



Obesity Treatment **Much More Than Pharmacotherapy**

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Disclosures

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Objectives



01

Pathophysiology

Understanding the genetic, epigenetic, and environmental factors, as well as the pathophysiology of the condition

02

Gathering a History

Using history taking to assess contributing environmental and social factors

03

Individualizing Treatment

Consider individual risk factors, comorbidities, and health disparities

04

Intensive Lifestyle Intervention

Implementing behavioral counseling strategies

05

Dietary Counseling

Providing dietary counseling to support nutritional interventions.

06

Pharmacologic Treatment

Using clinical trials and guidelines to make decisions

Pathophysiology

Understanding the genetic, epigenetic, and environmental factors, as well as the pathophysiology of the condition

Epigenetics and Genetics

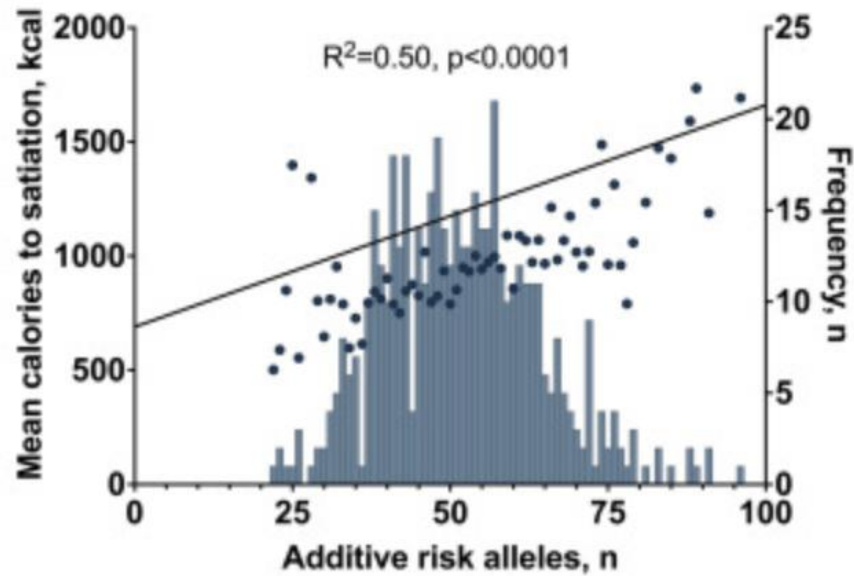
- Epigenetic Contributions: Overnutrition, saturated fat, physical inactivity, stress, sleep deprivation, gut microbiome, and early life nutrition can all affect whether genes are expressed or not. There is a 5-40% discordance rate of obesity in monozygotic twins (decreases as BMI increases)
- Polygenetic obesity: A conglomeration of various inherited genes that collectively amass to contribute to obesity risk. It is considered the largest risk factor for obesity. If a sibling has obesity up to a 50% risk the individual of interest will also have obesity. If both parents have obesity, 80% chance of adulthood obesity.
- Polymorphisms (e.g. PPARG, FABP4, LPL)
- Monogenetic obesity: either recessive or dominant inheritance of a single gene contributing to early and lifelong obesity risk.

Gene or disorder	Estimated prevalence in the United States ^{a,b}
POMC deficiency obesity ³	~100 to 500 individuals
LEPR deficiency obesity ³	~500 to 2,000 individuals
Bardet-Biedl syndrome ³	~1,500 to 2,500 individuals
Alström syndrome ³	~500 to 1,000 individuals ^c
POMC or LEPR heterozygous deficiency obesity ³	>20,000 individuals
SRC1 deficiency obesity ³	>23,000 individuals
SH2B1 deficiency obesity ³	>24,000 individuals
MC4R deficiency obesity ³	~10,000 individuals ^d
Smith-Magenis syndrome ³	~2,400 individuals
Prader-Willi syndrome ⁴	>7,000 individuals

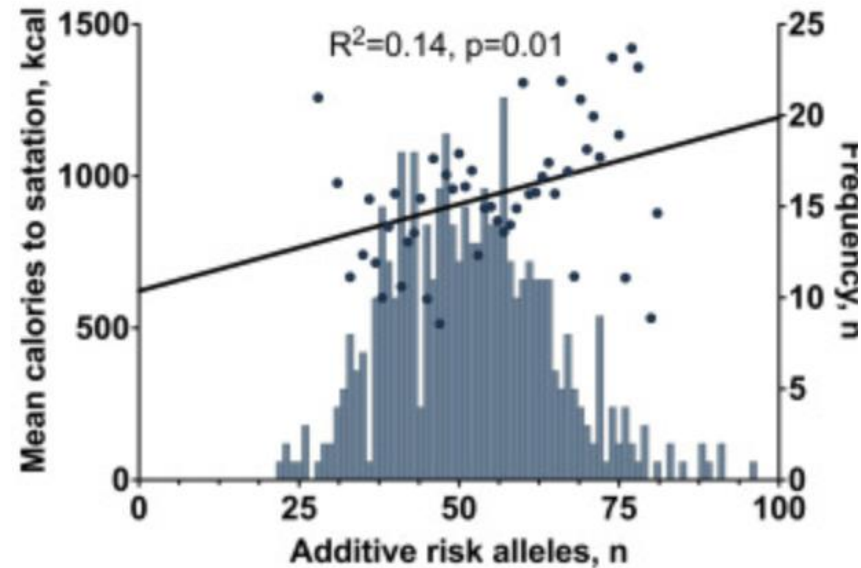
^aNumbers reflect individuals appearing in detailed case histories from published literature or conference proceedings and do not include those appearing in reports such as genomic analyses or population screening studies. Analysis performed in June 2019.³ ^bA list of LOF variants in *LEPR*, *POMC*, and *PCSK1* was compiled from published literature and supplemented with computationally predicted deleterious missense variants. The frequency of carriers, homozygotes, and compound heterozygotes for each gene was calculated using data from gnomAD sequencing data and the number of individuals with LOF variants of interest was estimated using Hardy-Weinberg proportions. Prevalence was estimated using a US population size of 300 million.² ^cEstimated prevalence worldwide. ^dEstimated prevalence with addressable variants of *MC4R*.

1. Heymsfield et al. *Obesity (Silver Spring)*. 2014;22(suppl 1):S1-S17. 2. Ayers et al. *J Clin Endocrinol Metab*. 2018;103:2601-2612. 3. Data on file, Rhythm Pharmaceuticals. 4. Prader-Willi Syndrome Association (USA). <https://www.pwsausa.org/pws-statistics/>. Accessed March 30, 2020.

