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Evidence-Based Obesity Medicine

Update on Changing Landscape of Obesity Management

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Disclosures

- Mochi Health – Founder and CEO
- I will clarify when I discuss Non-FDA approved medications currently being researched.

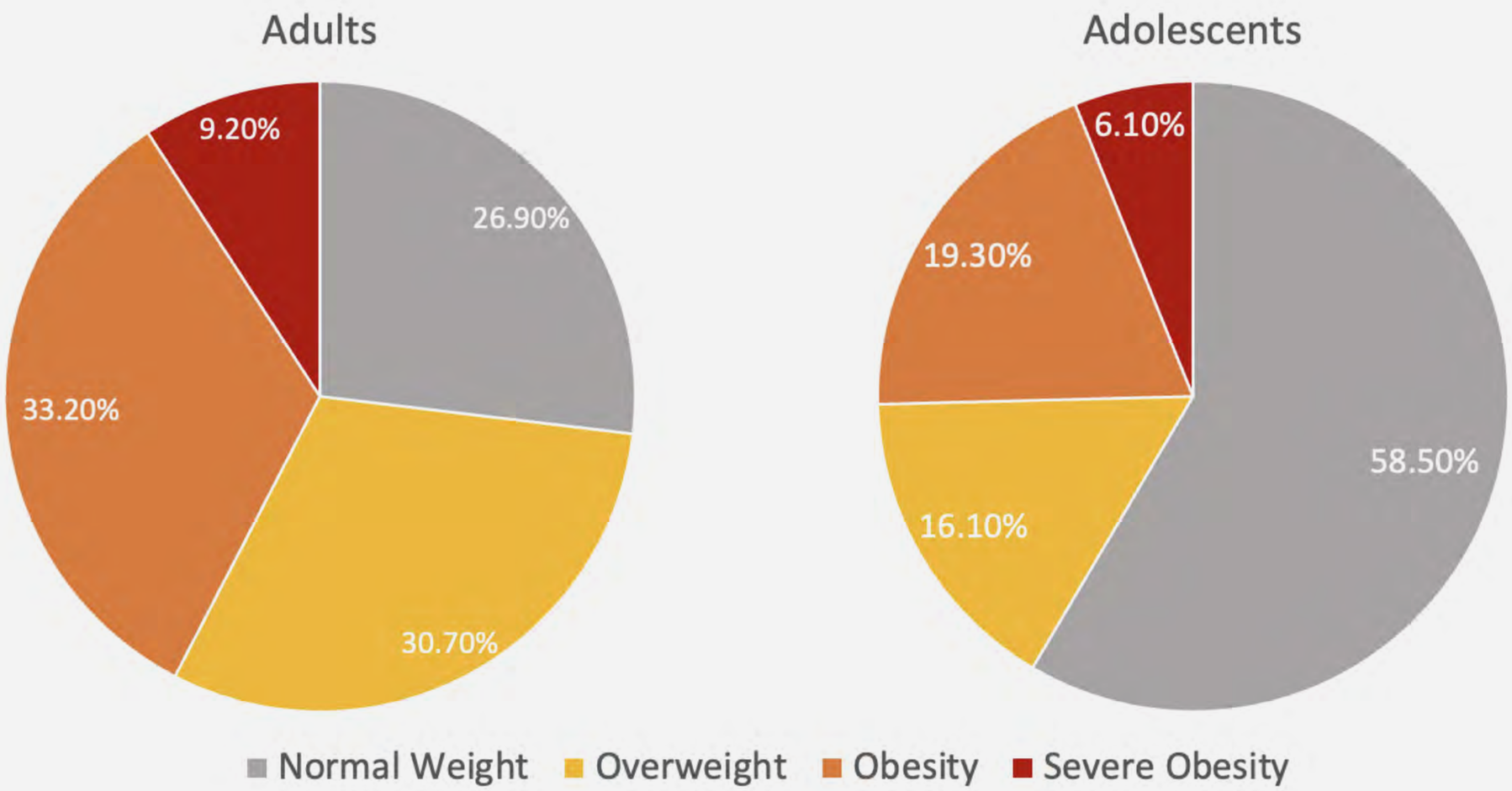
Objectives

- **Review current guidelines** intended to support practitioners in decisions about pharmacological interventions in management of obesity in **adults**.

- Discuss the guidance from American Academy of Pediatrics outlining **obesity management in adolescents**, and the evidence supporting these recommendations.

Outline

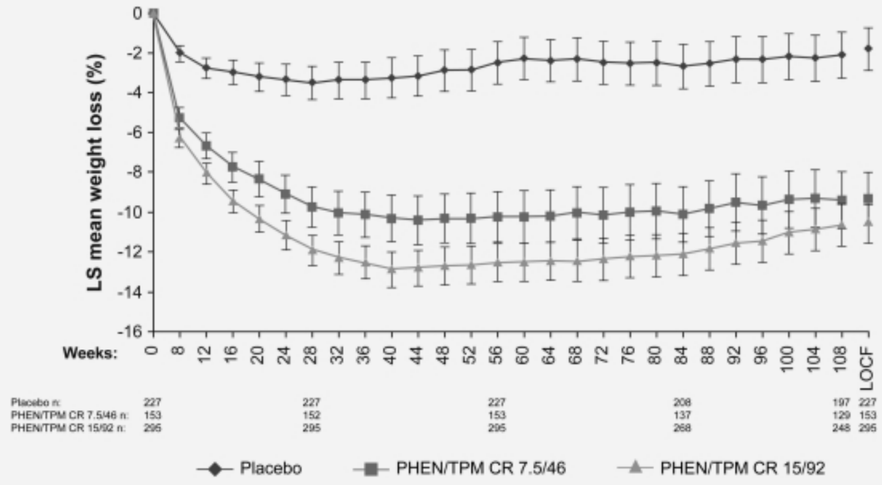
- Scale of the issue
- Pharmacologic treatments
  - Older Medications
  - Recent Advances
  - Diet and Nutrition
  - Adjunctive Benefits
  - Ongoing Trials
- Real-world applications
  - Switching medications
  - Stopping medications
  - Adolescents
  - Adverse Effects of GLP-1 drugs
- Genetic Obesity



Data from: 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, 2017-2018.

Older Medications - Qsymia (Phentermine-topiramate)

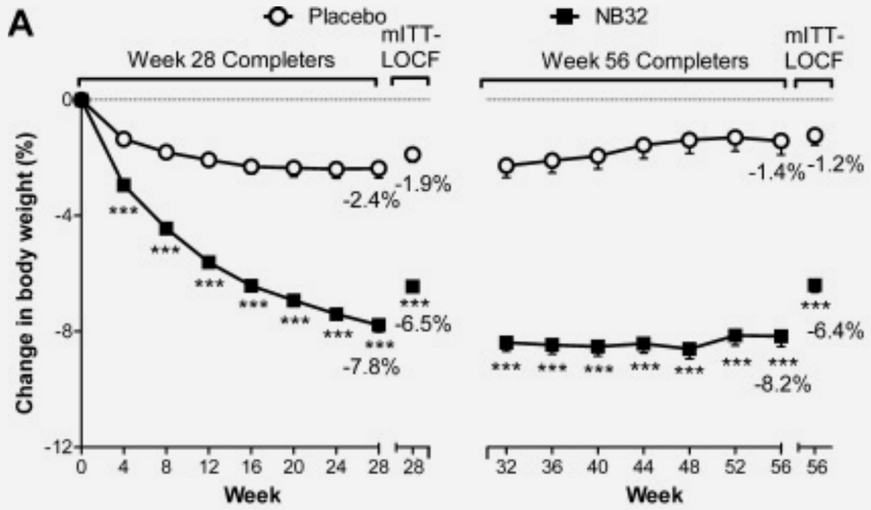
- Topiramate increases half-life of phentermine, prevents evening/nighttime binges
- CONQUER/SEQUEL trials published 2011
  - 10.7% weight loss in low-dose, 14% in high-dose groups over 2 years
- REMS program due to risk of birth defects
- Start at 1 tablet (Phentermine 3.75 mg/topiramate 23 mg) PO daily x2 weeks
  - Increase as tolerated to phentermine 7.5 mg/topiramate 46 mg once daily for 12 weeks, then evaluate weight loss
  - If ≥3% not lost, either taper off Qsymia or dose-escalate
  - Maximum dose 4 tablets daily (phentermine 15 mg/topiramate 92 mg)



Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, Schwiers M, Day WW, Bowden CH. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. Am J Clin Nutr. 2012 Feb;95(2):297-308. doi: 10.3945/ajcn.111.024927. Epub 2011 Dec 7. PMID: 22158731; PMCID: PMC3260065.

