Life Beyond GLP-1s: Maximizing the Surgeon's Pharmacological Toolkit for Precision Obesity Care

azurity pharmaceuticals

Featured faculty

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Chair, WOF Clinical Care Committee
President IFSO Global (2024-2025)
Past President SBCBM (2011-2012)
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Metabolic and Bariatric Surgery: Pathways to Better Outcomes

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Disclosures

Ricardo Cohen, MD

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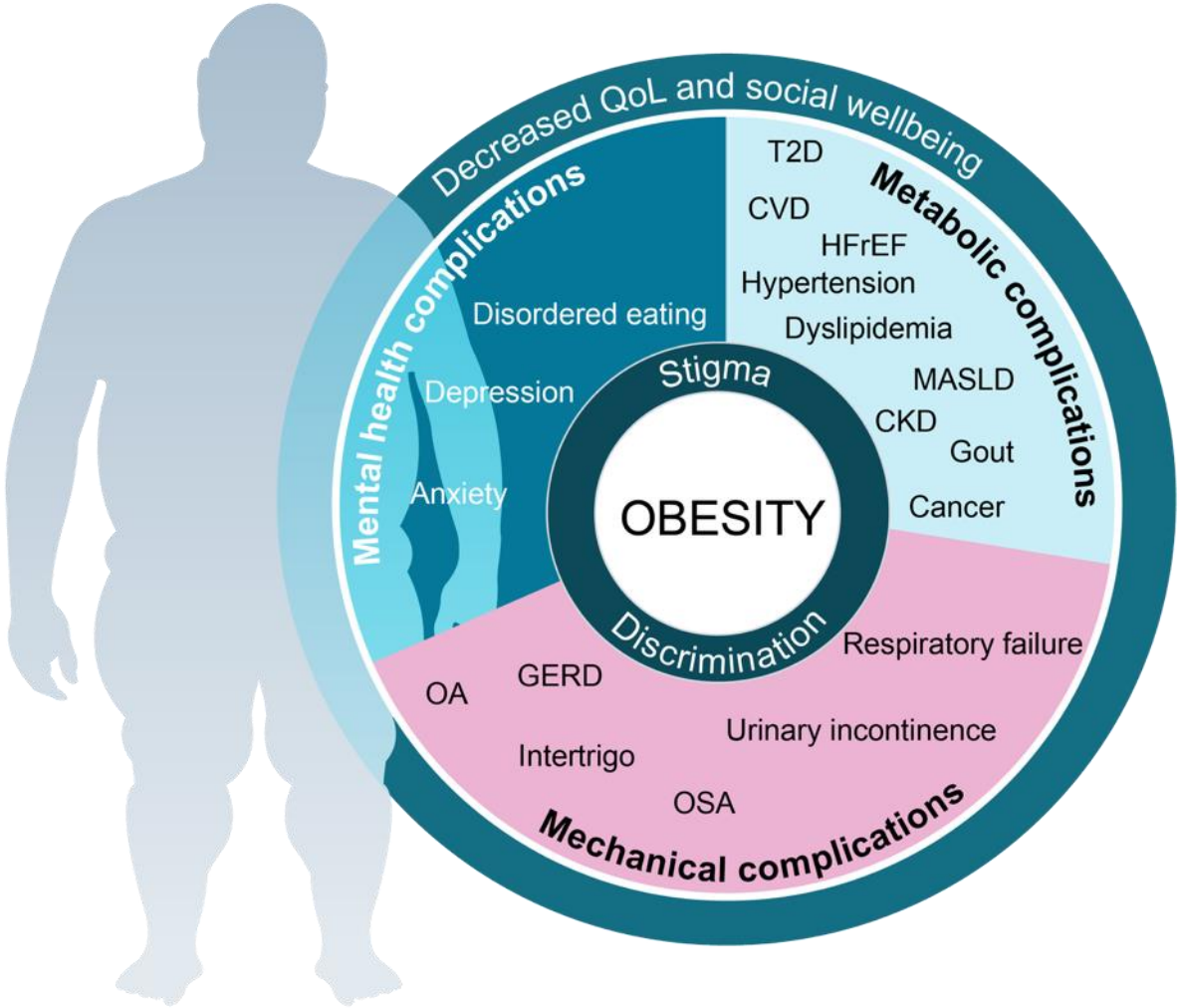
Obesity is not just “weight”



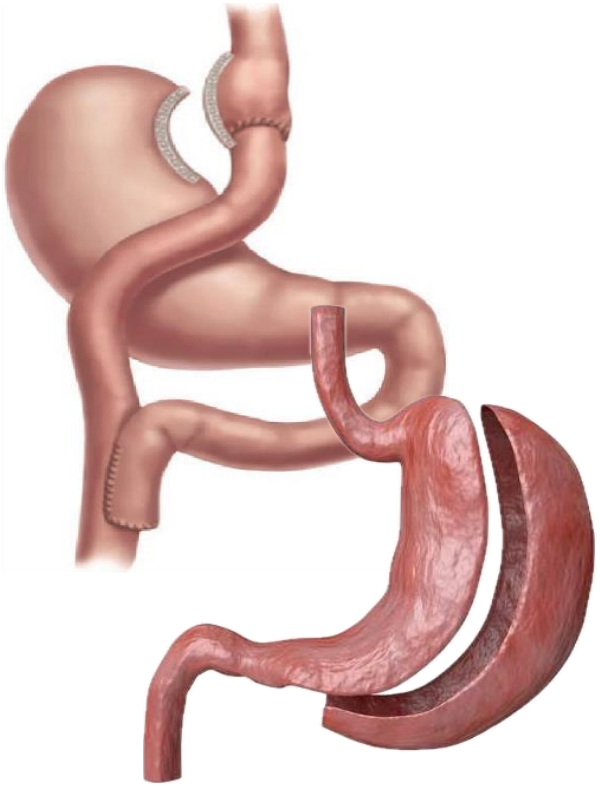
Clinical obesity is a multifaceted complex disease with signs, symptoms, and complications.

CKD, chronic kidney disease; CVD, cardiovascular disease; GERD, gastroesophageal reflux disease; HFrEF, heart failure with reduced ejection fraction; MASLD, metabolic dysfunction-associated steatotic liver disease; OSA, obstructive sleep apnea; T2D, type 2 diabetes.

1. Lingvay I,,, Cohen RV et al. *Lancet.* 2024;404:972-987. **2.** Nadolsky K et al. *Endocrine Pract.* 2025;31:1351-1394. **3.** Bae JP et al. *BMC Public Health*. 2025;25:273.

Bariatric/metabolic surgery

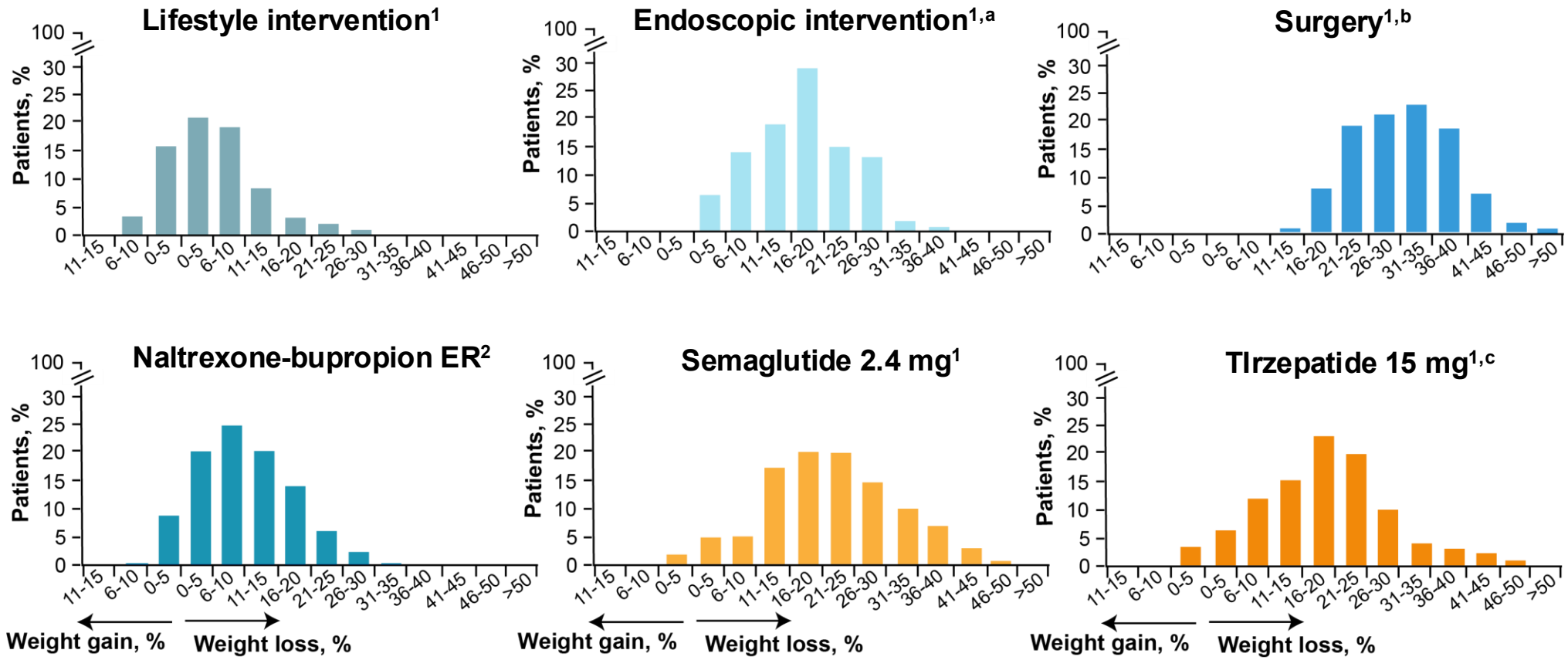
- ✓ Long-term significant weight loss[1]
- ✓ Physiologic mechanisms[2]
- ✓ Durable T2D remission (glucocentric endpoint)[3]
- ✓ Renoprotective[4]
- ✓ Decrease CV risk factors[1]
- ✓ Decrease CV events and mortality[5]
- ✓ Safe[6]



1. Sjöstrom L et al. *JAMA*. 2012;307(1):56-65. **2.** Cummings D et al. *Diabetes Care*. 2006. **3.** Courcoulas A et al. *JAMA*. 2024; 332(1):76-77. 4. Cohen RV et al. *Lancet EC*. 2022. **5.** Aminian A et al. JAMA. 2019;322(13):1271-1282. **6.** Arterburn D et al. *JAMA*. 2022.

Heterogeneity of response to weight loss interventions

Heterogeneity in weight loss response after approximately 12 months[1,2]



Only treatments for which 1-year data were available have been included. To enable comparison between different treatment modalities, percentage changes for total bodyweight are presented, as placebo-subtracted data are not usually reported in studies of lifestyle interventions and bariatric surgery. [a]For endoscopic intervention, mean results for intragastric balloon and endoscopic gastroplasty are shown for which data were available. [b]For surgery, mean results for sleeve gastrectomy and Roux-en-Y gastric bypass have been given as they account for 95% of all bariatric surgeries worldwide. [c]For tirzepatide, since published data reached only 25% weight loss or more, the proportion of participants obtaining higher weight losses has been presumptively assigned following the unimodal distribution observed for other anti-obesity medications.

1. Perdomo CM… Cohen RV. *Lancet.* 2023;401:1116-1130. **2.** Data on file. Currax Pharmaceuticals LLC.

There is no magic bullet for obesity

*Ildiko Lingvay, Priya Sumithran, Carel W le Roux, *Ricardo V Cohen*
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Lancet DE, July 2023

There is no magic bullet for obesity

Treating obesity has wide-ranging benefits on health and wellbeing.[1] Advances in medications for obesity have sparked interest, and excessive unregulated media attention has driven unprecedented demand for these new agents. However, the media coverage risks propagating the view that there is a magic bullet treatment for obesity.

Obesity is a chronic and relapsing condition with a complex multifactorial pathophysiology that spans genetics, metabolic maladaptation, neuroendocrine abnormalities, and major shifts in lifestyle, food composition, and societal inequities. An effective approach to obesity treatment must be multifactorial, individualised, and adaptable over time. The treatment will often require a combination of modalities and long-term therapy, akin to the accepted approach for other chronic diseases. The new medications will neither cure obesity nor render other approaches obsolete, including lifestyle interventions and metabolic surgery.

Although the latest generation of medications for obesity shows average results of 15–20% body weight loss per patient, seemingly even without major lifestyle interventions,[2] a few points are worth noting. First, weight loss observed in clinical trials using any obesity treatment has a Gaussian distribution, and up to 20% of participants do not experience clinicaly significant weight loss. Additionally, up to 10% of patients will struggle to tolerate the side effects from the medications.[2] Second, even people who meet the treatment goals with obesity pharmacotherapy might decide to explore metabolic surgery for long-term maintenance of weight loss and health gains. Third, the benefits of obesity medications cease if the medications are stopped.[3] Fourth, regardless of the weight loss method or its effect on bodyweight, a healthy lifestyle remains the cornerstone of optimising health.

Lifestyle interventions also are a valid and independent obesity management strategy. For up to 20% of patients, optimising nutritional quality, eating habits, eradicating maladaptive behaviours, and incorporating physical activity will successfully sustain weight loss and health gains.

Metabolic surgery also remains an effective therapy for obesity, reducing cardiovascular events, microvascular complications, some types of cancer, and all-cause deaths. As obesity is progressive, 10–20% of patients might regain a substantial amount of weight after surgery, often resulting in suboptimal control or relapses of the health issues related to obesity, and necessitate additional weight loss interventions (eg, use of medications). The inverse is also likely to be true for pharmacotherapy.

Combining surgical and medical approaches is standard practice in chronic disease management (eg, coronary disease). In oncology, a range of adjunctive treatments (eg, chemotherapy, radiotherapy, or immunotherapy) might be used in addition to surgery to improve outcomes. Likewise, in the treatment of type 2 diabetes and obesity, a combination of metabolic surgery and medications is associated with excellent glycaemic control, weight loss, and even reversal of diabetic complications.[5] Patients with advanced forms of obesity often have suboptimal responses to lifestyle, medical, or surgical interventions alone; thus, combination treatment might be necessary.

A chronic multifactorial disease requires an approach that is long term, multifactorial, flexible over time, and tailored to the individual. We should not promote one form of treatment by dismissing the other options. We need to combine our efforts and use the right tools, at the right time, and for the right person to achieve optimal care and maximise health benefits for our patients.