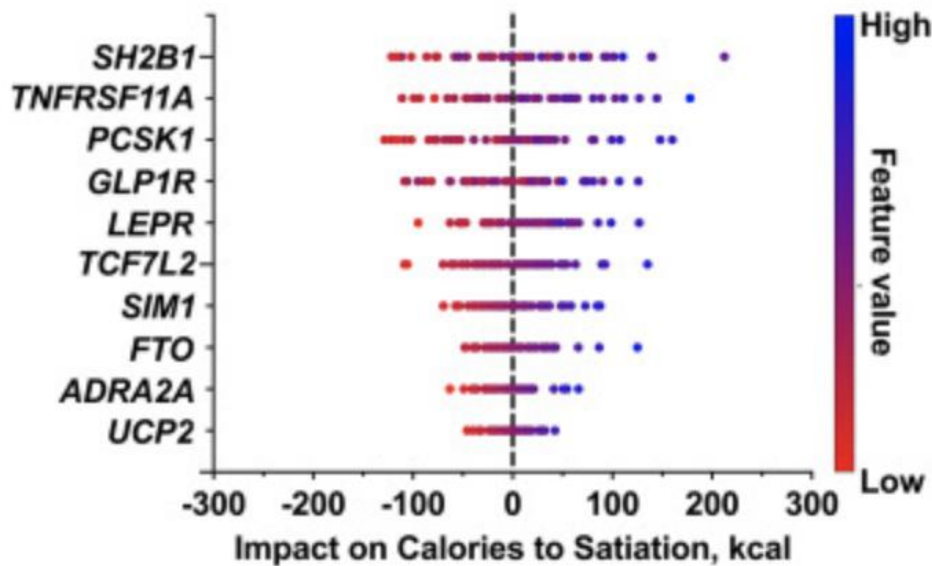
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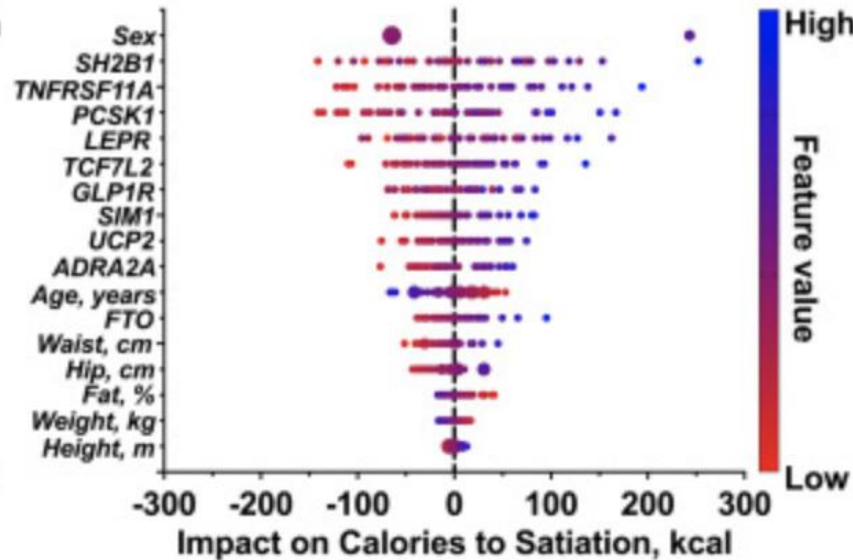
B



C



D



•**SH2B1** → leptin & insulin signaling

•**LEPR** → leptin receptor

•**PCSK1** → prohormone
• processing (GLP-1, PYY, insulin)

•**GLP1R** → GLP-1 receptor (very clinically relevant)

•**TCF7L2** → metabolic signaling / diabetes risk

•**SIM1** → hypothalamic satiety neurons

•**FTO** → energy intake regulation

•**UCP2 / ADRA2A** → energy efficiency / sympathetic tone

~500 CTS/meal

Figure 3 Genetic influence on CTS across risk alleles and key variants

Rare Genetic Disorders Present With a Variety of Clinical Characteristics

Disorder	Early-onset obesity	Hyperphagia (insatiable hunger)	Growth	Endocrine abnormalities	Other
LEP deficiency ^{1,2}	✓	✓	Normal linear growth with reduced adult height	Hypogonadotropic hypogonadism, hypothyroidism	Alterations to immune function Responsive to leptin therapy
LEPR deficiency ^{1,2}	✓	✓	Normal linear growth with reduced adult height	Hypogonadotropic hypogonadism, hypothyroidism	Alterations to immune function Not responsive to leptin therapy
POMC deficiency ³⁻⁵	✓	✓	Accelerated childhood growth ⁶	Adrenocorticotrophic hormone deficiency, mild hypothyroidism	Red hair, light skin
PCSK1 deficiency ^{4,7,8}	✓	✓ ^{9,a}	Failure to thrive in early infancy	Hypoglycemia, hypothyroidism, adrenocorticotrophic hormone deficiency	Intestinal malabsorption, diarrhea
MC4R deficiency ^{1,4,10,b}	✓	✓	Increased lean body mass, accelerated linear growth	Hyperinsulinemia	May have lower blood pressure
Alström syndrome ^{11,12}	✓	✓	Short stature	Type 2 diabetes mellitus, insulin resistance, hypogonadism, hyperandrogenism in females, hypothyroidism	Visual impairment, hearing loss, cardiomyopathy, hepatic dysfunction, renal failure

^aPrevalence based on an analysis of published case studies (n=43 individuals). Prevalence calculated by number of cases with the characteristic divided by total number of cases. It is accepted in the literature that excess hunger is a characteristic of individuals with PCSK1 deficiency; however, patient hunger level, excess hunger, and hyperphagia were not mentioned as patient characteristics in 79% of cases. ^bSeverity of phenotype has been shown to correlate with the in vitro function of MC4R variants.⁹
^{1.} Farooqi and O'Rahilly. *J Endocrinol.* 2014;223:T63-T70. ^{2.} Huvenne et al. *Obes Facts* 2016;9:158-173. ^{3.} Coll et al. *J Clin Endocrinol Metab.* 2004;89:2557-2562. ^{4.} Styne et al. *J Clin Endocrinol Metab.* 2017;102:709-757.
^{5.} Mendiratta et al. *Int J Pediatr Endocrinol.* 2011;2011:5. ^{6.} Data on file, Rhythm Pharmaceuticals, Inc. ^{7.} Stijnen et al. *Endocr Rev.* 2016;37:347-371. ^{8.} Martin et al. *Gastroenterology.* 2013;145:138-148. ^{9.} Argente et al. Poster presented at: 21st European Congress of Endocrinology; May 18-21, 2019; Lyon, France. ^{10.} Farooqi et al. *N Engl J Med.* 2003;348:1085-1095. ^{11.} Marshall et al. *Eur J Hum Genet.* 2007;15:1193-1202. ^{12.} Han et al. *J Clin Endocrinol Metab.* 2018;103:2707-2719.

Rare Genetic Disorders Present With a Variety of Clinical Characteristics

Disorder	Early-onset obesity	Hyperphagia (insatiable hunger)	Growth	Endocrine abnormalities	Other
Bardet-Biedl syndrome ¹	✓	✓	Wide range in height; does not differ significantly from population mean ²	Hypogonadism	Visual impairment, cognitive disabilities, polydactyly, renal dysfunction
Smith-Magenis syndrome ^{3,4}	✓ Often by adolescence	✓ Often by adolescence	Short stature	Disrupted melatonin signaling	Self-injurious behaviors, sleep disturbances, craniofacial abnormalities, intellectual disability
SRC1 deficiency ⁵	✓	Under investigation ⁶	n/a	Impaired leptin-induced <i>POMC</i> expression	n/a
SH2B1 deficiency ^{7,8}	✓	✓	Reduced adult height	Hyperinsulinemia	Delayed speech and language development, aggressive behavior
Prader-Willi syndrome ^{1,9}	✓ Often by school age	✓ Neonatal period: decreased sucking, failure to thrive; age 4-8 y: excess hunger with major food impulsiveness	Short stature	Growth hormone deficiency, hypogonadism	Severe neonatal hypotonia, body composition abnormalities, intellectual deficiency, behavioral difficulties, dysmorphia
16p11.2 microdeletion syndrome ^{1,10}	✓ Often by adolescence	✓	Slightly below average or average height	n/a	Developmental delay, intellectual disability, autism spectrum disorders, impaired communication and socialization skills
Sim1 deficiency ^{1,11}	✓	✓	Short stature	Hypopituitarism	Developmental delay, neonatal hypotonia, facial dysmorphisms

1. Huvenne et al. *Obes Facts*. 2016;9:158-173. 2. Beales et al. *J Med Genet*. 1999;36:437-446. 3. Truong et al. *BMC Med Genet*. 2010;11:142. 4. Alaimo et al. *Res Dev Disabil*. 2015;47:27-38. 5. Yang et al. *Nature Commun*. 2019;10:1718. 6. Lu et al. *J Mol Endocrinol*. 2019;62:37-46. 7. Doche et al. *J Clin Invest*. 2012;122:4732-4736. 8. Bochukova et al. *Nature*. 2010;463:666-670. 9. Cassidy and Driscoll. *Eur J Hum Genet*. 2009;17:3-13. 10. Miller et al. *GeneReviews*®. 2015. 11. Bonnefond et al. *J Clin Invest*. 2013;123:3037-3041.

