Obesity Medication Selection to Manage Weight Gain after Metabolic and Bariatric Surgery

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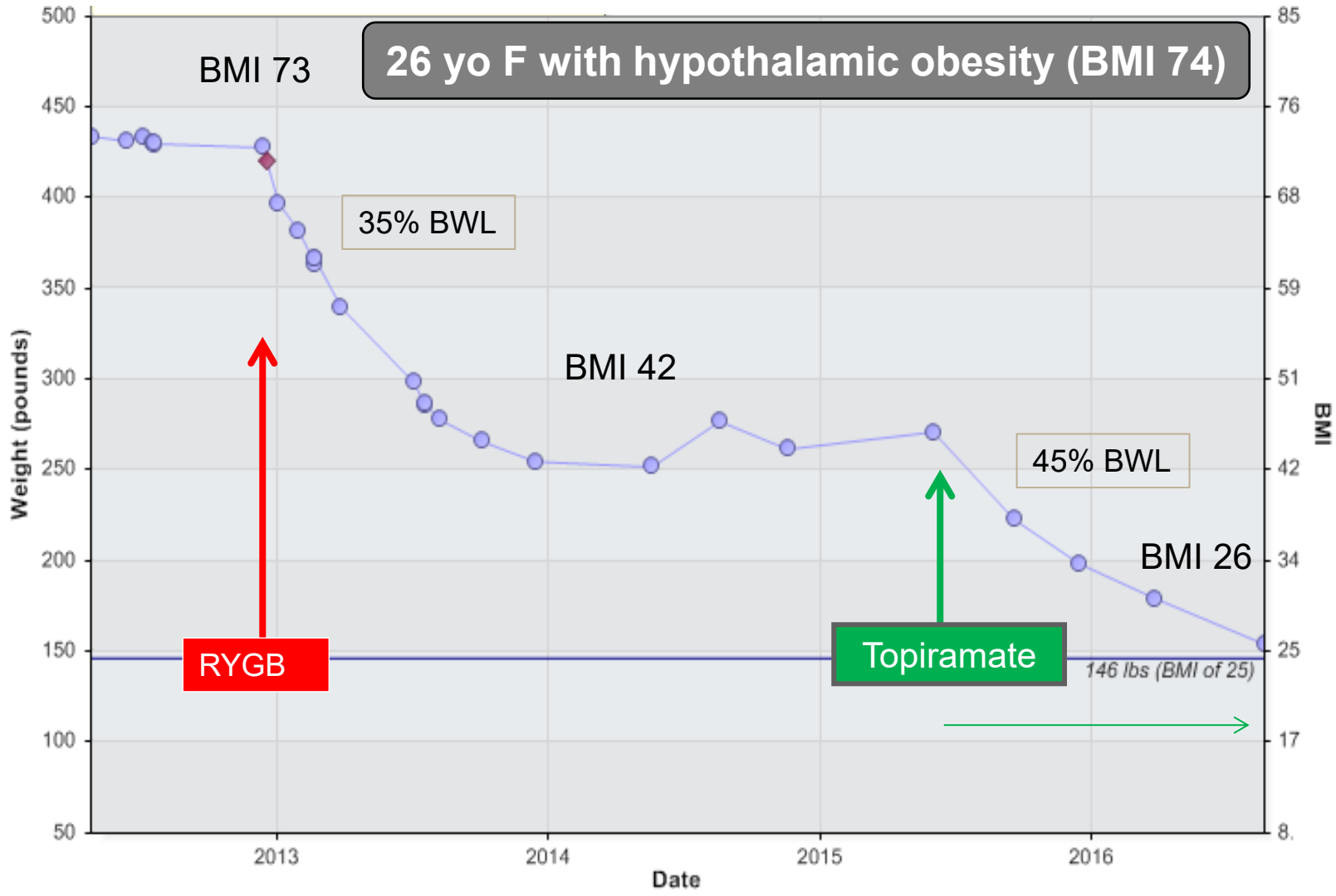
Objectives

- Recognize the use of obesity management medications (OMMs) as adjunctive therapies for weight gain after metabolic and bariatric surgery(MBS)
- Understand the need to individualize pharmacotherapy given lack of data to determine which OMM is best
- Identify obesity-related comorbidities and eating behaviors to help OMM selection
- Recognize many questions remain about the selection of OMM including timing of initiation and outcome measures

Adjuvant Obesity Therapy for Obesity after Metabolic and Bariatric Surgery



Use of Liraglutide is effective in Weight Recurrence after RYGB

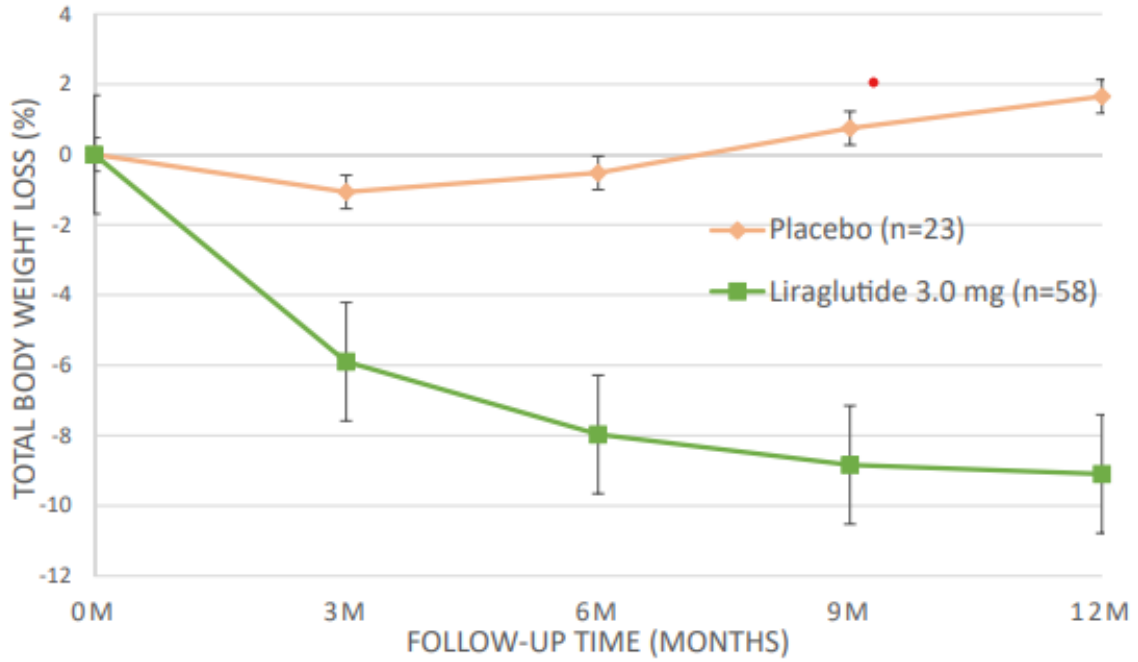


Fig 1. Mean percentage change in total body weight from baseline to 12 months

1.1%

8.8%

52wk RCT, n=81
18-120 mo s/p RYGB
>25%BW loss+10%BW gain
Liraglutide 3.0 vs Placebo