IL received grants paid to the Institution from Novo Nordisk, Pfizer, Merck, Sanofi, Boehringer-Ingelheim, and Mylan; and received consulting fees, covered travel expenses from Novo Nordisk, Eli Lilly, Johnson & Johnson, Merck, Pfizer, Sanofi, Boehringer Ingelheim, Zealand, Bayer, Intercept, Valeritas, Structure, Carmot, Shionoghi, Mediflix, and WebMD. PS received research grants paid to their institution from National Health and Medical Research Council; and declares co-authorship of manuscripts with medical writing assistance from Novo Nordisk. RVC received a research grant paid to the Institution from Johnson & Johnson, Medtech, and Medtronic; received honoraria for lectures, presentations, and speakers bureaus from Johnson & Johnson, Medtech, Medtronic, Janssen Pharmaceuticals, Novo Nordisk, and Abbott; and is a member of the Scientific Advisory Board for Baritek and GI Dynamics. CWIR reports grants from the Irish Research Council, Science Foundation Ireland, Anabio, and the Health Research Board; serves on advisory boards and speakers panels of Novo Nordisk, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Glia, Irish Life Health, and Boehringer Ingelheim, Currax, and Rhythm Pharma; CWIR is a member of the Irish Society for Nutrition and Metabolism; he was the chief medical officer and director of the Medical Device Division of Keyron in 2021; CWIR was gifted stock holdings in Keyron and divested all of them in 2021; CWIR continues to provide scientific advice to Keyron for no remuneration and provides obesity clinical care in the Beyond BMI clinic and is their shareholder.

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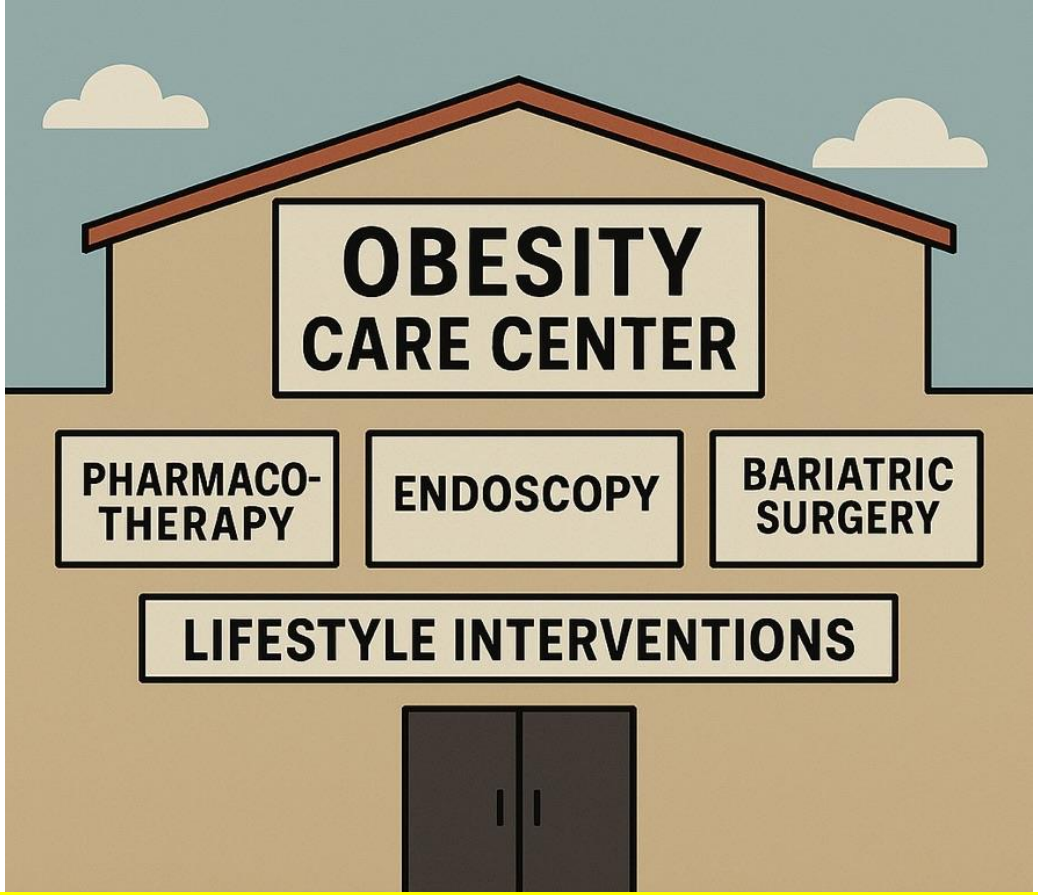
1 Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. *Lancet* 2022; **399:** 394–405.
2 Perdomo CM, Cohen RV, Sumithran P, Clément K, Frühbeck G. Contemporary medical, device, and surgical therapies for obesity in adults.*Lancet* 2023; **401:** 1116–30.
3 Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes Obes Metab* 2022; **24:** 1553–64.
4 Look ARG. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. *Obesity* 2014; **22:** 5–13.
5 Cohen RV, Pereira TV, Aboud CM, et al. Gastric bypass *versus* best medical treatment for diabetic kidney disease: 5 years follow up of a single-centre open label randomised controlled trial. *EClinicalMedicine* 2022; **53:** 101725.

DECISIONS ARE AS IMPORTANT AS INCISIONS

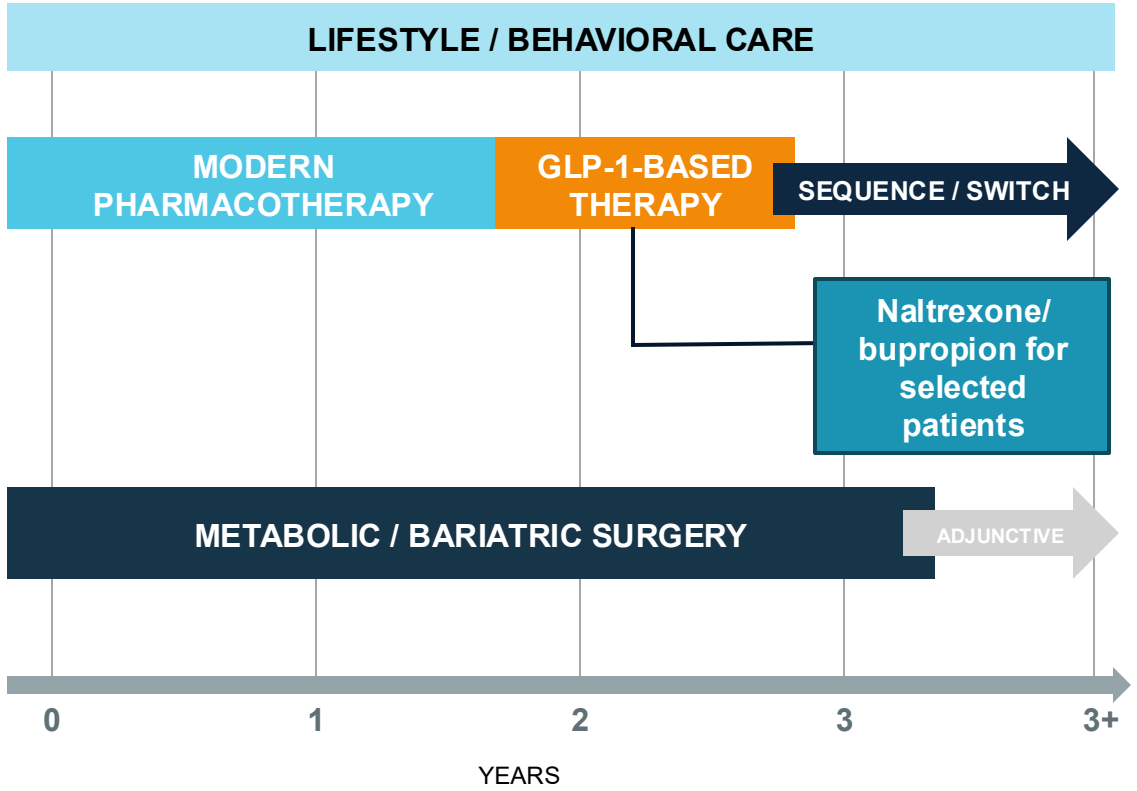
BEST OUTCOMES



INTERNATIONAL FEDERATION FOR THE SURGERY AND OTHER THERAPIES FOR OBESITY

From competition to sequencing: Obesity care in the era of modern pharmacotherapy

A chronic pathway: sequence, switch and combine when clinically appropriate



Modern obesity care is about sequencing — not either/or

- Modern pharmacotherapy extends beyond a single class
- Medication and surgery can be sequenced, switched or combined
- Treatment follows the patient, not the molecule

There is life beyond GLP-1

For selected patients, naltrexone/bupropion offers a different mechanism within a multimodal treatment pathway.

1. Sjöstrom L et al. *JAMA*. 2012;307(1):56-65. **2.** Cummings D et al. *Diabetes Care*. 2006. **3.** Courcoulas A et al. *JAMA*. 2024; 332(1):76-77. 4. Cohen RV et al. *Lancet EC*. 2022. **5.** Aminian A et al. JAMA. 2019;322(13):1271-1282. **6.** Arterburn D et al. *JAMA*. 2022.

Obesity Surgery
https://doi.org/10.1007/s11695-020-04934-1

BRIEF COMMUNICATION

Bariatric Surgery: There Is a Room for Improvement to Reduce Mortality in Patients with Type 2 Diabetes

Carel W. le Roux [1] · Johan Ottosson [2,3] · Erik Näslund [2,4] · Ricardo V. Cohen [5] · Erik Stenberg [2,3] · Magnus Sundbom [2,6] · Ingmar Näslund [2,3]

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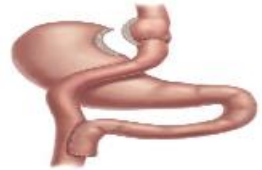
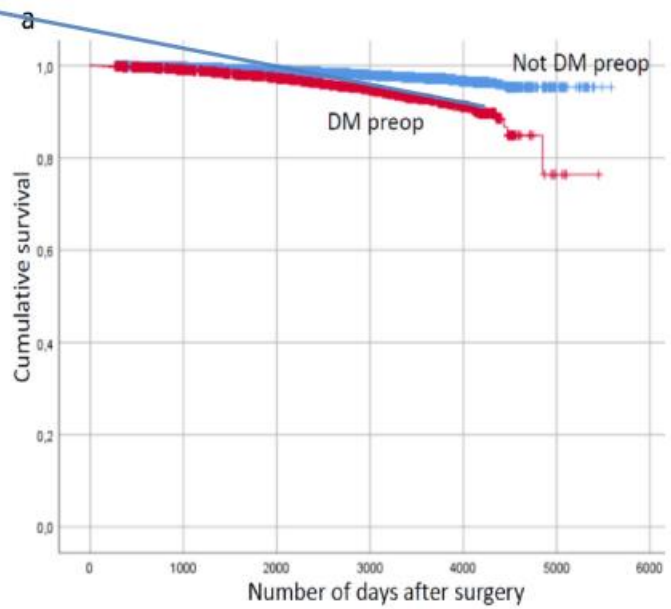


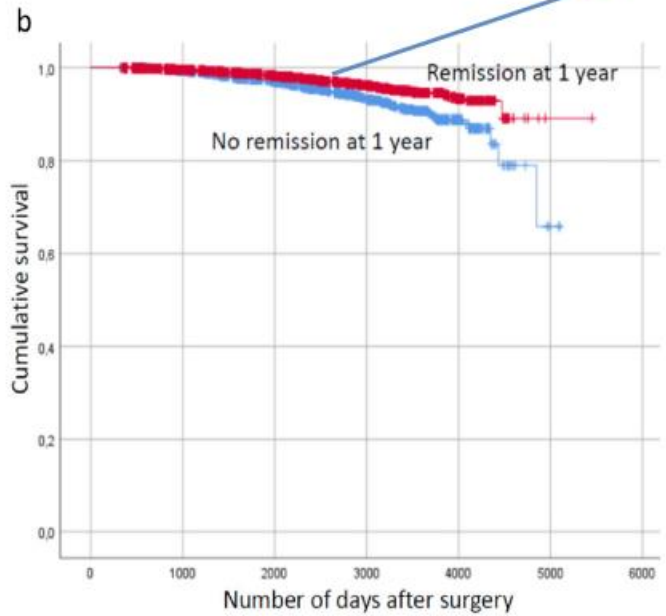
SoReg, Scandinavian Obesity Surgery Registry

65,345 pts up to 10y FU, all after RYGB

Operated pts with uncontrolled T2D @ 1 year have higher mortality during FU

Adjuctive pharmacotherapy





Published evidence
The Foundation: IFSO International Consensus

BJS, 2024, znae283
https://doi.org/10.1093/bjs/znae283
Collaborative Research Proceedings

OXFORD Collaborative Research

International consensus position statement on the role of obesity management medications in the context of metabolic bariatric surgery: expert guideline by the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO)

Ricardo V. Cohen[1,*], Luca Busetto[2], Randy Levinson[3], Carel W. Le Roux[4], Paulina Salminen[5,6] and Gerhard Prager[7] on behalf of the experts of the International Consensus on the Role of Obesity Management Medications in the Context of Metabolic Bariatric Surgery

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Members of the International Consensus on the Role of Obesity Management Medications in the Context of Metabolic Bariatric Surgery are co-authors of this study and are listed under the heading Collaborators.

Introduction

Metabolic bariatric surgery (MBS) is the most effective long-term treatment option for clinical obesity and its complications[1]. Nonetheless, modern pharmacotherapy involving intestinal hormonal analogues, such as semaglutide and tirzepatide, have shown good weight loss outcomes in the short and medium term[2–4]. Potentially, such obesity management medications (OMMs) may be synergistic with or additive to MBS for selected patients before and/or after MBS regarding improved outcomes.

The impact of pharmacotherapy before surgery is unclear, with a lack of high-level evidence regarding the efficacy of preoperative OMMs in reducing intraoperative risks and complications[5]. Similarly, the evidence is scarce for the use of OMMs as an adjunct therapy to MBS or in patients with a suboptimal initial clinical response or with recurrent weight gain after surgery[6–8]. For these reasons, the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) asked a multidisciplinary group of international experts in obesity management to develop evidence-based recommendations to serve as a global reference for using OMMs before and after MBS. These recommendations were developed through a Delphi process, identifying areas of expert consensus after a systematic review of the published literature and highlighting areas warranting further research[9].

