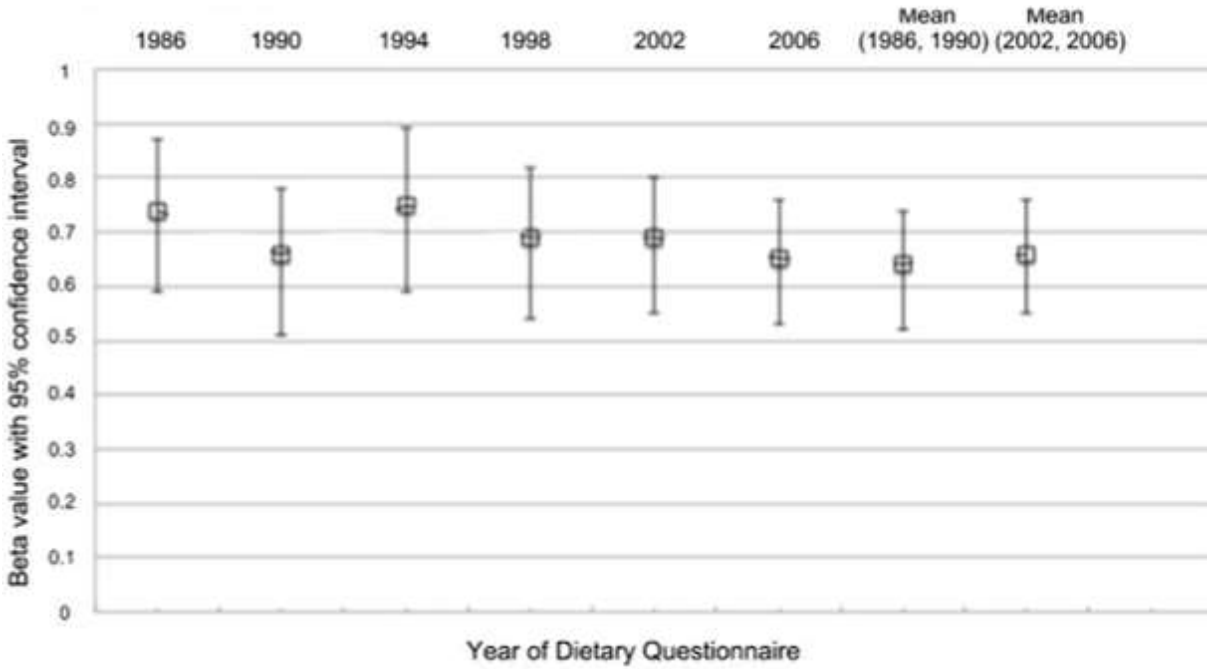


[1]McLaughlin, K et al. The effects of chronic stress on hippocampal morphology and function: an evaluation of chronic restraint paradigms. Brain research. 2007. 1161, 56-64.

[2]Danziger S et al. Extraneous factors in judicial decisions. Proceedings of the National Academy of Sciences. 2011. 108(17), 6889-6892.

Diet and Cognitive Functioning

- Mediterranean diet associated with
  - Better cognitive function, lower rates of cognitive decline and reduced AD[1]
  - Highest adherence to diet correlated with lower odds of poor self-reported subjective cognitive function (OR 0.64)[2]



[1]Lourida I et al. Mediterranean diet, cognitive function, and dementia: a systematic review. Epidemiology. 2013. 24(4), 479-489.

[2]Bhushan A. Adherence to Mediterranean diet and subjective cognitive function in men. European journal of epidemiology. 2017. 1-12.

Diet and Cognitive Functioning

- 2008 study of 449 people followed for 21 years showed high saturated fat diets associated with poorer global cognitive function, prospective memory, executive function, and psychomotor speed compared to polyunsaturated fat diets[1]
- 2012 study of 6183 nurses studied over 5 years with serial cognitive testing showed those with high saturated fat diets had more significant cognitive decline compared to those with high monounsaturated fat diets[2]
- 2015 cohort study from 40 countries (n=27860), followed for 56 months, showed that those eating the most nuts, veggies, fruit, fish higher relative to meat and eggs, and whole grains (high fiber) had lower rates of cognitive decline (HR 0.76 healthiest vs least)[3]

[1]Eskelinen MH et al. Fat intake at midlife and cognitive impairment later in life: a population-based CAIDE study. International journal of geriatric psychiatry. 2008. 23(7), 741-747.

[2]Okereke OI et al. Dietary fat types and 4-year cognitive change in community-dwelling older women. Annals of neurology. 2012. 72(1). 124-134.

[3]Smith A. Healthy eating and reduced risk of cognitive decline: A cohort from 40 countries. Neurology. 2015. 84(22). 2258-2265.

Omega-3s and Cognitive Functioning

- 2008 animal study showed higher omega-3 diet had better working memory and reference memory[1]
- 2012 meta-analysis found that high omega-3 intake helped with cognitive impairment but not dementia with attention, processing speeds, and immediate recall[2]
- 2013 study of children aged 7-9 with lower DHA and EPA in their blood had a small associated poorer reading ability and working memory performance[3]
- 2022 study of 1416 patients in France found that those who had fish weekly had decreased incidence of developing dementia over 7 years of follow up (HR 0.66)[4]

[1]Chung WL et al. WL et al. Fish oil supplementation of control and (n-3) fatty acid-deficient male rats enhances reference and working memory performance and increases brain regional docosahexaenoic acid levels. The Journal of nutrition. 2008. 138(6), 1165-1171.
[2]Mazereeuw G et al. Effects of omega-3 fatty acids on cognitive performance: a meta-analysis. Neurobiology of aging. 2012. 33(7), 1482-e17.
[3]Montgomery P et al. Low blood long chain omega-3 fatty acids in UK children are associated with poor cognitive performance and behavior: a cross-sectional analysis from the DOLAB study. PloS one. 2013. 8(6), e66697.
[4]Barberger-Gateau P et al. Fish, meat, and risk of dementia: cohort study. BMJ: British Medical Journal. 2022:325(7370), 932-933.

Diet and Cognitive Functioning

- Avoiding high sugar diet
  - High fat and refined sugar diet in rats decreased BDNF and neuroplasticity[1]
    - BDNF also likely contributes to mood
  - 2012 study following 937 subjects for 3.7 years found that those in the highest grouping for total carbohydrate and sugar had almost double the risk for developing cognitive impairment, whereas those with high protein or fat had lower risk[2]

[1]Molteni R et al. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. Neuroscience. 2002:112(4), 803-814.
[2]Roberts RO et al. Relative intake of macronutrients impacts risk of mild cognitive impairment or dementia. Journal of Alzheimer's Disease. 2012:32(2), 329-339.

Ketogenic Diet and Mental Health

- Dr. Christopher Palmer has theorized that there is a direct connection between metabolic health and mental health
  - Theory: Mental health disorders are metabolic disorders of the brain involving mitochondrial dysfunction
- First discovered to help with pediatric epilepsy in 1921
- This theory is controversial
  - Psychiatric diseases are likely impacted by many factors
    - Genetic, epigenetic, histological, endocrine, and inflammatory
  - Increasing evidence that this diet can be very beneficial for some patients with severe mental illnesses: SZP, BP, MDD
  - RCTs are underway

Ketogenic Diet and Mental Health

- Exercise
  - Increases BDNF -> increases mitochondria count and health
  - Higher plasticity and more neurogenesis
- Ketogenic Diet
  - Low carbohydrate, high protein, high fat diet
  - Body enters a state of ketosis burning fat instead of glucose
  - Influences GABA, glutamate, and ATP
  - Inflammasone inhibition: decreases inflammation
  - Changes gut microbiome
  - Improves insulin signaling to the brain
  - May help with
    - DMII, obesity, PCOS, migraines, ASD, neurodegeneration, SUDs
- Ketogenic diet for mental health differs from diet for weight loss
  - Patient should be monitored by trained specialist and dietician

Ketogenic Diet: Monitoring

- Contraindications
  - Rare metabolic disorders, SGLT2is, severe liver/pancreatic diseases
- Loss of electrolytes: 2/2 glycogen depletion (diuresis) and reduced insulin (electrolyte loss)
  - Na+: 1.5-2 tsps added daily (especially first 4 weeks)
  - K+: 3000-4700mg per day
- Mg++: 300-400mg/day
- Selenium: Diet may result in deficiency which in rare cases can be fatal
- Increase water intake
- Medications
  - Lithium, VPA, CBZ: levels may be affected
  - HTN/DMII medications: may need to be lowered
  - P450 system may be affected by high fat diet

Ketogenic Diet: Monitoring

- Labs
  - CMP: kidney/liver fx, electrolytes, glucose
  - CBC, iron panel
  - Fasting lipids
  - Vitamin D
  - Vitamin B12
  - L-carnitine: low levels: mitochondria may not be able to burn ketones efficiently
  - TSH
  - A1C
  - HOMO-IR: useful for tracking insulin sensativity
  - Uric acid: may increase
  - Tissue transglutaminase AB IgA and immunoglobulin A
  - Copper and ceruloplasmin

Ketogenic Diet and Mental Health

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- McClernon FJ et al. The Effects of a Low-Carbohydrate Ketogenic Diet and a Low-Fat Diet on Mood, Hunger, and Other Self-Reported Symptoms. Obesity. 2007; 15(1), 182-187.
- Phelps JR et al. The Ketogenic Diet for Type II Bipolar Disorder. Neurocase. 2013; 19(5), 423, 426.

Mindful Eating

- Slow down
  - Take a moment of gratitude
    - Don't pick up your silverware right away
    - Take a deep breath before eating
  - Pause after a few bites to take a breath
  - Chew thoroughly
- Make something you've never made before
- Make food from scratch with your partner/family
- Try new ingredients and foods
- Make subtle changes to recipes
- Grow your own food
  - Sprouts and herbs are easy for anyone

Barriers to Healthy Eating: Getting Started

- Challenge
  - Overcoming the inertia
- Strategy
  - Make any meaningful change today
  - Don't dive in too hard and fast
  - Make small changes over time

Barriers to Healthy Eating: Diet Trends

- Challenge
  - Difficulty keeping up with and discerning good nutritional advice
  - Advice is often coming from untrustworthy sources that are not backed by scientific evidence and are driven by profit
  - Scientific evidence for what is healthy can appear to change frequently
- Strategy
  - Keep nutritional advice simple
    - Concentrate on food groups and not individual foods
    - Eat less processed foods and sugar
    - Eat real foods
    - Not too much
    - Mostly plants

Barriers to Healthy Eating: Cost

- Challenge
  - Many healthy foods are expensive
    - Organic, cage-free, grass-fed, etc
- Strategy
  - Healthy foods are often cheaper
    - Many processed foods can be expensive
      - These foods often provide little nutrition, are not filling, and are mostly just calories; eliminating them can save money
    - Many take supplements which can be expensive with limited efficacy
    - Many vegetables, fruits, and whole grains are affordable
      - These foods are nutrient dense and more filling
      - Dried legumes, frozen veggies, some canned veggies
      - Fruits and vegetables in season
    - The SMILES trial showed that people actually saved money by incorporating food categories rather than adhering to strict diets

Barriers to Healthy Eating: Time

- Challenge
  - Most of us have a lifestyle which doesn't make room for exercise, good sleep, and a healthy diet
- Strategy
  - Make a healthy lifestyle a priority
  - Prepare quick meals that save a trip to the fast food joint
  - Prepare larger servings that can be used as prep for subsequent days
  - Cut back on screen time or allow while cooking or gardening
  - Make cooking an activity to do with your partner or family

Barriers to Healthy Eating: New Foods

- Challenge
  - Adding new foods can be a challenge especially with kids
- Strategy
  - Introduce new foods to meals you already make
    - Turn canned salmon into burgers
    - Add kale to macaroni and cheese
    - Substitute a whole grain or just replace 50% with whole grain
    - Add more vegetables to a pasta sauce
    - Put more leafy greens in your sandwich
    - Substitute healthier condiments for unhealthy ones
  - Make snacks healthier
    - Nuts, salsa, fruit, smoothies with kefir and fruit

Barriers to Healthy Eating: Others

- Food served in our institutions (schools, hospitals, military, senior facilities) promotes obesity
- Federal subsidies of commodity crops, especially soy and corn
- Nutritional education of health professionals is nonexistent to substandard
- The food industry designs foods to be addictive so people eat more and more and the food industry makes lots of money

Take a Dietary History

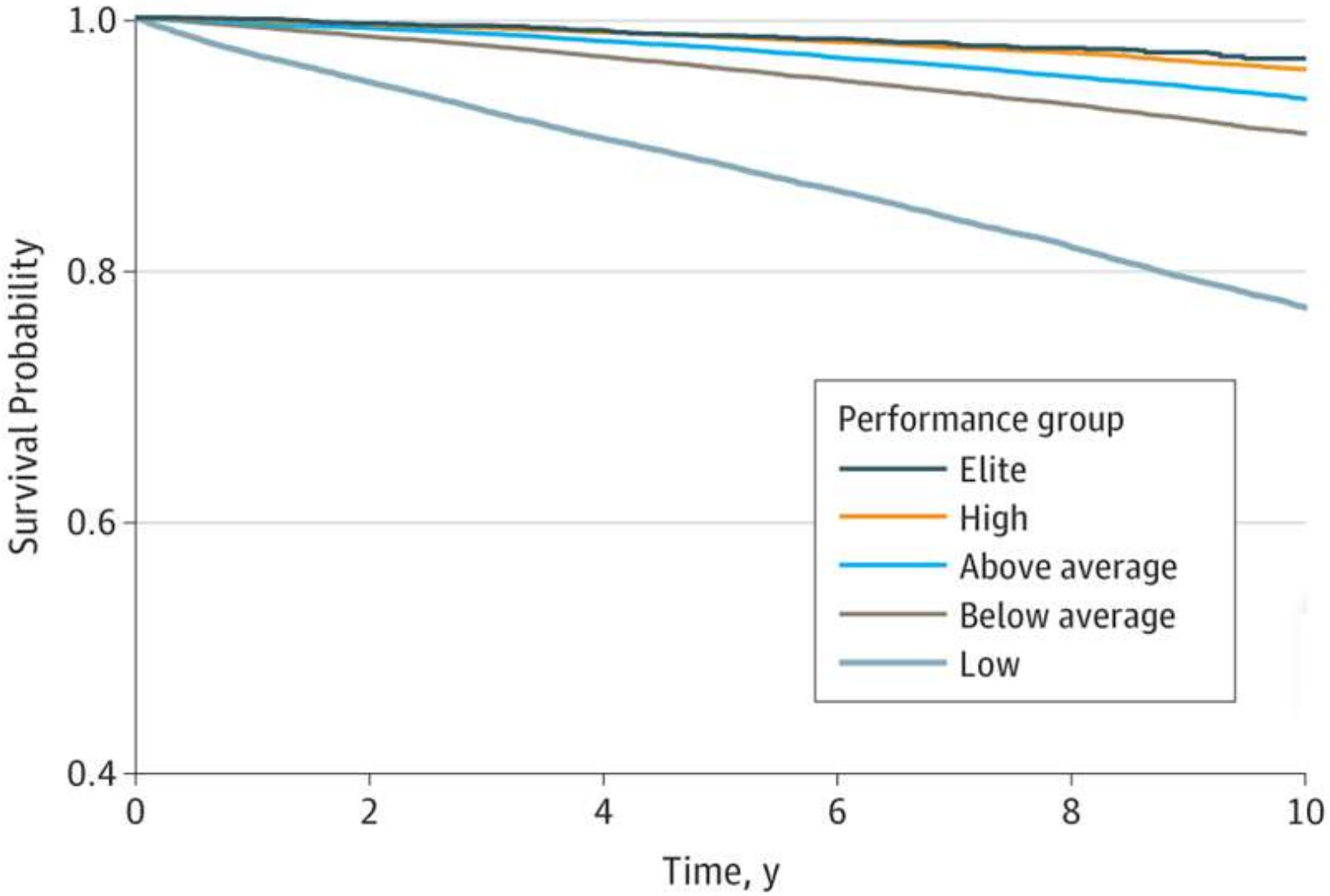
- Start with specific questions and frequency and typical meals and quantity
- Include questions about eating habits, foods preferred or enjoyed, typical meals and snacks, amounts eaten, and digestive function
  - Suspected deficiencies or insufficiencies can be identified and later confirmed through specific diagnostic testing