Older Medications - Contrave (naltrexone-bupropion)

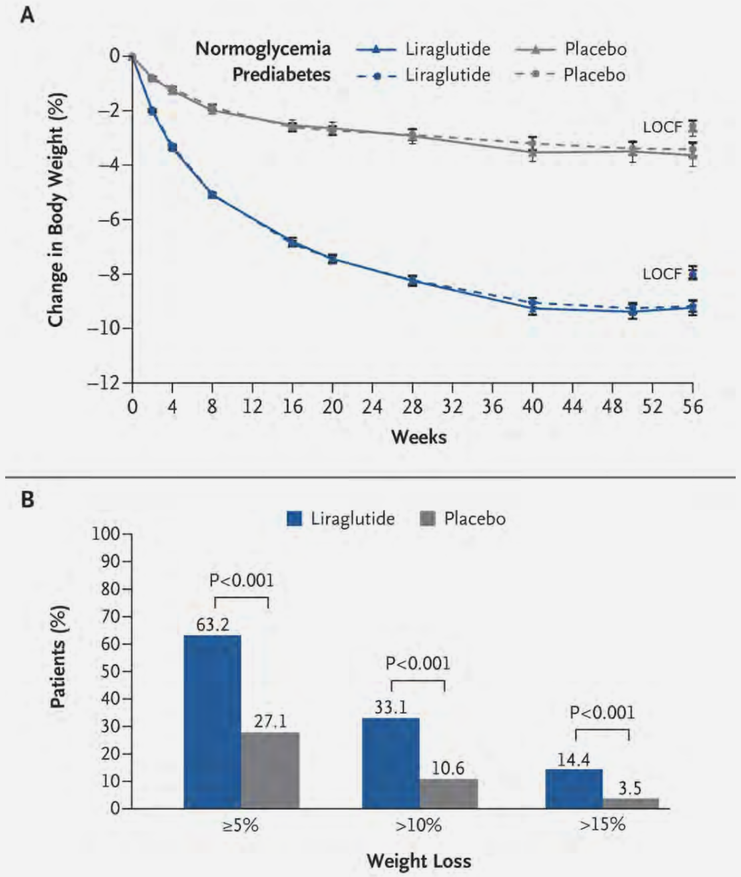
- COR-I, COR-II, COR-BMOD, and COR-Diabetes trials 2010-2013
  - 8.1-11.5% weight loss over 2 years
- CurAccess program - $99/m maximum regardless of insurance
- Start at 1 tablet (naltrexone 8 mg/bupropion 90 mg) PO qam x1 week, increase as tolerated weekly
  - 1 tablet PO BID x1 week; then 2 tablets PO qam & 1 tablet PO qpm x1 week; then 2 tablets PO BID
  - Max dose 4 tablets/day (naltrexone 32 mg/bupropion 360 mg total)



Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, Kim DD, Dunayevich E; COR-I Study Group. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2010 Aug 21;376(9741):595-605. doi: 10.1016/S0140-6736(10)60888-4. Epub 2010 Jul 29. Erratum in: Lancet. 2010 Aug 21;376(9741):594. Erratum in: Lancet. 2010 Oct 23;376(9750):1392. PMID: 20673995.

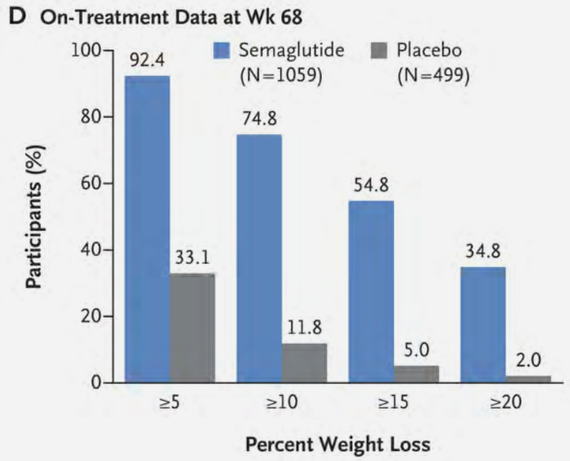
Recent Advances – Saxenda (liraglutide)

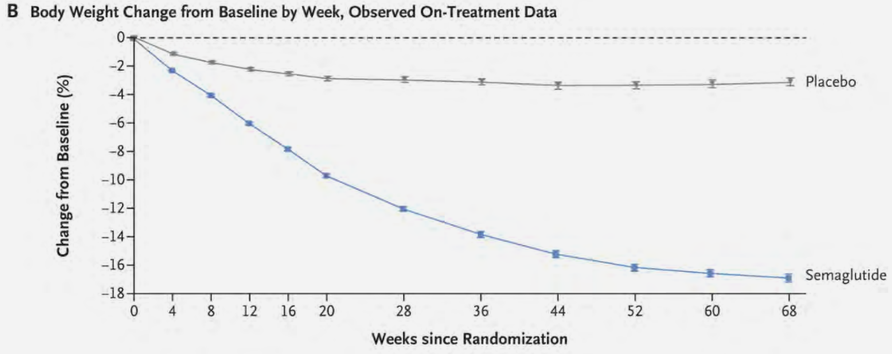
- GLP-1 agonist, daily subQ injection
- Saxenda for weight management, Victoza for DM2
- SCALE trials in 2015
  - 63.2% of liraglutide group lost at least 5% body weight, 33.1% lost at least 10% body weight
- Start at 0.6 mg SubQ daily x1 week, increase as tolerated weekly
  - Target dose and max dose 3 mg SubQ daily
  - If unable to tolerate dose increase, slow escalation
    - Pen has prefilled cartridge and can be dialed to select any dose
- Unique AEs and contraindications to GLP-1 medications



Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, le Roux CW, Violante Ortiz R, Jensen CB, Wilding JP; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. N Engl J Med. 2015 Jul 2;373(1):11-22. doi: 10.1056/NEJMoa1411892. PMID: 26132939.