Methods

Definitions and nomenclature

Clinical obesity is a condition in which the risk to health associated with excess adiposity has already materialized and can be objectively documented by specific signs and symptoms reflecting biological alterations of tissues and organs that are consistent with extant illness[10]. In 2023, IFSO created a global consensus to standardize MBS outcomes[11], defining a suboptimal initial clinical response and recurrent weight gain as the standard nomenclature. Modern OMMs are the second-generation intestinal hormonal analogues (single or dual analogues), whereas OMMs include all available pharmacotherapy that may be adjunctive to MBS and are not restricted to only modern agents.

Partner organizations and selection of voting experts

The core scientific committee (R.V.C., G.P., and L.B.) and the partner organizations—the World Obesity Federation (WOF), the European Association for the Study of Obesity (EASO), and the International Diabetes Federation (IDF)—tasked a multidisciplinary group of 40 international authorities to develop evidence-based recommendations. Voting experts were entirely chosen from academia, without representatives from industry. The names and details of these experts, as well as those of an internationally recognized Delphi expert (R.L.), with knowledge of endocrinology

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#1 **Most downloaded paper**

Br J Surgery 2025

Reflects the scale of clinical demand for clear guidance on combining OMMs with metabolic bariatric surgery

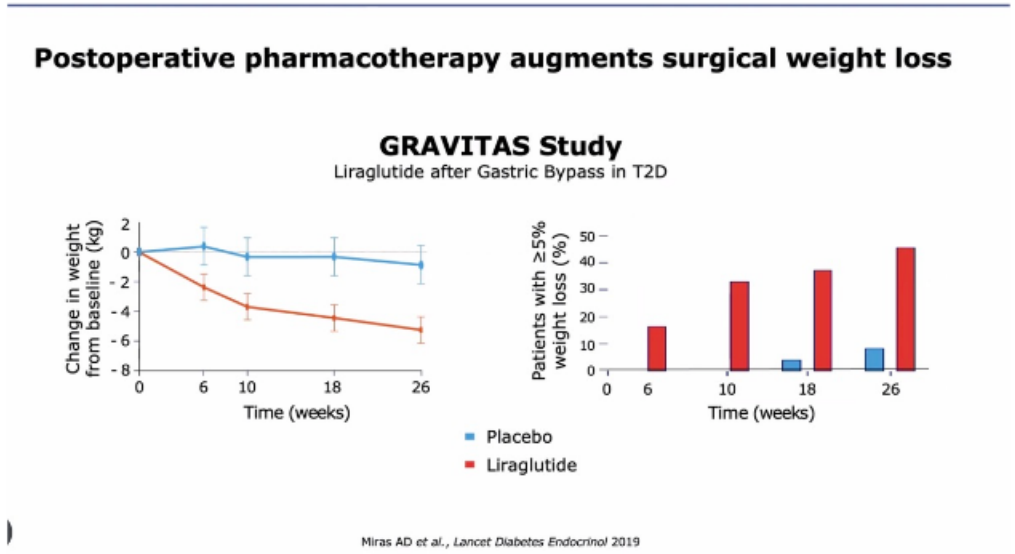
Cohen RV et al. *Br J Surg.* 2024;111(12):znae283.

OMMs After MBS: *A Comparable Response*

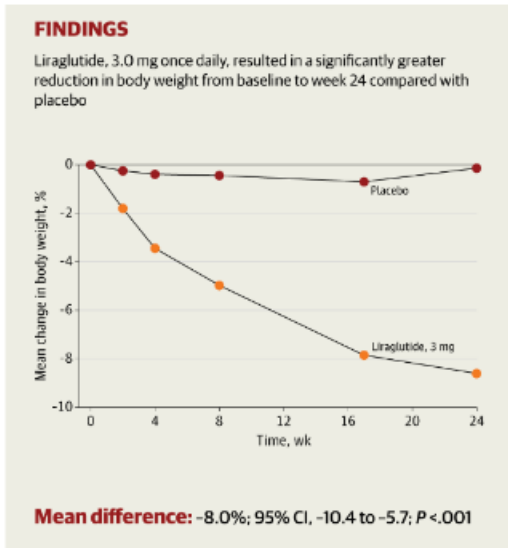
> *Emerging evidence indicates that the weight loss induced by OMMs is **similar** among people who have or have not undergone MBS.*

A+ IFSO CONSENSUS GRADE

GRAVITAS- Liraglutide T2D, after SG and RYGB



BARI-OPTIMISE — Liraglutide 3.0 mg after MBS



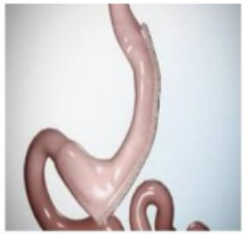
Cohen RV et al, BJS, 2024 · 100% consensus, 2 rounds, 36 votes

nature medicine

Article https://doi.org/10.1038/s41591-026-04416-4 online 22 May 2026

Semaglutide versus placebo in individuals with poor weight loss after bariatric surgery: a double-blinded, randomized, placebo-controlled trial

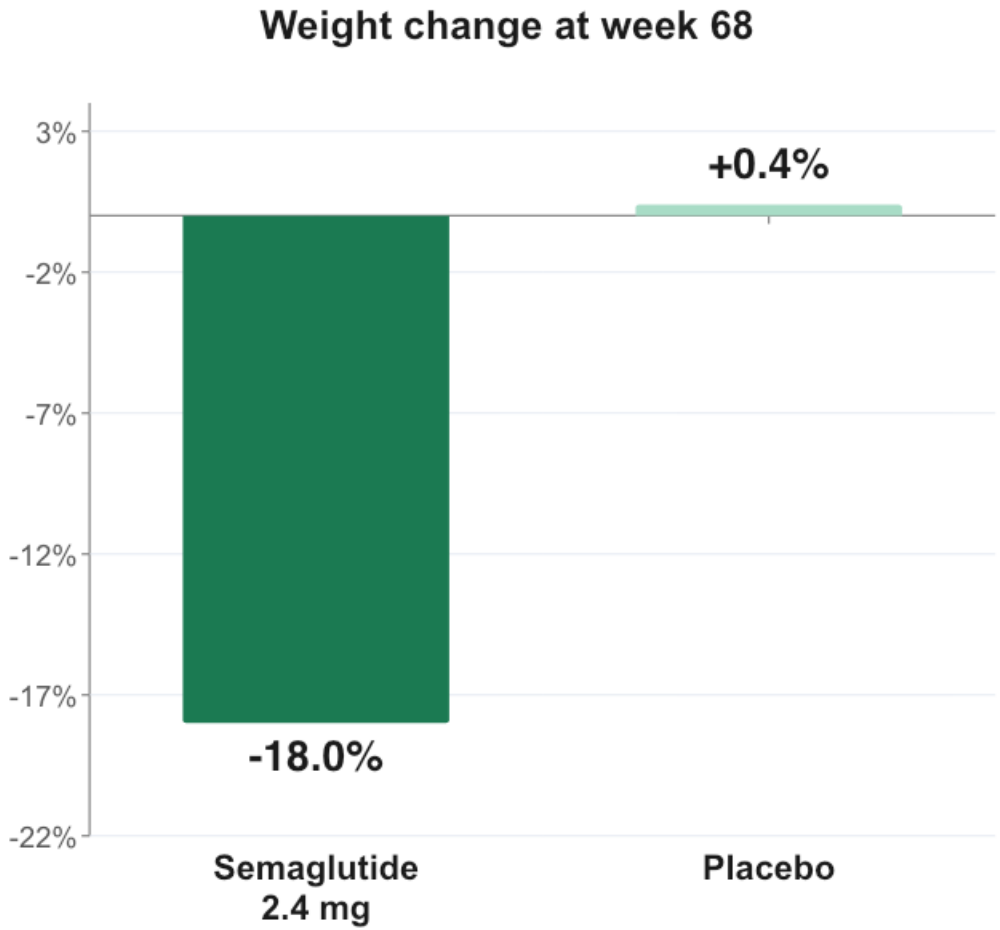
Population: Post-MBS patients with **weight regain or suboptimal weight loss** (lost less than 20% of body weight since surgery)



78.6% sleeve gastrectomy (55/70 participants)

Semaglutide 2.4 mg (34 patients) vs placebo (29 patients) for 68 weeks, with adjunctive lifestyle therapy

Mild side effects (GI symptoms); no treatment-related deaths



Adjusted difference: **-19.1%** (95% CI -23.4 to -14.8)
P < 0.001

OMMs After MBS: Safety Profile

> *When used after MBS, there appears to be **no increased incidence of side effects** of OMMs compared to non-surgical cohorts.*

A IFSO CONSENSUS GRADE

Side Effects Reported with Liraglutide post-MBS in BARI-OPTIMISE compared with SCALE

Adverse Events (AE)• in the BARI-OPTIMISE Study Population

Event	Participants who experienced an AE, No. (%)		
	Placebo (n = 35)	Liraglutide (n = 35)	Total (N = 70)
Total	20 (57)	28 (80)	48 (67)
Total AEs, No.•	55	37	112
Gastrointestinal events			
Nausea	7 (20)	18 (51)	25 (36)
Diarrhea	2 (6)	2 (6)	4 (6)
Constipation	2 (6)	9 (26)	11 (16)
Vomiting	1 (3)	1 (3)	2 (3)
Abdominal pain	1 (3)	2 (6)	3 (4)
Abdominal bloating	0	1 (3)	1 (1)
Dyspepsia	0	1 (3)	1 (1)

Mck et al. JAMA Surg 2023 (BARI-OPTIMISE); SCALE. Pi-Sunyer NEJM 2015

Side Effects Reported with Liraglutide post-MBS: Retrospective study of 117 patients compared to SCALE

TABLE 2 Side effects for liraglutide 3.0 mg

Symptom	n [%]*
Nausea	34 [29.1%]
Constipation	13 [11.1%]
Diarrhoea	8 [6.8%]
Fatigue	7 [6.0%]
Headache	4 [3.4%]
Rash	4 [3.4%]
Indigestion	3 [2.6%]
Vomiting	3 [2.6%]
Dry mouth	3 [2.6%]
Bloating	2 [1.7%]
Sweating	2 [1.7%]
Other†	9 [7.7%]

*Percent calculated as [(number of patients reporting the side effect)/(117)] x 100.
†Other includes abdominal pain (n = 1), bruising (n = 1), decreased glomerular filtration rate (n = 1), depression (n = 1), flu-like symptoms (n = 1), heartburn (n = 1), hot flashes (n = 1), gas (n = 1) and pancreatitis (n = 1).

Wharton S, et. al. Clinical Obesity. 2019;9:e12323; SCALE. Pi-Sunyer NEJM 2015

Real-world efficacy of naltrexone/bupropion for weight management in obesity and after bariatric surgery

- Real-world NB cohort
  - 111 surgery-naive patients (72.5%)
  - 40 post-MBS patients (26.1%)
- Predominantly female (77.5% surgery-naive, 75.0% post-MBS)
- Median age: 45.0 years (surgery-naive), 51.5 years (post-MBS)

www.nature.com/ijo International Journal of Obesity

ARTICLE

Bariatric Surgery

Real world efficacy of naltrexone/bupropion for weight management in obesity and after bariatric surgery

Marie Yskout[1], Nele Steenackers[2,3], Jarne Hoste[4], Sofia Pazmino[2], Caroline Simoens[2], Nele Mattelaer[2], Ellen Deleus[2,5], Matthias Lannoo[2,6], Ann Mertens[1,2], Bart Van der Schueren[1,2] and Roman Vangoitsenhoven[1,2]✉

BACKGROUND: Insufficient weight loss or weight regain after metabolic and bariatric surgery (MBS) is frequent, and evidence to support the use of pharmacotherapy for weight management is limited.
METHODS: In this single-centre retrospective cohort study, the effectiveness of naltrexone/bupropion (NB) for weight control in surgery-naive and post-MBS patients was evaluated. Data was collected between 2016 and 2022 on all patients started on NB after multidisciplinary consult. Patients received weekly dose escalation up to 32/360 mg daily per the manufacturer's protocol, with submaximal doses administered in cases of adverse effects or sufficient therapeutic response. Weight evolution, metabolic status, adherence and adverse events were analysed at 4 and 12 months after NB initiation. Data are presented as median (interquartile range).
RESULTS: A total of 151 patients were included, 111 were surgery-naive and 40 with prior MBS. The median time after MBS was 7.1 years (4.2, 14.9). Among the post-MBS patients, 18 (45%) patients had undergone Roux-en-Y gastric bypass and 11 (27.5%) sleeve gastrectomy. Four months after initiation of NB, 46.8% of the surgery-naive patients and 67.5% of the post-MBS patients continued using NB, with a median weight loss of 6.4% (3.0, 10.1) and 6.3% (2.3, 12.1) respectively. At 12-months, 38.5% of surgery-naive patients and 63.0% of post-MBS patients had continued NB, with median weight loss of 8.8% (5.0, 16.7) and 10.0% (4.5, 16.5) respectively. There was no statistically significant difference in weight loss between the surgery-naive and post-MBS group. Weight loss was not significantly influenced by whether the maximal dose was reached in both the surgery-naive patients ($p = 0.38$) and the post-MBS patients ($p = 0.72$).
CONCLUSION: Real-world data show that NB treatment is equally effective in surgery-naive patients and in patients experiencing weight regain after bariatric surgery, regardless of the maximal dose administered.

International Journal of Obesity (2025) 49:2102–2109; https://doi.org/10.1038/s41366-025-01870-x

INTRODUCTION

Treatment options for obesity have expanded in recent years, with major advancements in pharmacotherapy including the development of medicines like naltrexone/bupropion (NB) and glucagon-like peptide 1 (GLP-1) analogues. Surgical interventions for weight loss have improved greatly, rendering metabolic and bariatric surgery (MBS) a safe, effective and durable treatment for patients with severe obesity [1, 2]. According to data from The American Society for Metabolic and Bariatric Surgery, the most common surgical procedures performed in the U.S. in 2021 were laparoscopic sleeve gastrectomy (SG) at 58% and Roux-en-Y Gastric Bypass (RYGB) at 21% [3].

Despite these advancements, there is still a considerable number of patients who experience weight regain or insufficient weight loss after MBS [4]. The prevalence of poor weight loss outcomes ranges between 3.9 and 71% depending on the criteria used and the type of bariatric surgery performed [5]. While insufficient weight loss has been defined as less than 50% excess weight loss or a BMI above 35 kg/m², there is no consensus on the definition of weight regain [6]. Both are mitigated by factors such as dietary non-adherence, as well as hormonal and metabolic changes [5, 7]. As obesity is a chronic disease, individual variety and sensitivity in postoperative nutrient stimulated hormonal responses may play a role, such as those involving pancreatic peptide YY, ghrelin and glucagon like peptide [5, 7]. The optimal way to approach patients with weight regain or insufficient weight loss remains unclear, as limited data has been published on the effectiveness of different multidisciplinary strategies.