Lofton H et al *Surg Obes Rel Dis* 2025;21:135-45

Current Obesity Pharmacotherapy in the United States

FDA Approved Medications

1st Gen obesity medications (OMs)
- Phendimetrazine
- Benzphetamine
- Diethylpropion
- Phentermine

2nd Generation OMs
- Orlistat
- Phentermine/Topiramate
- Naltrexone/Bupropion
- Liraglutide 3.0 mg

3rd Generation OMs
- Semaglutide 2.4mg
- Tirzepatide

for monogenetic obesity
- Setmelanotide

Off Label Medications

for diabetes
- Metformin
- Pramlintide — Amylin Agonist
- Exenatide — GLP1R Agonist
- Liraglutide 1.8mg — GLP1R Agonist
- Dulaglutide — GLP1R Agonist
- Semaglutide 1mg — GLP1R Agonist
- Tirzepatide — GIPR-GLP1R Agonist
- Can/Emp/Dapagliflozin — SGLT2 Inhibitor

for seizures, migraines
- Topiramate
- Zonisamide

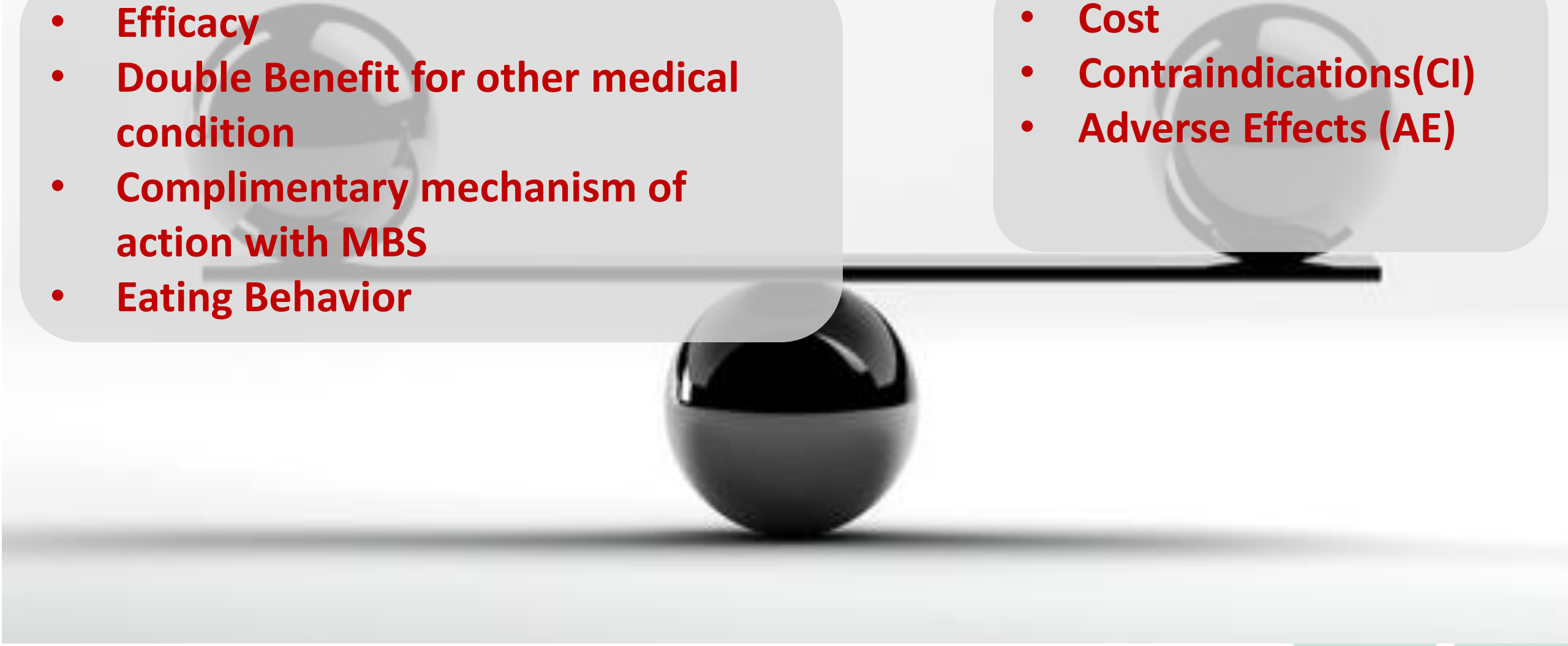
- Bupropion — for depression
- Naltrexone — for addiction

Slide: W. Scott Butsch

How do you choose an appropriate OMM for Patients with Weight Gain after MBS?

- Efficacy
- Double Benefit for other medical condition
- Complimentary mechanism of action with MBS
- Eating Behavior

- Cost
- Contraindications(CI)
- Adverse Effects (AE)



Efficacy of Obesity Management Medications

Witkamp RF. Pharm Res., 2011;28: 1792.; Gadde K. Arch Int Med, 2013; Apovian CM et al. Obesity. 2013;21; Powell AG et al. Clin Pharm Ther, 2011;90 ; Torgerson JS . Diab Care, 2004; Smith et al. NEJM, 2010;363.; Garvey WT. AJCN. 2012.; Bonora,E. Diabetes Obes Metab. 2021;23. Wilding JA, et al. NEJM, 2021. Jastreboff A, et al NEJM 2022

Where Obesity Treatments Work

Anti-Obesity Medications
Hypothalamus

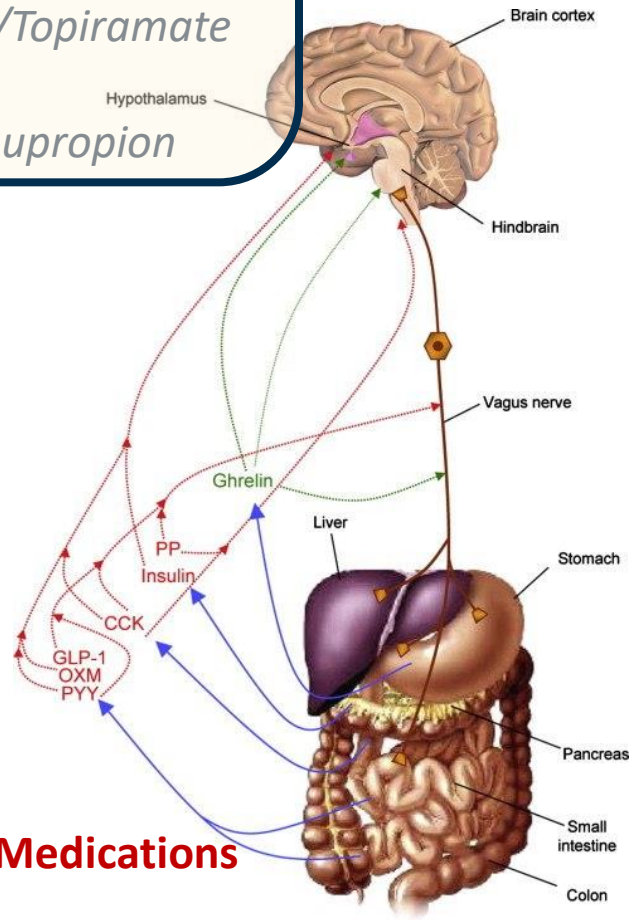
Phentermine
Diethylpropion
Topiramate , Zonisamide
Phentermine/Topiramate
Bupropion
Naltrexone/Bupropion