Recent Advances – Wegovy (semaglutide)





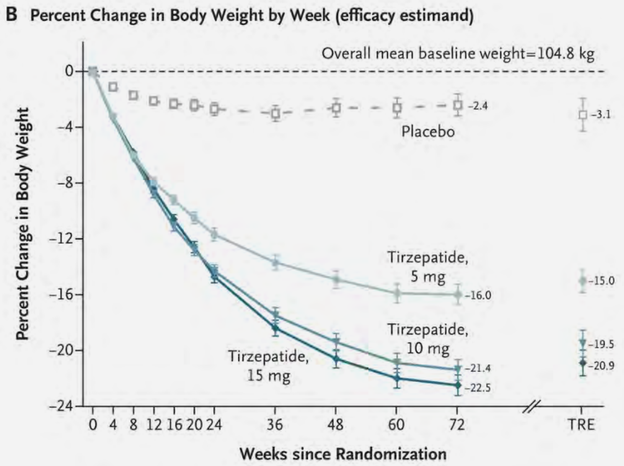
- GLP-1 agonist, weekly subQ injection
- Wegovy for weight management, Ozempic for DM2
- STEP 1 trial in 2021
  - 14.9% mean weight loss in semaglutide group
- Requires special needles to be prescribed
- Start at 0.25 mg SubQ weekly x4 weeks
  - Increase dose when outside 1-2 lb lost/week
  - Max frequency of increase q4 weeks
    - 0.25 mg, then 0.5 mg, then 1 mg, then 1.7 mg, then 2.4 mg
  - Max dose 2.4 mg SubQ weekly
  - If unable to tolerate dose increase, slow escalation rate
- If requiring Zofran regularly, decrease dose
- Prefilled pens available in any dose

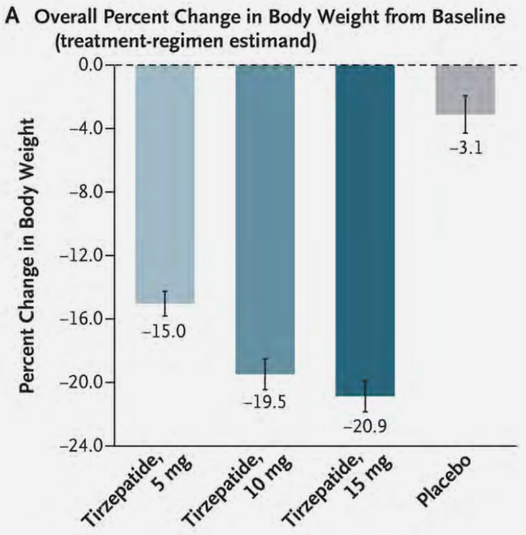
Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF; STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021 Mar 18;384(11):989-1002. doi: 10.1056/NEJMoa2032183. Epub 2021 Feb 10. PMID: 33567185.

Recent Advances – Mounjaro (tirzepatide)

- GLP-1, GIP dual agonist, weekly subQ injection
- Approved for DM2, on FDA fast-track for weight management with approval expected 12/2023
- SURMOUNT and SURPASS trials
  - 15-20.9% weight loss over 72 weeks

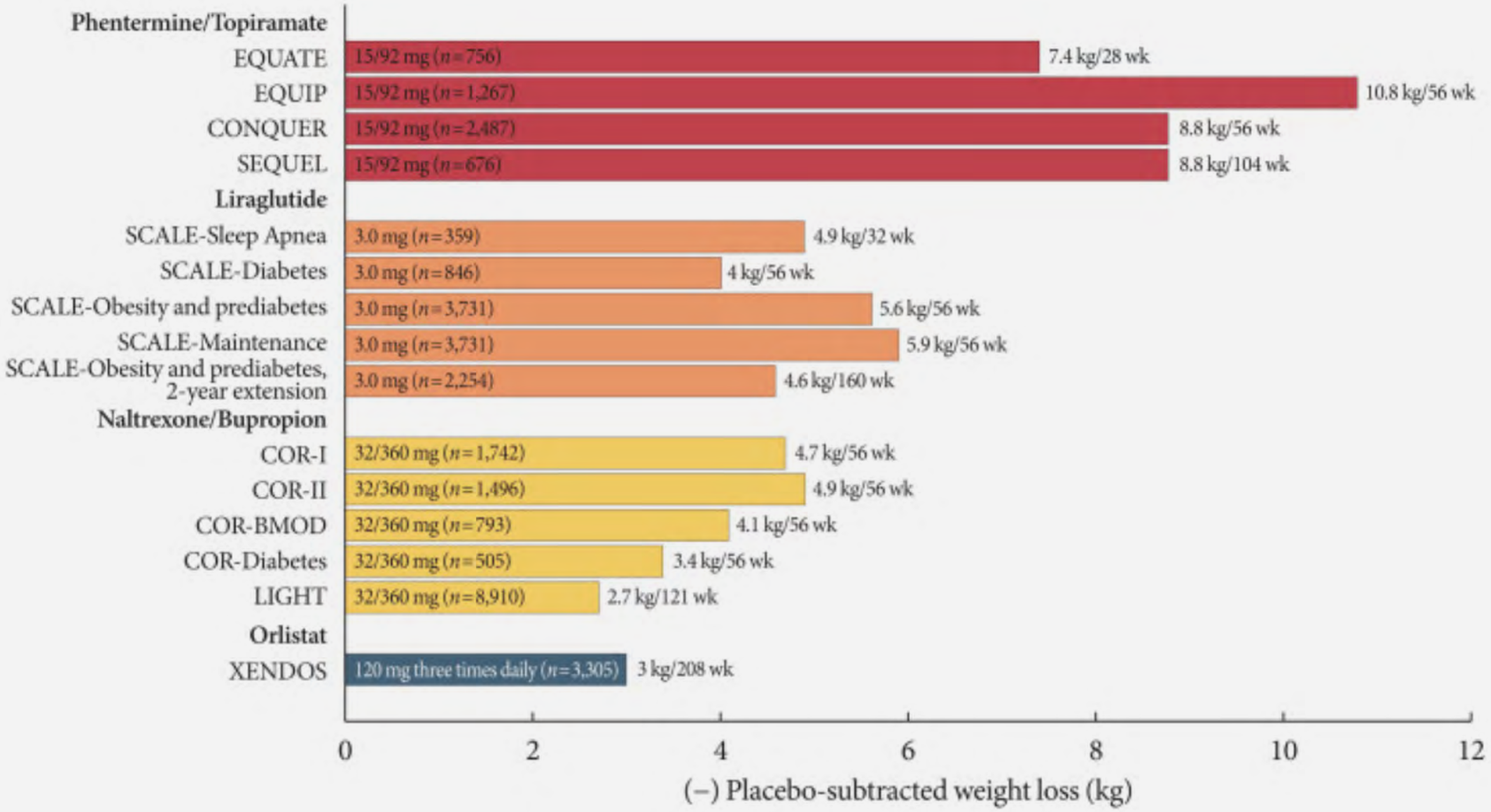
- Start at 2.5 mg SubQ weekly x4 weeks
  - Increase dose when outside 1-2 lb/week weight loss
  - Max frequency of increase q4 weeks
    - 5 mg, then 7.5 mg, then 10 mg, then 12.5 mg, then 15 mg
  - Max dose 15 mg SubQ weekly
  - If unable to tolerate dose increase, slow escalation rate
  - If requiring Zofran regularly, decrease dose





Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial,The Lancet,Volume 398, Issue 10295, 2021, Pages 143-155, ISSN 0140-6736, https://doi.org/10.1016/S0140-6736(21)01324-6.