Beyond Genetics

Physiology of Glucose & Insulin & Adipose Tissue

- Adipose cells increase in size (hypertrophy) to a point, then this triggers a stress pathway that activates macrophages (M1) and inflammatory cytokines → inflammation + mechanical stress and adipokine imbalance signal adipocyte progenitor cells to divide and create new adipose cells (hyperplasia). For the most part, once an adipocyte is created, it does not go away.
- Excess calories + excess FAs + insulin → insulin resistance with impaired mitochondrial oxidation → accumulation of intramyocellular lipids (DAG, ceramides) → DAGs activate serine kinases that cause inhibitory serine phosphorylation of IRS-1, impairing insulin signaling downstream of the insulin receptor.
- 50% of post-prandial portal insulin is immediately cleared by liver, the remaining insulin acts on insulin receptors to ultimately translocate GLUT4 transporter in various tissues to the cell surface –the predominant one being skeletal muscle
- 70-90% of glucose uptake happens in skeletal muscle, 90% of muscle glucose which is stored as glycogen and 10% is metabolized through glycolysis to pyruvate and ultimately generates ATP via mitochondrial oxidative phosphorylation.
- That means 10-30% of glucose that escaped skeletal muscle uptake remains to contribute to ectopic tissue. In those with T2DM, glucose uptake by be as low as 50% in skeletal muscle.

Pathophysiology

...Continued

- As insulin resistance develops and adipose cells are already jammed packed full, insulin is less able to suppress lipolysis, causing a release of NEFAs, which travel to the liver to stimulate hepatic VLDL production.
- Saturated fats (especially palmitate) and NEFAs induce TLR4-mediated inflammation peripherally and contribute to microglial activation centrally, which disrupts POMC neurons. The ceramides cause ER stress and inflammation and POMC damage via other pathways.

Metabolic Compensation

- Biggest Loser Study
- Adaptive Thermogenesis and Improved skeletal muscle efficiency (Low leptin → SNS downregulation, UCP1 downregulation, fT3 and rT3 affect mitochondrial biogenesis and oxidative phosphorylation)
- Hormonal changes (decreased insulin (central vs peripheral), increased Ghrelin, decreased GLP1 and PYY, leptin resistance)
- Genetic predisposition (Un-luxurious energy expenditure and variable response to overfeeding or caloric restriction)
- NEAT suppression
- Intestinal nutrient absorption changes

But Don't Take My Word For it...

American Academy of Family Physicians (AAFP) ⁱ

American Academy of Pediatrics (AAP) ⁱⁱ

Academy of Nutrition and Dietetics ⁱⁱⁱ

American Medical Association (AMA) ^{iv} (**since 2013**) American Academy of Orthopaedic Surgeons (AAOS) ^v American Association of Clinical Endocrinology (AACE) ^{vi}

American College of Cardiology (ACC) ^{vii}

American College of Obstetricians and Gynecologists (ACOG) ^{viii}

American Gastroenterological Association (AGA) ^{ix} American Heart Association (AHA) ^x

American Society of Metabolic and Bariatric Surgery (ASMBS) ^{xi} Centers for Disease Control and Prevention (CDC) ^{xii}

Endocrine Society ^{xiii}

Internal Revenue Service (IRS) ^{xiv} National Institutes of Health (NIH) ^{xv} Obesity Action Coalition (OAC) ^{xvi} Obesity Medicine Association (OMA) ⁱ

Strategies to Overcome and Prevent (STOP) Obesity Alliance ^{xvii}

The Obesity Society (TOS) ^{xviii}

World Health Organization (WHO) ^{xix} (**Since 1997**)

World Obesity Federation (WOF) ^{xx}

i. <https://www.aafp.org/about/policies/all/obesity.html>

ii. <https://publications.aap.org/pediatrics/article/151/2/e2022060641/190440/Executive-Summary-Clinical-Practice-Guideline-for>

iii [https://www.jandonline.org/article/S2212-2672\(15\)01636-6/fulltext](https://www.jandonline.org/article/S2212-2672(15)01636-6/fulltext)

iv <https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/about-ama/councils/Council%20Reports/council-on-science-public-health/a13csaph3.pdf>

v. <https://www.aaos.org/contentassets/1cd7f41417ec4dd4b5c4c48532183b96/1184-the-impact-of-obesity-on-bone-and-joint-health1.pdf>

vi <https://www.aace.com/trending-topics/patient-news-global-health/march-4th-world-obesity-day-what-adiposity-based-chronic>

vii <https://www.jacc.org/doi/10.1016/j.jacc.2017.11.011>

viii <https://www.acog.org/-/media/project/acog/acogorg/clinical/files/committee-opinion/articles/2019/01/ethical-considerations-for-the-care-of-patients-with-obesity.pdf>

ix [https://www.cghjournal.org/article/S1542-3565\(16\)30988-0/fulltext](https://www.cghjournal.org/article/S1542-3565(16)30988-0/fulltext)

x <https://www.ahajournals.org/doi/10.1161/CIR.0000000000000973>

xi <https://asmbs.org/patients/disease-of-obesity>

xii <https://www.cdc.gov/obesity/index.html>

xiii <https://academic.oup.com/jcem/article/100/2/342/2813109>

xiv <https://www.irs.gov/pub/irs-drop/rr-02-19.pdf>

xv <https://www.niehs.nih.gov/health/topics/conditions/obesity/index.cfm>

xvi <https://www.obesityaction.org/>

xvii <https://stop.publichealth.gwu.edu/LFD-jul23>

xviii <https://onlinelibrary.wiley.com/doi/10.1002/oby.22378>

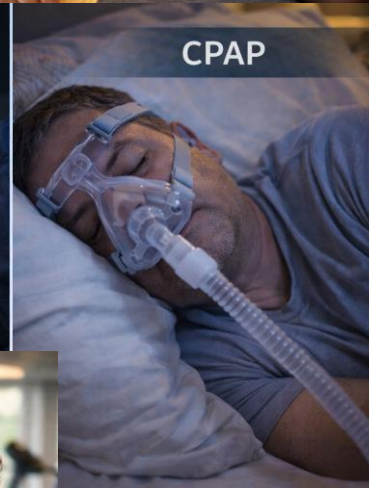
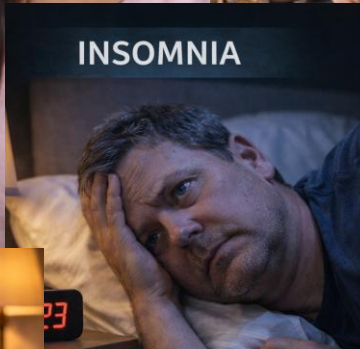
xix https://www.who.int/health-topics/obesity/#tab=tab_1

xx <https://onlinelibrary.wiley.com/doi/10.1111/obr.12551>



Gathering a History

Using history taking to assess contributing environmental and social factors





Individualizing Treatment

Consider individual risk factors, comorbidities,
and health disparities

Disordered Eating

Binge Eating Disorder
Concomitant ADHD
Food Addiction
ARFID
AN/BN



Food Insecurity

UPF
Food Deserts
Cost/Access



Other Causes

Genetic:
BBS
PCSK1
POMC
LEPR Def

Other Health issues:
CHF/CKD
Hypothyroidism



Mental Health

Parental influence
Prior Trauma
Depression
Anxiety



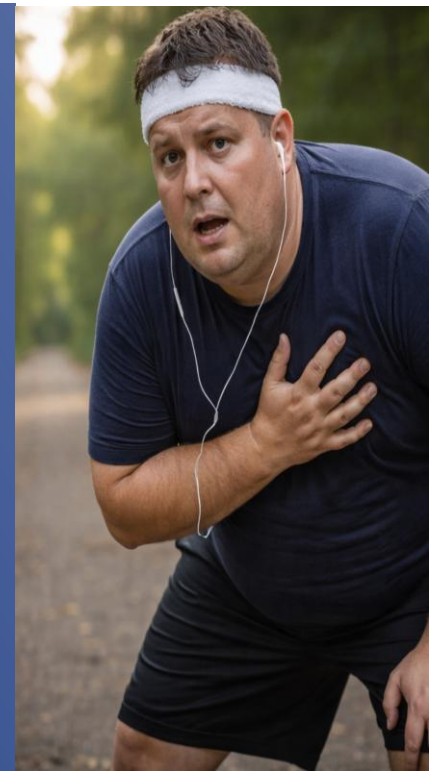
Sleep

Night Eating Syndrome
Sleep apnea
Sleep hygiene



Physical Limitations

Fear
Deconditioning
Arthritis & Pain





Intensive Lifestyle Intervention & Behavioral Therapies

Implementing behavioral counseling strategies

Mindfulness

- Physical hunger vs Head hunger
- Frequent check-ins
- Post-eating evaluation

Eating Slowly

- Non-dominant hand
- Focusing on conversation
- Counting chews
- Sips of water
- Setting a timer
- Slowest eater