NB, a combination of naltrexone (an opioid antagonist) and bupropion (a norepinephrine and dopamine reuptake inhibitor),

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MBS, metabolic and bariatric surgery.
Yskout M et al. *Int J Obes.* 2025;49:2102-2109.

Treatment protocol and dosing

Starting dose: 8 mg naltrexone/90 mg bupropion daily (one tablet)

Target dose: 32 mg naltrexone/360 mg bupropion daily (2 tablets twice daily)

Escalation: Weekly increases per manufacturer protocol

Flexibility: Submaximal doses allowed for:

- Adverse effects management
- Sufficient therapeutic response

Follow-up visits were scheduled at 4 and 12 months after treatment initiation.

Standard dosing for CONTRAVE[a]

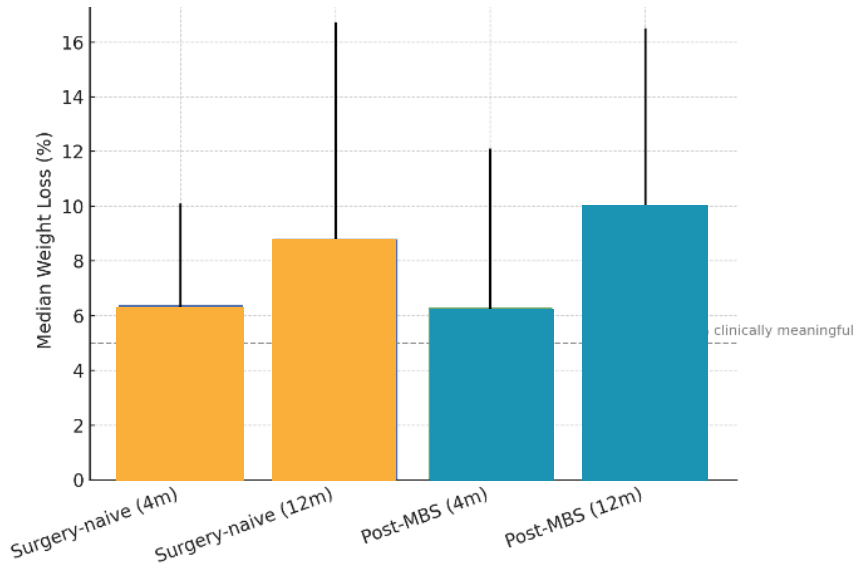
	AM	PM
Week 1		
Week 2		
Week 3		
Week 4		

The full recommended dose is reached at Week 4.

[a]Dose adjustments are needed for patients with moderate, severe, or end-stage renal impairment and hepatic impairment. Maximum recommended daily doses are as follows: moderate or severe renal impairment: 2 pills per day (1 in the AM, 1 in the PM). Moderate hepatic impairment: 2 pills per day (1 in the AM, 1 in the PM). End-stage renal disease or severe hepatic impairment: not recommended for use in these patients. Concomitant use with CYP2B6 inhibitors: 2 pills per day (1 in the AM, 1 in the PM).
CONTRAVE® extended-release tablets. Prescribing information. Currax Pharmaceuticals, LLC; 2025.

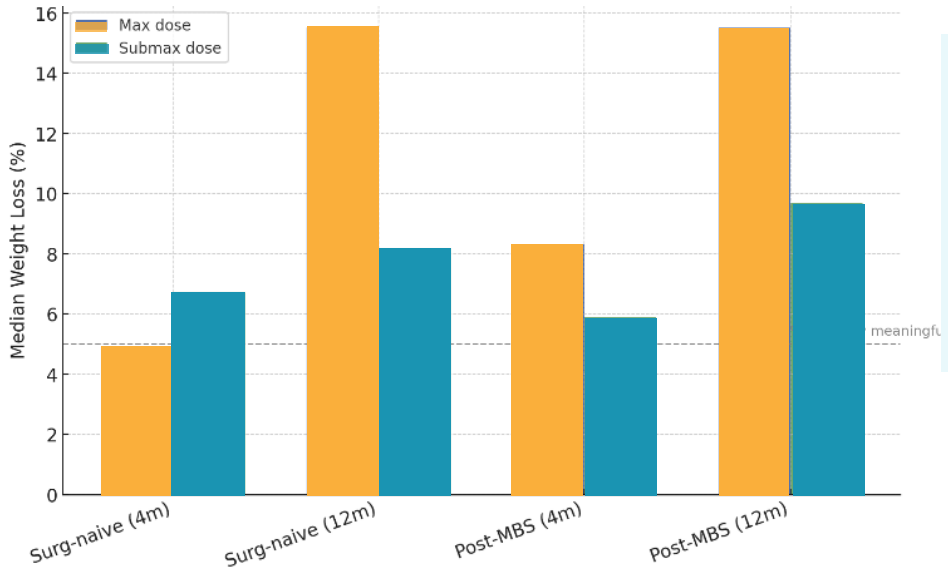
Real-world efficacy of NB for weight management in obesity and after bariatric surgery

Naltrexone/bupropion in surgery-naïve vs post-MBS patients



No significant difference between groups

Dose-dependent effect of NB



No significant difference between maximal and submaximal dose

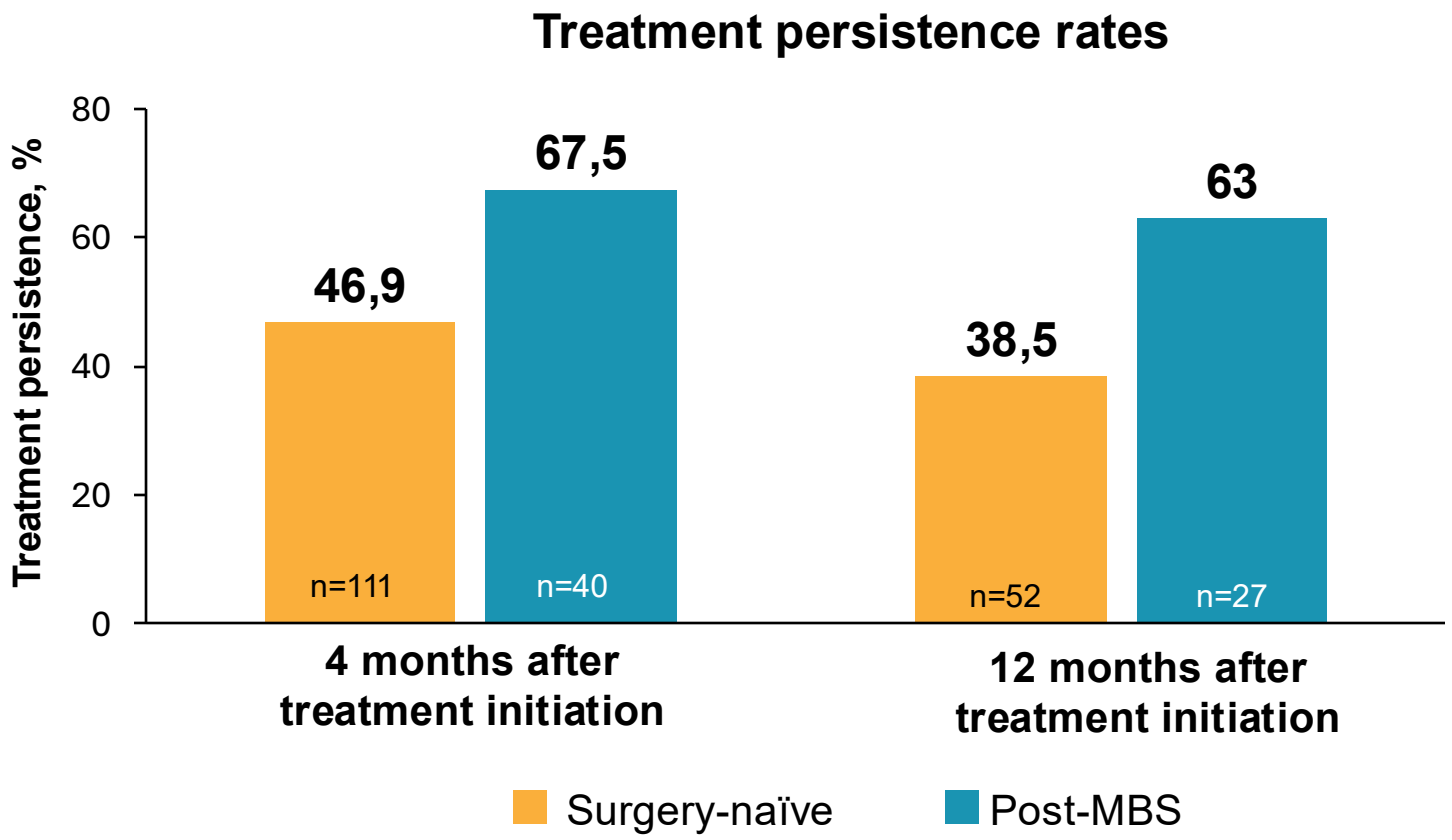
Sufficient subjective effect

62.1% Surgery-naive

63.6% Post-MBS

MBS, metabolic and bariatric surgery.
Yskout M et al. *Int J Obes.* 2025;49:2102-2109.

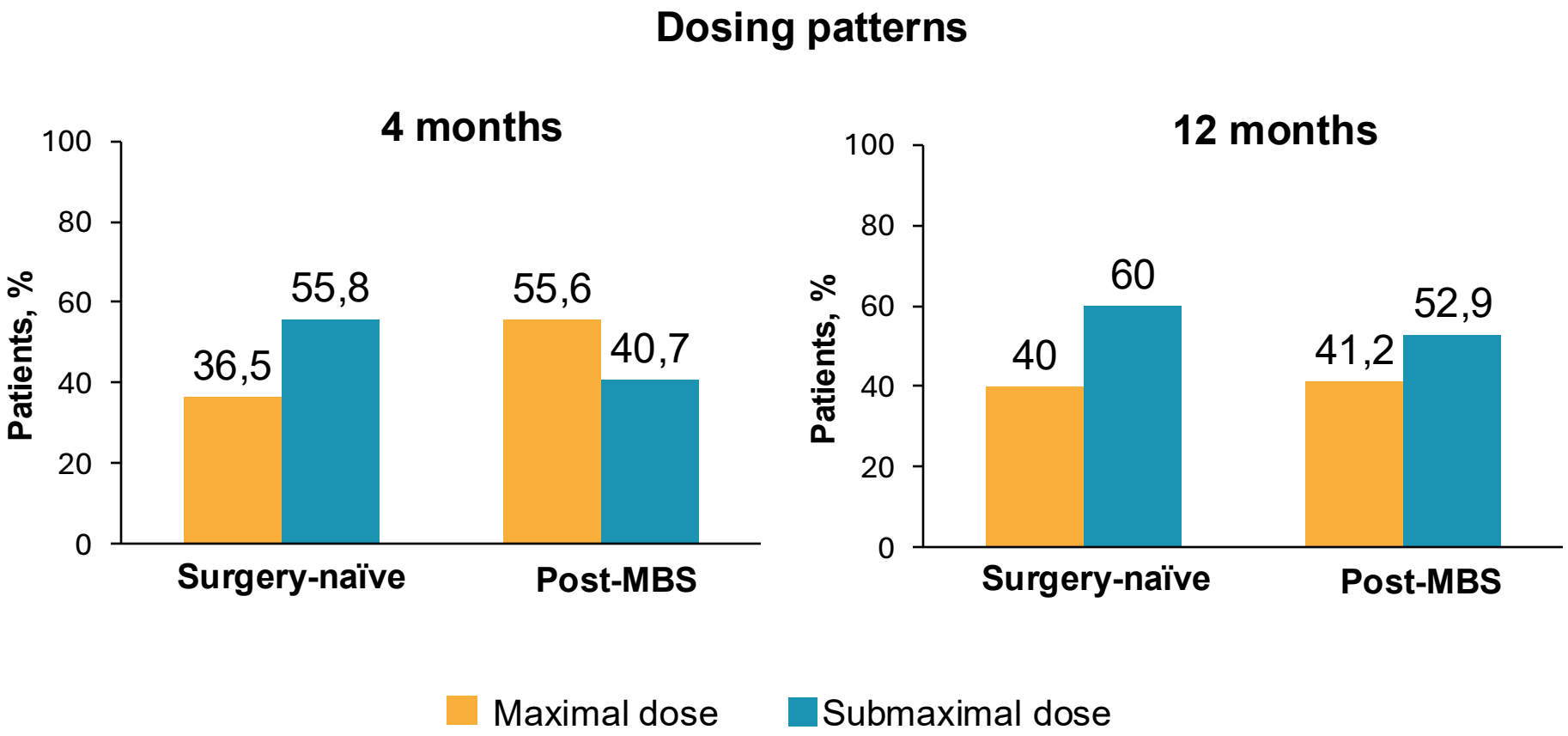
Treatment persistence rates



Post-MBS patients showed significantly higher treatment persistence rates at both time points.

MBS, metabolic and bariatric surgery.
Yskout M et al. *Int J Obes.* 2025;49:2102-2109.

Dosing patterns and tolerance



Most patients used submaximal doses successfully with no significant difference in weight loss outcomes.

MBS, metabolic and bariatric surgery.
Yskout M et al. *Int J Obes.* 2025;49:2102-2109.

Study conclusions

1. Effective in surgery-naive and post-MBS patients
2. No notable differences at 4 or 12 months
3. No meaningful maximal vs submaximal dose difference
4. Most continuing patients achieve ≥5% weight loss
5. RCT confirmation is still needed

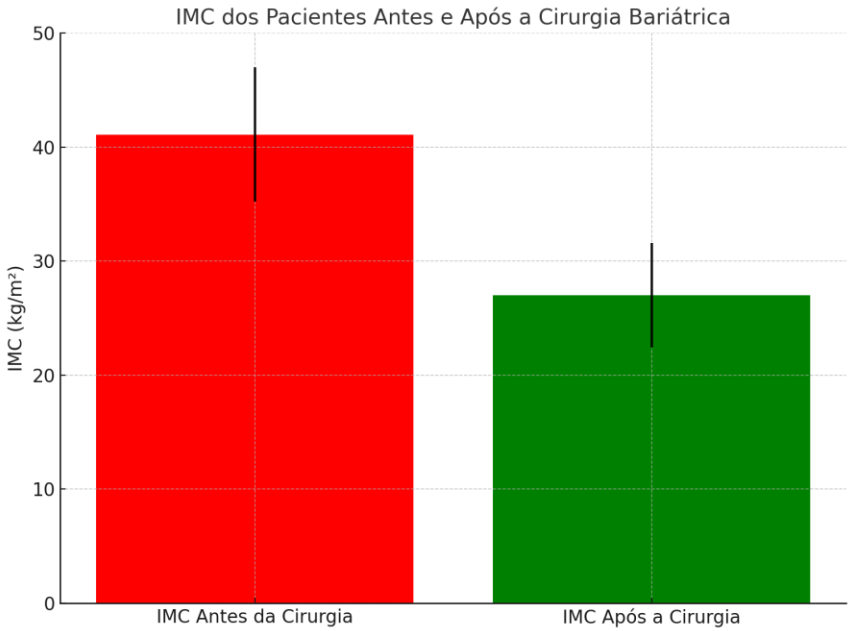
MBS, metabolic and bariatric surgery.
Yskout M et al. *Int J Obes.* 2025;49:2102-2109.