Side-by-Side Comparison



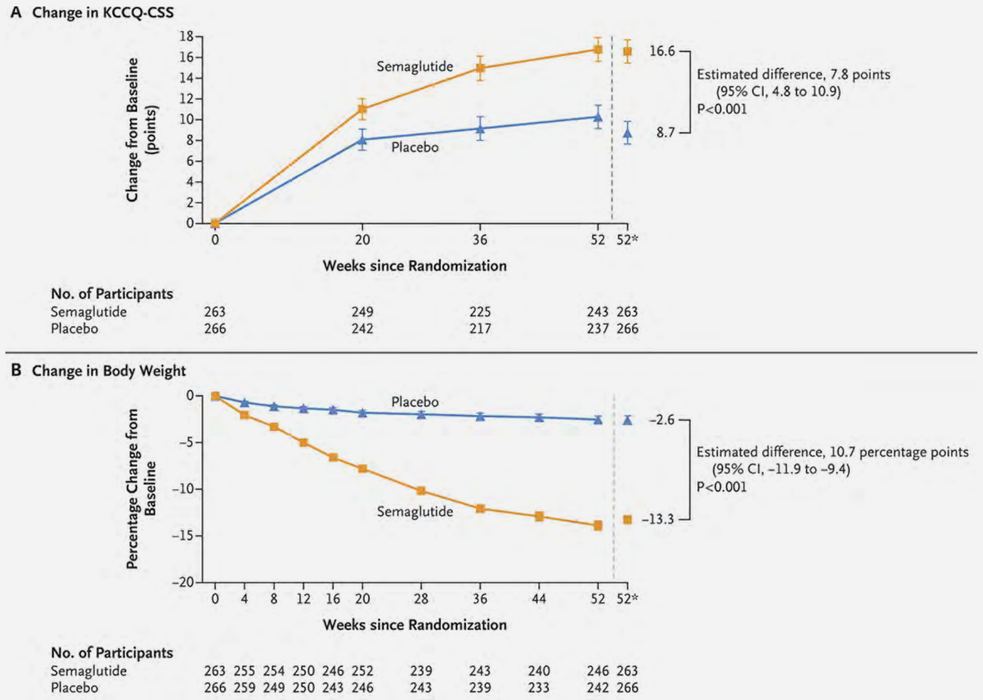
Son JW, Kim S. Comprehensive Review of Current and Upcoming Anti-Obesity Drugs. Diabetes Metab J. 2020 Dec;44(6):802-818. doi: 10.4093/dmj.2020.0258. Epub 2020 Dec 23. PMID: 33389955; PMCID: PMC7801751.

Dietary/Nutrition Changes

- **SCALE (liraglutide):** advised to exercise 150 minutes/week, maintain 500 kcal deficit, recommended macronutrient distribution was 30% fat, 20% protein, 50% carbohydrate
- **STEP (semaglutide):** individual counseling sessions every 4 weeks to help them adhere to 150 minutes exercise/week and 500 kcal deficit
- **SURMOUNT (tirzepatide):** regular lifestyle counseling sessions with dietitian or other qualified health professional to help them adhere to at least 150 minutes of exercise/week and 500 kcal deficit with “healthful, balanced meals”

Son JW, Kim S. Comprehensive Review of Current and Upcoming Anti-Obesity Drugs. Diabetes Metab J. 2020 Dec;44(6):802-818. doi: 10.4093/dmj.2020.0258. Epub 2020 Dec 23. PMID: 33389955; PMCID: PMC7801751.

Adjunctive Benefits – HFpEF

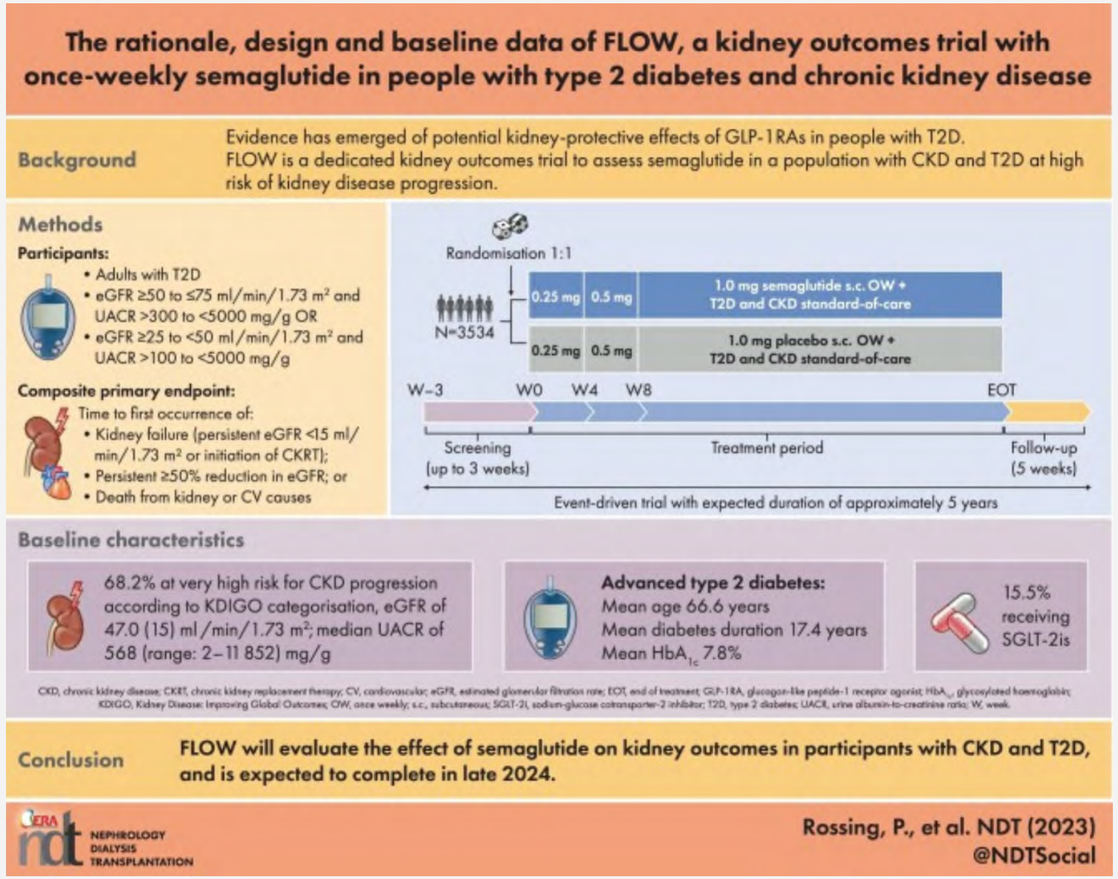


- STEP-HFpEF trial, 52 weeks long
  - 529 patients with HFpEF and BMI >30, placebo vs semaglutide 2.4 mg weekly
- Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (0-100, higher scores mean fewer symptoms/ limitations)
  - + 16.6 points with semaglutide
  - + 8.7 with placebo; p<0.001
- Body weight
  - -13.3% with semaglutide
  - -2.6% with placebo; p<0.001
- CRP level
  - -43.5% with semaglutide
  - -7.3% with placebo; p<0.001
- 6-minute walk distance
  - + 21.5 m with semaglutide
  - + 1.2 m with placebo; p<0.001