Emotional Regulation

- Relaxation techniques
- Redirecting focus
- Identifying emotions
- Reduce emotional vulnerability
- Letting go
- Opposite Action

Stress Management

- Diaphragmatic breathing
- Breath focus
- Progressive muscle relaxation
- Journaling/Mantra
- Exercise

Social Support

- Practical support
- Emotional support
- Appraisal support
- Companion support
- Spiritual support

Habit Formation/Goal

Setting

- Smaller starting goal
- Habit stacking
- Re-evaluating goals
- Picking start date & time

Stimulus Control

- Environmental control
- Stimulus discovery
- Anticipating triggers

Problem Solving

- List solutions
- Pros and cons of each
- Rank & Re-evaluate

Self-Monitoring

- CICO
- Journaling
- BIA, waist measurements

Medication

Compliance

- Evaluating % compliance
- Evaluating barriers
- Identifying solutions

Motivation

- Setting expectations
- Motivational Interviewing
- Identifying non-scale victories

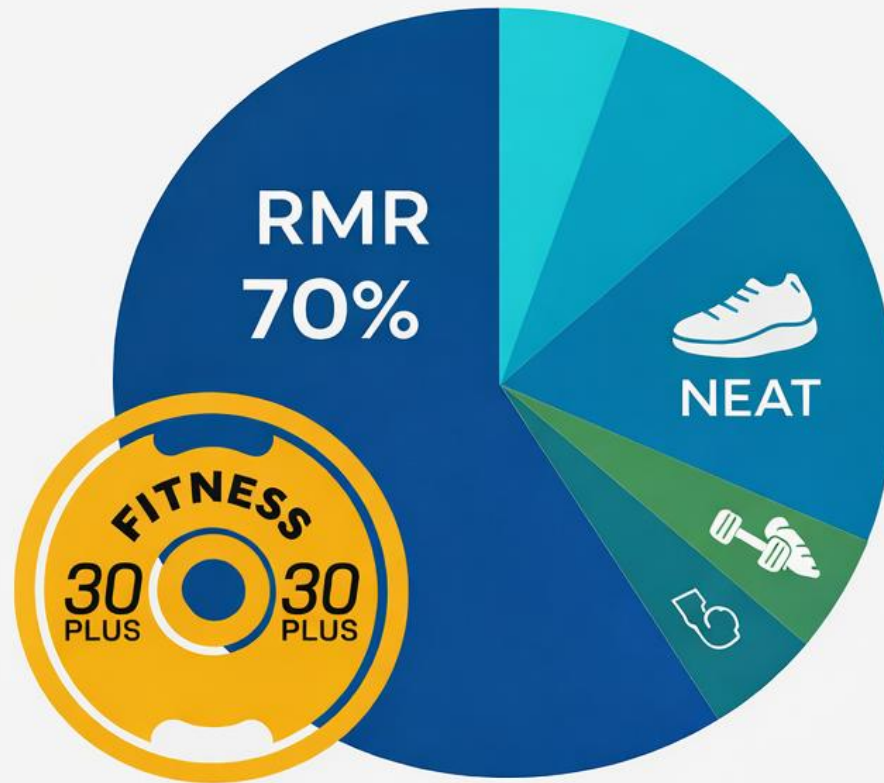
Sleep Hygiene

- 8 hours is goal
- Limiting ETOH/carbs
- Room temp/noise/light
- Routine
- Bedmates
- Journaling



TDEE

Total Daily Energy Expenditure is the total number of calories your body burns in a day, including rest, daily activity, exercise, and digestion.



70%

RMR 70%

Basal Metabolic Rate is the number of calories your body needs to perform basic functions like breathing, circulation, and cell production while at rest.



NEAT

NEAT is the energy burned from everyday movements like walking, cleaning, and fidgeting—outside of formal exercise.

10%

TEF 10%

Thermic Effect of Food) is the energy your body uses to digest, absorb, and process the food you eat.



Exercise

Exercise Activity Thermogenesis is the calories burned during intentional physical activity like workouts or sports.



EPOC < 5%

Dietary Counseling

Providing dietary counseling to support nutritional interventions

Atkins	5.46	5.14	3.30	-2.75	3.41	0.64
Zone	4.07	3.46	2.33	-2.89	-0.33	0.27
DASH	3.63	4.68	2.84	3.93	-1.90	NA
Mediterranean	2.87	2.94	1.03	4.59	-0.61	0.25
Paleolithic	5.31	14.56	3.85	7.27	-2.52	0.52
Low fat	4.87	3.95	2.22	1.92	-2.13	0.33
Jenny Craig	7.77	7.86	7.81	0.21	-2.85	0.19
Volumetrics	5.95	2.93	1.95	7.13	-0.13	NA
Weight Watchers	3.90	2.80	1.03	7.13	-0.88	0.87
Rosemary Conley	3.76	2.39	1.44	7.15	-2.04	NA
Ornish	3.64	0.69	0.20	4.71	-4.87	1.11
Portfolio	3.64	5.97	3.98	21.29	-3.26	-0.37
Biggest Loser	2.88	3.17	2.20	3.90	-0.01	NA
Slimming World	2.15	NA	NA	NA	NA	NA
South Beach	9.86	NA	NA	-0.64	0.36	NA
Dietary advice	0.31	0.58	0.40	-2.01	-1.71	-1.15

■ “Among the most effective” with moderate to high certainty

■ “Inferior to the most effective/superior to the least effective” with moderate to high certainty

■ “Among the least effective” with moderate to high certainty

■ “Maybe among the most effective” with very low to low certainty

■ “Inferior to the most effective/superior to the least effective” with very low to low certainty

“Differences between diets are, however, generally trivial to small, implying that people can choose the diet they prefer from among many of the available diets (fig 6) without concern about the magnitude of benefits.”