Fitness

Fitness and Mortality

- Association of Cardiorespiratory Fitness With Long-term Mortality Among Adults Undergoing Exercise Treatmill Testing. JAMA Netw Open. 2018.
  - Cohort study (n=122,007) over 23 yrs, mean age 53.4, median follow-up 8.4 yrs
  - Patients were stratified by age- and sex-matched cardiorespiratory fitness into 5 performance groups
    - Low (<25th %tile), below average (25-49th %tile), above average (50-74th %tile), high (75-97.6th %tile), and elite (>=97.7th %tile)
  - All-cause mortality associated with reduced cardiorespiratory fitness
    - Low vs elite (raw HR 9.11, adjusted HR 5.04), below vs above (1.41)
    - Compare to clinical risk factors
      - Coronary artery disease (1.29), Smoking (1.41), diabetes (1.40)

Patient Survival by Performance Group

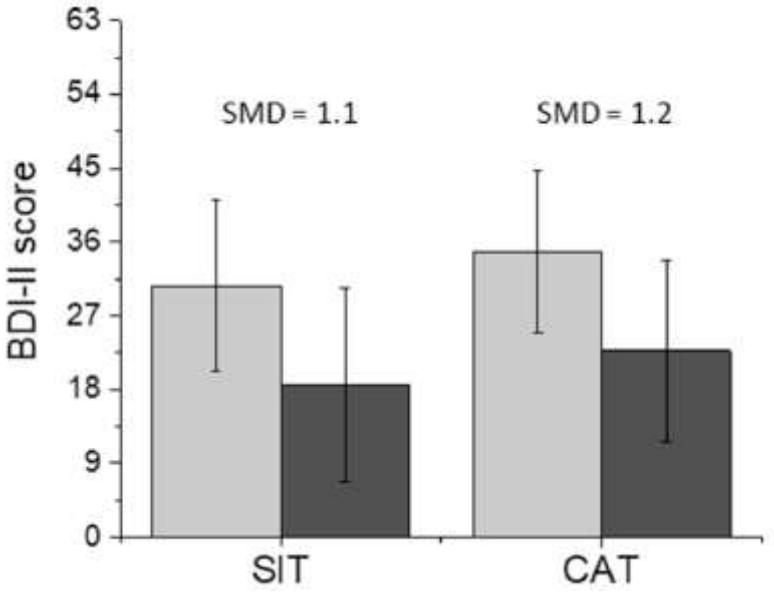


Strength Training and Mood

- Association of Efficacy of Resistance Exercise Training With Depressive Symptoms: Meta-analysis and Meta-regression Analysis of Randomized Clinical Trials. JAMA Psychiatry. 2018.
  - 33 studies (n=1877)
  - Resistance training associated with effect size of 0.66 for depression reduction, NNT 4 (AD effect size is ~0.25-0.4)
  - Volume of resistance training, health status, and previous strength did not affect results
- Moderating Effects of Exercise Duration and Intensity in Neuromuscular vs. Endurance Exercise Interventions for the Treatment of Depression: A Meta-Analytical Review. Front Psychiatry. 2018.
  - 27 RCTs, 1452 depressed adults
  - Strength exercise vs control with effect size of -1.14
  - Endurance exercise vs control with effect size of -0.79
- The Handgrip Strength and Risk of Depression Symptoms: A Prospective Study and Meta-Analysis. The Lancet. 2019. (n=6392)
  - Incidence of 11.9%, 15.5%, and 22.1% related to strong, moderate, and weak handgrip strength

Aerobic Exercise and Mood

- 2017 RCT of 34 inpatients with MDD, comparing HIIT to moderate continuous training on depression severity[1]
  - HIIT (ES 1.48), CAT (1.40) comparing pre- and post-
- 2018 RCT of 59 inpatients with MDD found sprint interval training comparable to continuous aerobic training in reduction of depressive symptoms (12.5 min vs 20 min) (ES 1.1 comparing pre- and post-)[2]

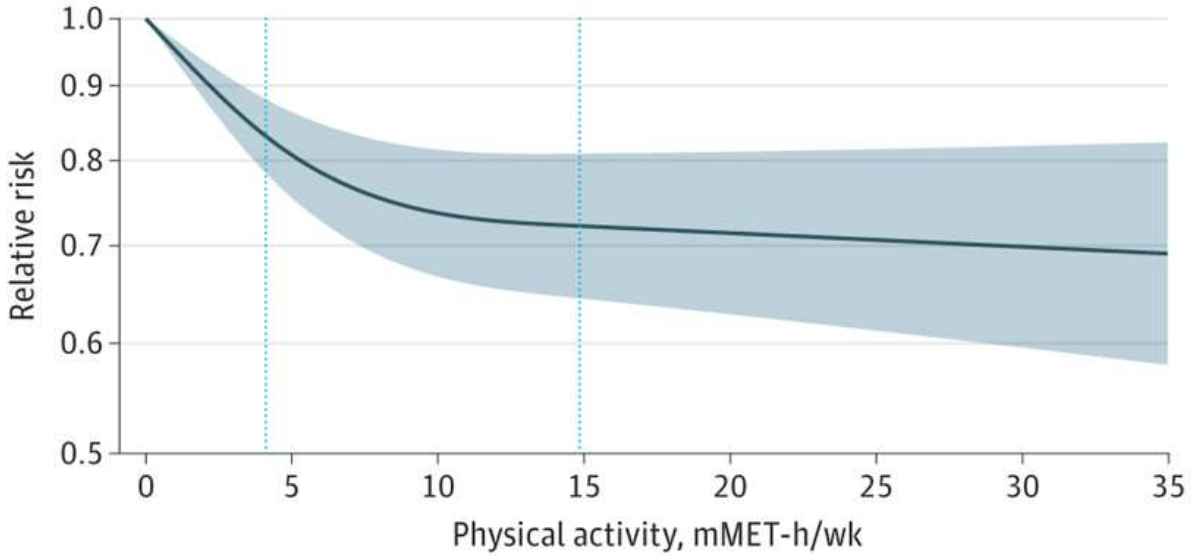


[1]Hanssen H. Effects of Endurance Exercise Modalities on Arterial Stiffness in Patients Suffering from Unipolar Depression: A Randomized Controlled Trial. Front Psychiatry. 2017; 8:311.
[2]Minghetti A. Sprint interval training (SIT) substantially reduces depressive symptoms in major depressive disorder (MDD): A randomized controlled trial. Psychiatry Res. 2018;265:292-297.

Physical Activity and Mood

- Association Between Physical Activity and Risk of Depression: A Systematic Rewview and Meta-analysis. JAMA Psychiatry. 2022.
  - 15 studies (n=191,130), prospectively monitored over 3-25 years
  - Recommended physical activity from WHO is moderate physical activity 30 mins 5x/wk (8.8 METs)
    - 4.4 mMET-h/wk had 18% lower risk of depression
    - 8.8 mMET-h/wk had 25% lower risk of depression; minimal change higher METs

Figure 1. Association Between Physical Activity and Incidence of Depression



Physical Activity Recommendations

- Decrease sedentary behavior
- Cardio for 30+ mins 5-7x per week
- Resistance Training
  - Important for preventing muscle loss
  - Exercises that use the most muscle mass possible
  - Exercises that train over the greatest range of motion
  - Squat, deadlift, overhead press, bench press
  - Progression and consistency
    - Start with the bar practicing good form and increase weight by 5 lbs each session; decrease to 2.5 as needed
    - 3 sets of 5 reps (1 set for deadlifting)
    - Alternate overhead and bench pressing days
    - 3x/wk for <65 yo, 2x/wk for >= 65 yo
  - Competitive powerlifting has around 20x less injuries than competitive soccer

Barriers to Physical Activity

- Getting Started
  - Just get out there today and do something
    - Go for a walk
    - Go to the gym and do anything
  - Don't go too fast and burn out
- Continued Motivation
  - Set small interval goals which are achievable
  - Make a game out of it
    - Play a sport, Reps challenge, Fitness tracker, Reward yourself
    - Dance, Meditative activities, Martial arts
  - Work out with friends and family
  - Hire a coach
    - Plentiful
    - Many virtual options
    - Barbell Logic
  - Make it a habit
    - Work out 3-4 days a week
    - Do light exercise like a walk on other days
  - Change it up

Barriers to Physical Activity

- Cost
  - Set of dumbbells are inexpensive
  - Resistance exercises with bands, body weight, household items
  - Many free training videos and podcasts online
  - Good fitness will save money
    - Medical costs
    - Injuries, falls, loss of ability to work
    - Improved mental health
- Time
  - Can be done at home
  - Can be done while attending to daily routines
    - Taking stairs, parking further away, walking short distances
    - While watching TV, listening to audiobook, other screen time
  - Replace unhealthy hobbies with healthy ones

Toxins

Smoking and Vaping

- Frequent vaping is associated with 2.4x increased odds of depression[1]
- Higher frequency of vaping is associated with more severe depressive symptoms[2]
- Vaping is associated with worsened mood, anxiety, suicidal ideation, and overall mental health. Dual use with smoking has even worse results.[3]
- Smoking cessation is linked to better mental health[4]
- Former smokers with current e-cigarette use do not show an improvement in depressive symptoms as is seen with those that are not current e-cigarette users[5]

Smoking Status	Depressive Symptoms %
Smoking	
Never smoking	5.49
Currently smoking	12.5
Former smoking	5.77
E-cigarette use	
No	6.56
Yes	14.69
Former smokers by e-cig use status	
E-cigarettes not used	5.55
E-cigarettes used	**16.10**

[1]Obisesan OH et al. Association Between e-Cigarette Use and Depression in the Behavioral Risk Factor Surveillance System, 2016-2017. *JAMA network open.* 2019;2(12), e1916800.

[2]Lechner WV et al. Bi-directional associations of electronic and combustible cigarette use onset patterns with depressive symptoms in adolescents. *Prev Med.* 2017;96:73-78.

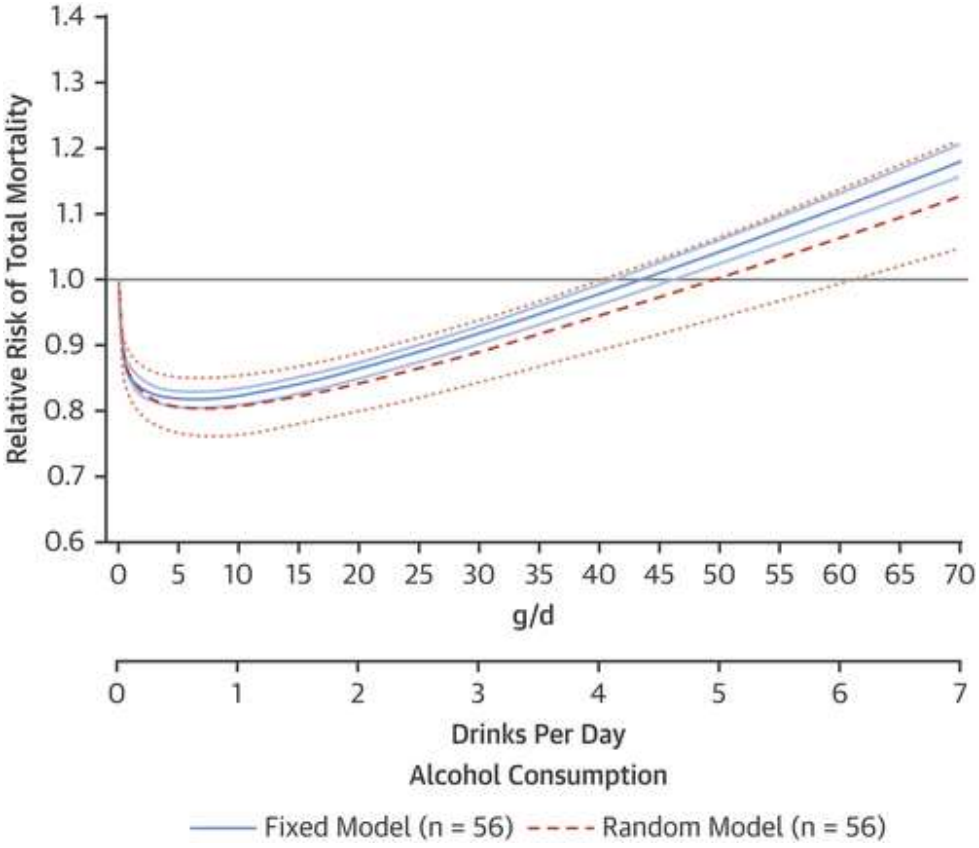
[3]Pham T et al. Electronic cigarette use and mental health: A Canadian population-based study. *Journal of affective disorders*;2020:260, 646–652.

[4]Taylor G et al. Change in mental health after smoking cessation: systematic review and meta-analysis. *BMJ (Clinical research ed.)*, 2014;348.

[5]Dahal R et al. Smoking Cessation and Improvement in Mental Health Outcomes: Do People Who Quit Smoking by Switching to Electronic Cigarettes Experience Improvement in Mental Health? *Canadian Journal of Psychiatry*. 2020;65(7):512–514.

Alcohol Consumption

- Previous large population-based studies have shown a link between light-moderate alcohol use and cardiovascular benefits with J-shaped curve
  - Very low levels have moderate risk
  - Moderate levels (4-7 drinks/wk) showed the lowest mortality
  - More drinks led to higher mortality



De Gaetano, G, Costanzo S. Alcohol and Health: Prasie of the J Curves*. J Am Coll Cardiol. 2017 Aug, 70 (8) 923-925.

Alcohol Consumption

- 2022 JAMA Biddinger et al study refutes these findings
  - Light-moderate consumption associated with healthier lifestyle factors
    - Non-smokers, healthier weight, increased physical activity, vegetable consumption, red meat consumption, and self-reported health
  - Adjustment for these factors attenuated the cardioprotective epidemiologic associations with modest intake
  - Association with light-moderate drinking is still minimal
    - 16 people would have to give up alcohol to prevent 1 case of HTN
    - 94 would have to give up alcohol to prevent one MI
  - Conclusion is that light-moderate use is not cardioprotective
  - Risk likely goes up at 7 drinks/wk and not 14 drinks/wk

Biddinger KJ, Emdin CA, Haas ME, et al. Association of Habitual Alcohol Intake With Risk of Cardiovascular Disease. JAMA Netw Open. 2022;5(3):e223849.