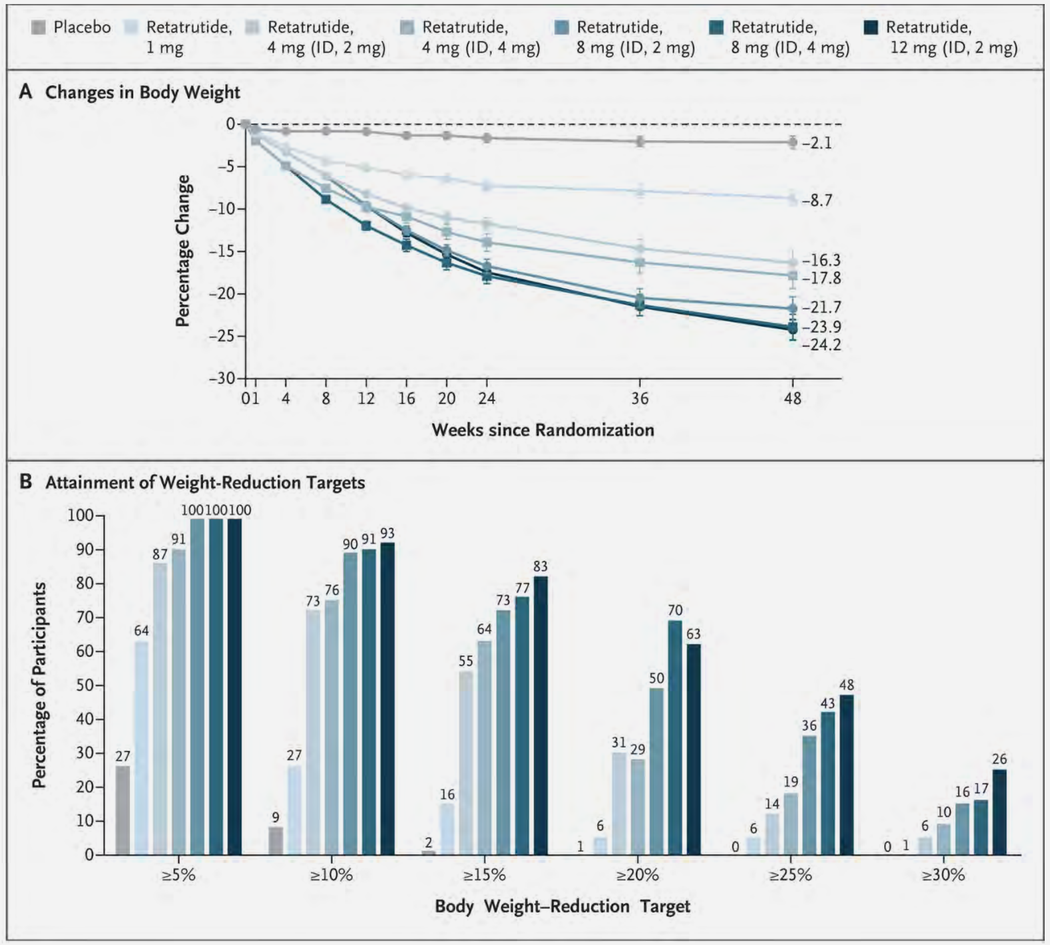
Kosiborod, M. N. et al, (2023). The New England Journal of Medicine, 389 (12), 1069-1084. doi: 10.1056/NEJMoa2306963.

Adjunctive Benefits and Ongoing Trials – Renal Function

- FLOW trial: randomised, double-blind, parallel-group, multinational, phase 3b
- Semaglutide vs placebo in patients with CKD and DM2
- Designed to examine progression of kidney disease and progression to kidney failure
- Will also track renal and CV disease mortality



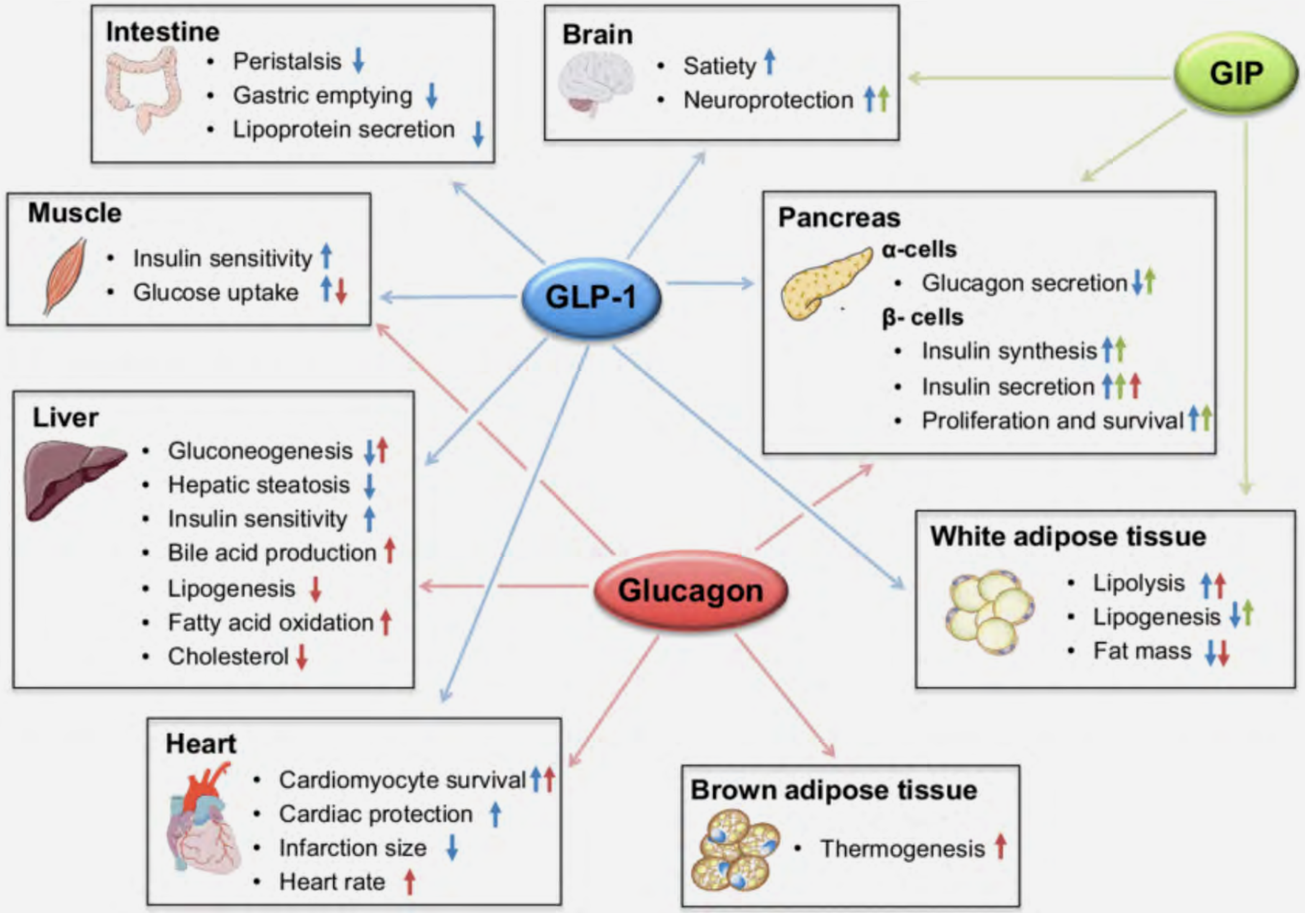
Ongoing Trials - Retatrutide



- GIP, GLP-1, and glucagon **triple agonist**, weekly SubQ injection
- Phase 2 trial published August 2023
  - 8.7-24.2% weight loss at 48 weeks
  - Increased efficacy in women, BMI >35
  - 100% of participants at 8 mg and 12 mg doses lost >5% of body weight
  - 63% of participants at 12 mg dose lost >20% of body weight, 48% lost >25% of body weight, and 26% lost >30% body weight
  - Participants still losing weight at trial endpoint