- ~50% of American diet is composed of carbohydrate, while 40-65% of Japanese dietary intake is composed of carbohydrate
- Japan has a 4-6% obesity rate
- The USA has an obesity rate of 40%

Main Principle

- It's ultimately about CALORIES
- Diet > Exercise for weight loss
- Mifflin St. Jeor Equation
- Katch-McArdle Equation
- Metabolic compensation



Providing Options

- Intermittent Fasting
- CICO
- Logging vs Mindfulness
- Tracking macronutrients
- Stylized diet (e.g. Mediterranean, keto, Atkins)
- Meal replacements

Support

- Dietitian vs Nutritionist
- IAEDP or other local resources
 - Accountability
- Food insecurity resources
- Tips for when eating out or time constraints

Nutrition

- Fruits and veggies
 - Protein intake
 - Whole grains
 - Snacking
- Caloric Beverages
 - Healthy fats
- Micronutrients
 - Microbiota

Other Dietary Considerations





Pharmacologic Therapy

Using clinical trials and guidelines to make
decisions

Organizations Recommending Rx for Obesity

- American Association of Clinical Endocrinology (AACE)
- Endocrine Society
- American Gastroenterological Association (AGA)
- Obesity Medicine Association (OMA)
- American Diabetes Association (ADA)
- The Obesity Society (TOS)
- American Heart Association (AHA)
- American College of Cardiology (ACA)

American Association of Clinical Endocrinology (AACE)

<https://www.aace.com/disease-state-resources/nutrition-and-obesity/clinical-practice-guidelines-treatment-obesity> Endocrine Society

<https://www.endocrine.org/clinical-practice-guidelines/pharmacological-management-of-obesity> American Gastroenterological Association (AGA)

<https://gastro.org/clinical-guidance/pharmacological-interventions-for-adults-with-obesity/> Obesity Medicine Association (OMA)

<https://obesitymedicine.org/obesity-algorithm/> American Diabetes Association (ADA)

<https://diabetesjournals.org/care/issue> (see "Standards of Care in Diabetes" → Obesity & Weight Management section) The Obesity Society (TOS) *(via joint guideline with AHA/ACC)*

<https://www.ahajournals.org/doi/10.1161/01.cir.0000437739.71477.ee> American Heart Association (AHA) *(joint guideline)*

<https://www.ahajournals.org/doi/10.1161/01.cir.0000437739.71477.ee> American College of Cardiology (ACC) *(joint guideline)*

<https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2014/11/07/15/20/2013-aha-acc-tos-guideline-for-management-of-overweight-and-obesity>

Shared Decision Making



Buy-in

- Does patient agree Rx necessary?
- Life-long treatment
- Expectations



- Side-effects
- Cost
- Prior Rx
- Concomitant diagnoses



Counseling

- Discussing side-effects
- How to mitigate negative effects
- Escalation plan
- How to administer/take Rx

Medication (generic; brand)	FDA Indication(s)	Pivotal Trial(s) (Labeling)	Duration	Mean Weight Change vs Placebo
Semaglutide 2.4 mg weekly; Wegovy	Chronic weight management (overweight/obesity) + MACE reduction + MASH	STEP 1 ("Study 2" in label)	68 weeks	-14.9% vs -2.4% (placebo-adjusted ≈ -12.4%)
Semaglutide 7.2 mg weekly (higher-dose Wegovy)	Chronic weight management only (no current MACE/MASH indication)	STEP-UP	72 weeks	-20.7% total and 18.7% (placebo-adjusted)
Semaglutide oral (up to 25 mg daily)	Chronic weight management + MACE reduction (no current MASH indication)	OASIS-4	64 weeks	-15.1% weight loss (-12.4% placebo-adjusted)
Tirzepatide weekly; Zepbound	Chronic weight management	SURMOUNT-1	72 weeks	-21% total loss at highest dose (-17.8% placebo adjusted)
Tirzepatide weekly; Zepbound	Moderate-severe obstructive sleep apnea	SURMOUNT-OSA	~52 weeks	-18.1-20.0% total loss at highest dose (placebo adjusted -16.8 to 17.7% weight loss)

Medication	FDA indication	Pivotal trial(s) used for FDA approval / labeling	Trial duration	Mean % weight loss
Phentermine / Topiramate ER (Qsymia)	Chronic weight management	Study 1 and Study 2 in FDA label; commonly referred to as EQUIP and CONQUER	56 weeks	Top dose (15/92 mg): -10.9% in Study 1 and -9.8% in Study 2; placebo -1.6% and -1.2%, respectively
Liraglutide 3.0 mg daily (Saxenda)	Chronic weight management	Study 1 in label (adult obesity/overweight with comorbidity; commonly tied to the SCALE obesity/prediabetes program)	56 weeks	-7.4% vs -3.0% placebo
Naltrexone / Bupropion ER (Contrave)	Chronic weight management	COR-I, COR-BMOD, COR-Diabetes in FDA labeling	56 weeks	COR-I: -5.4% vs -1.3%; COR-BMOD: -8.1% vs -4.9%; COR-Diabetes: -3.7% vs -1.7%
Setmelanotide (Imcivree)	Reduce excess body weight and maintain long-term reduction in specific genetic/syndromic obesity and acquired hypothalamic obesity	Trial 1 (acquired hypothalamic obesity), Trial 2 (BBS), Trials 3 & 4 (POMC/PCSK1 and LEPR deficiency)	56-60 weeks for Trial 1; 52 weeks for BBS; 1 year for Trials 3 & 4	Trial 1 HO: placebo-adjusted BMI change -18.4% at 52 weeks; Trial 2 BBS: mean BMI change -7.9% at 52 weeks; Trial 3 POMC/PCSK1: mean weight change -23.1% at 1 year with 80% achieving ≥10% weight loss; Trial 4 LEPR: mean weight change -9.7% at 1 year with 46% achieving ≥10% weight loss

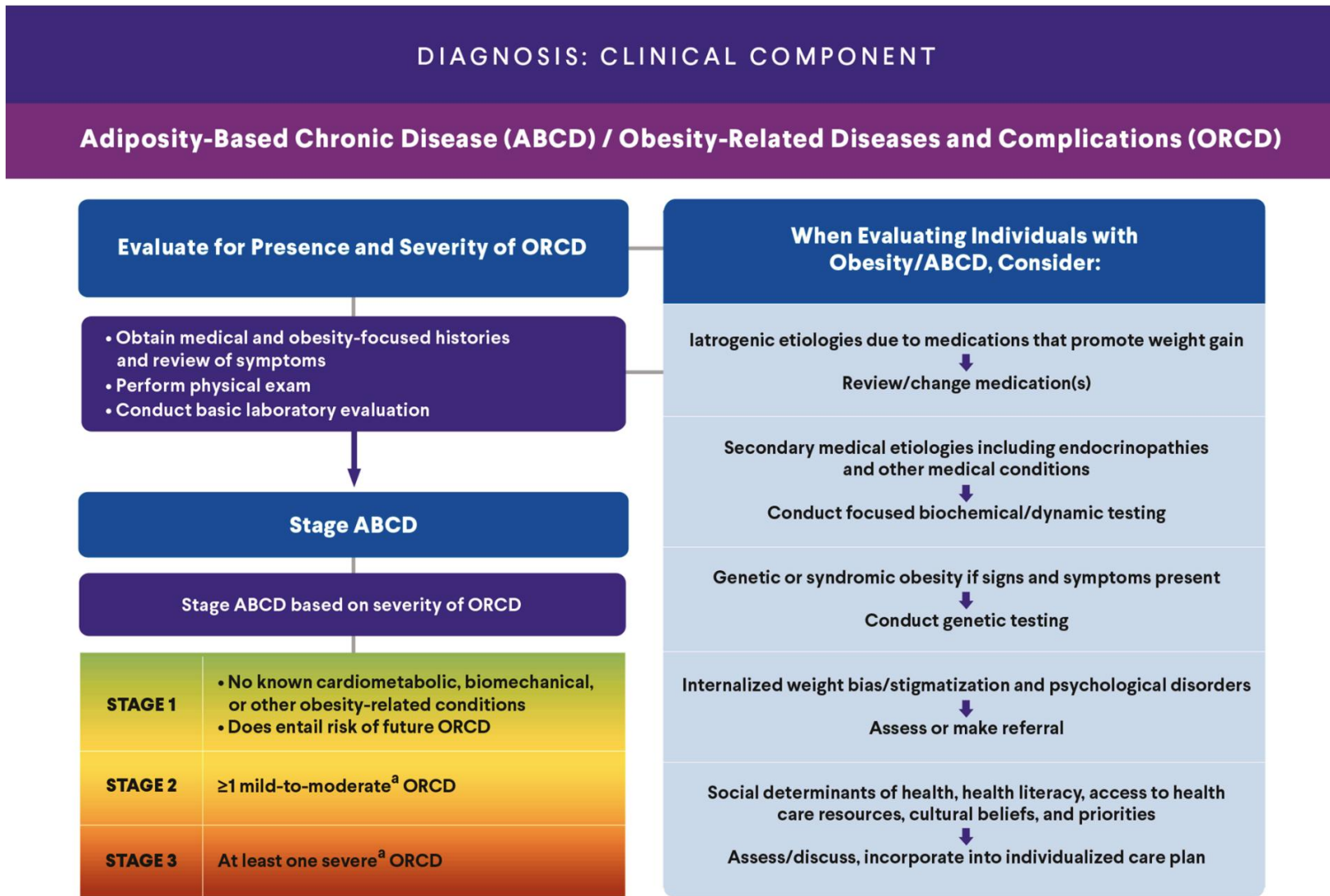
Medication	FDA status	Trial	Population	Duration	Mean % weight loss	Placebo-adjusted
Orforglipron (Foundayo; oral GLP-1)	FDA-approved	ATTTAIN-1 / ATTTAIN-2	Adults with obesity ± T2D	72 weeks	~-11.1% to -12.4% (36 mg) vs ~-2.1% placebo	~-9-10%