Naltrexone/bupropion for weight regain following bariatric surgery: Real world data

Retrospective study of NB in recurrent weight gain after MBS

9 RYGB
4 SG
2 AGB
e 1 Mason operation

33.9% TBWL



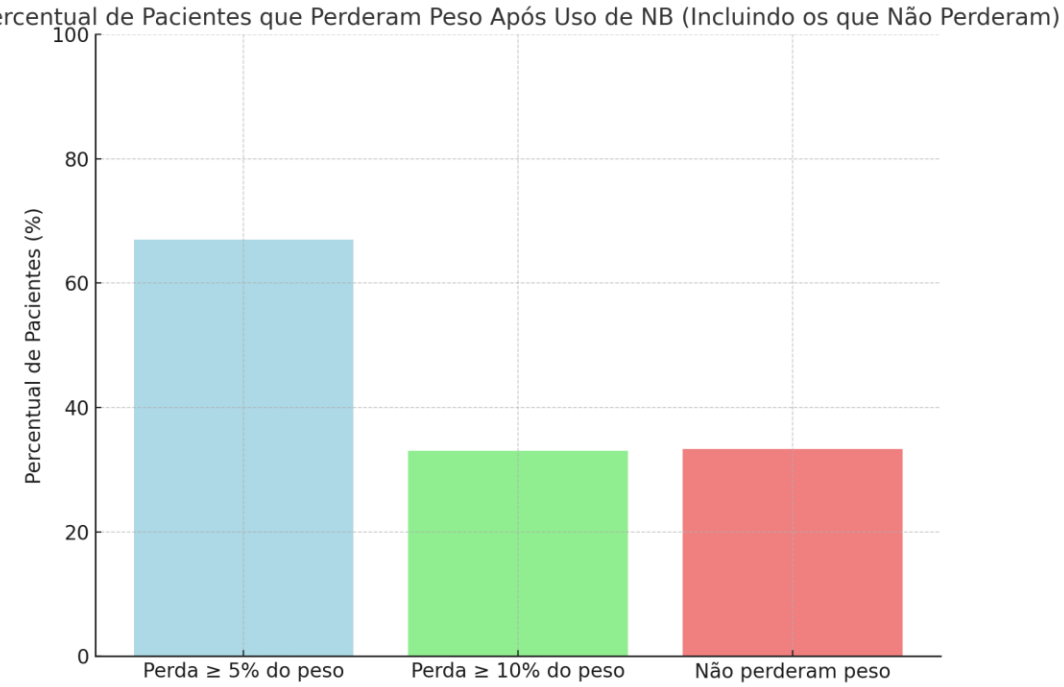
MBS, metabolic and bariatric surgery.
Leuven et al. Abstract presented at the 40th Annual Meeting of the Obesity Society at Obesity Week®. 2022.

Naltrexone/bupropion for weight regain following bariatric surgery: Real world data

Retrospective study of NB in recurrent weight gain after MBS

After 4 months of treatment

9 RYGB
4 SG
2 AGB
e 1 Mason operation



RWG when starting NB:
28.2 16.0 % (from nadir)

MBS, metabolic and bariatric surgery.
Leuven et al. Abstract presented at the 40th Annual Meeting of the Obesity Society at Obesity Week®. 2022.

IFSO CONSENSUS 2024 · AFTER SURGERY

OMMs After MBS: *When to Start*

> *Treatment with OMMs after MBS should generally be **withheld until the weight plateau** is reached — unless there is a compelling clinical need for earlier initiation.*

A+ IFSO CONSENSUS GRADE

RATIONALE

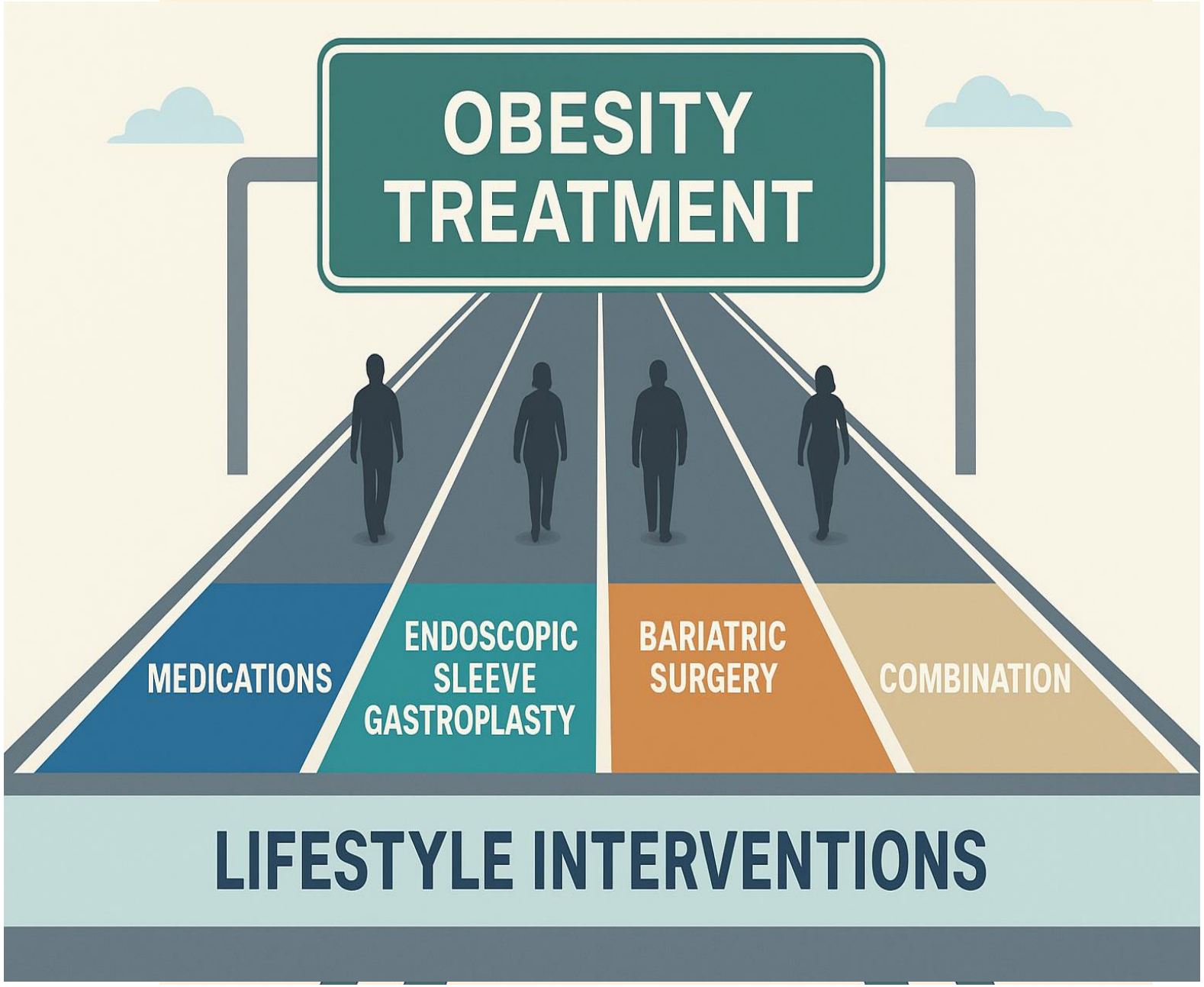
- Lets patients and physicians see the full effect of surgery before adding pharmacotherapy

EXCEPTION

- **BMI > 60 kg/m² — early initiation at 2–3 months postop**

IFSO Consensus 2024 · Cohen RV et al, BJS, 2024 · 100% consensus, 3 rounds, 33 votes

Evidence-based



Better predictors are the next step

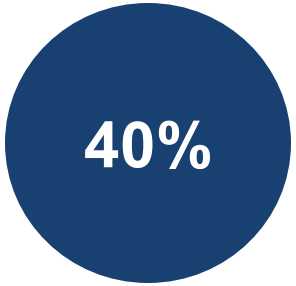
	Grade	Consensus (%)	Number of rounds	Total votes, N
Future research is needed to identify predictors of which patients are likely to derive substantial benefit from combined pharmaco-surgical therapy for obesity and its complications	A+	100	3	35

- ✓ **Next step**
- ✓ **Predict who benefits most from combined therapy**

Cohen RV et al. *Br J Surg*. 2024;111(12):znae283.

Precision medicine

Four phenotypes can guide treatment selection



Hungry brain

Satiation

More calories consumed per meal

TREATMENT SIGNAL

Phentermine / topiramate

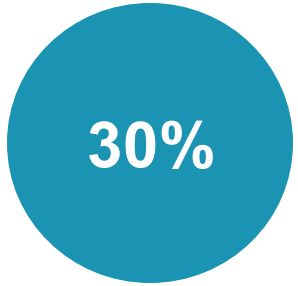
Hungry gut

Satiety

Hunger returns quickly after a meal

TREATMENT SIGNAL

GLP-1 analogue



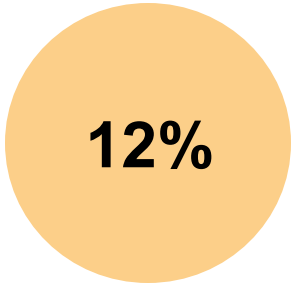
Emotional hunger

Emotion / reward

Eating to cope with positive or negative emotions

TREATMENT SIGNAL

Naltrexone / bupropion ER



Slow burning

Energy expenditure

Low resting metabolic rate

TREATMENT SIGNAL

Phentermine + resistance training

Acosta A et al. *Gastroenterology*. 2015;148:537-546.

Naltrexone/bupropion in multimodal care

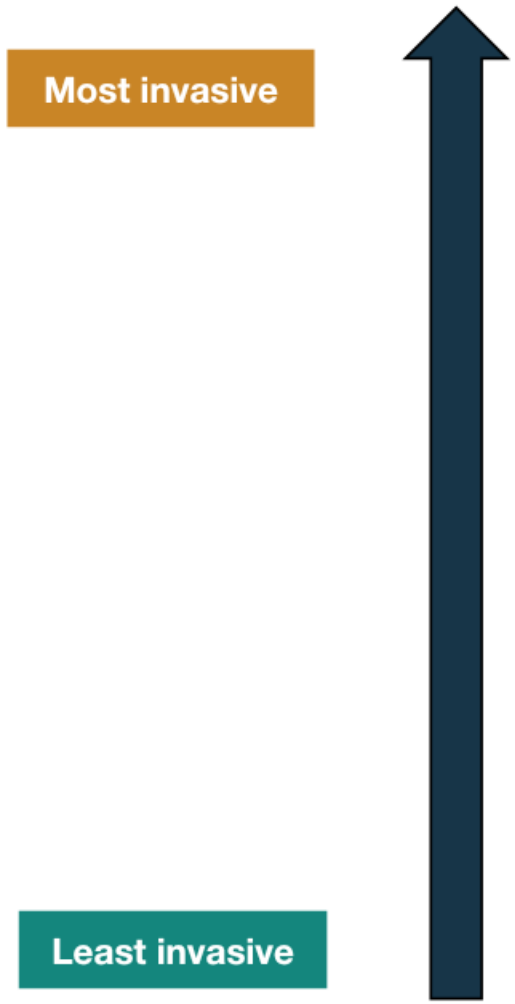
1. Review safety with other CNS agents
2. Consider adjunctive use with other OMMs and MBS/ESG

Acosta A et al. *Gastroenterology*. 2015;148:537-546.

Obesity treatment TODAY

Oncology model
What would an oncologist do ?

Access to full spectrum of therapy



Reoperative therapy

Adjuvant therapy

Combination therapy, when needed

Obesity Management Medications

Surgical treatment

Adapted from Lingvay I , Cohen R, Lancet 2024

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@rvcohen(twitter)

OSWALDO CRUZ

CENTRO ESPECIALIZADO EM **OBESIDADE E DIABETES**

Precision Obesity and Bariatrics: **The Next Frontier**

Alex Miras
Professor of Endocrinology
Ulster University

azurity pharmaceuticals

Faculty disclosures

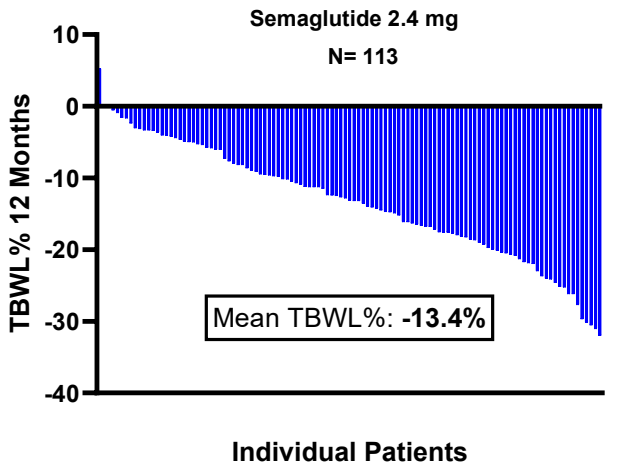
Alexander Miras, MD

Grants/Research Support: Fractyl, Novo Nordisk, Boehringer Ingelheim, Randox, Gila, Anabio

Other Financial or Material Support/Honorarium: Eli Lilly, Novo Nordisk, GI dynamics , AstraZeneca, Boehringer Ingelheim, Ethicon, Medtronic, Azurity, BeyondBMI, Screen Health, Algorithm

Obstacles In the obesity pandemic

HETEROGENEOUS OUTCOMES[1]