Oral Capsules
Stomach

Absorbant Polymers

Anti-Obesity Medications
Gut Hormones/Incretins

Pramlintide (Amylin)
Exenatide (GLP-1Ra)
Liraglutide 3.0mg (GLP-1Ra)
Dulaglutide (GLP-1Ra)
Semaglutide 2.4mg (GLP-1Ra)
Tirzepatide (GIP/GLP-1Ra)



Anti-Obesity Medications
Intestines

Orlistat

Electrical Stimulation Devices
Vagus nerve

V-BLOC™

Endoscopic Devices
Stomach, Intestines

Gastric Balloons
Endoscopic Sleeve Gastroplasty
Duodenal-Jejunal Bypass Liner
Duodenal Mucosal Resurfacing

Bariatric and Metabolic Surgery
Stomach, Intestines

Sleeve Gastrectomy
Gastric Bypass
SADI
Biliopancreatic Diversion/DS
Adjustable Gastric Band

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Mechanisms of AOMs should complement Surgery

RYGB, SG**

- Increase GLP-1, PYY
- Decrease ghrelin
- Increase bile acids
- Altered microbiome

+

AOM

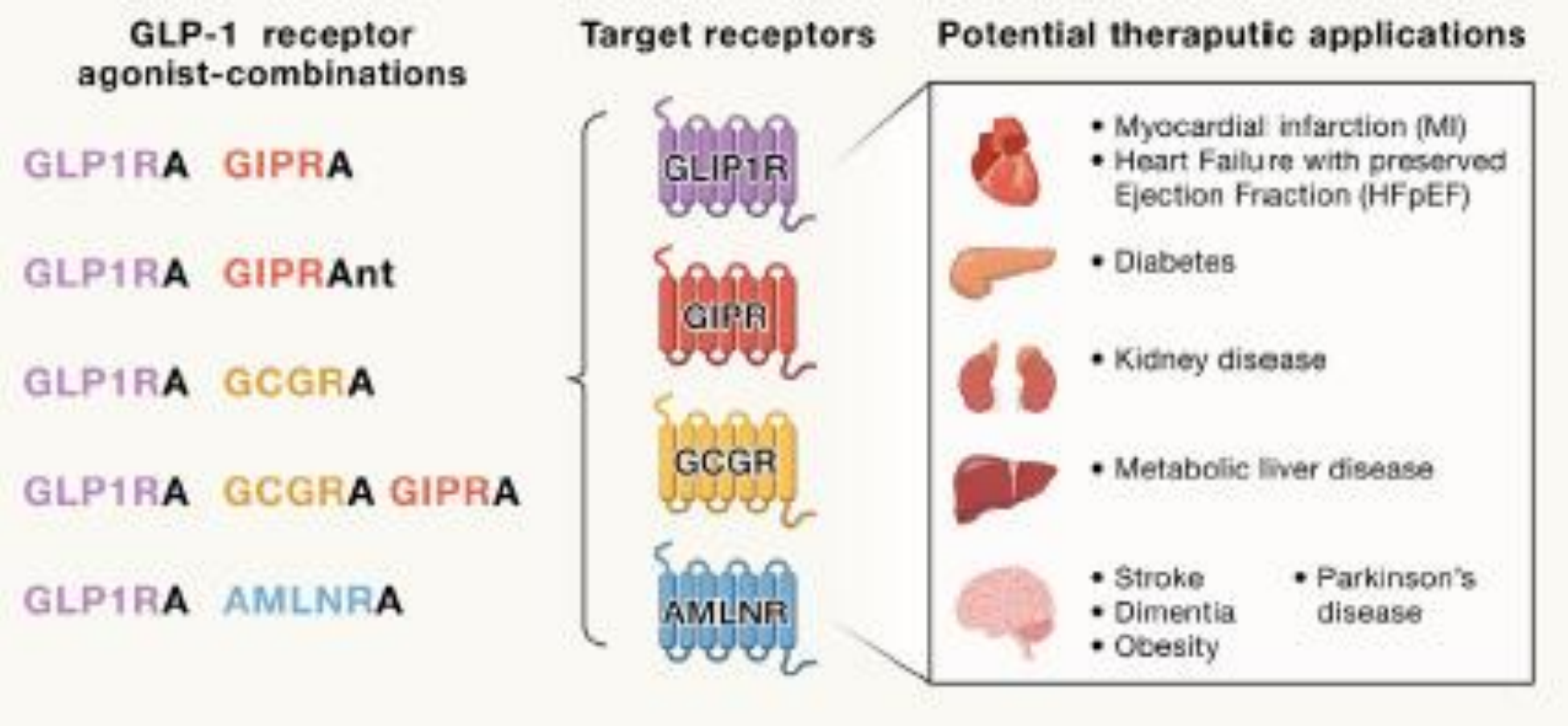
- Increase Norepinephrine
- Decrease Dopamine
- Increase GLP-1
- Increase μ-opioid
- Increase Amylin