Efficacy Estimand Results				
	Orforglipron 6 mg	Orforglipron 12 mg	Orforglipron 36 mg	Placebo
Primary Endpoint				
Mean percent change in body weight from avg. baseline (101.4 kg; 223.5 lbs) ^j	-5.5% (-5.5 kg; -12.1 lbs)	-7.8% (-7.9 kg; -17.4 lbs)	-10.5% (-10.4 kg; -22.9 lbs)	-2.2% (-2.3 kg; -5.1 lbs)
Key Secondary Endpoints				
Percentage of participants achieving body weight reductions of ≥10% ⁱ	23.9 %	35.5 %	50.1 %	7.0 %
Percentage of participants achieving body weight reductions of ≥15% ⁱⁱ	7.3 %	17.7 %	28.4 %	1.9 %
A1C reduction from avg. baseline of 8.1% ⁱ	-1.3 %	-1.6 %	-1.8 %	-0.1 %
Percentage of participants achieving A1C <7% ⁱ	70.0 %	78.0 %	85.1 %	23.0 %
Percentage of participants achieving A1C ≤6.5% ⁱ	56.2 %	67.5 %	75.0 %	10.6 %

ⁱSuperiority test was adjusted for multiplicity with all three doses.

ⁱⁱSuperiority test was adjusted for multiplicity with the 12 mg and 36 mg doses.

Medication	FDA indication	“Pivotal trial name”	Typical labeled duration	Mean weight loss to show
Phentermine	Short-term adjunct in obesity	No current named FDA pivotal program: best-cited evidence is older short-term RCTs/meta-analyses	Short-term (“a few weeks”)	~3.6 kg placebo-subtracted over 2–24 weeks; a newer 28-week RCT cited in reviews reported ~6.1% vs 1.7% placebo
Diethylpropion	Short-term adjunct in obesity	No current named FDA pivotal program: best-cited evidence is older RCTs/meta-analyses	Short-term (“a few weeks”)	~3.0 kg placebo-subtracted in meta-analysis; one 6-month RCT reported ~9.8% vs 3.2% placebo
Phendimetrazine	Short-term adjunct in obesity	No current named FDA pivotal program	Short-term (“a few weeks”)	Best slide estimate: modest short-term loss, likely ~1–3% placebo-adjusted over ~12 weeks
Benzphetamine	Short-term adjunct in obesity	No current named FDA pivotal program	Short-term (“a few weeks”)	Best slide estimate: modest short-term loss, likely ~1–3% placebo-adjusted over ~12 weeks



^a The degree of severity for ORCD is based on clinical judgment, incorporating findings from physical examination, laboratory testing, and/or other diagnostic procedures, as well as a person's symptomatology, in ways that apply to each individual complication.

Algorithm Figure 4 - Diagnosis: Clinical Component

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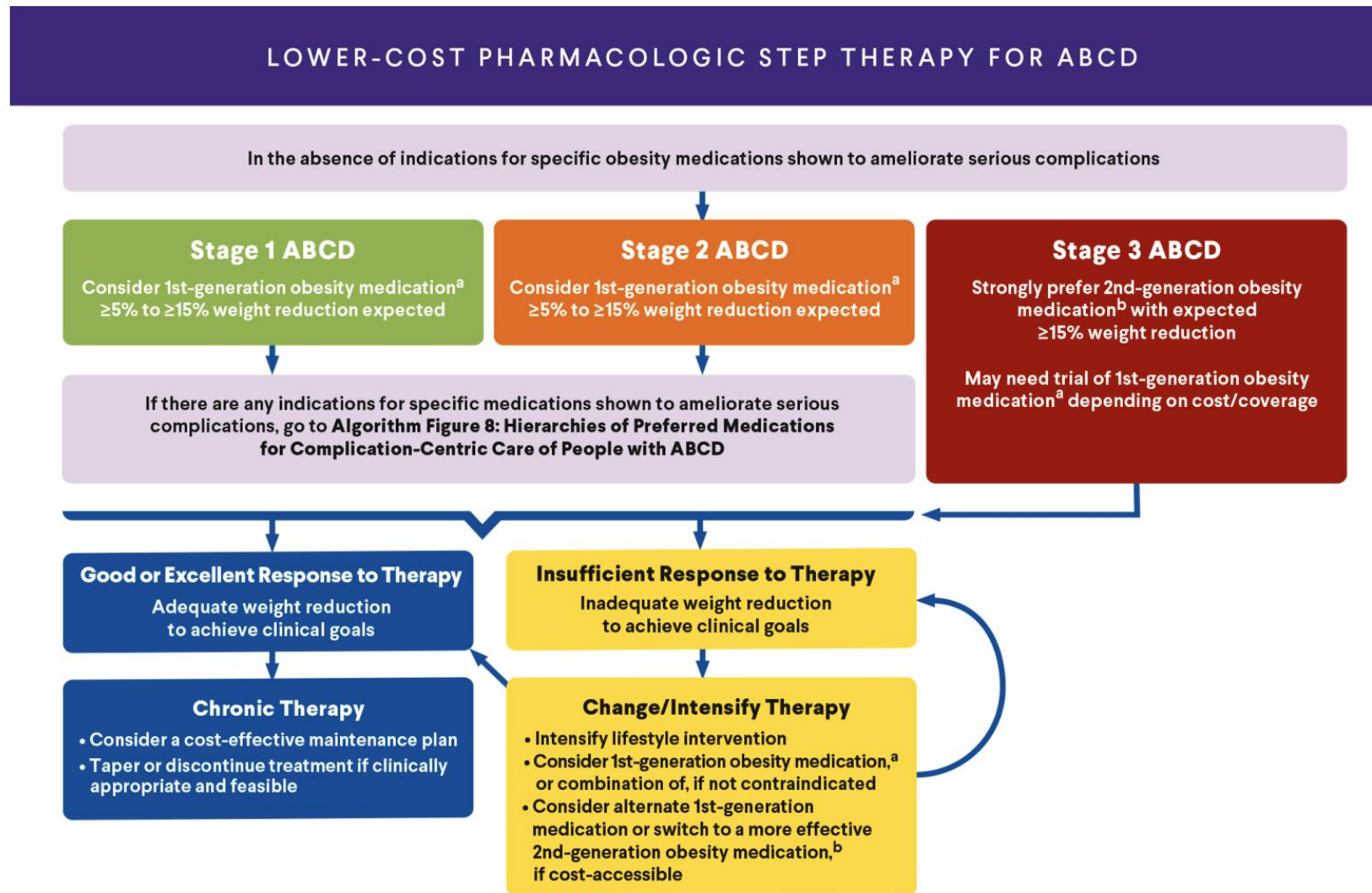
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Examples of ORCD that May Be Detected in the Clinical Evaluation of ABCD