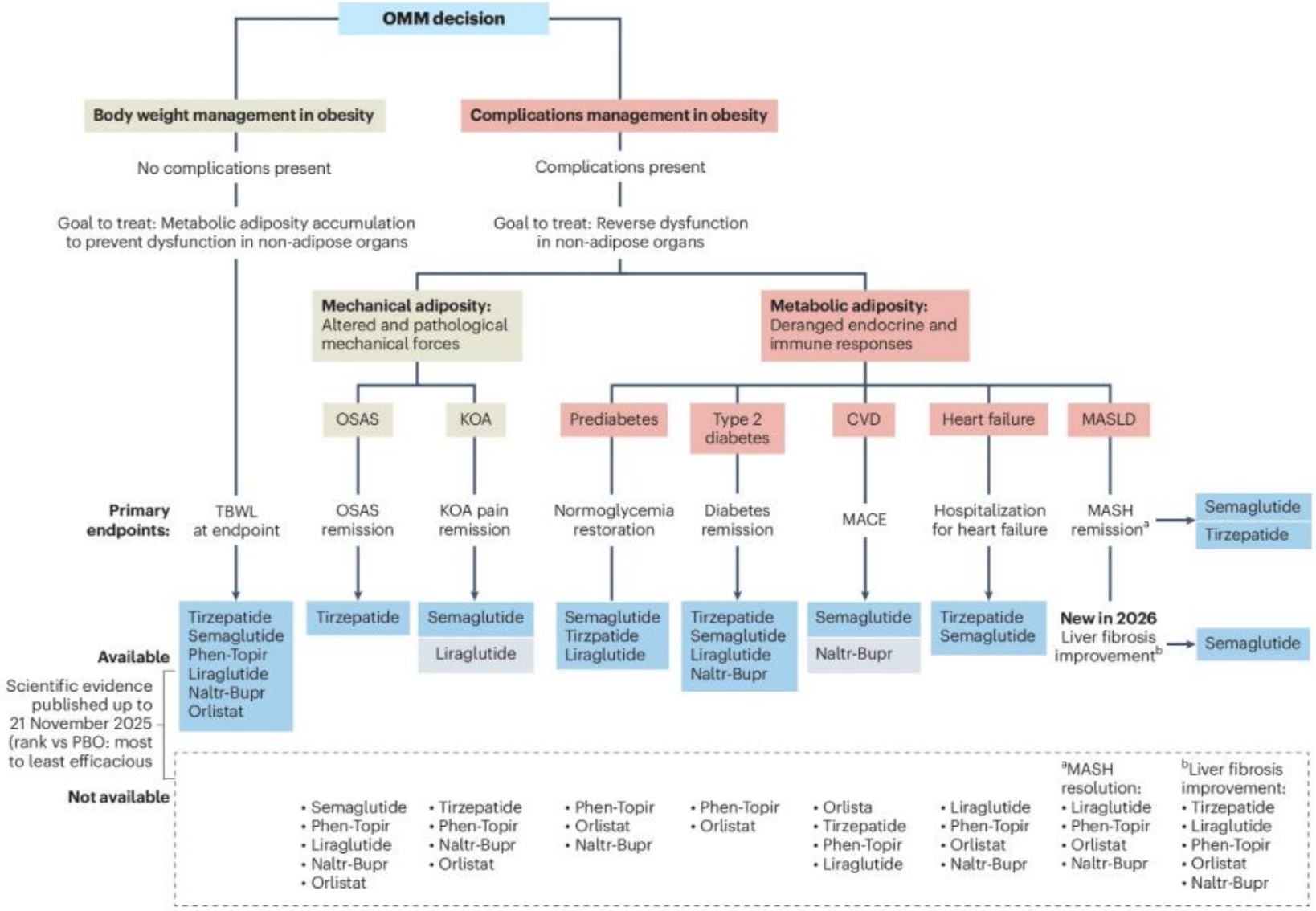


HIGH COST[2]

LIMITED PATIENT ACCESS[3]

1. Modified from Ghusn W, IJO, 2022; **2.** Trujillo JM et al. *Ther Adv Endocrinol Metab*. 2021;12:2042018821997320. **3.** Ard J et al. *Adv Ther*. 2021;38(6):2821-2839.

EASO pharmacotherapy framework



Phentermine–topiramate is not approved for chronic weight management by Health Canada

Ciudin et al, Nature Medicine, 2026

2026 TOS, OMA, OAC evidence-based recommendations for OMMs

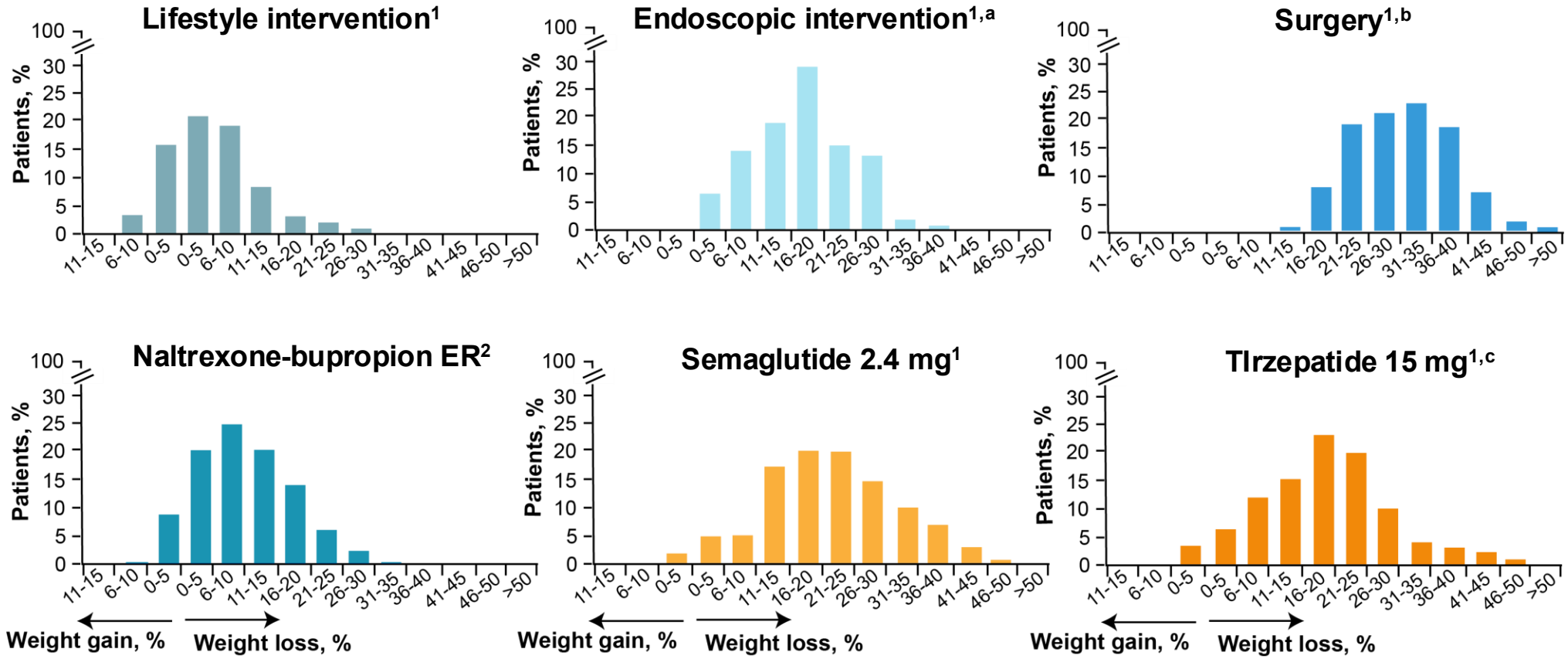
	Recommendation	Strength of recommendation	Certainty of evidence
In adults ≥18 years with overweight or obesity, TOS, OMA, and OAC…	**suggests** using orlistat	Conditional	⨁⨁◯◯ Low
	suggests using phentermine-topiramate	Conditional	⨁⨁◯◯ Low
	recommends using NB-ER	Strong	⨁⨁⨁◯ Moderate
	suggests using liraglutide	Conditional	⨁⨁◯◯ Low
	recommends using semaglutide and tirzepatide	Strong	⨁⨁⨁◯ Moderate

Phentermine–topiramate is not approved for chronic weight management by Health Canada

OAC, Obesity Action Coalition; OMA, Obesity Medicine Association; TOS, The Obesity Society.
Alexander L et al. Obesity Pillars. 2026;18:100254.

Heterogeneity of response to weight loss interventions

Heterogeneity in weight loss response after approximately 12 months[1,2]



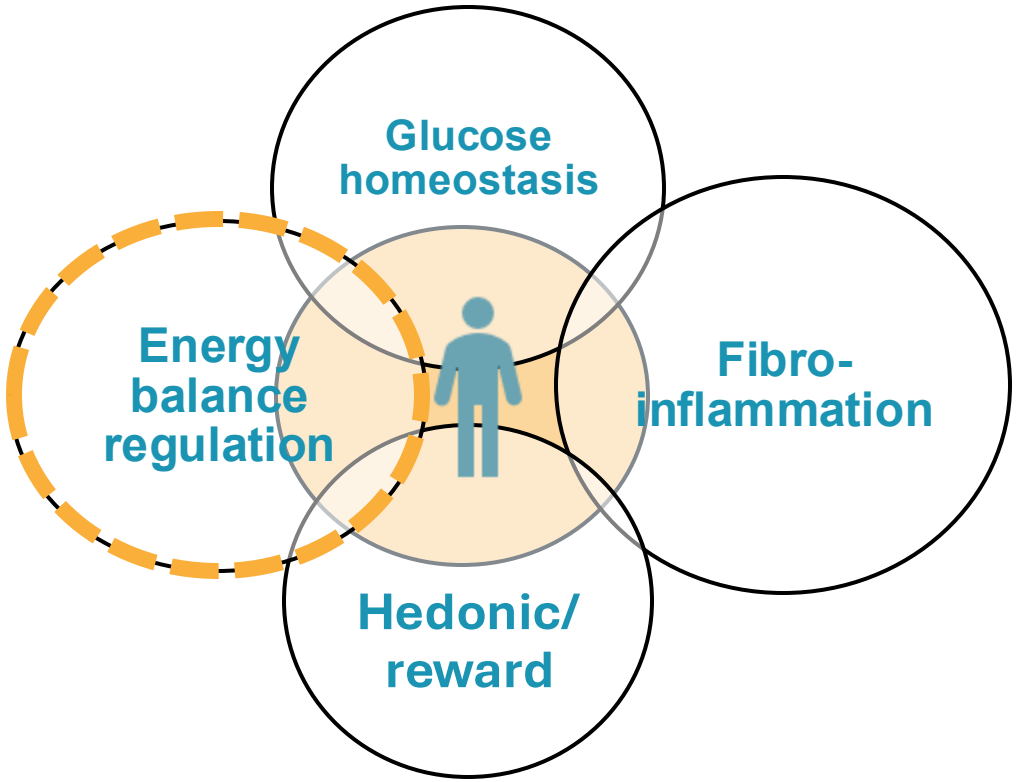
Only treatments for which 1-year data were available have been included. To enable comparison between different treatment modalities, percentage changes for total bodyweight are presented, as placebo-subtracted data are not usually reported in studies of lifestyle interventions and bariatric surgery. [a]For endoscopic intervention, mean results for intragastric balloon and endoscopic gastroplasty are shown for which data were available. [b]For surgery, mean results for sleeve gastrectomy and Roux-en-Y gastric bypass have been given as they account for 95% of all bariatric surgeries worldwide. [c]For tirzepatide, since published data reached only 25% weight loss or more, the proportion of participants obtaining higher weight losses has been presumptively assigned following the unimodal distribution observed for other anti-obesity medications.

1. Perdomo CM et al. *Lancet.* 2023;401:1116-1130. **2.** Data on file. Currax Pharmaceuticals LLC.

Heterogeneity and complexity of obesity

Obesity-related Diseases

- Diabetes
- HTN
- CVD
- Cancer (some)
- +280 diseases



OMICS

- Exposomics
- Proteomics
- Metabolomics
- Epi-Genetics
- Genetics

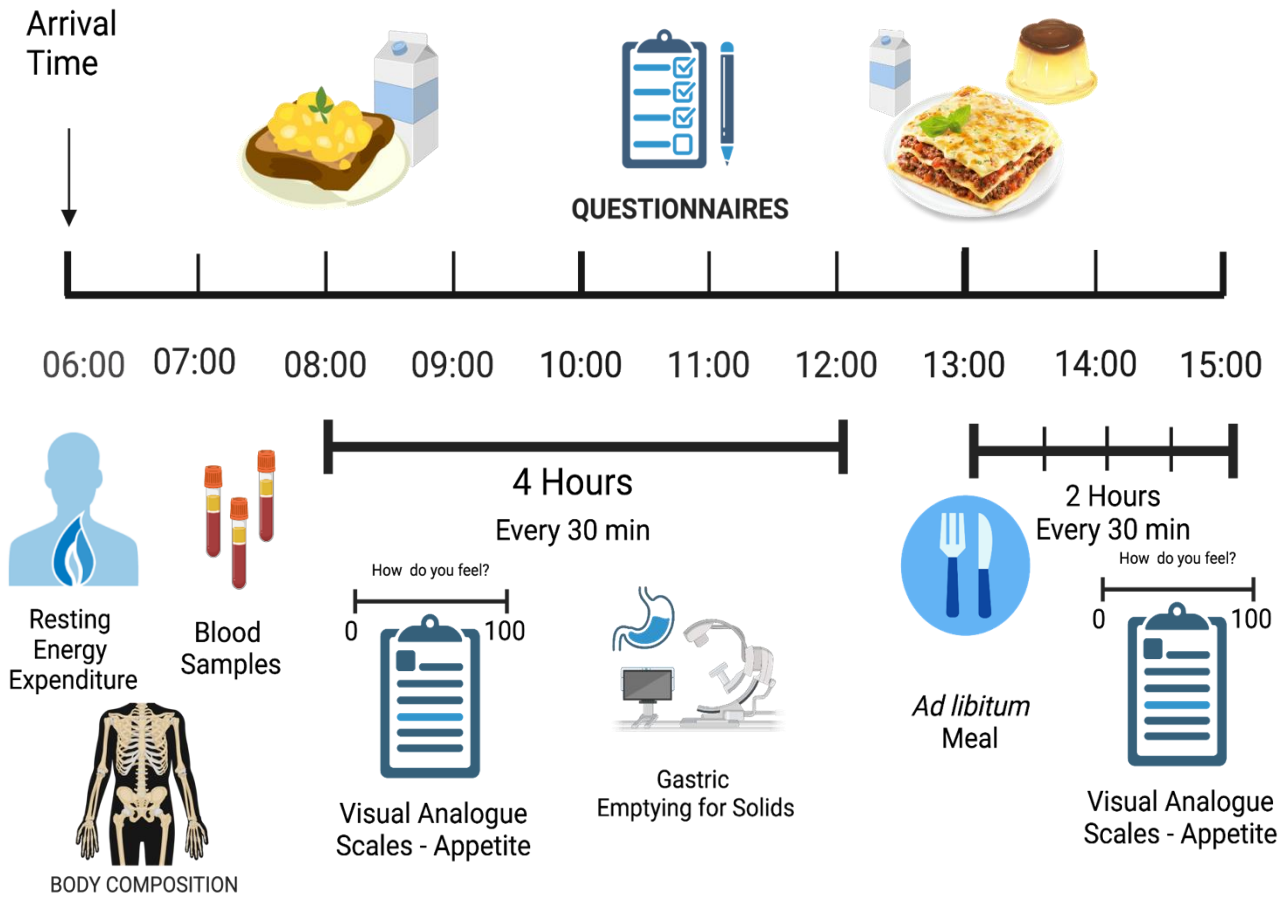
Obesity Severity = BMI - fat mass

Social Determinants of Health

BMI, body mass index; CVD, cardiovascular disease; HTN, hypertension

Understanding the heterogeneity of obesity through energy balance phenotypes

- We stratify obesity based on energy balance and behavioral phenotypic traits[1]