Medication Treatments

Medication Treatment Indications

- Non-pregnant
- BMI >30
- BMI >27 with comorbidities
  - DM2, IGT, dyslipidemia, HTN, or OSA)
- Pediatrics (>= 12 years old)
  - >95%tile
- Trial of lifestyle modifications for 6 months

Medication Treatment Indications

- Treatment goals
  - 1-2lbs per week
  - Sustained loss
  - Improved health
    - Diabetes:
      - 5% loss -> 50% reduced risk
      - 10% loss -> 80% reduced risk
      - 15% loss -> 95% reduced risk
      - Even a temporary loss conveys reduction of risk
    - A1C, BP, Lipids: >=3-5% loss
    - OSA: 10% loss improves AHI and symptoms
    - Fatty liver
      - 5% loss reduces steatosis
      - 7% loss resolve inflammation
      - 10% loss improves fibrosis

Compound	Brand	Type	FDA Approval	Year	Weight Loss	Schedule
Phentermine	Adipex, Lomaira	NRA	Weight (short-term)	1959	5-7%	IV
Diethylpropion	Tenuate	NRA	Weight (short-term)	1959		IV
Phendimetrazine	Anorex	NDRA	Weight (short-term)	1959		III
Amphetamine salts	Obetrol	NDRI, DRA	Withdrawn	1960		
Benzphetamine	Didrex	NDRI, DRA	Weight (short-term)	1973		III
Fenfluoramine	Pondimin	SRA	Withdrawn	1973		
Fenfluoramine-Phentermine	Fen-Phen	SRA/NRA	Withdrawn	1973		
Metformin	Glucophage	AMPK, cAMP	DM2	1995		
Topiramate	Topamax	Carbonic anh	Seizure, Migraine pph	1996		
Sibutramine	Meridia	SNRI	Withdrawn	1997		
Orlistat	Xenical, Alli	Pancreatic lipase inh	Weight (chronic)	1999	2.5-4.0%	
Exenatide	Byetta, Bydureon	GLP1 agonist	DM2	2005		
Pramlintide	Symlin	Amylin	DM2	2005		
Lorcaserin	Belviq	5HT2C	Withdrawn	2012		
Phentermine-Topiramate	Qsymia	NRA/carbonic anh	Weight (chronic)	2012	9.3%	IV
Naltrexone-Bupropion	Contrave	Opioid ant/NDRI	Weight (chronic)	2014	5.2%	
Dulaglutide	Trulicity	GLP1 agonist	DM2	2014	6-10lbs	
Gelesis100	Plenity	Hydrogel	Weight (chronic)	2019	2%	
Setmelanotide	Imcivree	MC4 agonist	Weight (chronic)	2020		
Liraglutide	Saxenda	GLP1 agonist	Weight (chronic)	2020	5.6g	
Semaglutide	Wegovy	GLP1 agonist	Weight (chronic)	2021	12.5%	
Tirzepatide	Zepbound	GLP1/GIP agonist	DM2	2022	17.8%	
Retatrutide	LY-3437943	GLP1/GIP/GCGR	Phase II		24%	
Rimonabant	Acomplia	CB1	Never approved			

Stimulants

Norepinephrine suppresses appetite

Phentermine (Adipex®) (1959)

- Norepinephrine Releasing Agent (serotonin and dopamine release to lesser extent)
  - Appetite suppression without euphoria (not shown to be addictive)
- Substituted amphetamine
- FDA approved for short-term weight loss (~5-7%) >= 17 yo
  - Some states do not allow long-term use (>12 weeks) (ie Ohio, Florida)
  - However, it can be safely managed long-term
  - Can take 1 month break in between dosing if needed per requirements or with tolerance
- Off-label use for concentration
- Dosing
  - 15-18.5mg qAM; 30-37.5mg split 1-2x/day; 8mg 30min before meals (Lomaira®)
- Adverse Effects: HR, BP, insomnia, anxiety
  - Bupropion more likely to cause tachycardia and HTN
  - Fears of danger are overstated (historic connection to fenfluoramine)
  - Monitor VS with dose changes
  - Consider stopping if VS are elevated
- Contraindications
  - CVD (arrhythmias, heart failure, CAD, stroke, uncontrolled HTN)
  - Hyperthyroidism, glaucoma, agitation, hx of drug abuse, use of MAOi within 14 days
  - Pregnancy, breastfeeding

Diethylpropion (Tenuate®) (1959)

- Norepinephrine Releasing Agent
- AKA Amfepramone
- Prodrug of Ethcathinone
- FDA approved for short-term weight loss >=17 yo
- Dosing: 25mg TID, CR 75mg qAM
- Adverse Effects: HR, BP, insomnia
- Contraindications
  - CVD (arrhythmias, heart failure, CAD, stroke, uncontrolled HTN)
  - Hyperthyroidism, glaucoma, agitation, hx of drug abuse, use of MAOi within 14 days
  - Pregnancy, breastfeeding

Phendimetrazine (Anorex®) (1959)

- Norepinephrine-Dopamine Releasing Agent
- Substituted amphetamine
- Prodrug of Phenmetrazine
  - Withdrawn from the market in the 1980s
  - Phendimetrazine produces steadier long-acting blood levels
- FDA approved for short-term weight loss >= 17 yo
- Dosing: 17.5-35mg B/TID, ER 105mg qAM
- Adverse Effects: HR, BP, insomnia
- Contraindications
  - CVD (arrhythmias, heart failure, CAD, stroke, uncontrolled HTN)
  - Hyperthyroidism, glaucoma, agitation, hx of drug abuse, use of MAOi within 14 days
  - Pregnancy, breastfeeding

Amphetamine Salts (Obetrol®) (1960)

- Norepinephrine-Dopamine Reuptake Inhibitor
- Dopamine Releasing Agent
- Obetrol® **withdrawn** in 1973 by the FDA due to concerns of abuse
- Methamphetamine was removed from Obetrol®
  - Current form as mixed amphetamine salts rebranded as Adderall® which was available but not FDA approved until 1996 for ADHD
- Current FDA approved treatments for obesity
  - Lisdexamfetamine (Vyvanse® 30-70mg qAM)
    - Prodrug R-enantiomer amphetamine
    - FDA approved for binge eating disorder (adults only)
      - Criteria for binge eating disorder is very broad
  - Amphetamine sulfate (base) (Evekeo® 5-30mg qAM (can divide))
    - Exogenous obesity (children >= 12 yo)
  - Dextroamphetamine (ProCentra® or Zenzedi® 5mg qAM (max 10mg BID)
    - Obesity secondary to hypothalamic-pituitary dysfunction (children >=2 yo)

Benzphetamine (Didrex®) (1973)

- Norepinephrine-Dopamine Reuptake Inhibitor
- Dopamine Releasing Agent
- Prodrug of Dextroamphetamine and Dextromethamphetamine
- FDA approved for short-term weight loss >= 17 yo
- Dosing: 25-50mg qAM; Max 50mg TID
- Adverse Effects: HR, BP, insomnia
- Contraindications
  - CVD (arrhythmias, heart failure, CAD, stroke, uncontrolled HTN)
  - Hyperthyroidism, glaucoma, agitation, hx of drug abuse, use of MAOi within 14 days
  - Pregnancy, breastfeeding

Fenfluoramine (Finlepta®) (1973)

- Serotonin Releasing Agent
- Fenfluoramine is still available
  - Dravet syndrome and Lennox-Gestaut syndrome
- Fenfluoramine-Phentermine (Fen-Phen®)

  - SRA + NRA
  - Very popular effective weight loss treatment in the 90s
  - Obesity indication **withdrawn** in 1997
    - Cardiotoxicity in the form of valvular disease

Sibutramine (Meridia®) (1997)

- Serotonin-Norepinephrine Reuptake Inhibitor
- Withdrawn from the market by the FDA in 2010 due to association with increased heart attacks in strokes in patients with a history of CV disease (11.4% vs 10% controls)
- May still be found in supplements marketed as “natural,” “traditional,” or “herbal remedies.”

Phentermine/Topiramate (Qsymia®) (2012)

- NRA + carbonic anhydrase inhibitor
  - Phentermine: appetite suppression, affects proopiomelanocortin (POMC) neurons suppressing appetite
  - Topiramate ER: may help with sugar craving due to adverse taste
- FDA approved for **chronic** weight loss >= 12 yo (phentermine is only approved for short-term weight loss)
- Average weight loss: 10%
- Dosing
  - 3.75-23mg every morning for 2 weeks, then 7.5-46mg for 12 weeks
  - If <3% weight loss, discontinue or increase to 11.25-69mg for 2 weeks then 15-92mg
- Possible to prescribe separately
  - Start phentermine first and titrate 15 to 30/37.5 qAM
  - Add topiramate and titrate 25 to 100mg QHS
  - Advantages: cheaper, no prior auth, no REMS, dose separately qAM and QHS which may be better tolerated
- REMS requirement due to teratogenic risk (orofacial clefts)
  - Purpose is to inform of risk (RR 9.6); there are no contraceptive requirements; BHCG recommended
  - REMS required for males as well despite no risk
  - Pharmacy must be certified; not available in the Navy
- Adverse Effects: HR, BP, insomnia, cognitive dysfunction, parathesias, nephrolithiasis, dysgeusia
- Contraindications
  - CVD is NOT listed, however contraindications of phentermine and topiramate individually should be considered
  - Hyperthyroidism, glaucoma, agitation, hx of drug abuse, use of MAOi within 14 days
  - Hypersensitivity, pregnancy, breastfeeding
  - Reduced dose with GFR <50, contraindicated with GFR <30

Naltrexone/Bupropion (Contrave®) (2014)

- Substituted amphetamine + Naltrexone
  - Norepinephrine-Dopamine Reuptake Inhibitor: appetite suppression
  - μ-opioid receptor antagonist: cravings, emotional eating
  - Synergistically affect POMC
- FDA approved for chronic weight loss >=18 yo
- Average weight loss: 5%
  - Compared to placebo: (48% vs 16% lost 5%), (25% vs 7% lost 10%)
- Dosing
  - Wk1 (8-90mg qAM), Wk2 (8-90mg BID), Wk3 (16-180mg qAM, 8-90mg qPM), Wk4 (16-180mg BID)
- Possible to prescribe separately
  - Naltrexone 25 to 50mg qAM with bupropion XL 150 to 450mg qAM
- May also help with concentration, depression, alcohol/nicotine abuse
- Warnings/precautions: nausea, HR, BP, SI, hepatotoxicity
- Contraindications
  - Uncontrolled HTN, hx of seizure disorder, bulimia/anorexia
  - Use with other bupropion- or naltrexone-containing product
  - Chronic opioid use (hold prior to surgery)
  - Abrupt discontinuation of alcohol, benzos, barbiturates, and antiseizure drugs
  - Use within 14 days of MAOI
  - Pregnancy
  - Decompensated cirrhosis

Others

Various mechanisms

Metformin (Glucophage®) (1995)

- MOAs not fully understood and are multiple
  - Decreases gluconeogenesis
  - Effects on various hormones and proopiomelanocortin
  - Increased release of leptin
    - Counters increase in neuropeptide Y seen in AP use up to 750mg only; higher doses worse
- FDA approved for DMII >=10 yo
- **NOT** FDA approved for weight loss
- Used off-label for antipsychotic-induced weight gain
  - More effective in prevention than loss (use if 5% weight gain)
- Dosing: 250-500mg BID, up to 1000mg BID for obesity without AP use
- Can be used safely in pregnancy and breastfeeding
- Adverse Effects: GI upset, lactic acidosis, B12 deficiency
- Contraindications
  - Severe renal dysfunction (eGFR <30)
  - History of lactic acidosis or ketoacidosis **(BBW)**
  - Risk of lactic acidosis
    - Excessive alcohol intake, hepatic dysfunction, IV contrast, surgery, CHF

Topiramate (Topamax®) (1996)

- Several MOAs
  - Sodium channels, calcium channels, GABA, AMPA, carbonic anhydrase
  - May affect weight through leptin and insulin signaling
    - Early satiety
- **NOT** FDA approved for weight loss
- FDA approved for migraine prophylaxis (>=6 yo) and seizures (>=2 yo)
- Used off-label
  - Antipsychotic-induced weight gain and binge eating disorder
- Dosing: 25mg QHS, increase 25mg weekly to 100-150mg QHS
- May be most effective for evening food cravings
- Adverse Effects
  - Cognitive dysfunction, parathesias
  - Metabolic acidosis, nephrolithiasis, ocular effects, oliogohydrosis, dysgeusia

Orlistat (Xenical®) (1999)

- Pancreatic lipase inhibitor: reduces lipid absorption
- Saturated derivative of lipstatin from *Streptomyces toxytricini*
- Alli® is OTC formulation (only FDA-approved OTC weight loss med)
- Average 3kg (2.5-4% over placebo) weight loss
- FDA approved for chronic weight loss >=12 yo
- May improve cholesterol, BP, glycemic control, diabetes prevention, MASLD, MASH
- Dosing: 120mg TID with meal containing fat (Alli® is 60mg TID)
- Adverse Effects: Oily rectal leakage (less likely with lower fat diet), GI upset, ADEK vitamin malabsorption
  - Recommend to take ADEK vitamin supplement
- Contraindications
  - Chronic malabsorption syndrome
  - Cholestasis
  - Pregnancy
  - Bariatric surgery patients

Pramlintide (Symlin®) (2005)

- Amylin analogue
  - Slows gastric emptying
  - Promotes satiety
  - Inhibits inappropriate secretion of glucagon
  - Currently there are 2 medications undergoing phase II trials that combine this with GLP1
- Up to 8kg weight loss
- FDA approved for DM2, **NOT** weight loss >=18 yo
- Dosing: 60mcg SQ prior to major meals, increase to 120mcg
- Adverse Effects: GI upset, severe hypoglycemia
- Contraindications
  - Gastroparesis
  - Hypoglycemia unawareness
  - Caution with coadministration with insulin

Lorcaserin (Belviq®) (2012)

- Serotonin 5-HT_{2C} agonist
  - SGAs and mirtazapine antagonize this receptor
- Withdrawn from the market by the FDA in 2020 due to association with increased occurrence of pancreatic, colorectal, and lung cancers
  - Higher incidence of cancer-related death is not conclusive, however conducting further trials to confirm or refute the signal is not feasible

Gelesis100 (Plenity®) (2019)

- Considered a device and not a medication
  - Cellulose and citric acid hydrogel
  - Absorbs water and grows to fill the stomach
  - Water is reabsorbed in the intestines and it is excreted unchanged
- FDA-cleared for chronic weight loss
  - Can be used for BMI >25 (lower than other options)
  - Can only e-prescribe through GoGoMeds Pharmacy
    - Not covered by TRICARE ($98/month)
- Average weight loss: 6.4% (2% over placebo)
  - 10% weight loss seen in 27% of patients vs 15% forplacebo
- Dosing: 2.25g BID (before lunch and dinner) with 2 glasses of water
  - Gel expands to 100x its volume
- Adverse effects: GI upset
- Alternative: Glucomannan (konjac fiber)
  - Available OTC
  - $25/month
  - Expands to 50x its volume
  - May have more GI adverse effects
- Contraindications: only hypersensitivity

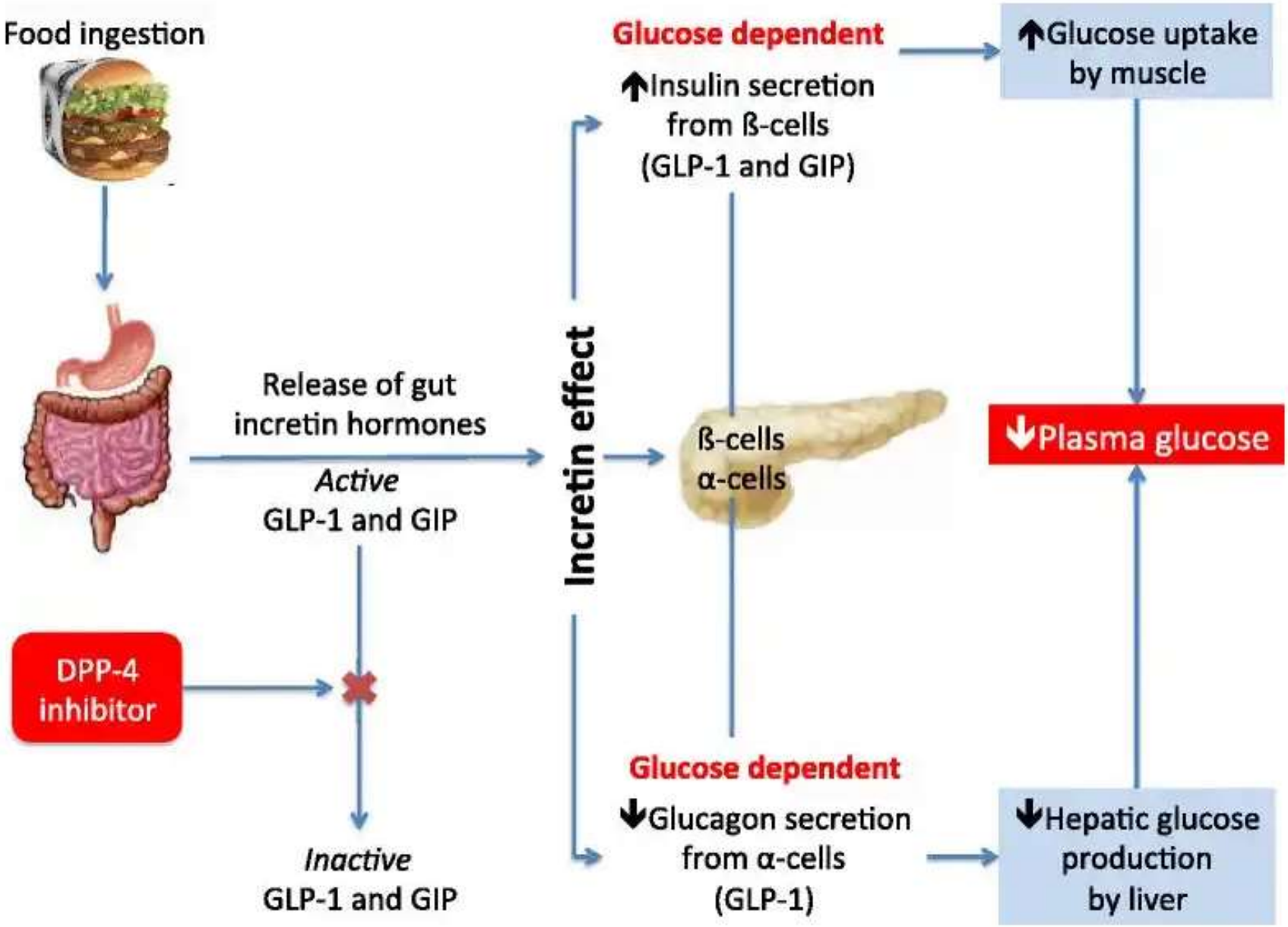
Setmelanotide (Imcivree®) (2020)