**These factors are associations and have not been shown to be causal

Tailoring Anti-Obesity Medications with Dual Benefit

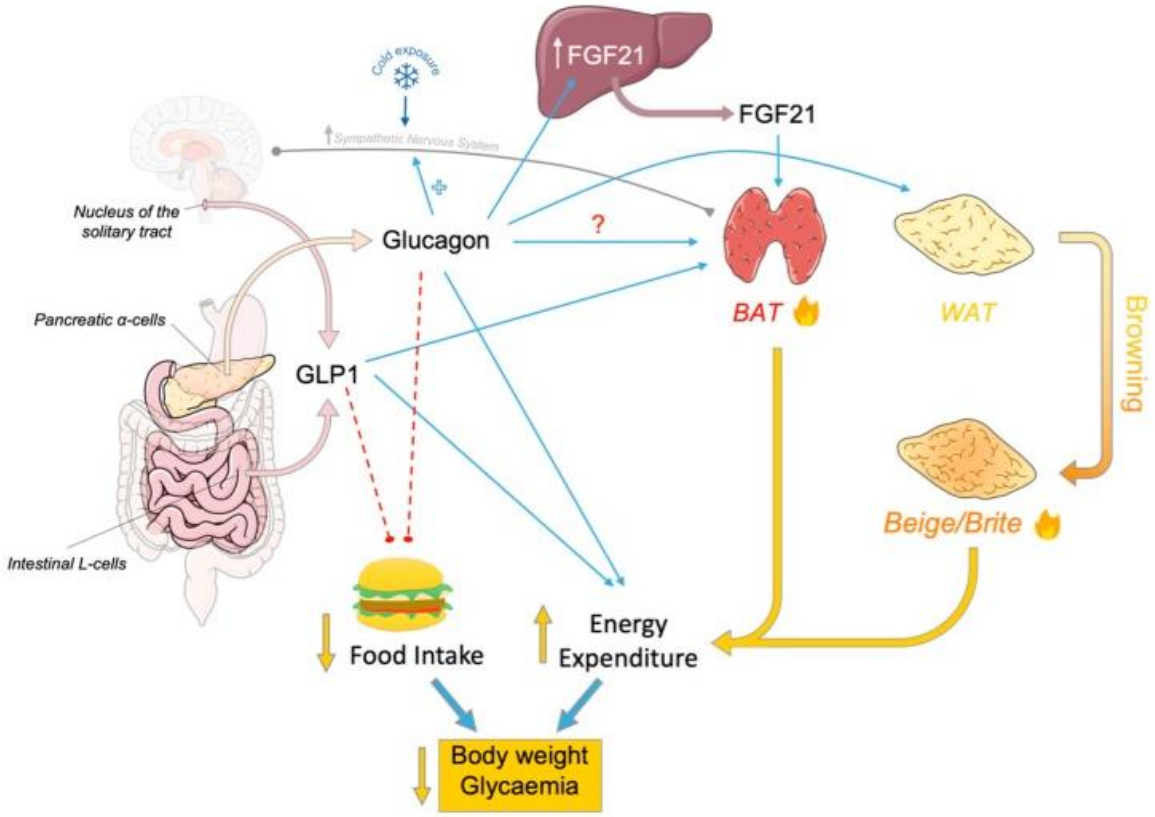
Additional Condition	Medication to Consider * Off Label Use
Diabetes	Liraglutide 1.8mg; Dulaglutide, Semaglutide 1.0 (*2.4mg); Cana/Empa/Dapa-gliflozin, Tirzepatide
Depression	Bupropion
Migraines	Topiramate, Zonisamide
Bipolar disorder (on psychotropic medications)	Metformin*
Sleep dysfunction	Topiramate*, Zonisamide*
Elevated LDL,TG	Orlistat
Smoking, Cravings	Naltrexone-bupropion, Bupropion, Topiramate*
Pain	Naltrexone, Topiramate

GLP1 with other Metabolic Peptide Combination Therapies Target Cardiometabolic Conditions