1. Acosta A et al. *Gastroenterology*. 2015;148:537-546.

Understanding the heterogeneity of obesity through energy balance phenotypes

- We stratify obesity based on energy balance and behavioral phenotypic traits[1]

 Satiation **Hungry Brain**	 Post-prandial satiety **Hungry Gut**
 Emotional eating **Emotional Eater**	 Energy expenditure **Slow Burn**

1. Acosta A et al. *Gastroenterology*. 2015;148:537-546.

Understanding the heterogeneity of obesity through energy balance phenotypes

- We stratify obesity based on energy balance and behavioral phenotypic traits[1]
- Obesity interventions that target a specific obesity phenotype improves weight loss outcomes by **1.7 to 2 fold**[2-11]

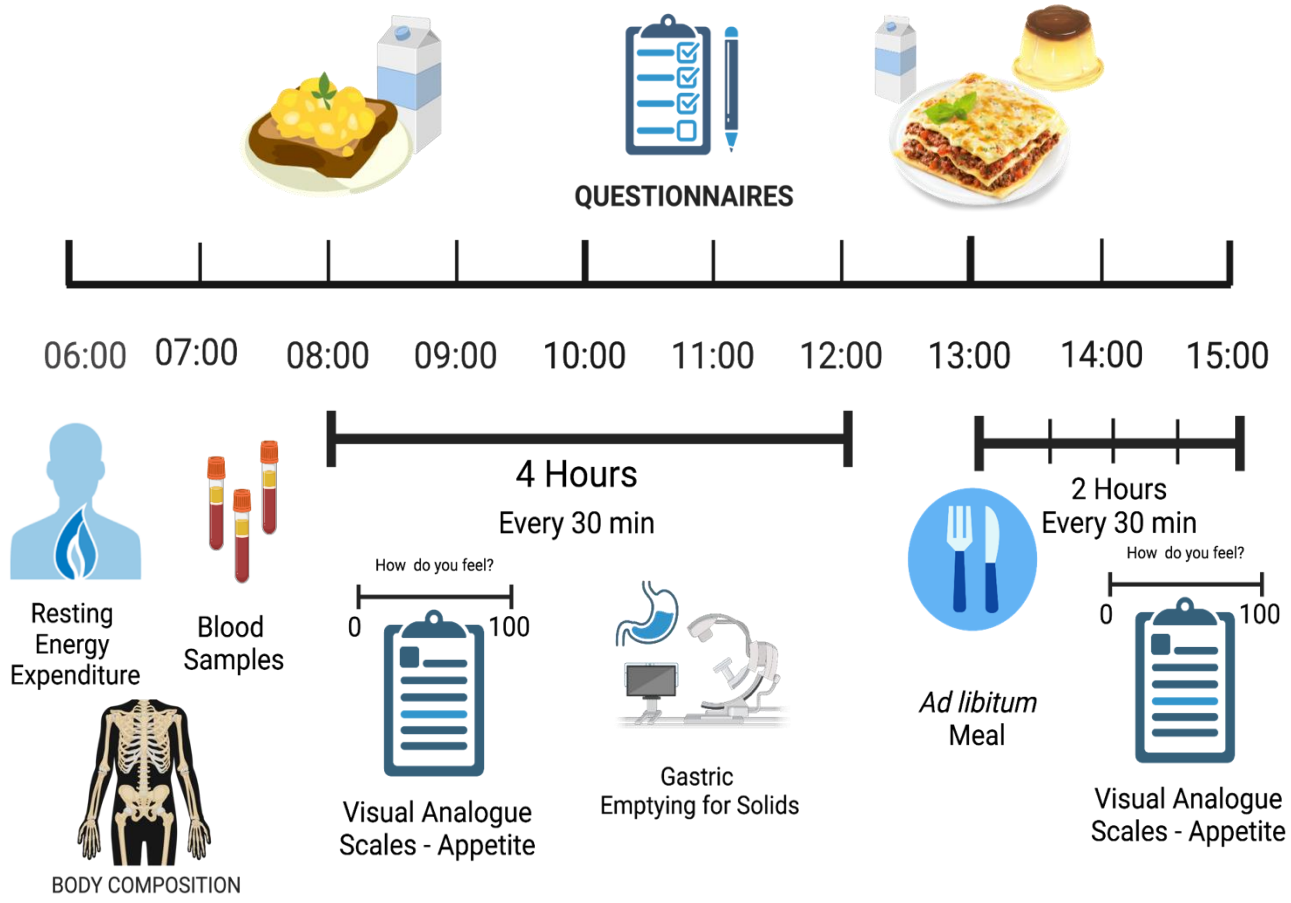
	Hungry brain	Hungry gut	Emotional hunger	Slow Burn
LIFESTYLE INTERVENTION	Hungry brain diet	Hungry gut diet	Behavioral therapy Hungry feelings diet	• Intense exercise plan • Slow burn diet
MEDICATION[a]	Phentermine-topiramate ER	Liraglutide Semaglutide Tirzepatide	Naltrexone-bupropion ER	
ENDOSCOPY[a]	Vagal nerve block	Intragastric balloons Endoscopy sleeve gastroplasty		
SURGERY	Laparoscopic sleeve gastrectomy	Roux-en-Y gastric bypass		

Phentermine–topiramate is not approved for chronic weight management by Health Canada

1. Acosta A et al. *Gastroenterology*. 2015;148:537-546. 2. Acosta A et al. *Physiol Rep.* 2015;3(11):e12610. **3.** Halawi H et al. *Lancet Gastroenterol Hepatol*. 2017;2(12):890-899. **4.** Gómez V et al. Obesity (Silver Spring). 2016;24(9):1849-1853. **5.** Abu Dayyeh BK et al. *Clin Gastroenterol Hepatol.* 2017;15(1):37-43.e1. **6.** Vargas EJ et al. *BMJ Open Gastroenterol.* 2019;6(1):e000273. **7.** Acosta A et al. *Obesity (Silver Spring).* 2021;29(4):662-671. **8.** Campos A et al. *Obesity Surgery*. 2022;32(8):2632-2640. **9.** Cifuentes L et al. *EClinical Medicine*. 2023;58:101923. **10.** Vargas EJ et al. *Gut.* 2023;72(6):1073-1080. **11.** Gala K et al. *Obesity Surg.* 2023;33(4):1284-1288.

Understanding the heterogeneity of obesity through energy balance phenotypes

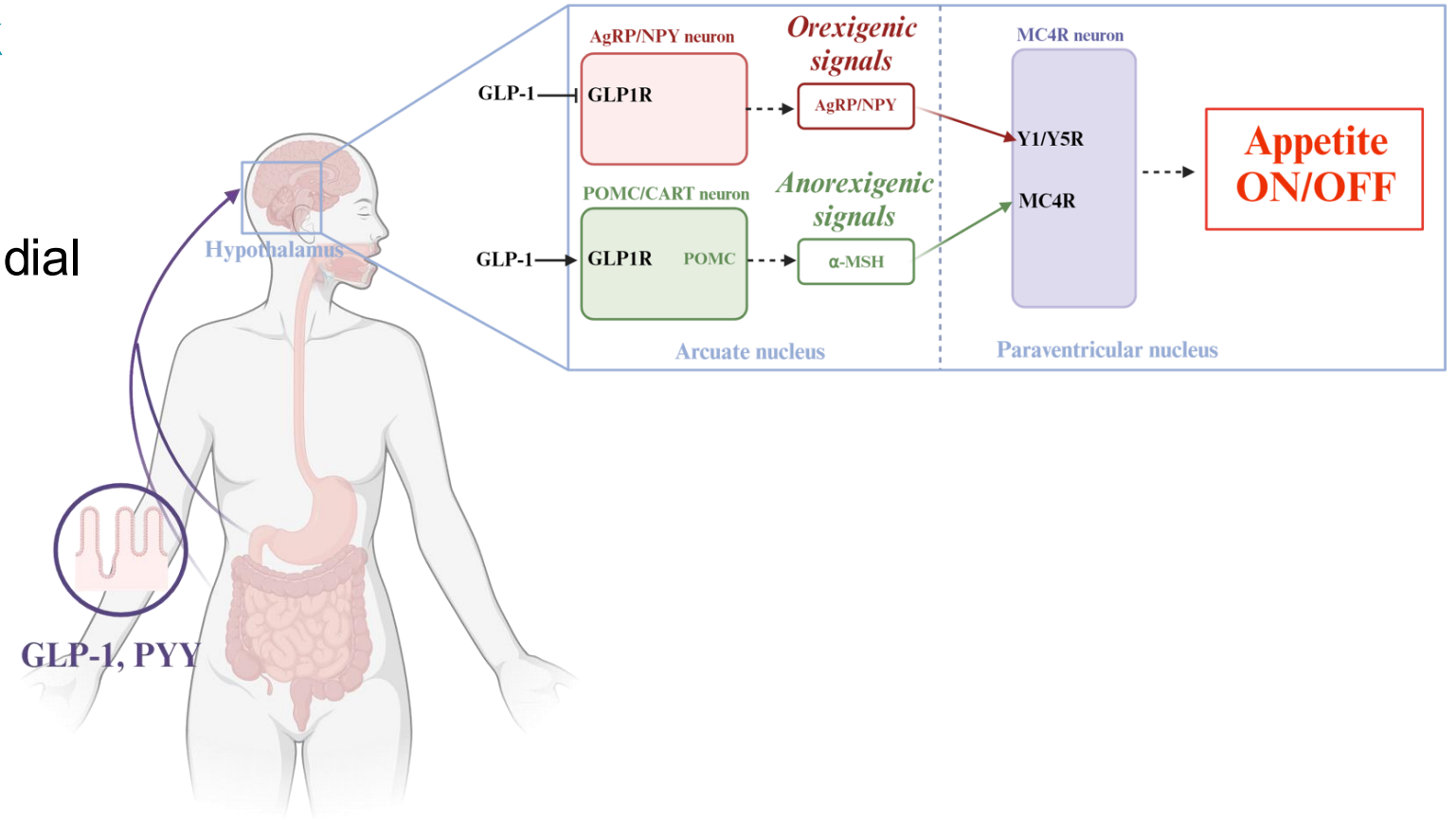
- We stratify obesity based on energy balance and behavioral phenotypic traits[1]
- Obesity interventions that target a specific obesity phenotype improves weight loss outcomes by **1.7 to 2 fold**[2-11]
- Phenotyping is not scalable; it is expensive, time-consuming and limited to a few academic centers[12]



1. Acosta A et al. *Gastroenterology*. 2015;148:537-546. 2. Acosta A et al. *Physiol Rep.* 2015;3(11):e12610. **3.** Halawi H et al. *Lancet Gastroenterol Hepatol*. 2017;2(12):890-899. **4.** Gómez V et al. Obesity (Silver Spring). 2016;24(9):1849-1853. **5.** Abu Dayyeh BK et al. *Clin Gastroenterol Hepatol.* 2017;15(1):37-43.e1. **6.** Vargas EJ et al. *BMJ Open Gastroenterol.* 2019;6(1):e000273. **7.** Acosta A et al. *Obesity (Silver Spring).* 2021;29(4):662-671. **8.** Campos A et al. *Obesity Surgery*. 2022;32(8):2632-2640. **9.** Clfuentes L et al. *EClinical Medicine*. 2023;58:101923. **10.** Vargas EJ et al. *Gut.* 2023;72(6):1073-1080. **11.** Gala K et al. *Obesity Surg.* 2023;33(4):1284-1288. **12.** Anazco D, Acosta A. *Int J Obes (Lond)*. 2025;49(3):452-463.

Biomarker for obesity phenotypes

- **Machine-learning gene risk score (ML-GRS)** to predict **appetite** phenotypes
  - Hungry Gut (abnormal postprandial satiety) and Hungry Brain (abnormal satiation)
  - 41 candidate genes from the gut-adipose-brain pathway



Cifuentes L et al. *Cell Metab*. 2025;37(8):1655-1666.e5.