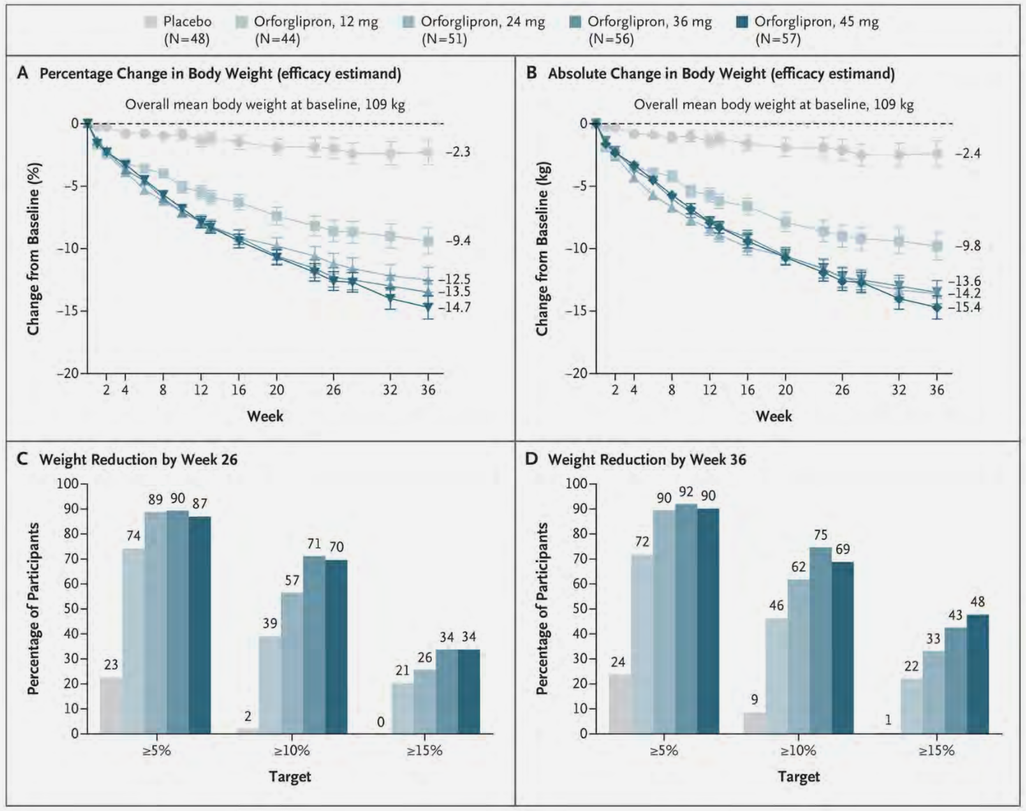
Jastreboff AM, Kaplan LM, et al. Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial. N Engl J Med. 2023; 389:514-526. DOI: 10.1056/NEJMoa2301972

Retatrutide – the Triple Agonist Advantage



Brandt SJ, Müller TD, DiMarchi RD, Tschöp MH, Stemmer K. Peptide-based multi-agonists: a new paradigm in metabolic pharmacology. J Intern Med. 2018 Dec;284(6):581-602. doi: 10.1111/joim.12837. Epub 2018 Oct 23. PMID: 30230640.

Ongoing Trials - Orforglipron

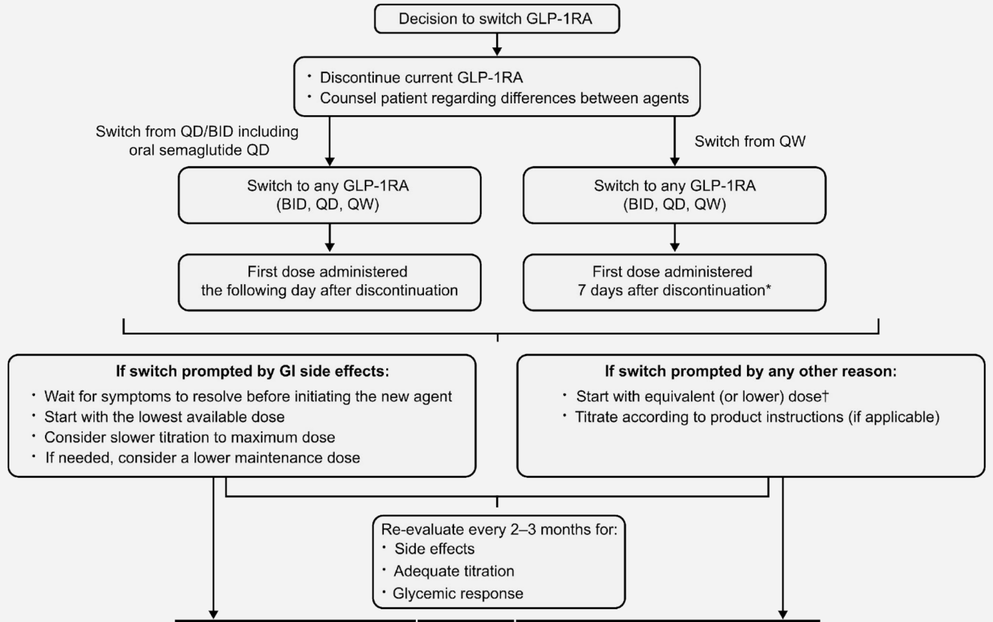


- **Non-peptide** GLP-1 agonist, daily **oral** dosing
  - Theoretically easier and cheaper to produce
- Phase 2 trial published September 2023
  - 9.4-14.7% weight loss in 36 weeks
  - Participants still losing weight at trial endpoint
- MOA at GLP-1 receptor produces cAMP signals similar to native GLP, but has reduced activation of receptor internalization pathway mediated by β-arrestin
  - Potential for reduced desensitization/improved agonist activity
  - Similar to tirzepatide in this respect

Wharton S, Blevins T, et al. Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity. N Engl J Med 2023; 389:877-888. DOI: 10.1056/NEJMoa2302392

Switching GLP-1 Agonists

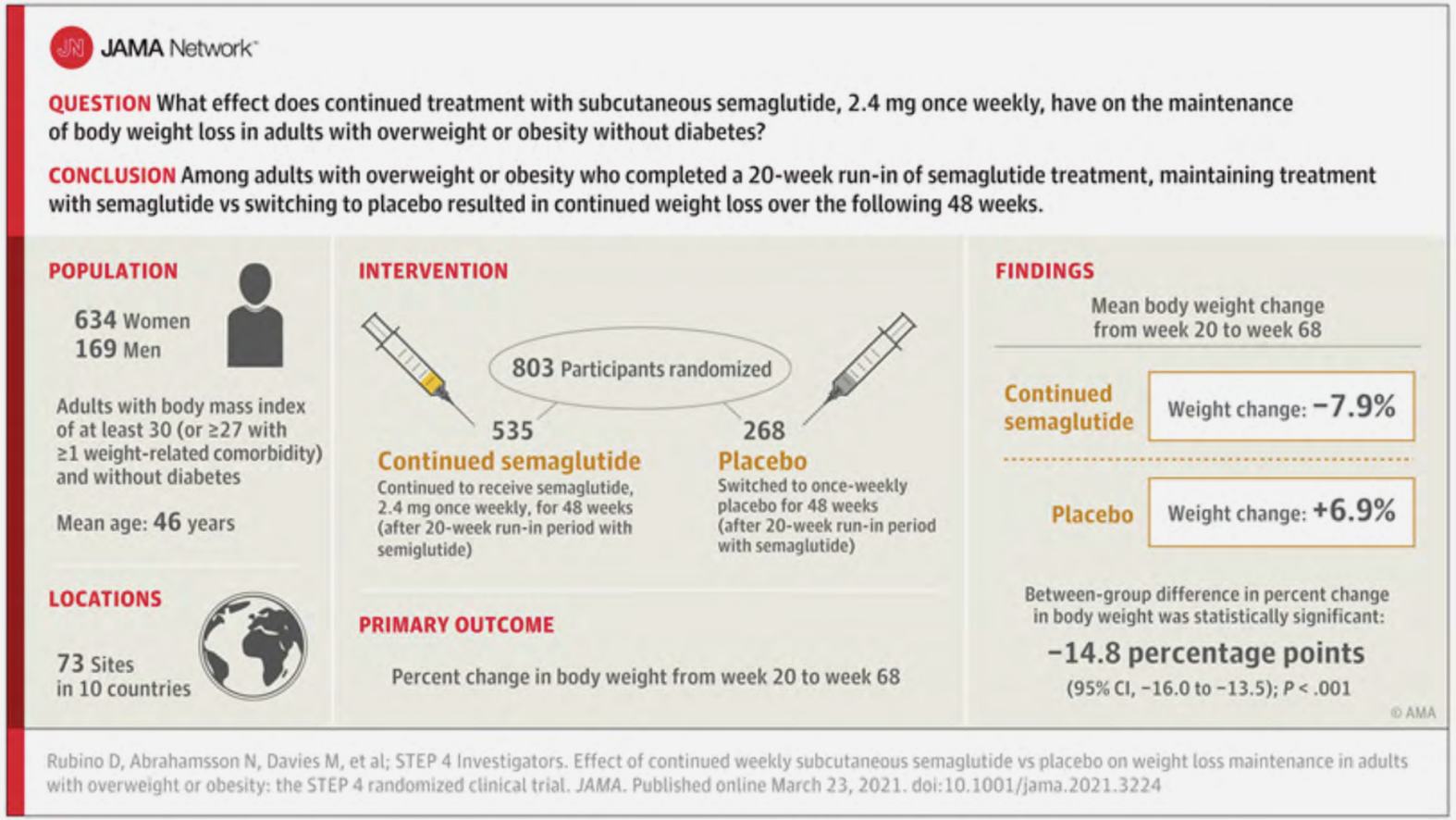
- Many reasons to switch, no consensus protocol
- If switching due to AEs, start at lower relative dose
- If switching from max dose of one GLP to another, skip the initial starting dose and go directly to second dosing step
- Ongoing phase 4 trials with tirzepatide vs increasing dulaglutide and tirzepatide vs other GLP-1 agonists
    - SURPASS-SWITCH, SURPASS-SWITCH-2 started 2023