ABCD Stage 1	ABCD Stage 2 or 3	
No ORCD identified following intake evaluation	<p>Obesity Complications*</p> <ul style="list-style-type: none"> • OA (knee, hip) • OSA • Obesity hypoventilation syndrome • Lymphedema • Stress urinary incontinence • GERD • Prediabetes and metabolic syndrome • MASLD • Obesity glomerulopathy, CKD • HFpEF • ASCVD • Thromboembolism • Idiopathic intracranial hypertension • Disability limiting activities of daily living 	<p>Obesity-Related Diseases*</p> <ul style="list-style-type: none"> • T2D • MASH • HFrEF • Atrial fibrillation • Certain cancers • Cholelithiasis, cholecystitis • Asthma • Depression, anxiety • Internalized weight bias • Stigmatization • Disordered eating • Cognitive decline, dementia • Inflammatory skin diseases • Intertrigo
<p>*There can be overlap between complications and related diseases depending on the pathophysical role of obesity in individual patients. See Box A for definitions.</p>		

Fig. 2. Examples of ORCD that may be detected in the clinical evaluation of ABCD. Note that ABCD stages 2 and 3 in the AACE obesity algorithm do not differentiate between obesity complications and related diseases since both can be ameliorated by weight-loss therapy. *ABCD* = adiposity-based chronic disease; *ASCVD* = atherosclerotic cardiovascular disease; *CKD* = chronic kidney disease; *GERD* = gastroesophageal reflux disease; *HFpEF* = heart failure with preserved ejection fraction; *HFrEF* = heart failure with reduced ejection fraction; *MASH* = metabolic dysfunction-associated steatohepatitis; *MASLD* = metabolic dysfunction-associated steatotic liver disease; *OA* = osteoarthritis; *ORCD* = obesity-related complications and diseases; *OSA* = obstructive sleep apnea; *T2D* = type 2 diabetes. K. Nadolsky; W.T. Garvey; M. Agarwal et al. Endocrine Practice 31 (2025) 1351-1394.



^a 1st-generation obesity medications: phentermine, phentermine/topiramate ER, nalextrone/bupropion ER, liraglutide

^b 2nd-generation more effective obesity medications: semaglutide, tirzepatide

Abbreviations: **ABCD**, adiposity-based chronic disease; **ER**, extended release

Algorithm Figure 9 - Lower-Cost Pharmacologic Step Therapy

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MEDICATIONS FOR OBESITY: INDIVIDUALIZATION OF THERAPY^a

KEY: ■ Preferred (evidence of benefit) ■ Insufficient evidence to prefer ■ Monitoring indicated ■ Contraindicated (evidence of risk/harm)

OBESITY-RELATED CONDITION	ORLISTAT	PHENTERMINE	PHENTERMINE/ TOPIRAMATE ER	NALTREXONE ER/ BUPROPION ER	LIRAGLUTIDE	SEMAGLUTIDE	TIRZEPATIDE
DIABETES PREVENTION	Benefit via weight reduction		Benefit via weight reduction		Benefit via weight reduction and incretin effect	Benefit via weight reduction and incretin effect	Benefit via weight reduction and incretin effect
TYPE 2 DIABETES	Benefit via weight reduction		Benefit via weight reduction	Benefit via weight reduction	Benefit via weight reduction and incretin effect	Benefit via weight reduction and incretin effect	Benefit via weight reduction and incretin effect
HYPERTENSION	Benefit via weight reduction	Monitor heart rate, BP	Monitor heart rate, BP; BP benefit observed in trials ^b	Monitor heart rate, BP	BP benefit observed in trials; Monitor heart rate	BP benefit observed in trials; Monitor heart rate	BP benefit observed in trials; Monitor heart rate
		Contraindicated in uncontrolled HTN	Contraindicated in uncontrolled HTN	Contraindicated in uncontrolled HTN			
ASCVD		Contraindicated	Use with caution; Monitor heart rate, BP	Monitor heart rate, BP	Demonstrated prevention of ASCVD in T2D	Demonstrated prevention of ASCVD	Evidence in T2D and obesity pending
MASLD					Benefit observed in trials	Benefit observed in trials	Benefit observed in trials
DEPRESSION			Appropriate monitoring	Appropriate monitoring	Appropriate monitoring	Appropriate monitoring	Appropriate monitoring
ANXIETY		Appropriate monitoring	Appropriate monitoring	Appropriate monitoring			
CHRONIC KIDNEY DISEASE	Monitor for oxalate nephropathy		Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90mg twice a day	Benefit in T2D; Avoid vomiting and volume depletion	Benefit in T2D; Avoid vomiting and volume depletion	Benefit in T2D; Avoid vomiting and volume depletion
SEVERE KIDNEY IMPAIRMENT	Monitor for oxalate nephropathy	Urinary clearance of drug	Urinary clearance of drug	Urinary clearance of drug	Avoid vomiting and volume depletion	Avoid vomiting and volume depletion	Avoid vomiting and volume depletion
NEPHROLITHIASIS	Calcium oxalate stones		Calcium phosphate stones				
HEPATOBIILIARY IMPAIRMENT	Monitor for cholelithiasis	Do not exceed 8 mg per day	Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg daily	Monitor for cholelithiasis	Monitor for cholelithiasis	Monitor for cholelithiasis
SEVERE HEPATIC IMPAIRMENT	Not recommended						

^a All medications are contraindicated in pregnancy and breastfeeding. ^b Blood pressures are significantly decreased in clinical trials.

Abbreviations: **ASCVD**, atherosclerotic cardiovascular disease; **BP**, blood pressure; **ER**, extended release; **HTN**, hypertension; **T2D**, type 2 diabetes