- Melanocortin 4 (MC4) agonist
- FDA approved for chronic weight loss >=2 yo
  - Bardet-Biedl Syndrome (1 in 100,000)
  - POMC (50 cases), PCSK1 (<50), or LEPR deficiency (88)
- Dosing: 2-3mg SQ daily
- Adverse effects: SI, sexual dysfunction, skin pigmentation
- Contraindications: none

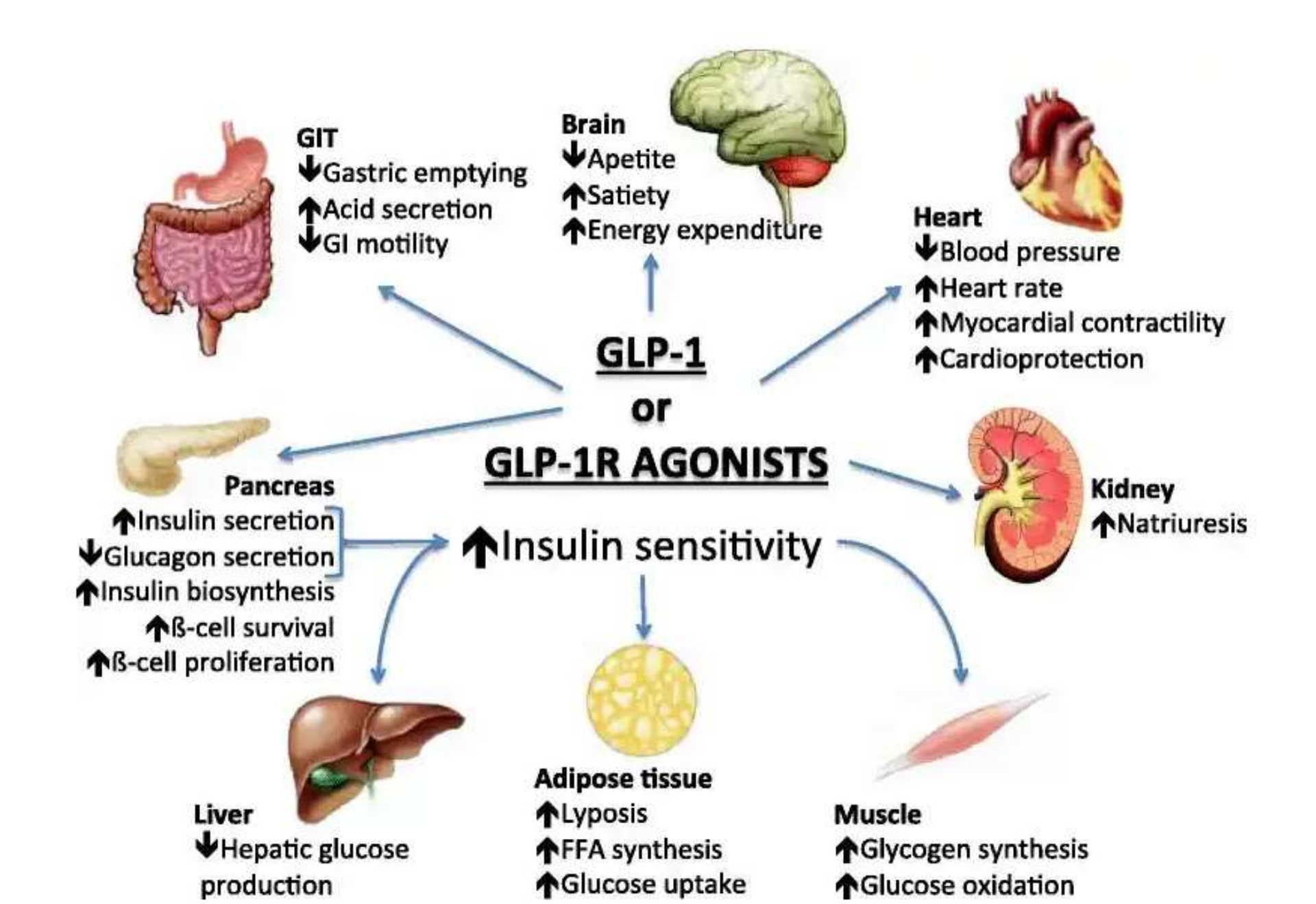
SGLT2 Inhibitors

- Sodium-glucose cotransporter 2
  - Responsible for glucose reabsorption in the kidneys
- Examples
  - Canagliflozin (Invokana®) (2013) >=18 yo
  - Dapagliflozin (Forxiga®) (2014) >=10 yo
  - Empagliflozin (Jardiance®) (2014) >=10 yo
- FDA approval for DM2 and heart failure
- Weight loss
  - 2-3% placebo-subtracted weight loss
  - Due to loss of glucose in urine
- Other benefits
  - Glycemic control (0.5-1 point drop in A1C)
  - BP and CV outcome improvement
  - Nephroprotective
- Adverse Effects
  - UTIs, euglycemic diabetic ketoacidosis, **hypotension**
  - Rare: AKI, bone fxs, lower limb amputation, hyperkalemia

Incretin Analogues



Saraiva FK et al. Cardiovascular effects of Glucagon-like peptide 1 (GLP-1) receptor agonists. Cardiovascular Diabetology. 13, Article number: 142 (2014).



Saraiva FK et al. Cardiovascular effects of Glucagon-like peptide 1 (GLP-1) receptor agonists. Cardiovascular Diabetology. 13, Article number: 142 (2014).

Glucagon-like peptide 1 (GLP-1) agonists

- Long-acting GLP-1 first isolated from gila monster saliva
  - Lizard only needs to eat twice a year
- GLP-1 (incretin) is produced in the ileum by enteroendocrine L-cells
  - Helps with glucose-dependent secretion of insulin
  - Reduces inappropriate glucagon secretion
  - Slows gastric emptying and digestion -> reduces appetite
- Faster/increased release with Roux-en-Y bariatric surgery
  - Endogenous GLP-1 is broken down too quickly (30 secs) to cross BBB
  - Synthetic GLP-1 is not broken down by DPP4 and crosses the BBB
    - Turns down emotional/reward of food in the brain leading to sustained weight loss
    - Will still enjoy food
- Does not cause hypoglycemia
  - Does not affect pancreas w/o hyperglycemia

GLP-1 Agonist Benefits

- Lifespan in the US
  - Lifespan for men is now only 73 in the US; 10 years behind other developed countries
  - Cardiac deaths related to obesity increased 2.8-fold from 1999-2020
    - Most affected: middle-aged men, black adults, midwesterners, rural
- Blood sugar control for patients with DM2
  - 50% of diabetic patients attain normal A1C
  - SURMOUNT-1 (tirzepetide): Risk of diabetes reduced by 94%
- Fertility (male and female)
  - Improvement of PCOS: weight loss and improved insulin resistance
- Renoprotective
  - GLP-1 receptors on afferent arterioles
  - GLP-1 influences secretion of angiotensin II and improves oxygenation
  - 24% relative risk reduction in kidney events

GLP-1 Agonist Benefits

- Cardioprotective
  - Likely mechanism
    - Weight and glucose control
    - Anti-inflammatory independent of obesity
    - Improved capillary health 2/2 anti-inflammation and reduced atherosclerosis
  - Semaglutide
    - 29% relative risk reduction in cardiac death
    - Study was done at only 1mg semaglutide vs current 2.4mg
    - Study ended early as not to deprive patients of life-saving medication
    - So true benefit may be even higher
    - Serious adverse events similar to placebo
  - Tirzepetide
    - 38% relative risk reduction of cardiac death
  - Direct effect on sinus node vs sympathetic system (other obesity meds) increasing heart rate: neg efffect likely outweighed by above

GLP-1 Agonist Benefits

- Cancer
  - 10 of the 13 cancers associated with obesity demonstrated to be reduced so far by GLP-1s
  - Colorectal cancer (CRC)
    - Reduced risk of early-onset (<50) CRC in patients with DMII
    - Cohort study with 1.8M patients with DMII (77K patients per group)
    - 0.4% risk vs 0.7% risk regardless of weight
    - Other studies have shown decreased risk for late-onset CRC as well
- Weight loss!!!
  - Details on weight loss on later slides
  - Weight loss in patients with DM2 is less than those without
    - Likely due to more diet advice given in weight loss trials

GLP-1 Agonist Benefits

- Obstructive sleep apnea
  - Tirzepetide
    - Received FDA approval for moderate to severe OSA in 2024
    - AHI drop of 25-29 vs 5 with lifestyle changes
    - 43-52% resolution of OSA vs 15%
- Preliminary studies show improvements in
  - Alcohol abuse
  - Drug abuse
- Anecdotal reports improving other addictive behaviors
  - Gambling
  - Hypersexual behavior
  - Skin picking
  - Nicotine

GLP-1 Agonist Benefits

- MASLD
  - Semaglutide 72 wk ESSENSE trial: 63% vs 34% placebo resolution
  - Tirzepatide smaller Phase II trial: 62% vs 30% placebo resolution
- Effects on the brain
  - Plasticity
  - Synaptogenesis
  - Antiapoptosis
  - Dementia
    - Amyloid causes inflammation, oxidative stress, mitochondrial dysfunction
    - GLP-1 is anti-inflammatory, anti-oxidative, and dissolve amyloid
    - EVOKE trials end of 2024
  - Lixisenatide shown to slow Parkinson's disease in mice

GLP-1 Agonists: Dosing

- Can titrate slower than package insert recommends if needed
- Not all patients will need the max dose
- After patient loses desired amount of weight
  - May need to lower dose
  - May dose every other day/week instead of daily/weekly
  - May take a few months off and restart after ~5% weight gain
  - Consider transition to other medication for weight loss maintenance
- Need to instruct patient on how to administer
  - Each medication has slightly different instructions
  - Multi-use injector pens: Byetta® and Saxenda®
    - Must order needles as well (patient may need to purchase separately)
  - Single-use injector pens: Bydureon®, Trulicity®, Wegovy®, Zepbound®
  - Vial: Zepbound® (Must order needles and syringe separately)

GLP-1 Agonists: Duration of Treatment

- Obesity is a chronic condition
- Weight regain is extremely common if medications are withdrawn
  - May be able to maintain on lower dose
  - Important to practice a healthy diet and exercise while on medication
    - Easier to achieve this diet with the help of GLP-1s
    - May be able to stop medication if able to maintain these healthy habits
  - Lisdexamfetamine use can be considered as replacement
- Optimal duration of medication treatments has not been established
  - Typically takes ~2 years to reach desired weight loss
- Short-term treatment (3-6 months) has not been demonstrated to produce long-term results
- ~1 in 6 people can maintain weight loss that stop these meds
- Patients with temporary weight gain from acute stressor may only need short-term use

GLP-1 Agonists: Contraindications

- PMH/FMH (1st degree) of medullary thyroid cancer or MEN2A/B
  - **Black box warning**
  - Seen in rodents with liraglutide
    - Rodents have GLP-1 receptors on C-cells; humans have significantly less
    - No cases in humans since first approval in 2005
    - Despite this, FDA insisted on the warning
  - Clues that patient or family had medullary thyroid cancer
    - Radioactive iodine treatment is never done for medullary thyroid cancer
    - Excess thyroid hormone is not given with medullary thyroid cancer
- Pregnancy
  - Contraception is recommended
  - No adverse outcomes to date
- Hypersensitivity

GLP-1 Agonists: Adverse Effects

- Pancreatitis
  - Very unlikely to cause in absence of diabetes as the medication does not affect the pancreas w/o hyperglycemia
  - With diabetes
    - Hx of Cholecystitis
      - OK, but go slow with hx due to gall stone sludge
      - Hx of cholecystectomy: OK to use
      - Hx due to hypertriglyceridemia: they respond very well to GLP-1 agonists
    - Caution with use if prior history of pancreatitis
    - Don't use with ongoing alcohol use
    - Don't use if heterozygous for CF (don't need to check but ask about fam hx)
    - Don't use with pancreatic divisum
    - Avoid use if history of GLP-1-induced pancreatitis
- No increased risk of pancreatic cancer has been seen
  - Would not use if there is hx of pancreatic cancer
- Concern for macular generation highly likely not a concern

GLP-1 Agonists: Adverse Effects

- Acute gall bladder disease, cholestasis, cholelithiasis
  - FLOW trial (very large) demonstrated more with placebo
- Increase in thyroid cancer (non-medullary)
  - Seen but likely due to detection bias (mixed study results)
  - Easily treatable
- Diabetic retinopathy
  - SUSTAIN trial (DM, CVD, and obesity)
    - Improved CV outcomes
    - Diabetic retinopathy: 3% in semaglutide group vs 2% placebo
      - Non-arteritic anterior ischemic optic neuropathy (NAION)
        - Risk increased with OSA and HTN (overnight BP drop)
        - Make sure to reduce HTN medication as weight loss leads to improved BP
        - Need to stop medication immediately
  - SELECT trial (obesity, CVD): no difference from placebo
  - FLOW trial (Renal disease, obesity): Not seen

GLP-1 Agonists: Adverse Effects

- Reduction in desired rewarding behaviors
  - Dehydration (can take away thirst in addition to hunger)
    - Lightheadedness, syncope
    - Nephrolithiasis, AKI
  - **Exercising!!**
  - Sexual activity
- Mental health symptoms
  - They are being studied for use as an antidepressant
  - Anecdotal reports of worsened depression, anxiety, sleep, fatigue
    - 2025 meta-analysis from JAMA Psychiatry showed no AEs on mental health
    - May be from inadequate nutrition or fluid intake
- Risk of aspiration during surgery due to decreased GI motility
- Patient unwilling to use needles
  - Other options are on the way

Aureliane CS et al. Glucagon-Like Peptide 1 Receptor Agonists and Mental Healthl: A Systematic Review and Meta-Analysis. JAMA Psychiatry. 2025.