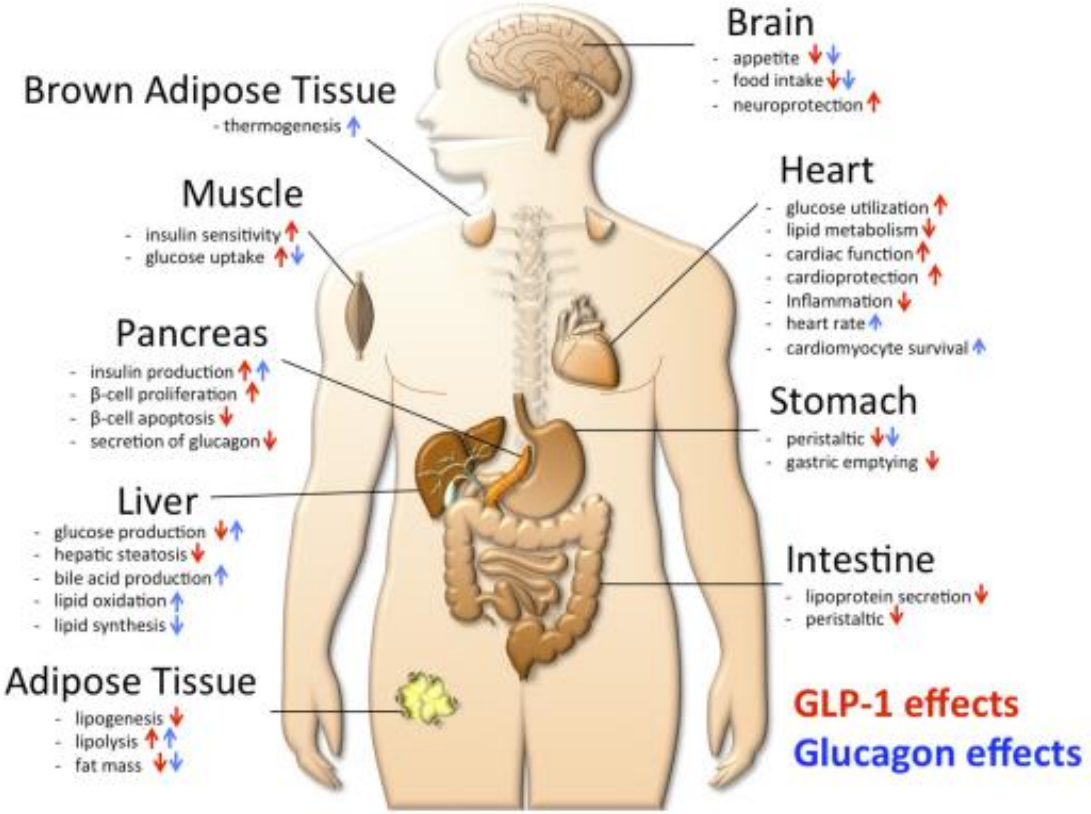


Abel ED et al. *Cell* 2024;187

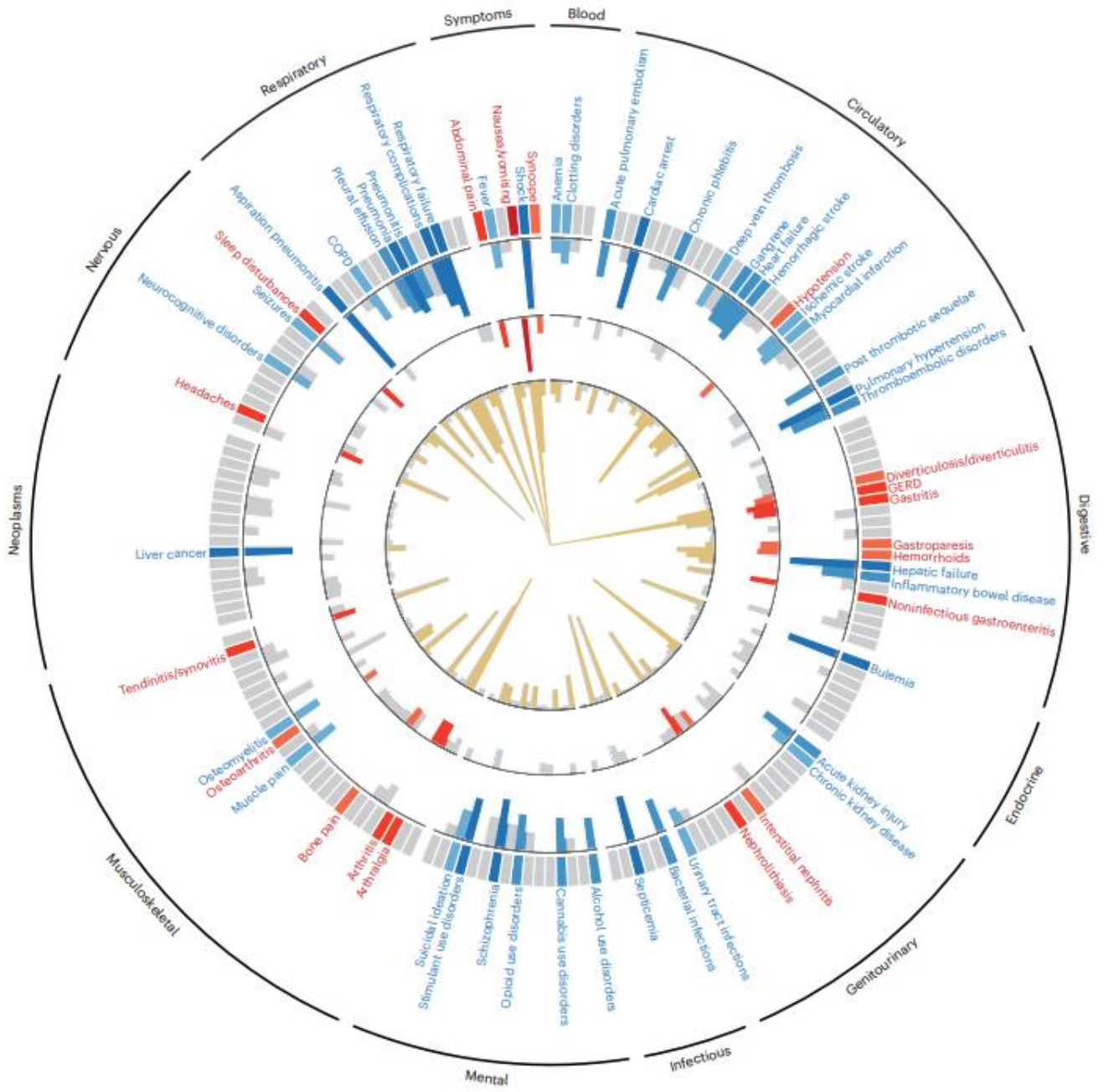
Glucagon Physiological Effects



González-García I, et al. Glucagon, GLP-1 and Thermogenesis. *Int J Mol Sci*. 2019



Muller TD et al. *Physiol Rev* 97: 721–766, 2017



nature medicine

Article

https://doi.org/10.1038/s41591-024-03412-w

Mapping the effectiveness and risks of GLP-1 receptor agonists

Received: 14 June 2024

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Yan Xie[1,2,3,4], Taeyoung Choi[1,2] & Ziyad Al-Aly[1,2,5,6,7]

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are increasingly being used to treat diabetes and obesity. However, their effectiveness and

Xia Y et al *Nature Med* 2025

VAMC, >1M T2D, 95%M, 2017-2023
215K on GLP1RA
GLP1RA v Sulfony, DPPIV, SGLT2i, Usual Care
175 Health Outcomes

- Neurocognitive disorders
- Substance use disorders
- Coagulation
- Cardiometabolic disorders

Understand Components of Appetite

Patient with sweet cravings

Hunger

Drive to consume

Wanting

Motivation to consume a specific food (craving)

Satiety

End state of satisfaction

(between-meal inhibition)

Fullness

Physical feeling experienced in the gut

Satiation

Negative feedback, leading to meal termination (within-meal inhibition)

Liking (hedonic)

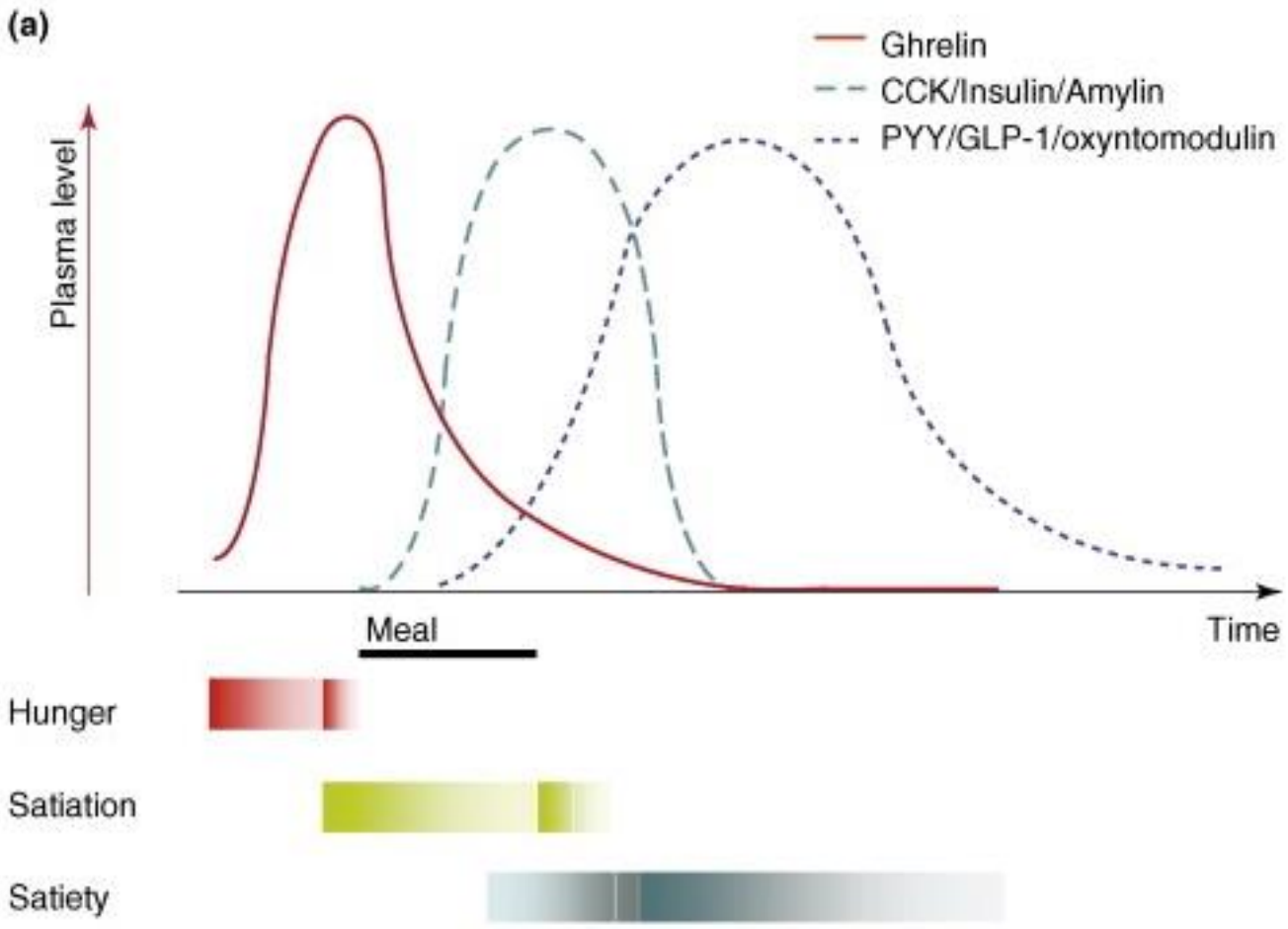
Sensory pleasure elicited by contact with food