Algorithm Figure 10 - Medications for Obesity: Individualization of Therapy

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MEDICATIONS FOR OBESITY APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION ^{a,b}							
	ORLISTAT	PHENTERMINE ^c	PHENTERMINE/ TOPIRAMATE ER	NALTREXONE ER/ BUPROPION ER	LIRAGLUTIDE	SEMAGLUTIDE	TIRZEPATIDE
CLASS/MECHANISM OF ACTION	Lipase Inhibitor	NE-Releasing Agent	NE-Releasing Agent GABA Receptor Modulation	Opioid-Receptor Antagonist DA-NE Reuptake Inhibitor	GLP-1 RA	GLP-1 RA	GIP/GLP-1 RA
AGE	≥12 years ^d	>16 years	≥12 years	≥18 years ^d	≥12 years ^e	≥12 years ^e	≥18 years ^d
DELIVERY	Oral	Oral	Oral	Oral	Subcutaneous Injection	Subcutaneous Injection	Subcutaneous Injection
STARTING DOSE	60 mg 3 times/day AC	8 mg or 15 mg QAM	3.75 mg/23 mg QAM	8 mg/90 mg QAM	0.6 mg QD	0.25 mg QWK	2.5 mg QWK
DOSE ESCALATION	Titrate up to needed dose Slow dose titration if side effects occur Formulations: 60 mg cap 120 mg cap	Titrate up to needed dose Slow down dose titration if side effects occur Formulations: 8 mg tab 15 mg cap 37.5 mg tab	Titrate up bi-weekly to needed dose Slow down dose titration if side effects occur 3.75 mg/23 mg QAM x 2 wk 7.5 mg/ 46 mg QAM x 12 wk 11.25 mg / 69 mg QAM x 2 wk 15 mg/92 mg QAM	Titrate up weekly to needed dose Slow down dose titration if side effects occur 8 mg/90 mg QAM x 1wk 8 mg/90 mg twice daily x 1 wk 16 mg/90 mg QAM and 8 mg/90 mg QPM x 1 wk 16 mg/90 mg twice daily	Titrate up weekly to needed dose Slow down dose titration if side effects occur 0.6 mg QD x 1 wk 1.2 mg QD x 1 wk 1.8 mg QD x 1 wk 2.4 mg QD x 1 wk 3.0 mg QD	Titrate up monthly to needed dose Slow down dose titration if side effects occur 0.25 mg QWK x 4 wk 0.5 mg QWK x 4 wk 1.0 mg QWK x 4 wk 1.7 mg QWK x 4 wk 2.4 mg QWK	Titrate up monthly to needed dose Slow down dose titration if side effects occur 2.5 mg QWK x 4 wk 5.0 mg QWK x 4 wk 7.5 mg QWK x 4 wk 10 mg QWK x 4 wk 12.5 mg QWK x 4 wk 15 mg QWK
MAXIMUM DOSE	120 mg 3 times/day AC	37.5 mg QAM ^f	15 mg/92 mg QD	16 mg/180 mg twice daily	3.0 mg QD	2.4 mg QWK	15 mg QWK
WEIGHT REDUCTION ^g	4% (52 weeks)	5%–6% (28 weeks)	9.6%–9.9% (52 weeks) dose dependent	4.2%–5.2% (52 weeks)	9.2% (56 weeks)	16.9% (68 weeks)	22.5% (72 weeks)
POTENTIAL SIDE EFFECTS ^h	Flatulence Fecal Urgency Oily Stools Fat-Soluble Vitamin and Drug Malabsorption Potential Drug-Drug Interactions	Restlessness Insomnia Headache Dry Mouth Tachycardia BP Elevation	Paresthesia, Dizziness Dysgeusia, Insomnia Constipation, Dry Mouth Fatigue Blurred Vision Mental Clouding Mood Changes	Nausea, Constipation Headache Vomiting Dizziness Insomnia Dry Mouth, Diarrhea Anxiety	Nausea Diarrhea Constipation Dyspepsia Vomiting Abdominal Pain GERD	Nausea, Diarrhea Constipation Dyspepsia Vomiting Abdominal Pain Headache Fatigue	Nausea, Diarrhea Constipation Dyspepsia Vomiting Abdominal Pain Headache Fatigue
CAUTIONS, RELATIVE AND ABSOLUTE CONTRAINDICATIONS ⁱ	Cholestasis Chronic Malabsorption Syndrome Nephrolithiasis Vitamin Malabsorption Encourage Supplementation Potential for Misuse	CAD, CVA, Arrhythmias, CHF, Uncontrolled HTN ^k Hypertension Agitated States History of Drug Abuse MAOI Use Angle-Closure Glaucoma	MAOI Hypertension Angle-Closure Glaucoma Monitor for Increased Heart Rate Nephrolithiasis Metabolic Acidosis ^c Monitor for Worsening Anxiety or Depression ^c	Seizure Disorder Uncontrolled HTN Chronic Opioid Use Anorexia Nervosa Bulimia Nervosa MAOI Use Abrupt Drug or Alcohol Withdrawal Angle-Closure Glaucoma Monitor for Worsening Anxiety or Depression ^c	History or Family History MTC/MEN2 Gallbladder Disease Pancreatitis Increased Heart Rate	History or Family History MTC/MEN2 Gallbladder Disease Pancreatitis Diabetic Retinopathy ^j	History or Family History MTC/MEN2 Gallbladder Disease, Diabetic Retinopathy ^j
ACCESS/COST	\$\$	\$	\$\$	\$\$	\$\$\$	\$\$\$\$	\$\$\$\$

^aMonogenic obesity treatment, devices for weight reduction, and setmelanotide can be found in narrative. ^bFDA-approved for CWM. ^cThis class of medications includes diethylpropion (or amfepramone), phendimetrazine, and benzphetamine. ^dEMA approved for age 18 years and above for CWM. ^eEMA approved for age 12 years and above for CWM. ^fMaximum dose allowed for phentermine; however, many patients will see results on 8 mg 3 times a day which is also considered a maintenance dose in patients with diabetes and obesity. ^gPercent body weight reduction in treatment in phase III trial. ^hComplications requiring caution or monitoring in order of observed frequency. ⁱAll FDA-approved medications for obesity are contraindicated in individuals who are pregnant or breastfeeding; effective birth control should be recommended/prescribed. A negative pregnancy test is recommended before initiating, with monthly monitoring. ^jIn patients with T2D and obesity. ^kBlood pressures are significantly decreased in clinical trials for phentermine/topiramate ER.

Abbreviations: AC, before meals; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; CWM, chronic weight management; DA, dopamine; EMA, European Medicines Agency; ER, extended release; FDA, U.S. Food and Drug Administration; GERD, gastroesophageal reflux disease; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HTN, hypertension; MAOI, monoamine oxidase inhibitors; MEN2, multiple endocrine neoplasia, type 2; MTC, medullary thyroid cancer; NE, norepinephrine; QAM, every morning; QD, every day; QPM, every afternoon or evening; QWK, every week; wk, week(s)

Algorithm Figure 11 - FDA-Approved Medications for Obesity: Prescribing Information

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Pharmacologic Phenotype

- Studied 450 people, measuring energy balance and eating behavior (body composition, resting energy expenditure, satiation/satiety, eating behavior, affect, physical activity). And then they classified people into phenotypes
- 85% had a phenotype. Of all participants 27% had 2 or more phenotypes
- 15% had no phenotype at all
- The Four Phenotypes
 - Hungry brain ate ~62% more calories before fullness
 - Evaluated with nutrient drink test
 - Phentermine/Topiramate ER
 - Emotional hunger had ~2.8× higher anxiety
 - Evaluated with validated questionnaires
 - Bupropion/Naltrexone ER
 - Hungry gut had ~31% faster gastric emptying
 - Evaluated with gastric emptying scintigraphy
 - Liraglutide (Saxenda)
 - Slow burn had ~12% lower predicted REE
 - Indirect calorimetry REE
 - Low dose Phentermine

At 12 months:

- Phenotype-guided: -15.9% mean weight loss
- Standard care: -9.0%
- Difference: -6.9% (95% CI -9.4 to -4.5), $P < 0.001$

Clinically meaningful responder rates:

- >10% weight loss: 79% phenotype-guided
 - Failure rate: 2% phenotype-guided
- >10% weight loss: 34–35% standard care
 - Failure rate 26% standard care



Upcoming Treatment Options

Expected to be Approved for 2026 or 2027

Retatrutide

Trial / program	Population	Duration	Mean weight loss	Placebo	Placebo-adjusted	Note
Phase 2 obesity (NEJM)	Obesity/overweight, no diabetes	24 weeks	17.5%	1.6%	15.9%	Highest-dose result
Phase 2 obesity (NEJM)	Obesity/overweight, no diabetes	48 weeks	24.2%	2.1%	22.1%	Highest-dose result
Phase 2 T2D (Lancet)	Type 2 diabetes with overweight/obesity	36 weeks	up to 16.9%	—	—	
TRIUMPH-4 phase 3	Obesity/overweight with knee osteoarthritis	68 weeks	28.7% (efficacy estimand)	2.1%	26.6%	Most up-to-date public phase 3 topline
TRIUMPH-4 phase 3	Obesity/overweight with knee osteoarthritis	68 weeks	23.7% (treatment-regimen estimand)	4.6%	19.1%	A pragmatic estimate



Thank You

Any Questions?

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APPENDIX

A top-down view of a desk with a laptop, a coffee cup, glasses, photos, and a person writing in a notebook. The scene is overlaid with a semi-transparent blue filter. The word "APPENDIX" is centered in white, bold, uppercase letters.

Pathophysiology

Normal Physiology of Insulin Receptor

- The insulin receptor (IR) has 2 extracellular α -subunits and 2 transmembrane β -subunits.
- The β -subunits contain 3 essential tyrosine residues that autophosphorylate when insulin binds.
- IRS-1 (insulin receptor substrate 1) binds to the receptor and becomes tyrosine-phosphorylated. Tyrosine-phosphorylated IRS-1 activates PI3K.
- PI3K (phosphoinositide 3-kinase) converts PIP2 (phosphatidylinositol 4,5-bisphosphonate) to PIP3 (phosphatidylinositol 3,4,5-triphosphate).
- PIP3 recruits and activates Akt (protein kinase B) and PDK1 (Akt activator). PIP3 inhibits GSK-3 (glycogen synthase kinase-3) downstream.
- Akt drives GLUT-4 translocation to the cell surface, allowing glucose uptake.