GLP-1 Agonists: Adverse Effects

- GI upset
  - Nausea
    - Increase satiety, so patients need to eat less (~1/2)
    - Smaller, less fatty meals
    - Avoid eating close to bedtime or lying down after eating
    - Titrate slower or use a lower dose
    - Less with tirzepatide
  - Constipation
    - Slows digestion: eat less, increase fiber and fluids
  - Caution in patients with gastroparesis
- Hair and skin
  - Hair loss
  - "Ozempic face" "Ozempic butt"
    - Skin loosening and wrinkles caused by rapid weight loss
  - May be mediated by controlled slower weight loss

GLP-1 Agonists: Adverse Effects

- Malnutrition
  - Iron, magnesium, B12, etc deficiencies due to decreased intake
  - Muscle loss in addition to fat loss
    - Lean body mass/soft tissue and fat free mass is not just skeletal muscle
      - Lean soft tissue is everything that isn't fat or bone and fat free mass includes bone
    - In one study 6.9kg of fat free mass loss reported (25% of total loss)
      - Only 1kg was skeletal muscle protein
    - Muscle loss is the same as seen in weight loss with calorie restriction
    - Chronic weight loss followed by gain equal to chronic dieting and relapsing
      - Can lead to worsened body fat% in the long run
    - Myostatin inhibitors are now being tested combined with GLP1s
      - Garetosmab, trevogrumab, bimagrumab
      - Unclear if there is functional improvement in the muscle or just hypertrophy
      - COURAGE Interim Phase II results: Monkeys lost 2x weight and GAINED muscle
  - Some patients lose weight too rapidly

GLP-1 Agonists: Adverse Effects

- Reflexive weight regain upon stopping medication
  - Decreased appetite leads to focus on maintaining nutrition
  - Return of appetite upon withdrawal leads to weight regain
- Recommendations
  - Maintain a well-balanced diet including adequate protein intake
  - Resistance training
  - Monitor closely for steady weight loss (adjust dose as appropriate)
  - If patient stops medication, follow closely for weight regain
  - For **MOST** patients, starting meds means maintaining indefinitely
- Use of these medications should be about health and not vanity
  - There are serious risks, cost, and supply issues
  - Focus on those with metabolic risk who have failed lifestyle changes
    - Prediabetes, HTN, HLD, central obesity, OSA, MASH

GLP-1 Agonists: Drug Interactions

- Most warnings are regarding enhanced hypoglycemia
  - Androgens
  - Beta-blockers
  - Direct acting antiviral agents
  - Insulin and other diabetic agents
  - MAOis and SSRIs
  - Fluoroquinolones
  - Salicylates
  - Thiazide and thiazide-like diuretics
  - Diabetic agents are risk class D, others are class C
- May increase serum levothyroxine level
- Tirzepetide may make oral birth control less effective

GLP-1 Agonists: Drug Interactions

- Not mentioned in package insert
  - Decreased gastric emptying may interfere with XR formulations and meds that need to be spaced out from food or other meds
  - Shouldn't negatively affect meds that act 24 hr
  - Stimulants lasting too long may cause insomnia
  - Sedatives lasting too long may cause grogginess
  - Examples
    - Mixed amphetamine salts XR (Adderall XR®)
    - Lisdexamfetamine (Vyvance®)
    - Concerta (Ritalin OROS®)
    - Zolpidem XR (Ambien XR®)
    - Others? (levothyroxine)
  - Recommendations
    - Lower dose of XR formulation
    - Switch to IR BID dosing
    - Take XR formulation earlier if possible

GLP-1 Agonists: Shortages

- Many patients are paying out of pocket
- Many prescribers are giving prescriptions to patients that do not meet appropriate criteria or lacking appropriate medical evaluation
  - Do not prescribe for vanity purposes!
- Has affected DM2 versions of medication even though they are not being used for DM2
- Saxenda® is more available as its pens are multiuse and can be dialed in to desired dose
- Wegovy® is available at higher doses
  - If lower doses unavailable, can initiate Saxenda® and titrate up to 3mg then switch to 2.4mg Wegovy®
  - Could consider skipping the 0.25mg or 0.5mg dose
  - Consider dosing by "clicks": full dose is 74 clicks, can dose lower
    - Other countries outside US have made dial in dosing easier
- Zepbound® has faced shortages as well
  - Has made vials available due to shortage of pens

GLP-1 Agonists: Cost

- Many insurers will not cover these medications
- Medicare/Medicaid will not pay for weight loss or gain medications
  - This includes fertility treatment, drugs for cosmetic purposes or hair growth, symptomatic relief of cough and cold, vitamins and minerals except pre-natals
  - Used to include smoking cessation, barbiturates and benzodiazepines
- Cost ~$1200 in the US
  - $100-400/month in most countries
  - Option to acquire reduced price product (~1/2) directly from the manufacturer
  - Compounding pharmacies provide easier access at a much lower cost
    - $200-500/month
    - Not covered by insurance
    - Dosed by syringe
      - Patients often confuse concentration, unit, and volume
      - Vial concentrations differ between pharmacies
      - Important to ensure patient understands how to dose with each pharmacy that they use

GLP-1 Agonists: Compounding

- Compounding is allowed if FDA declares a shortage
  - Designed to help patients already on medication; not start new patients
  - New patients may not be able to get medication once shortage ends
- Compounding is allowed if "not a commercially available copy" (drug, dose, route)
  - May add something like a vitamin or remove something like an inactive ingredient
  - May change the dose (>10% difference)
- Exception to above: Drugs on Demonstrably Difficult to Compound (DDC) List
  - Manufacturers are petitioning for this
  - Currently the compounders product is made in a different way, manufacturer argues this is a problem
- Quality control of these products has been a concern
  - Reports of not yet approved GLP-1s being compounded
  - Reports of unauthorized salt forms of GLP-1s being compounded (2022-2023)
  - Reports of being given at spas without a prescription
  - Impurities, counterfeits, and contamination concerns
  - **MUST come from FDA approved pharmacies**
  - American Diabetes Association recommends against use of these products due to these concerns
- How to safely prescribe
  - Ensure patients understand how to dose and deliver each time they use a different pharamcy
  - Ensure they are getting from an FDA licensed 503A or 503B compounding pharmacy
  - 503B pharmacies have stricter guidelines

Exenatide (Byetta® Bydureon®) (2005, 2012)

- GLP-1 receptor agonist
- Average 2.5kg weight loss
- FDA approved for DM2, **NOT** weight loss
- Dosing
  - Byetta® is SQ BID (>=18 yo)
    - Slightly better weight loss than Bydureon®
  - Bydureon® is SQ qWeekly (>=10 yo)

Dulaglutide (Trulicity®) (2014)

- GLP-1 receptor agonist
- Average weight loss: 6-10lbs
- FDA approved for DM2, **NOT** weight loss (>=10 yo)
- Dosing: 0.75-4.5mg SQ qWeekly

Lixisenatide+Glargine (Soliqua®) (2016)

- GLP-1 receptor agonist with insulin
- Lixisenatide (Adlyxin®) is no longer available as a stand alone product in the US
- FDA approved for DM2, **NOT** weight loss

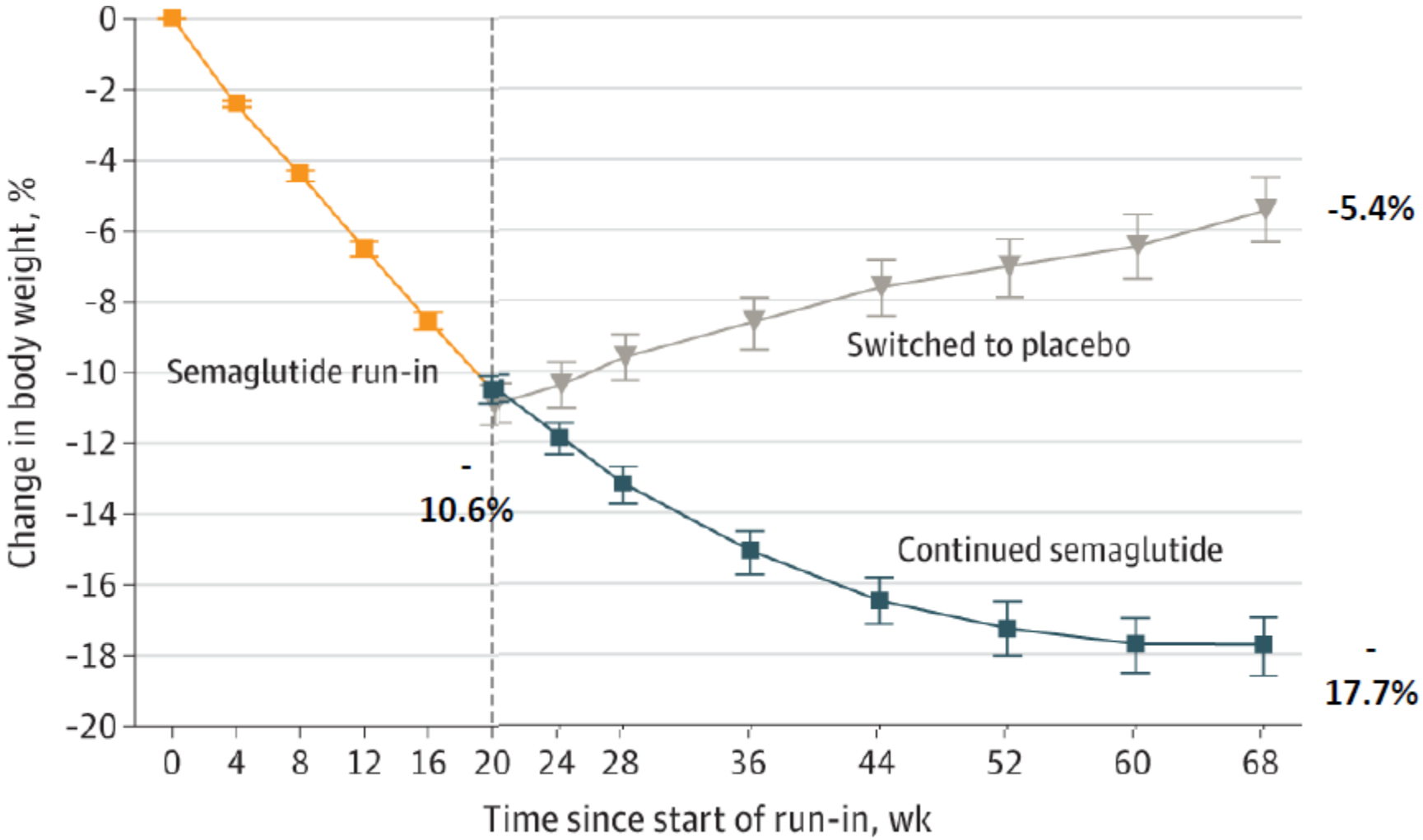
Liraglutide (Saxenda®) (2020)

- GLP-1 receptor agonist
- FDA approved for chronic weight loss and DM2 (Victoza® in 2010)
  - Approved for ages **>= 12** for weight loss (>=10 for DM2)
- Average weight loss: 8.4±7.3kg (-5.6kg compared to placebo)
- So far studies in AP-induced weight gain only show benefit for prevention
- Dosing: 0.6-3mg SQ **qDaily** (higher than Victoza®)
  - Pen injector is dialed to desired dose, needle is changed at each use
  - 0.6mg SQ once daily x 7 days
  - 1.2mg SQ once daily x 7 days
  - 1.8mg SQ once daily x 7 days
  - 2.4mg SQ once daily x 7 days
  - 3.0mg SQ once daily
- Advantages over Wegovy®
  - Often more available in supply
  - Dose titration takes only 5 weeks vs 17 weeks

Semaglutide (Wegovy®) (2021)

- GLP-1 receptor agonist
- FDA approved for chronic weight loss and DM2
  - Ozempic®: weekly SQ formulation approved for DM2 in 2017 (>=18 yo)
  - Rybelsus®: daily oral formulation approved for DM2 in 2019 (>= 18 yo)
  - Wegovy®: weekly SQ approved for ages **>= 12** for weight loss
- Average weight loss: STEP 1 trial: 15% (12% above placebo)
  - STEP 4 trial: switch to placebo at 20 wks vs continue to 68 wks: **17.7%**
  - STEP UP trial: triple dose, 7.2mg SQ once weekly: **20.7%** weight loss
- Head-to-head with liraglutide (16 vs 6% weight loss), (3 vs 13% stopped due to AEs)
- Dosing: 0.25-2.4mg SQ **qWeekly** (higher than Ozempic®)
  - 0.25mg SQ once weekly x 4 weeks
  - 0.5mg SQ once weekly x 4 weeks
  - 1mg SQ once weekly x 4 weeks
  - 1.7mg SQ once weekly x 4 weeks
  - 2.4mg SQ once weekly (28 day and 84 day supplies available)
- Advantages over Saxenda®
  - Greater weight loss on average
  - Weekly injection is more convenient than daily
  - Pen injector is simpler to use (single pen for each injection)