Prospective food consumption

How much an individual feels they would like to eat

Blundell *et al*. *Obes Rev* 2010;11:251–270; van Can *et al*. *Int J Obes* 2014;38:784–93

Symptoms of Appetite Control:
How to assess effectiveness of pharmacological interventions



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Tailoring selection of anti-obesity medication to *individual eating behaviors*

Table 1 Mechanism of action and effect on appetite expression, eating behaviour and CNS activity for weight loss pharmacotherapies

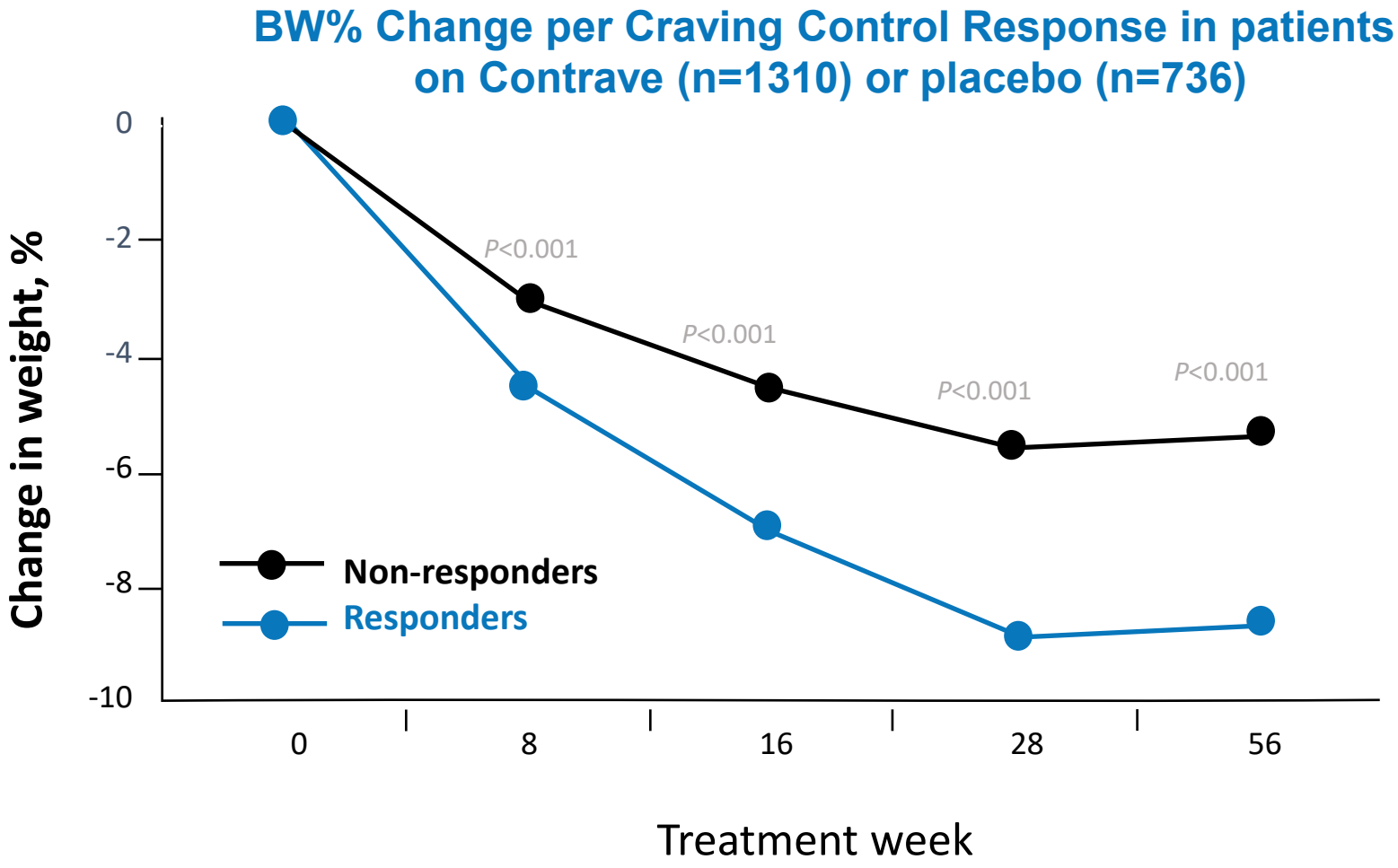
Drug	Mechanism of action	Effect on appetite expression, eating behaviour or CNS activity
Liraglutide	GLP-1 receptor agonist	Reduced intake, reduced post-meal hunger, increased post-meal satiety and fullness. Reduced CNS reward activity
Bupropion/naltrexone	Dopamine and norepinephrine reuptake inhibitor+opioid (mu and k) receptor antagonist	Increased fullness, reduced hunger, reduced desire for sweet, non-sweet or starchy foods, increased ability to control eating and resist craving. Increased activity in inhibitory control-related areas (anterior cingulate), reduced activity in hypothalamus
Lorcaserin	Selective $5HT_{2C}$ receptor agonist	Reduced food intake, decreased hunger, decreased activity in attention-related neural regions (parietal and visual cortices), reduced emotional and salience related limbic activity (insula and amygdala)
Phentermine/topiramate	TAAR1 agonist and norepinephrine releasing agent+sulphamate-substituted monosaccharide with action on GABA signalling	No published data

Characteristics of eating behaviors

- **Lack of fullness**
- Increased sweet cravings
- Increased Hunger
- Increased desire
- Inability to control eating

Roberts CA et al. Acta Diabetol 2017;54:715-25.

Responders to Craving Control lose more weight with Naltrexone/Bupropion



***P<0.001.

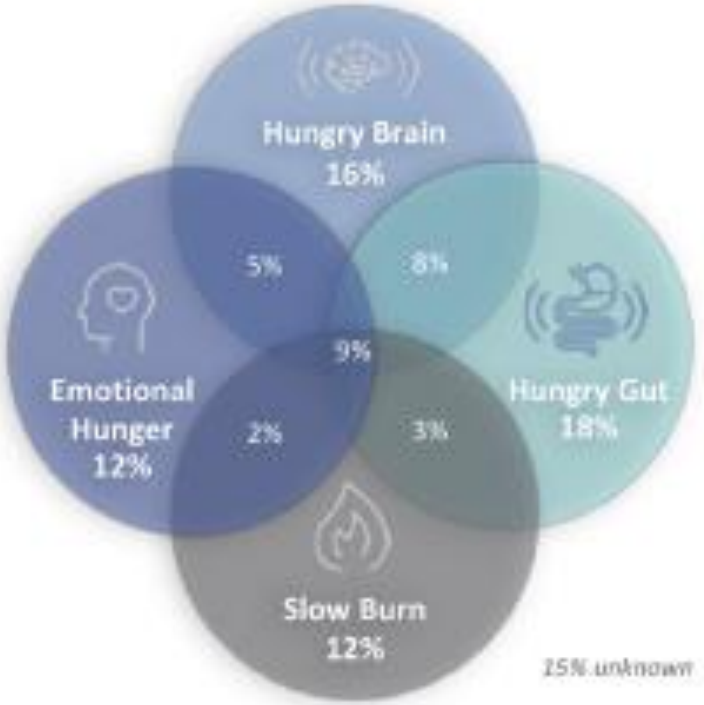
Responders were defined as patients who exhibited the greatest improvement in Craving Control subscale of the CoEQ at week 8. Non-responders exhibited the lowest Craving Control improvement at week 8.