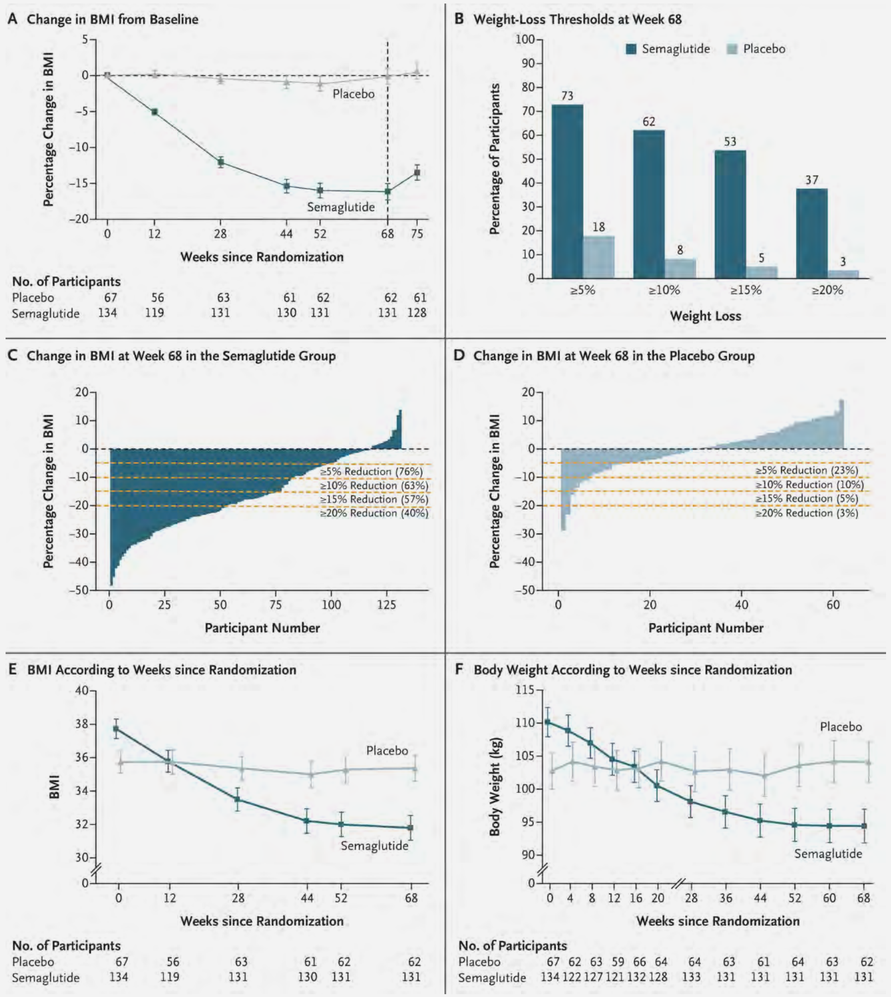
Agent	Frequency	Equivalent Dose†			
Exenatide	QW			2 mg	
Dulaglutide	QW		0.75 mg	1.5 mg	
Semaglutide	QW		0.25 mg	0.5 mg	1 mg
Liraglutide	QD	0.6 mg	1.2 mg	1.8 mg	
Lixisenatide	QD	10 µg	20 µg		
Oral semaglutide	QD	3 mg	7 mg	14 mg	
Exenatide	BID	5 µg	10 µg		

Almandoz JP, Lingvay I, Morales J, Campos C. Switching Between Glucagon-Like Peptide-1 Receptor Agonists: Rationale and Practical Guidance. Clin Diabetes. 2020 Oct;38(4):390-402. doi: 10.2337/cd19-0100. PMID: 33132510; PMCID: PMC7566932.

Stopping Medications – STEP 4 Trial



Adolescents



- STEP-TEENS trial of semaglutide vs placebo (both with lifestyle interventions)
  - Average BMI decreased 16.1% after 68 weeks
  - >5% body weight loss in 73% of participants on semaglutide
- American Academy of Pediatrics Guidelines, 2023
- Offer pharmacotherapy to adolescents 12+ with BMI >95th percentile in conjunction with “intensive health behavior and lifestyle treatments” (IHBLT)
  - Minimum 26 hours of family-based comprehensive care over 3-12 months to qualify as IHBLT
- Semaglutide, phentermine/topiramate, and liraglutide are approved for use in adolescents

Weghuber D, Barrett T, Barrientos-Pérez M, Gies I, Hesse D, Jeppesen OK, Kelly AS, Mastrandrea LD, Sørrig R, Arslanian S; STEP TEENS Investigators. Once-Weekly Semaglutide in Adolescents with Obesity. N Engl J Med. 2022 Dec 15;387(24):2245-2257. doi: 10.1056/NEJMoa2208601. Epub 2022 Nov 2. PMID: 36322838; PMCID: PMC9997064.

Adverse Effects of GLP-1 Medications

GI

- Nausea (16-44%)
- Diarrhea (9-30%)
- Vomiting (5-24%)
- Constipation (3-24%)
- Abdominal pain (6-20%)
- Cholelithiasis (0-4%)
- Pancreatitis (<1%)

Cardiac

- Hypotension (1-2%)
- Orthostasis (1-2%)
- Increased HR (postmarketing, thought to be related to GLP receptors in SA node)
- QT prolongation (postmarketing)

Other

- Headache (14-17%)
- Fatigue (11%)
- Rash (3%)
- Hypersensitivity Reactions (<1%)
- Acute Kidney Injury (postmarketing, often due to GI side effects)
- Medullary thyroid cancer (in rodents but not primates)

Genetic Obesity - Testing

- https://uncoveringrareobesity.com/ — 79 genes and 1 chromosome region
  - Must be ≤18 yo with BMI >97th percentile or ≥19 yo with BMI >40 and history of childhood obesity
  - Also eligible if symptoms suggest Bardet-Biedl or an immediate family member of some previously tested patients
  - Sample collected at home or office, results within ~3 weeks
- Rhythm Pharmaceuticals covers the cost of the test and provides collection kits
- Patient information available in both English and Spanish

Genetic Obesity – Treatment

Table 1: Adverse Reactions Occurring in 3 or More Patients Treated with IMCIVREE in Open Label Clinical Studies of 52-week Duration