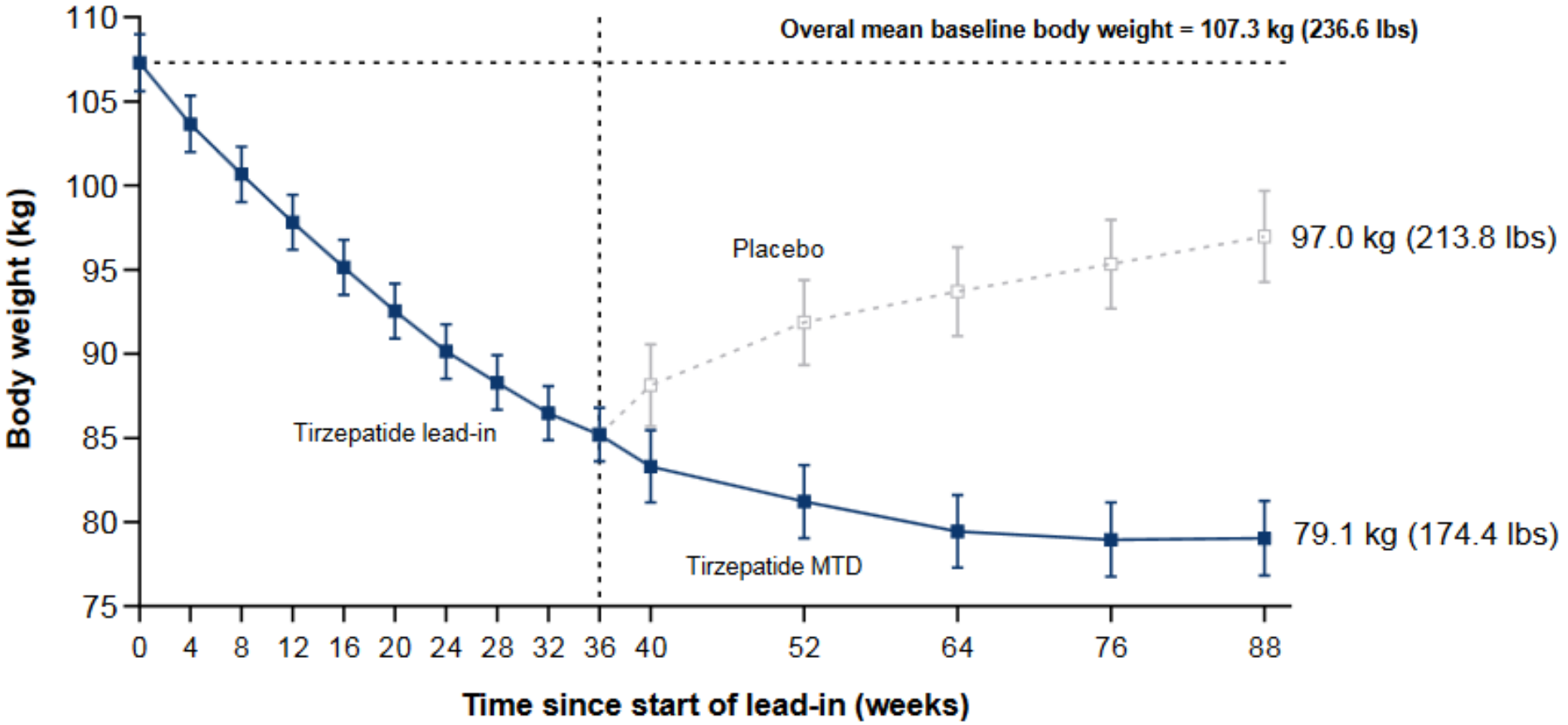
Semaglutide: Step 4 Trial



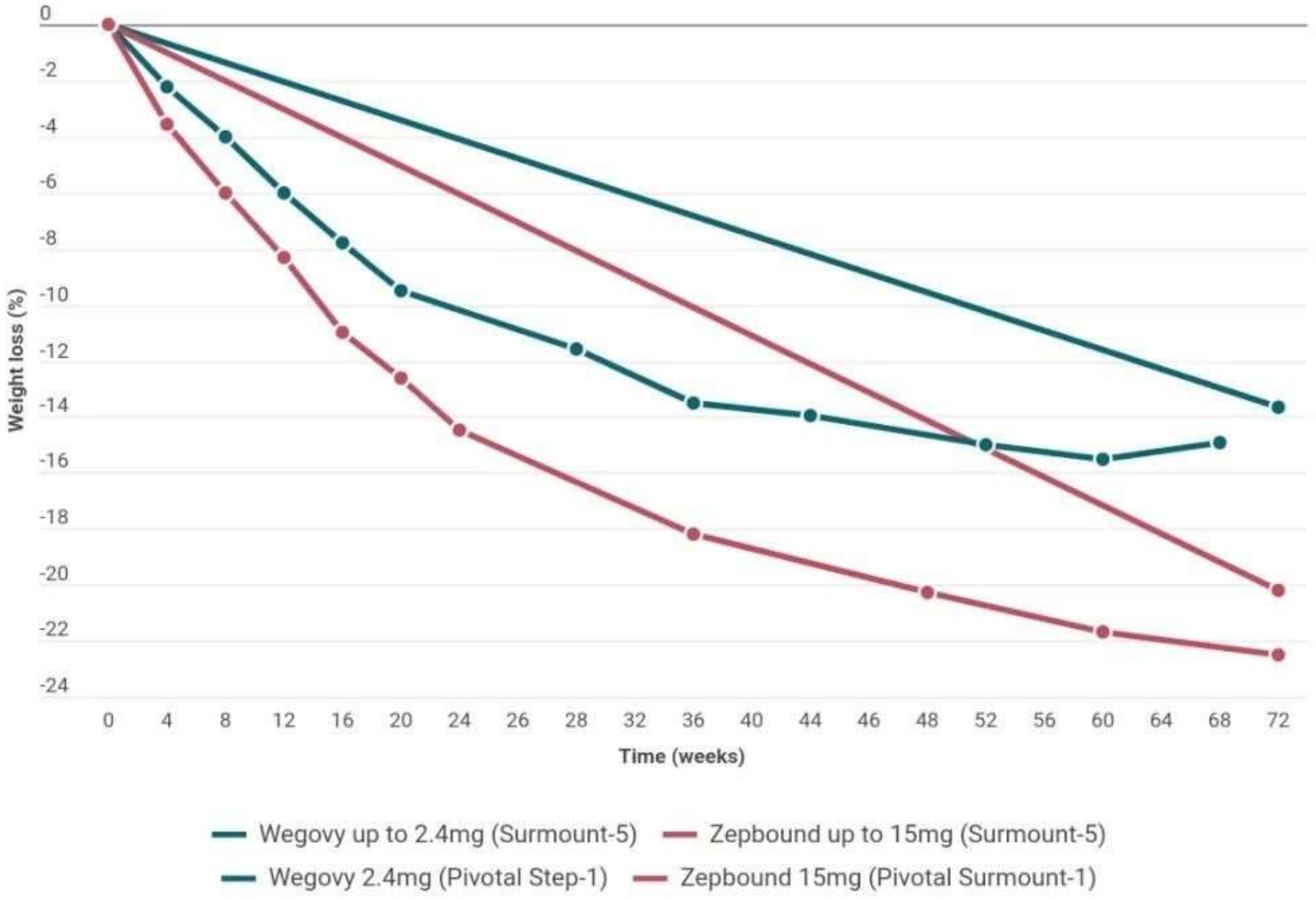
Tirzepatide (Zepbound®) (2023)

- "Twincretin"
  - GLP-1 receptor agonist
  - Mounjaro® approved by FDA in 2022 for DM2
  - Zepbound®: weekly SQ approved for ages **>= 18** for weight loss
  - Glucose-dependent insulinotropic polypeptide (GIP) receptor agonist
    - AKA Gastric inhibitory polypeptide
    - Produced in the duodenum and jejunum by enteroendocrine K-cells
    - GIP receptors are in the pancreas, brain (appetite), and adipocytes
- Average weight loss: 20% (18% above placebo)
  - Less GI adverse effects making it more likely to work
  - 88 week SURMOUNT-4 trial showed 25.3% weight loss
  - 72 week SURMOUNT-5 vs semaglutide: 20.2% vs 13.7%
- Dosing: 2.5-15mg SQ qWeekly, titrate by 2.5mg every 4wks
- Warning that hormonal contraceptive may be less effective and to use non-hormonal contraceptive for 4 wks after initiation/change

Tirzepatide: SURMOUNT-4 Trial

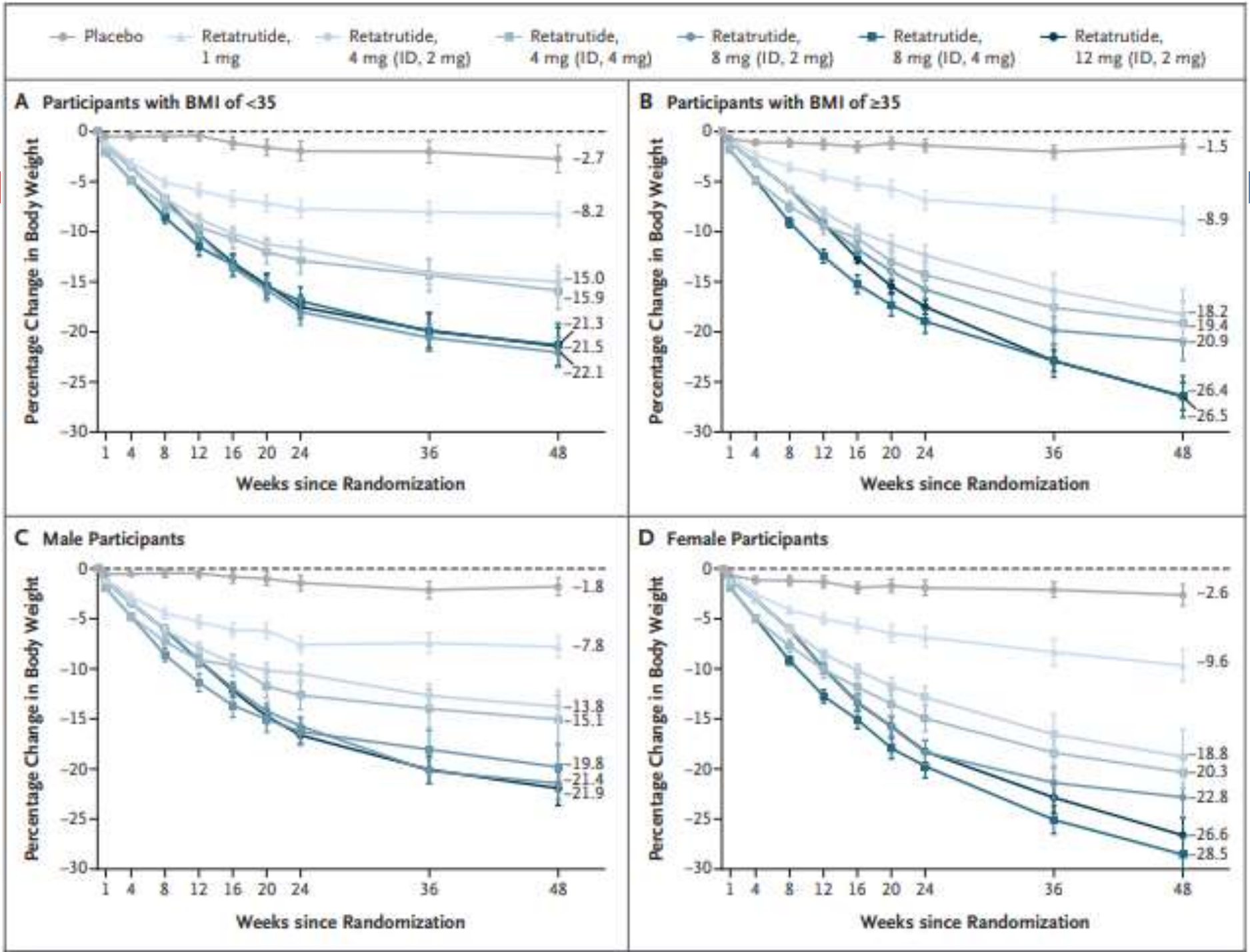


Tirzepatide vs Semaglutide: SURMOUNT-5



Phase II Trials

- Survodutide (BI-456906)
  - GLP-1 and Glucagon Receptor (GCGR) agonist
    - GCGR may help to improve lipids directly
  - Average weight loss: 18.7% at 46 weeks
  - Phase II trials for MASH and liver fibrosis
    - 62% improvement vs 13% placebo
  - Phase III trial begun in 2023 for obesity and 2024 for MASH/liver fibrosis
- Retatrutide (LY-3437943)
  - "Triple G": GLP-1, GIP, and GCGR agonist
  - Average weight loss
    - 24.2% average on highest 12mg dose at 48 weeks
    - 26.5% for those with BMI >=35 on 12mg at 48 weeks
    - 28.5% for females at 12mg at 48 weeks
    - Trend suggests continued weight loss beyond 48 weeks
  - Phase III trial for DM2, MASLD, and obesity
    - 28 Aug 2023 – 6 Feb 2026


Placebo
Retatrutide, 1 mg
Retatrutide, 4 mg (ID, 2 mg)
Retatrutide, 4 mg (ID, 4 mg)
Retatrutide, 8 mg (ID, 2 mg)
Retatrutide, 8 mg (ID, 4 mg)
Retatrutide, 12 mg (ID, 2 mg)
A Participants with BMI of <35
Percentage Change in Body Weight
0
−5
−10
−15
−20
−25
−30
−2.7
−8.2
−15.0
−15.9
−21.3
−21.5
−22.1
1 4 8 12 16 20 24 36 48
Weeks since Randomization
B Participants with BMI of ≥35
Percentage Change in Body Weight
−1.5
−8.9
−18.2
−19.4
−20.9
−26.4
−26.5
1 4 8 12 16 20 24 36 48
Weeks since Randomization
C Male Participants
Percentage Change in Body Weight
−1.8
−7.8
−13.8
−15.1
−19.8
−21.4
−21.9
1 4 8 12 16 20 24 36 48
Weeks since Randomization
D Female Participants
Percentage Change in Body Weight
−2.6
−9.6
−18.8
−20.3
−22.8
−26.6
−28.5
1 4 8 12 16 20 24 36 48
Weeks since Randomization

Phase II Trials

- Semaglutide
  - Oral GLP-1 agonist similar to Rybelsus®
  - OASIS 1 and PIONEER PLUS trials
    - 50mg dose associated with 17% weight loss (similar to Wegovy®)
    - Greater reduction in A1C than lower approved doses
  - Current max dose of 14mg (Rybelsus®) is associated with 5% weight loss
  - Manufacturer is requesting FDA approval for 25mg and 50mg doses for DM2 and weight loss in 2023
- Orforglipron (LY-3502970)
  - Daily oral GLP-1 agonist for weight loss
  - Phase II published Sep 2023
    - Average weight loss: 14.7% compared to 2.3% placebo
  - Phase III data expected April 2025
- Danuglipron (PF-06882961)
  - Twice daily oral GLP-1 agonist for weight loss
  - Phase II results in 2023 were underwhelming: 8-13% weight loss beyond placebo
  - Company is pivoting to a once daily preparation

Phase II Trials

- Amycretin
  - Oral dual GLP-1 agonist and amylin agonist
    - Amylin is secreted by beta cells (same as insulin) in the pancreas
    - Amylin may improve leptin sensitivity, which contributes to satiety
  - Phase I trial showed 13.1% weight loss in 12 weeks
  - Phase II trial began in 2024
- CagriSema®
  - Cagrilintide (amylin agonist) + semaglutide
  - Phase II trial showed 15.6% weight loss at 32 weeks
  - Phase III trial REDUCE 1
    - 23% weight loss (11% Cagri, 16% Sema, 2.5% placebo)
    - Similar to tirzepatide

GLP1RA Comparison

- Zepbound®
  - Studies show more weight loss and better tolerance
  - Warning that it may make oral contraceptives less effective
  - Flexible dosing: both pens and vials available
  - Not yet approved for <18 yo
- Wegovy®
  - Next most effective, but 7.2mg dose similar to tirzepatide
  - Less flexible dosing than Saxenda® but can dose by clicks
- Saxenda®
  - Least effective, though more effective than non-GLP1RAs
  - New TRICARE algorithm makes prescribing difficult
  - More flexible dosing and quickest titration to max dose
  - Must load syringe vs preloaded pens of Zepbound® and Wegovy®
  - Can use to bridge lower doses of Zepbound® and Wegovy® if lower doses of those medications are not available
  - Daily injections are more burdensome

Obesity in Pediatrics

- Age 2 and up
  - Dextroamphetamine (2nd to hypothalamic-pituitary dysfunction: from tumors or other organic brain disorders)
  - Setmelanotide (for specific rare obesogenic disorders)
- Age 10 and up
  - Victoza® (aka Saxenda®) (for DMII only)
- Age 12 and up
  - Evekeo®, Qsymia®, Orlistat, Saxenda®, Wegovy®
- Age 17 and up
  - Phentermine, diethylpropion, phendimetrazine, benzphetamine
- Age 18 and up
  - Contrave®, Zepbound®

Insurance Algorithm

TRICARE Treatment Algorithm – Effective 2 Aug 2023

- Age lowered for many medications to 12+
- Requirement to be enrolled in a Service-specific Health/Wellness Program AND adhere to Service policy, AND remain engaged throughout course of therapy was dropped
- Contrave®
  - Requirement to trial or have contraindication for benzphetamine, diethylpropion, AND phendimetrazine was dropped
- Saxenda® and Wegovy®
  - Requirement to trial on Xenical® was dropped
  - For those <18yo: only required trial of Qsymia®

TRICARE Treatment Algorithm – NEW Effective 28 Aug 2024

- PA removed for phentermine, benzphetamine, diethylpropion, phendimetrazine, and Lomaira®; added for Xenical®
- Contrave®, Qsymia®, Wegovy®, Zepbound®
  - Now only require a trial of phentermine, benzphetamine, diethylpropion, OR phendimetrazine
- Qsymia®
  - Now contraindication to phentermine counts for Qsymia®
- Wegovy®, Zepbound®
  - Trial of dulaglutide in those with diabetes has been removed
- Saxenda® and Xenical®
  - Now require trials of all of the above
- PAs now expire annually rather than at 4-6 months

Phentermine Prior Auth Requirements

- **No prior auth requirement anymore!**
- Prescribing guidelines
  - Age >= 17
  - BMI
    - BMI >30
    - BMI >27 AND (DM2, IGT, dyslipidemia, HTN, or OSA)
  - Trial of lifestyle modification
  - Contraindications
    - Pregnancy, CAD, arrhythmia, heart failure, stroke, uncontrolled hypertension, hyperthyroidism

Wegovy® and Zepbound® Prior Auth Requirements

- Age >= 12 (Wegovy®), >=18 (Zepbound®)
- BMI
  - Children: >= 95%tile BMI
  - Adults
    - BMI >30
    - BMI >27 AND (DM2, IGT, dyslipidemia, HTN, or OSA)
- Phentermine OR similar trial
  - 12 weeks w/ <5% weight loss
  - UNLESS contraindication or adverse reaction to phentermine
- Trial of lifestyle modification for at least 6 months
- Non-pregnant
- Must not use with another GLP1 agonist
- No fhx or phx of medullary thyroid cancer or MEN2
- Renewal after 12 months: >=4% loss (peds), >=5% (adults)

Qsymia® Prior Auth Requirements

- Age >= 12
- BMI
  - Children: >= 95%tile BMI, agreement to monitor weight
  - Adults
    - BMI >30
    - BMI >27 AND (DM2, IGT, dyslipidemia, HTN, or OSA)
- Phentermine, benzphetamine, diethylpropion, OR phendimetrazine trial: 12 weeks w/ <5% weight loss
- Contraindication or adverse reaction to phentermine
- Trial of lifestyle modification for at least 6 months
- Non-pregnant
- Agreement with REMS program
- Renewal 12 months: 3-5% weight loss depending on dose

Contrave® Prior Auth Requirements

- Age >= 18
- BMI
  - BMI >30
  - BMI >27 AND (DM2, IGT, dyslipidemia, HTN, or OSA)
- Phentermine OR similar trial
  - 12 weeks w/ <5% weight loss
  - UNLESS contraindication or adverse reaction to phentermine
- No concurrent opioid therapy, seizure d/o, or uncontrolled HTN
- No concurrent MAOi or other bupropion/naltrexone formulation
- Trial of lifestyle modification for at least 6 months
- Non-pregnant
- Renewal after 12 months: >=5% weight loss