Dalton M et al. *Int J Obesity*. 2017;41(8):1232-1236.

Phenotype-Guided Pharmacotherapy is effective

N=450 participants phenotyped
N=84 cases, 284 controls

- **Hungry Brain** (**Satiation**): Increased hunger, Short duration of satiety
  - **Visual Analog Scale (VAS) for Hunger and desire to eat**
  - **Satiation: calories consumed to reach fullness & terminate meal (ad libitum buffet)**
- **Hungry Gut** (**Satiety**): increased gastric emptying
  - **Satiety: duration of fullness, return to hunger – VAS for appetite at baseline, postprandial**
  - **Gastric emptying t½ (minutes)**
- **Slow Burn** (**Low Metabolism**): resting metabolic rate via IC
  - **Energy Expenditure: Indirect calorimetry**
  - **Reported non-exercise physical activity + Reported exercise**
- **Emotional Hunger** (**Hedonic Eating**): Hedonistic eating habits via questionnaire
  - **Hospital Anxiety and Depression Score (HADS)**
  - **Three Factor Eating Questionnaire (TFEQ-21)**
  - **Emotional Eating Questionaires**

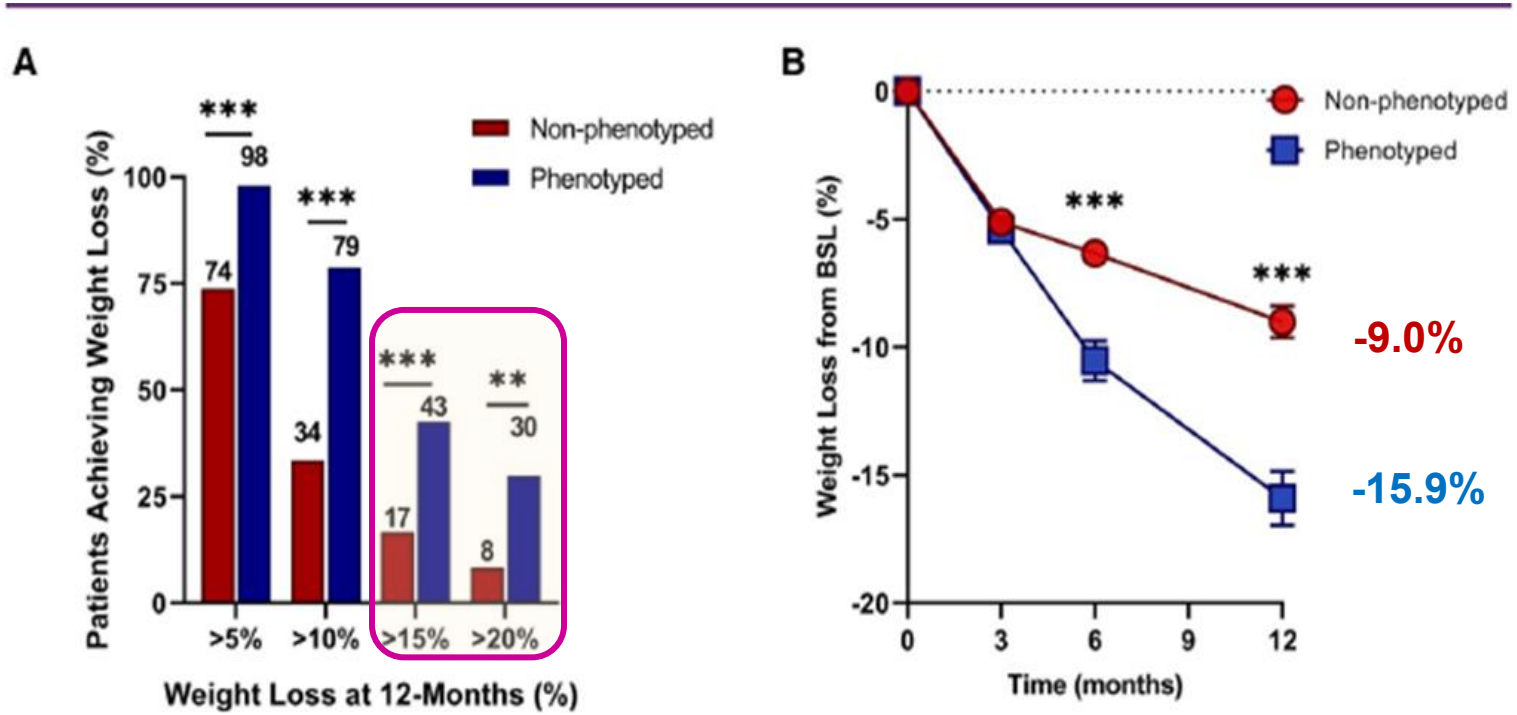


Acosta A et al. *Obesity* 2021; 29:662-71

Phenotype-Guided Pharmacotherapy is more effective than usual obesity care

Obesity Medications for Phenotype Classification

- **Hungry Brain** (Satiation): **Phentermine/Topiramate 7.5/46** ~~or Lorcaserin 20mg~~
- **Hungry Gut** (Satiety): **Liraglutide 3mg/day**
- **Slow Burn** (Low Metabolism): **Phentermine 15mg/d + Resistance Training**
- **Emotional Hunger** (Hedonic Eating): **Naltrexone/Bupropion 16/180mg twice daily**