	IMCIVREE-treated Patients N = 27 %
Injection site reaction [a]	96
Skin hyperpigmentation [b]	78
Nausea	56
Headache	41
Diarrhea	37
Abdominal pain [c]	33
Back pain	33
Fatigue	30
Vomiting	30
Depression [d]	26
Upper respiratory tract infection	26
Spontaneous penile erection [e]	23
Arthralgia	19
Asthenia	19
Dizziness	15
Dry mouth	15
Dry skin	15
Insomnia	15
Vertigo	15
Alopecia	11
Chills	11
Constipation	11
Influenza-like illness	11
Muscle spasm	11
Pain in extremity	11
Rash	11
Suicidal ideation	11

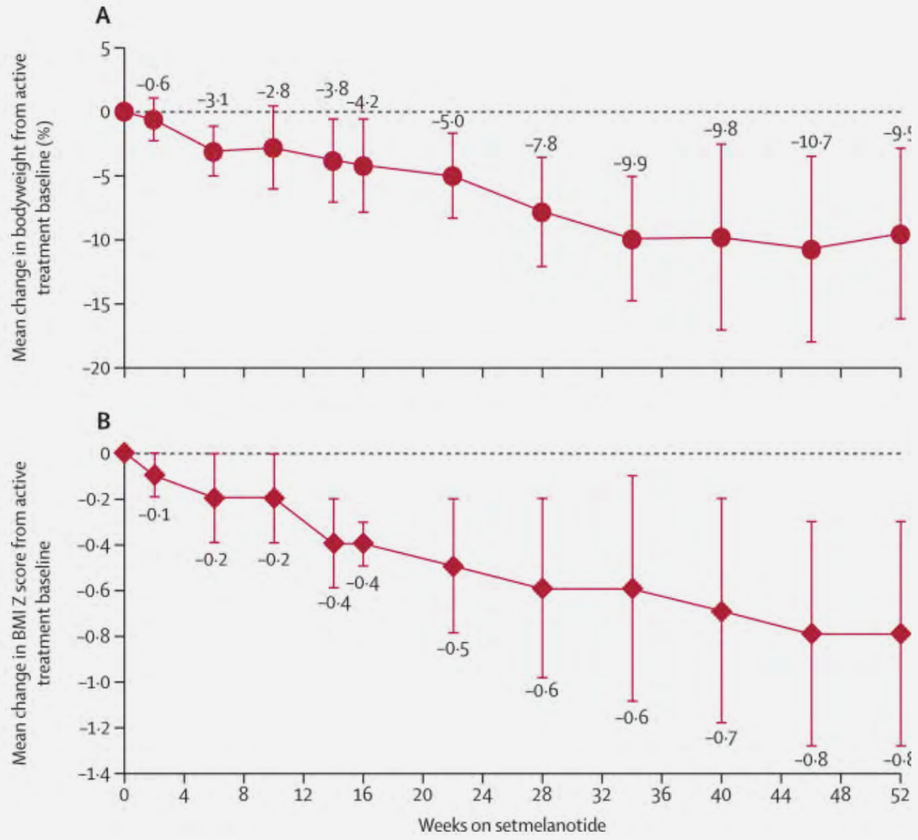
[a] Includes injection site erythema, pruritus, edema, pain, induration, bruising, hypersensitivity, hematoma, nodule, and discoloration
[b] Includes skin hyperpigmentation, pigmentation disorders, skin discoloration
[c] Includes abdominal pain and upper abdominal pain
[d] Includes depressed mood
[e] n = 13 male patients

- Setmelanotide (Imcivree) - MC4R, MC3R, MC1R agonist designed to restore upstream activity
  - MC1R - skin pigmentation
  - MC3R, MC4R - body weight
- FDA approved for Bardet-Biedl Syndrome (BBS), pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency in children and adults ≥6 years old
- Daily subQ injection, dose starts at 1 mg (<12 yo) or 2 mg (≥12 yo), max of 3 mg daily
- Cost starts at $330 per mg = $361,350 annually at max dose

Imcivree (setmelanotide) [package insert]. Boston, MA: Rhythm Pharmaceuticals; 2020.

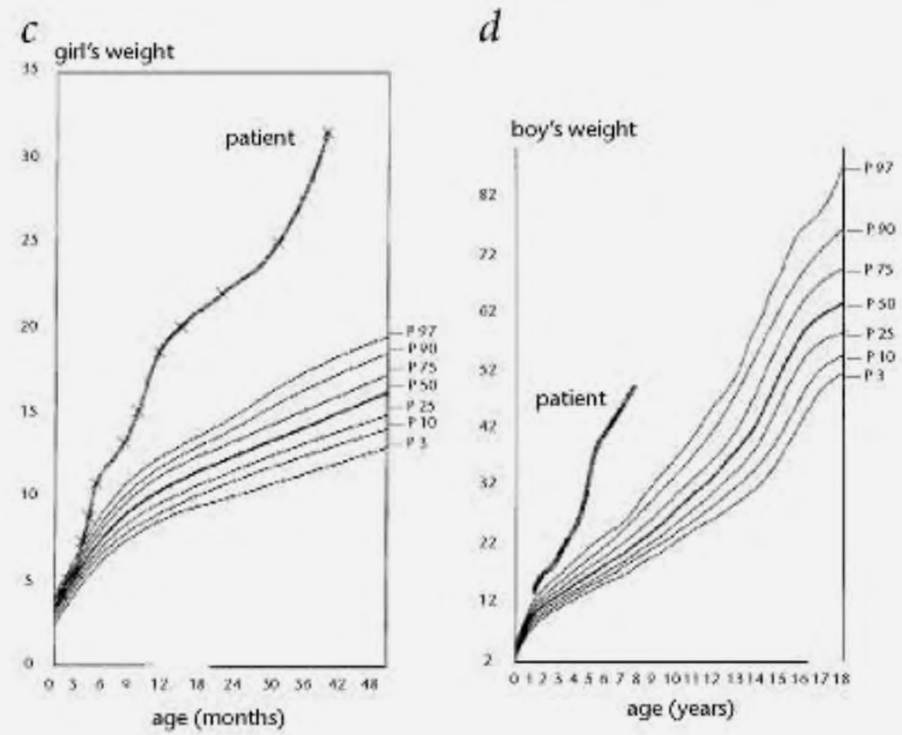
Genetic Obesity - Bardet-Biedl Syndrome (BBS)

- Multisystem ciliopathy, autosomal recessive; 21 BBS genes identified
- Incidence ~1 in 150,000-160,000 in North American and European populations
- Central obesity, rod-cone dystrophy, renal malformations, learning difficulties, polydactyly, hypogonadism
- Setmelanotide approved for BBS in 2022
  - Phase 3 trial, 38 patients randomized to setmelanotide or placebo for 52 weeks
  - 32.3% of patients age 12 or older lost ≥10% bodyweight; mean change -5.2%; p=0.0005
  - 62.5% of patients reached ≥25% reduction in average daily max hunger score, mean change -30.9%; p<0.0001



Genetic Obesity – Heterozygous POMC Deficiency

- Early-onset obesity, adrenal insufficiency, hyperphagia, cholestasis, red hair, decreased skin pigmentation
- POMC is cleaved to produce ACTH, lipotrophins, endorphins, and several melanocyte stimulating hormones which stimulate melanocortin receptors (MCRs)
  - MC1R - skin pigmentation
  - MC2R - cortisol
  - MC3R, MC4R - body weight
- Setmelanotide approved by FDA for POMC deficiency in 2020



Krude, H., Biebermann, H., Luck, W. et al. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. Nat Genet 19, 155–157 (1998). https://doi.org/10.1038/509

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