Saxenda® Prior Auth Requirements

- Age >= 12
- BMI
  - Children: >= 95%tile BMI
  - Adults
    - BMI >30
    - BMI >27 AND (DM2, IGT, dyslipidemia, HTN, or OSA)
- Ineffective trial (<5% weight loss) or contraindication (including poor tolerance) to
  - Phentermine OR similar (12 week trial)
  - Qsymia® (only this one for peds; 14 week trial)
    - A trial of phentermine combined with topiramate will likely be accepted
  - Contrave® (15 week trial)
  - Wegovy® AND Zepbound® (No Zepbound® for peds) (length??)
- Trial of lifestyle modification for at least 6 months
- Non-pregnant
- Must not use with another GLP1 agonist
- No fhx or phx of medullary thyroid cancer or MEN2
- Renewal after 12 months: >=4% loss (peds), >=5% (adults)

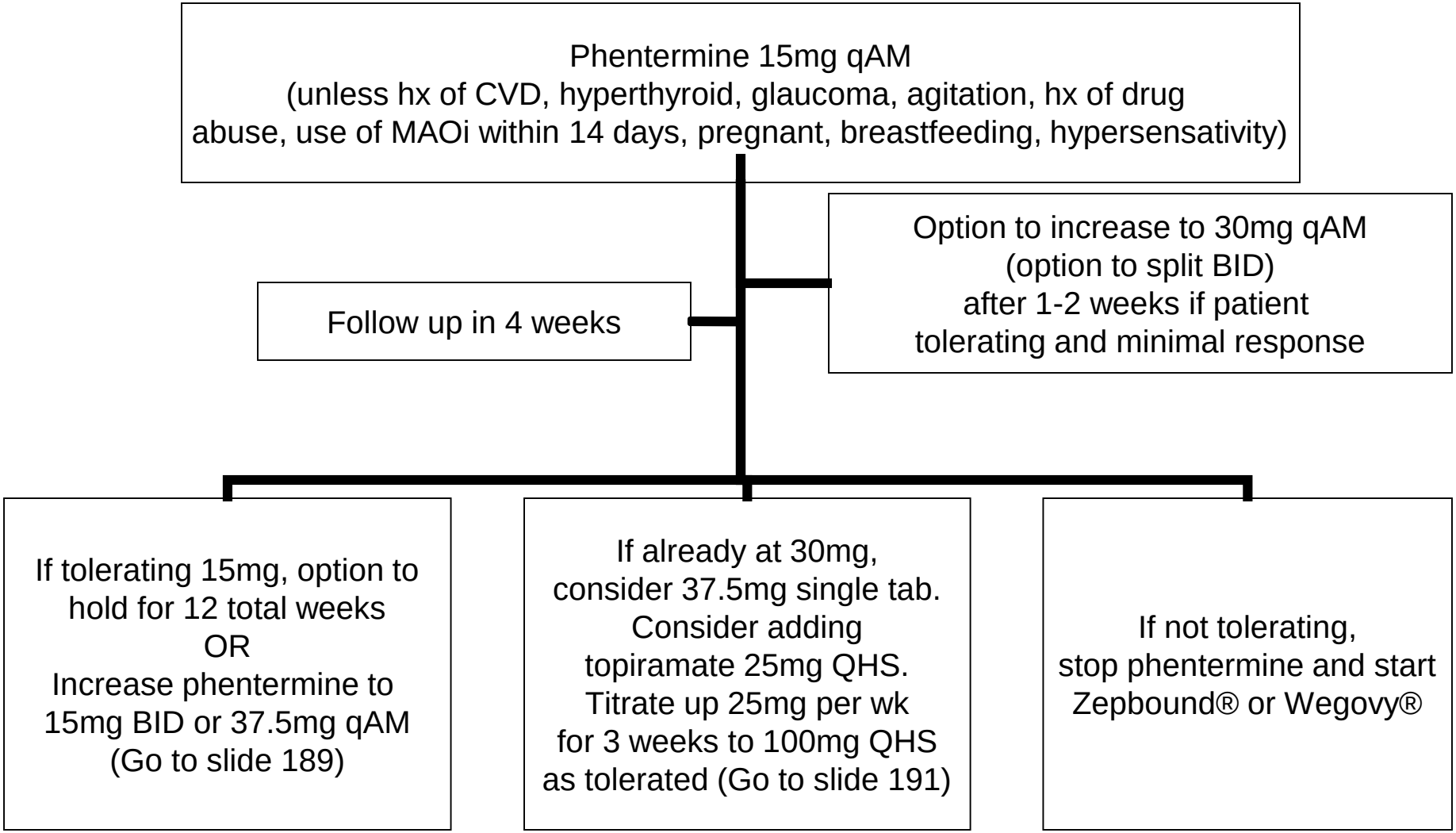
Xenical® Prior Auth Requirements

- Age >= 12
- BMI
  - Children: >= 95%tile BMI
  - Adults
    - BMI >30
    - BMI >27 AND (DM2, IGT, dyslipidemia, HTN, or OSA)
- Ineffective trial (<5% weight loss) or contraindication (including poor tolerance) to
  - Phentermine OR similar (12 week trial)
  - Qsymia® (only this one for peds; 14 week trial)
    - A trial of phentermine combined with topiramate will likely be accepted
  - Contrave® (15 week trial)
  - Wegovy® AND Zepbound® (No Zepbound® for peds) (length??)
- Trial of lifestyle modification for at least 6 months
- **Patient does not have chronic malabsorption syndrome or cholestasis**
- Non-pregnant
- Renewal after 12 months: BMI > 85%tile (peds), >=5% (adults)

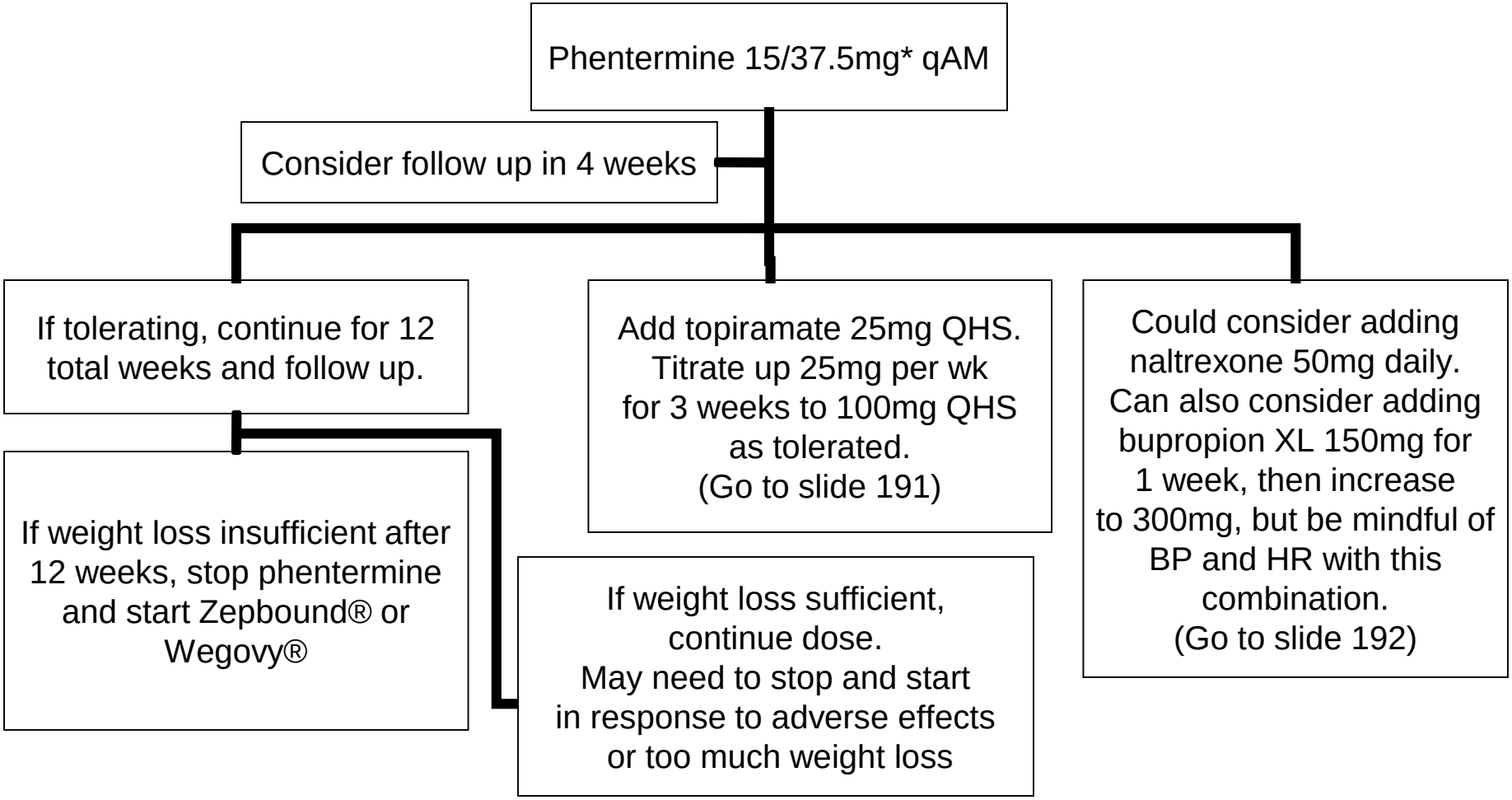
GLP1 agonist Prior Auth Requirements in Patients with DM2

- Trulicity®
  - Requires trial of metformin
- Ozempic® and Mounjaro®
  - Requires trial of metformin
    - However if obese, you can avoid this
- Victoza®, Byetta®, Bydureon® and (Adlyxin® discontinued in 2023)
  - Requires trial of metformin, Trulicity®, AND Ozempic®
- Rybelsus®
  - Trial of metformin
  - Not pregnant
  - No hx of pancreatitis
  - No personal of family hx of medullary thyroid carcinoma or MEN2
  - Acknowledge that Rybelsus® has not shown to reduce major CVEs in adults with DM2 and CVD
  - Acknowledge that patient can take on empty stomach with 4oz of water at least 30 minutes prior to first meal of the day

Medication Algorithm: Phentermine

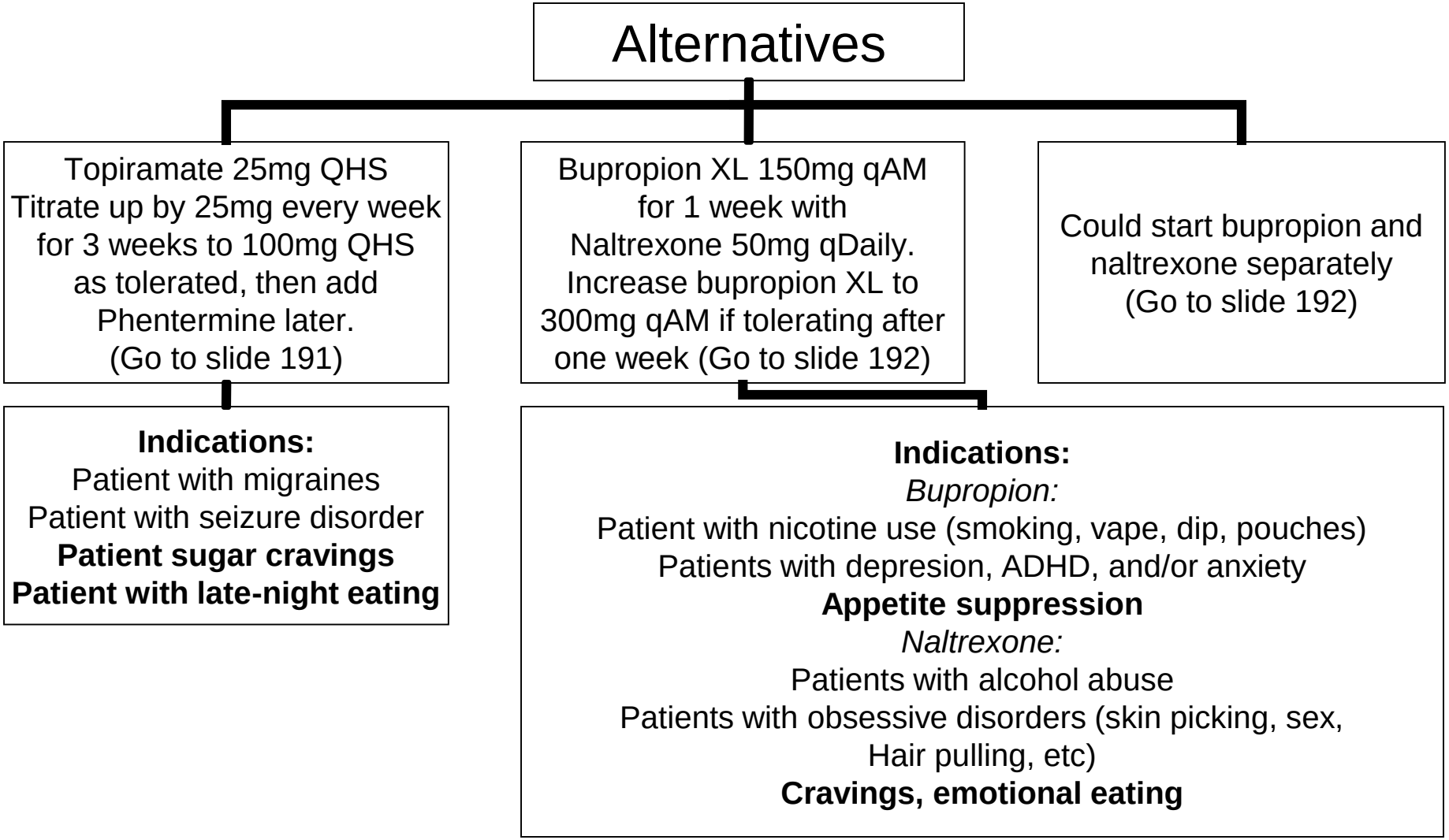


Medication Algorithm: Phentermine

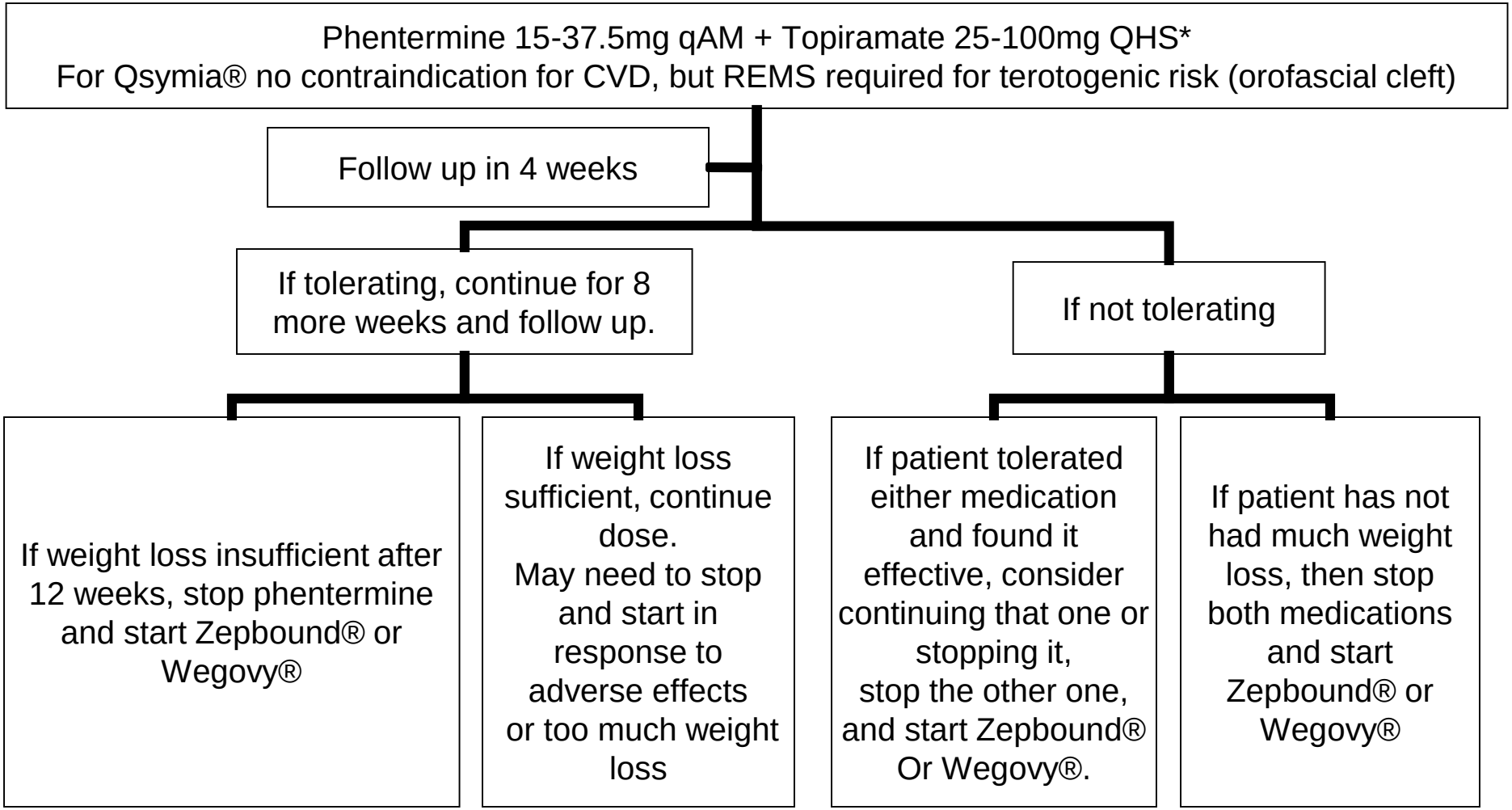


*Patient may be on phentermine 15, 30, or 37.5mg. Whichever lowest dose is most effective and tolerated

Medication Algorithm: Alternative to Starting with Phentermine



Medication Algorithm: Phentermine/Topiramate



*Patient should be on whichever doses are the lowest most effective and well tolerated doses.