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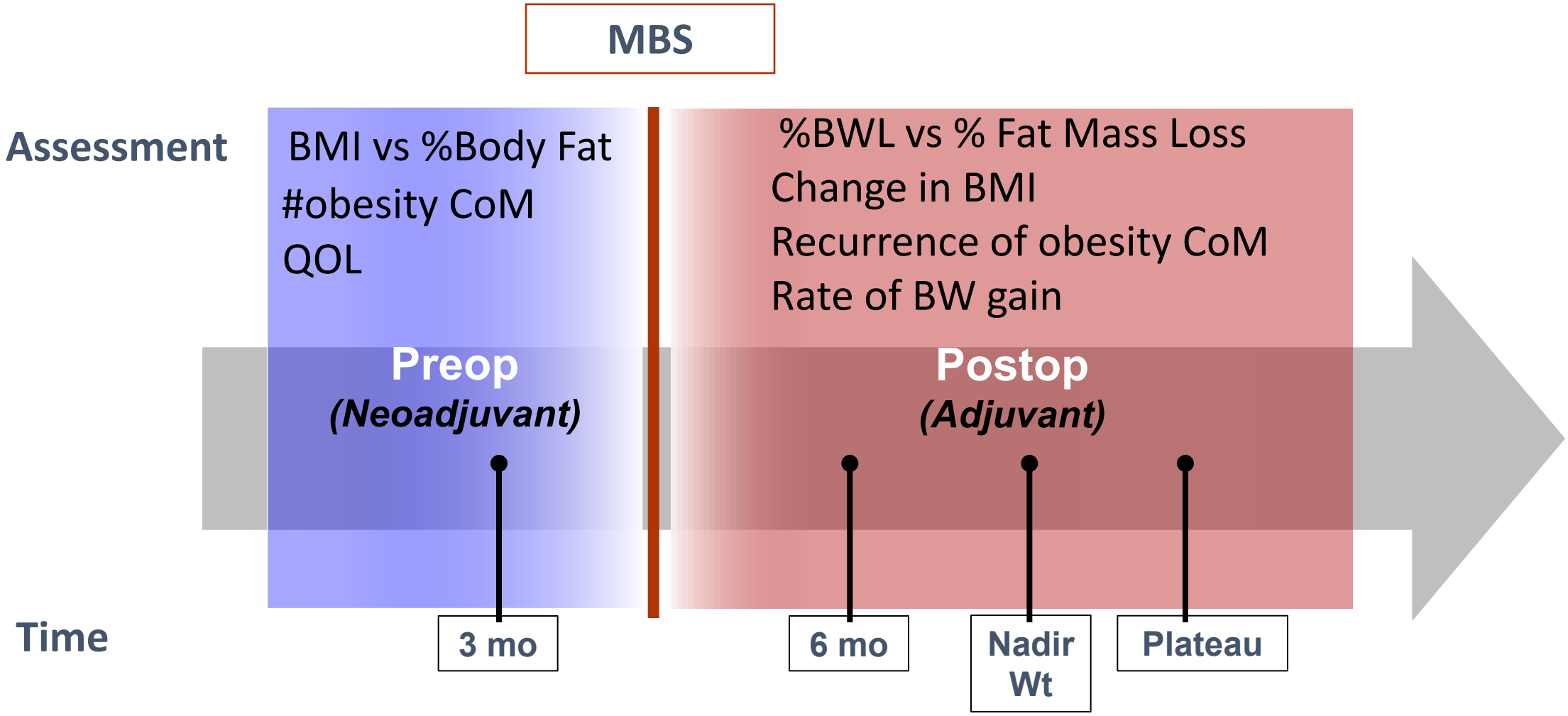
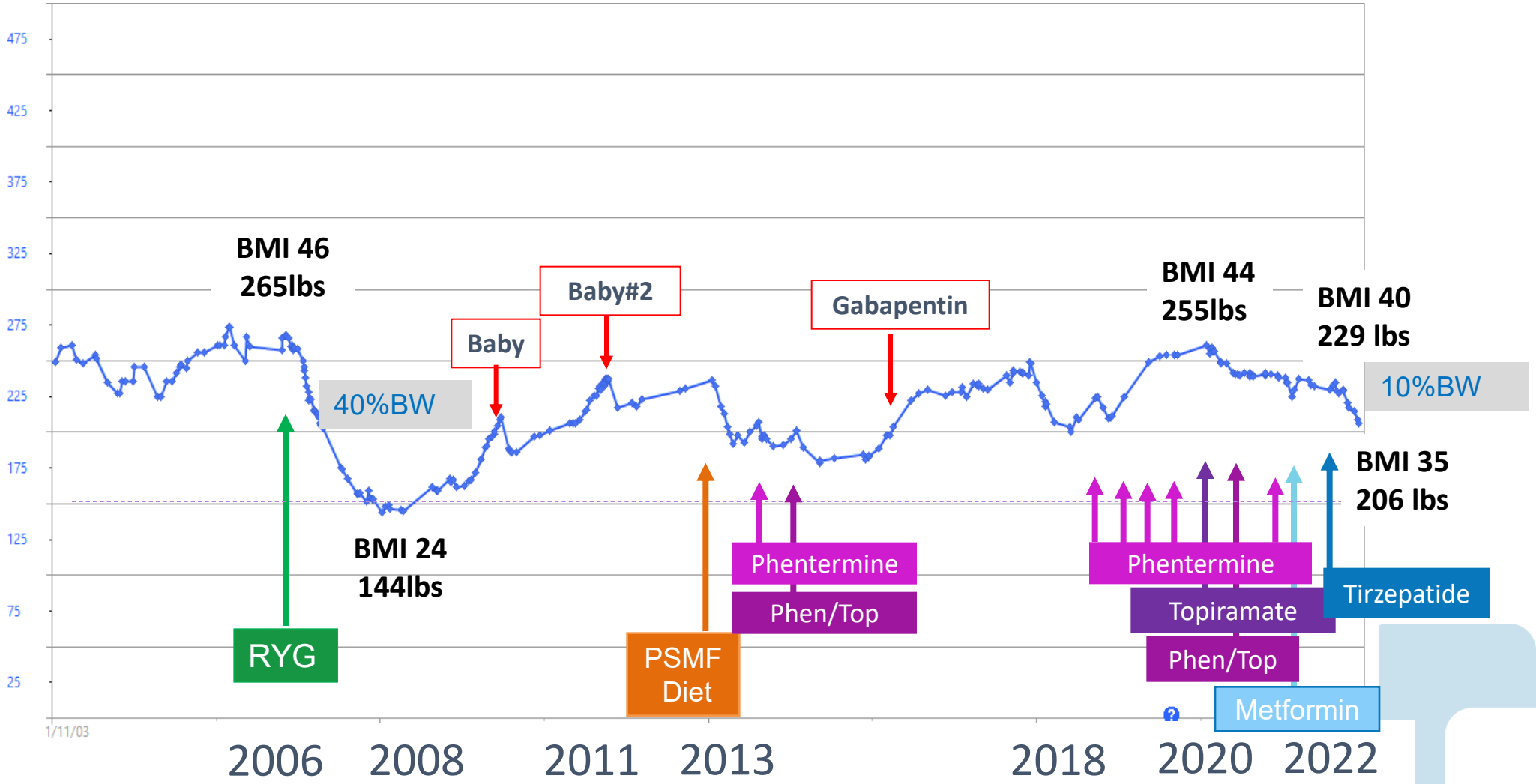
Challenges to Using Obesity Medications in MBS Pts

Timing and Metrics of Adjuvant Therapy is not clear



Don’t Stop Treating Obesity Seriously



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Summary

- **Use combination multimodal therapy early** with obesity medications in patients with Weight Gain
- **Individualize Pharmacotherapy** as there is **no data** to determine which OMM is best
- Most studies examining OMMs after MBS are observational, retrospective
- Consider **other factors** eg “dual benefit”, eating behaviors, and cost
- **Many questions remain about *initiation*, *selection*, and *outcome measures*** of OMMs

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