Medication Algorithm: Bupropion/Naltrexone

Bupropion 150-450mg qAM + Naltrexone 25-50mg qDaily*
(Bupropion contraindications: uncontrolled HTN, hx of seizure disorder, hx of anorexia/bulemia, abrupt cessation of alcohol, benzodiazepines, or barbiturates, use within 14 days of MAOi, hypersensativity)
(Naltrexone contraindications: chronic opioid use, hypersensativity)
(Contrave® contraindications: pregnant, if they are already on bupropion or naltrexone)

Follow up in 4 weeks

If tolerating, continue for 15 total weeks on both meds but can change dosing in the mean time. .

If weight loss insufficient after 15 weeks, switch to or add Zepbound® or Wegovy®

If weight loss sufficient, continue dose.
May need to stop and start in response to adverse effects/ too much loss

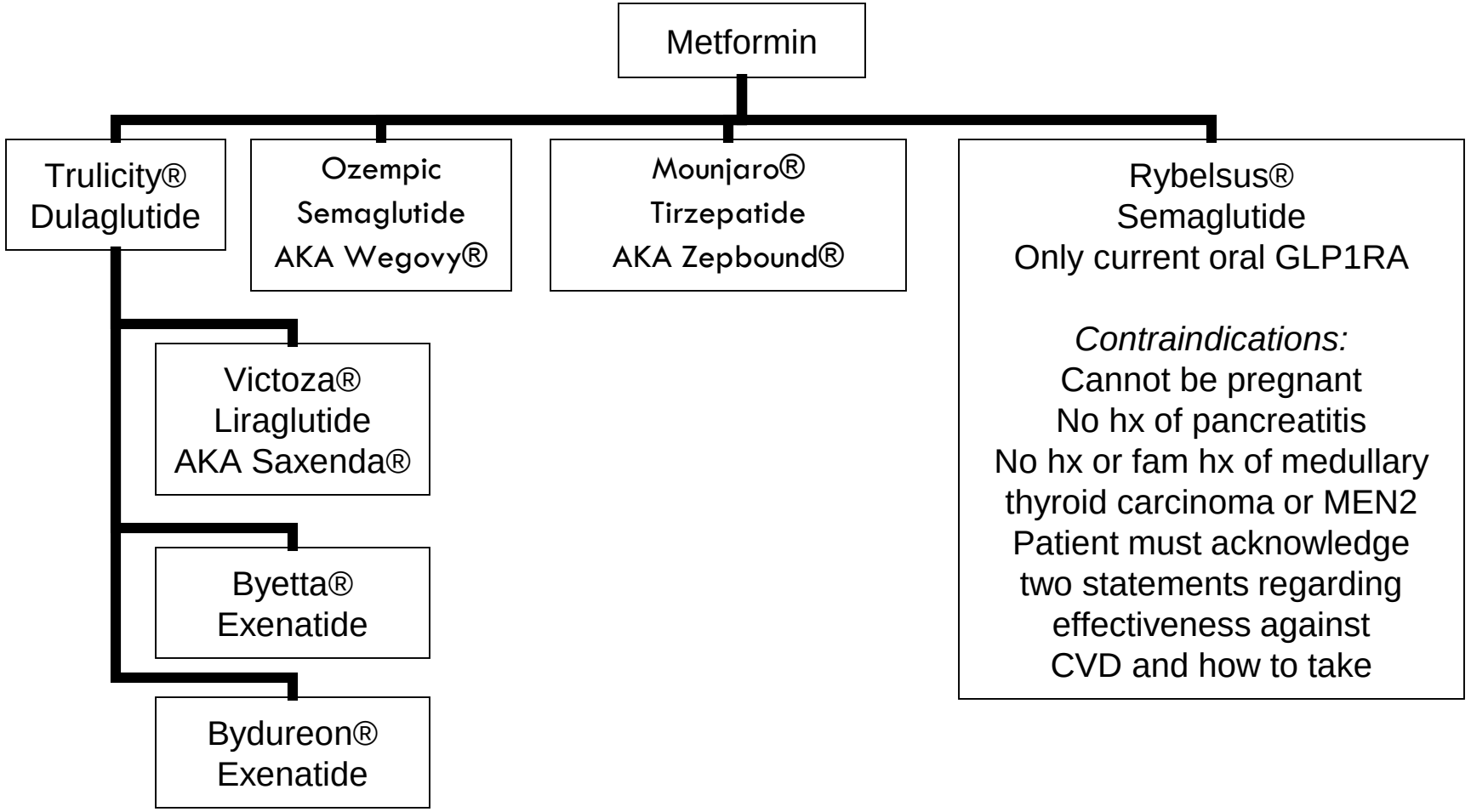
If not tolerating

If patient tolerated either medication and found it effective Consider continuing that one or stopping it, stop the other one, and start Zepbound® or Wegovy®

If patient has not had much weight loss, then stop both medications and start Zepbound® or Wegovy®.

*Patient should be on whichever doses are the lowest most effective and well tolerated doses.

Medication Algorithm for DM2: GLP-1RAs



Active Duty Policies

- Navy
  - Authorized use following TRICARE formulary
  - No prescriptions from civilian/non-federal providers
  - Policy under review
- Air Force
  - Routine use not authorized
  - Short-term use (3-6 months) authorized, BMI >=30 or BMI >=27 with 1 co-morbidity
- Army
  - Discourages weight loss dietary supplements
  - No mention of FDA approved weight loss medications
  - Policy under review

Obesity Treatment Procedures

Obesity Treatment Procedures

- Candidates
  - BMI >=40
  - BMI >=35 and >=1 co-morbid metabolic symptom
  - Lifestyle and medication trials first
- Types
  - Restrictive
    - Bariatric (surgical)
      - Gastric band, sleeve gastrectomy, sleeve gastroplasty
    - Endoscopic sleeve/balloon (GI procedure)
      - Less invasive and slows emptying vs increasing it
      - Sleeve vs GLP1: equally effective, cheaper, not covered by insurance, one time procedure
  - Hybrid
    - Restrictive, malabsorption, and hormonal
    - Bariatric (surgical)
      - Roux-en-Y, biliopancreatic switch, single anastomosis duodenal switch
    - Gastric ablation (GI procedure)
      - Less invasive
      - Reduces ghrelin: decreases appetite
      - Shrinks stomach
      - Average weight loss (8%) with wide variation; longer-term studies expected to be more

Obesity Treatment Procedures

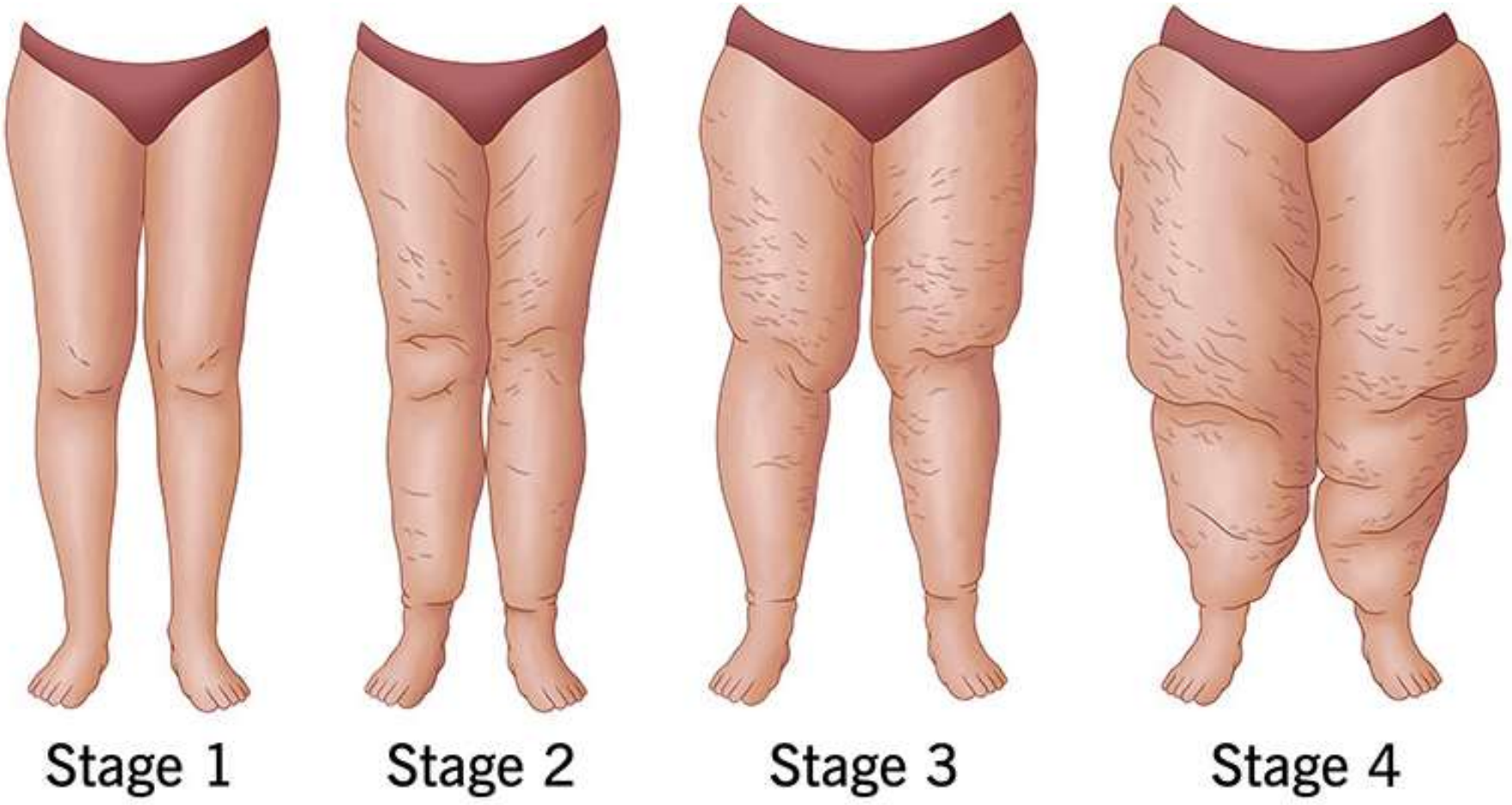
- **25-35% of pts regain >= 15% weight with 2-5 years**
  - Need for medication treatment to maintain weight lost
- Supplementation post-surgery
  - Restrictive: MTV with 2/3 of vitamins at 100% RDA
  - Hybrid: MTV with 2/3 of vitamins at 200% RDA
- Deficiencies
  - Thiamine, B12, folic acid, ADEK vitamins
  - Iron, zinc, copper, calcium
- Medications
  - pH changes differ by procedure and can affect absorption of medications
  - P450 system can be affected
  - <=2 months post-surgery medications should be chewable/crushed/liquid/open capsules

Lipedema

Lipedema

- Fat storage condition
  - Begins around puberty, pregnancy, menopause
- Affects ~11% of female population
  - Staged 1 to 4 from mild to advanced
- Autosomal dominant condition
  - Almost never expressed in males
- Symptoms
  - Column-like appearance from the groin to the ankle
  - Typically involves buttocks, legs, and sometimes arms
  - Tenderness to pressure in 90% of patients
  - Easy bruising, swelling
  - Connection with Ehlers Danlos Syndrome
  - Leaky gut syndrome

Lipedema



Lipedema

- Metabolically active fat that does not provide body with fuel
- Mostly unresponsive to diet, exercise, and medications
- Lower relative risk of metabolic disorders
- Possible pathophysiology (etiology is unknown)
  - Fat stem cells move through leaky lymphatic system
    - Differs from subcutaneous fat; whiter vs yellower color, etc
  - These cells divide and die
  - Chronic inflammation ensues to clean out dead cells
  - Fibrosis ensues and can involve the lymphatic system
    - Can lead to lipo-lyphedema

Lipedema Differential

	Lipedema	Lipo-lyphmadema	Lyphmadema	Obesity	Vascular insufficiency
Fat location	Legs, arms	Widespread	In one limb	Widespread	Near ankles
Sex	F	F	F/M	F/M	F/M
Onset	Hormonal shift	Hormonal shift	After surgery	Any age	Around obesity
Effect of diet	Restriction ineffective	Restriction ineffective	Restriction ineffective	Restriction effective	Restriction effective
Edema	Non-pitting	Much	Pitting	None	With/without
Stemmer's sign	No	Yes	Yes	No	Yes/No
Pain	Yes	Yes	No	No	Yes
Population	~11%	~3%	Rare	>=40%	>=30%
Cellulitis	No	Likely	Yes		Yes/No
Fam Hx	Yes	Yes	No	Yes	Yes

Lipedema

- Treatments
  - Foods to avoid
    - Gluten, grains, alcohol, sugar, dairy
  - Compression garments
  - Lymphatic therapy (ie massage)
    - Manual lymphatic drainage (MLD)
  - Pharmacologic
    - GLP1 agonist anecdotally may help with weight loss and particularly pain and swelling
  - Surgery
    - Similar to liposuction but specialized for lipedema

MASLD

MASLD and MASH

- MASLD is the leading cause of liver disease in North America and trending towards the leading cause of liver transplantation
  - Projected to be the leading cause worldwide surpassing viral hepatitis
  - World prevalene (~33%)
  - Those with DMII and obesity prevalence is ~66%
- Lipotoxic lipids drive hepatocyte injury, inflammation and stellate cell activation leading to fibrosis and hepatocellular cancer
- Intrahepatic hypothyroidism is associated with MASLD/MASH
- Resmetirom (Rezdiffra®) (2024): thyroid hormone receptor-β agonist
  - Significant improvement/resolution of MASH
- Now there is evidence of resolution with semaglutide (63% vs 34%)
- Bariatric surgery also with around 60% resolution

Jayakumar S. Liver transplantation for non-alhoholic fatty liver disease-a review. AME Medical Journal. 3:2. 2018.
Karim G et al. Resmetirom: An Orally Administered, Smallmolecule, Liver-directed, β-selective THR Agonist for the Treatment of Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatits.

Podcast

- This Is Your Brain On Drugs Psychiatry Podcast
  - Apple Podcasts
  - Spotify
  - Amazon Music
  - Should be on almost all others
- Website: www.punkrockpsychiatrist.com
- Facebook: Punk Rock Psychiatrist
- YouTube: @punkrockpsychiatrist
- Instagram: @punkrockpsychiatrist

Questions?