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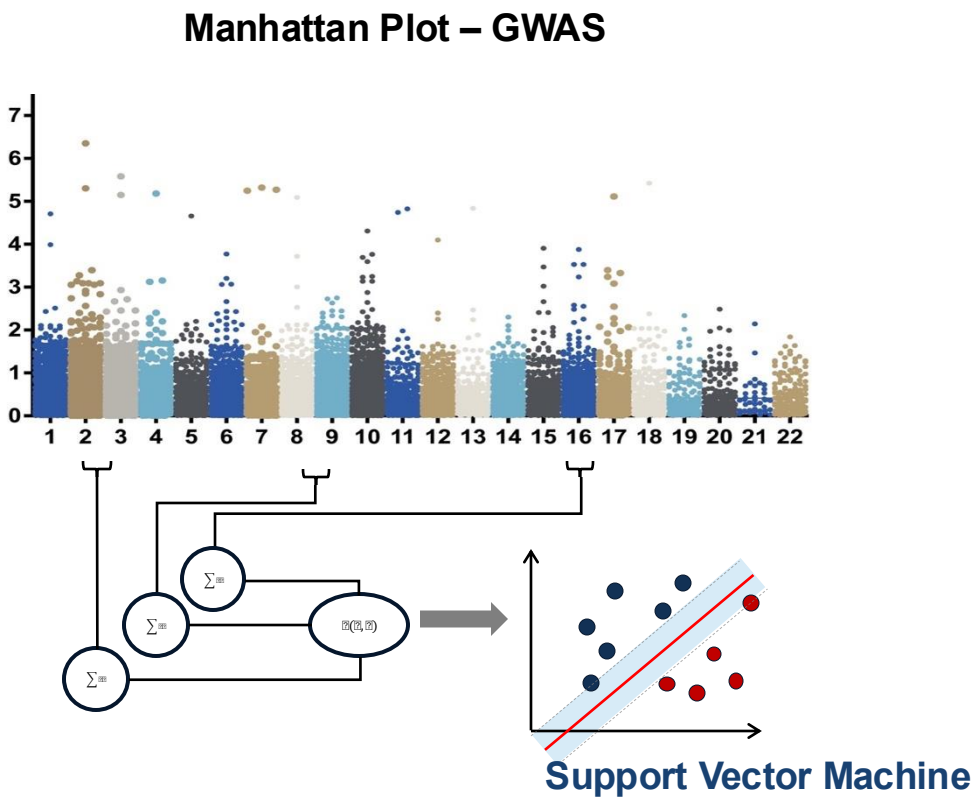
  - Using machine-learning techniques, the most informative GRS were selected to create the biomarker to predict hungry gut phenotype

Development of ML-GRS



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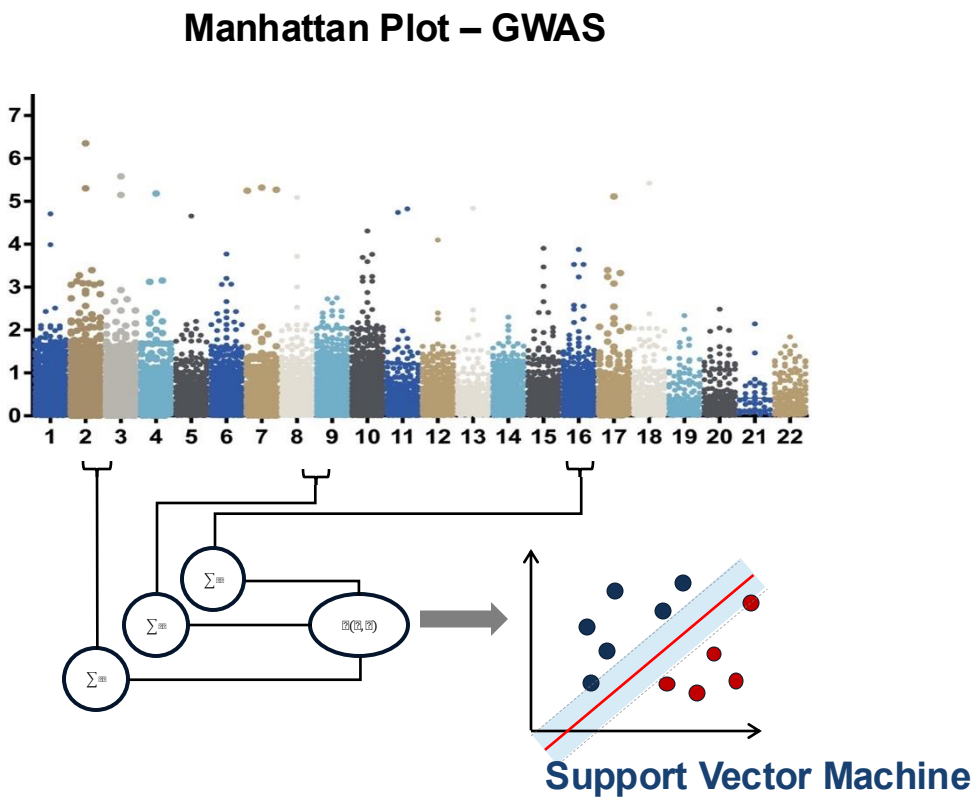
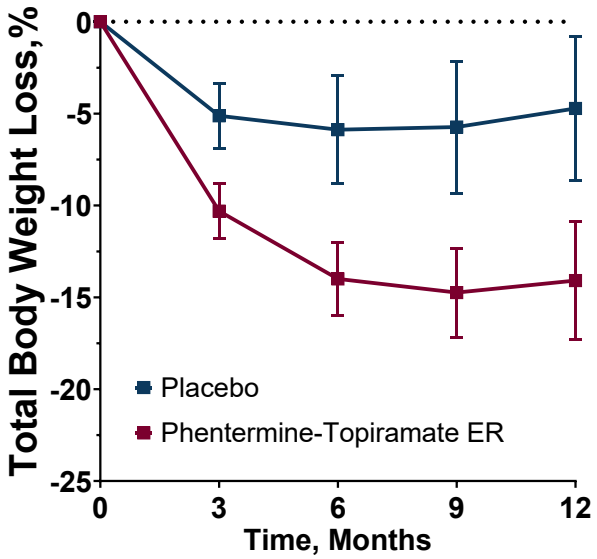
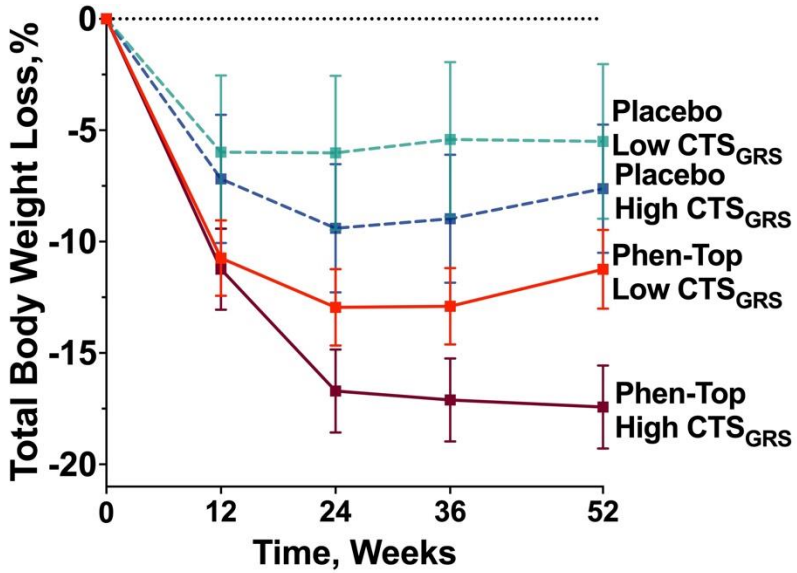


Satiation or CTS_{GRS} prediction of response to phentermine-topiramate ER

All



CTS_{GRS}



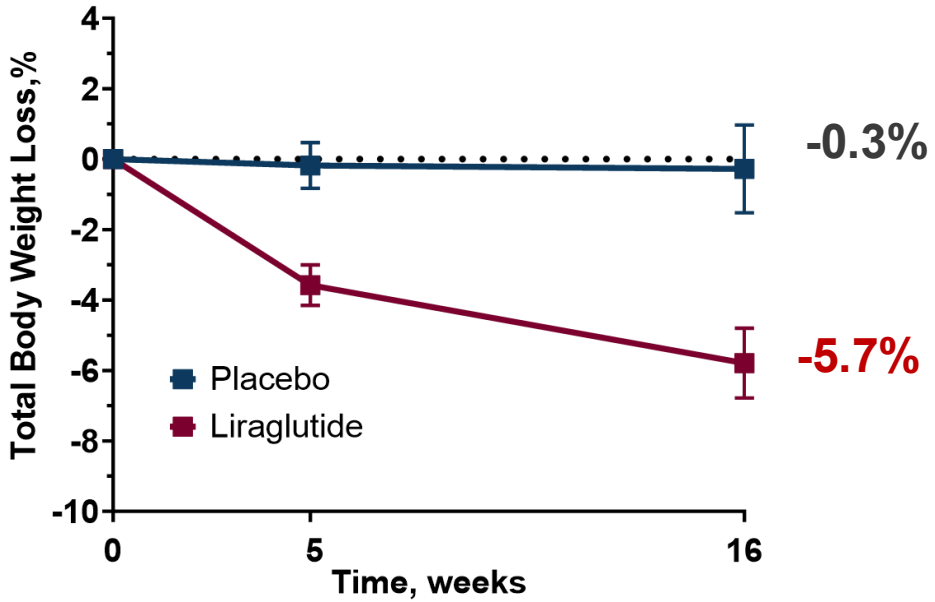
80 patients (BMI: 38 ± 6.9 kg/m^2)
From placebo-controlled, 52-week trial of
Phentermine-topiramate ER 7.5/46mg daily

Phentermine–topiramate is not approved for chronic weight management by Health Canada

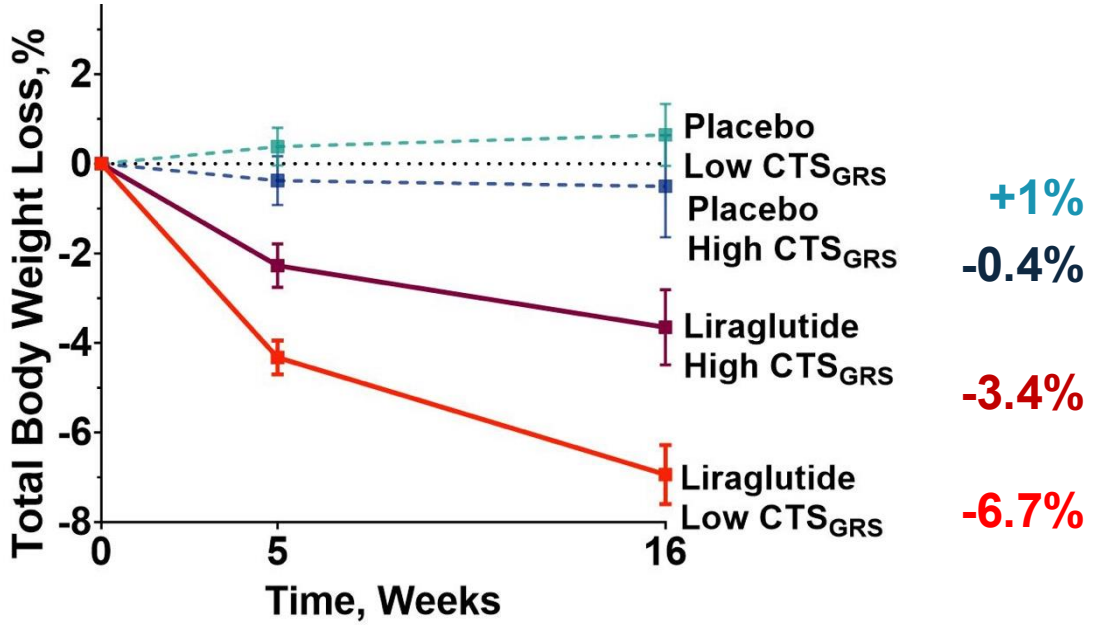
CTS, calories to satisfaction; GRS, genetic risk score.
Cifuentes L et al. *Cell Metab*. 2025;37(8):1655-1666.e5.

CTS_{GRS} prediction of response to liraglutide

All participants



CTS_{GRS}



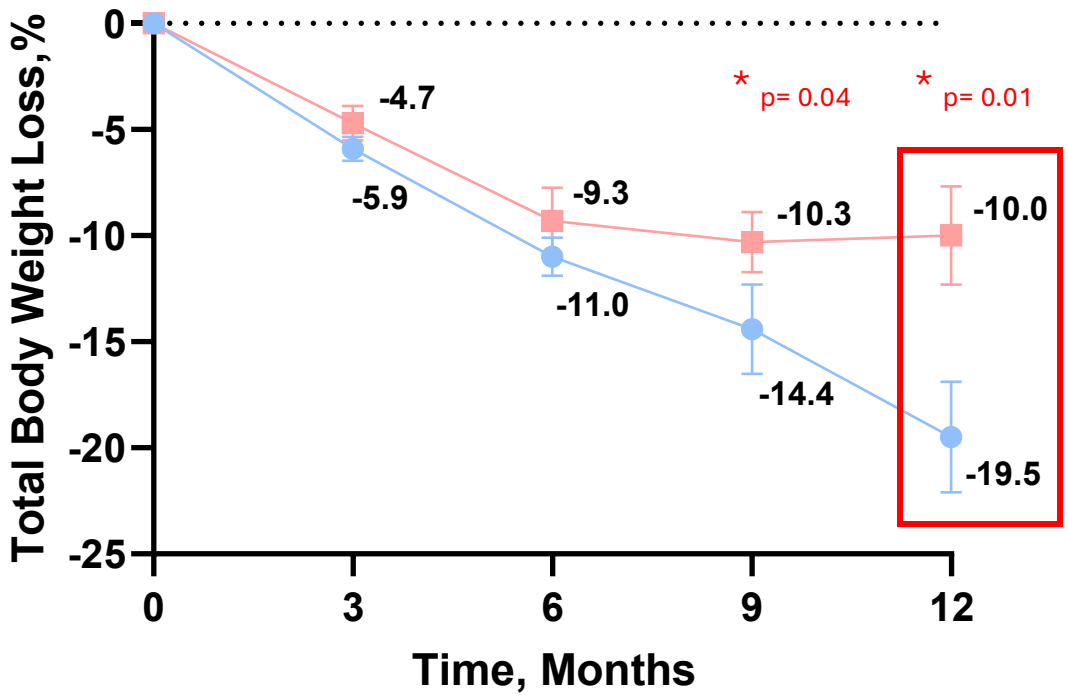
Randomized placebo-controlled, double-blinded trial[1]
Liraglutide 3 mg SC daily for 16 weeks
N=121 patients (BMI: 39.09 ± 7.40 kg/m^2)

CTS, calories to satisfaction; GRS, genetic risk score; SC, subcutaneous.

1. Maselli et al. *Obesity*. 2022;30(8):1608-1620. **2.** Cifuentes L et al. *Cell Metab*. 2025;37(8):1655-1666.e5.

Clinical utility: hungry gut test and weight loss outcomes to semaglutide

- Prospective cohort real-world evidence of semaglutide 2.4 mg SC weekly
- N=84 patients (BMI: 38 ± 7.40 kg/m^2)



CTS_{GRS} >0.50 (high)
Hungry gut-negative

CTS_{GRS} <0.50 (low)
Hungry gut-positive

	n/N[a]				
	Start	3 months	6 months	9 months	12 months
Hungry Gut +	51/51	**36**/50	**40**/45	**24**/32	**19**/22
Hungry Gut -	33/33	**26**/33	**24**/30	**24**/27	**16**/24

2-fold higher weight loss
associated with hungry gut-positive at 12 months compared with hungry gut-negative

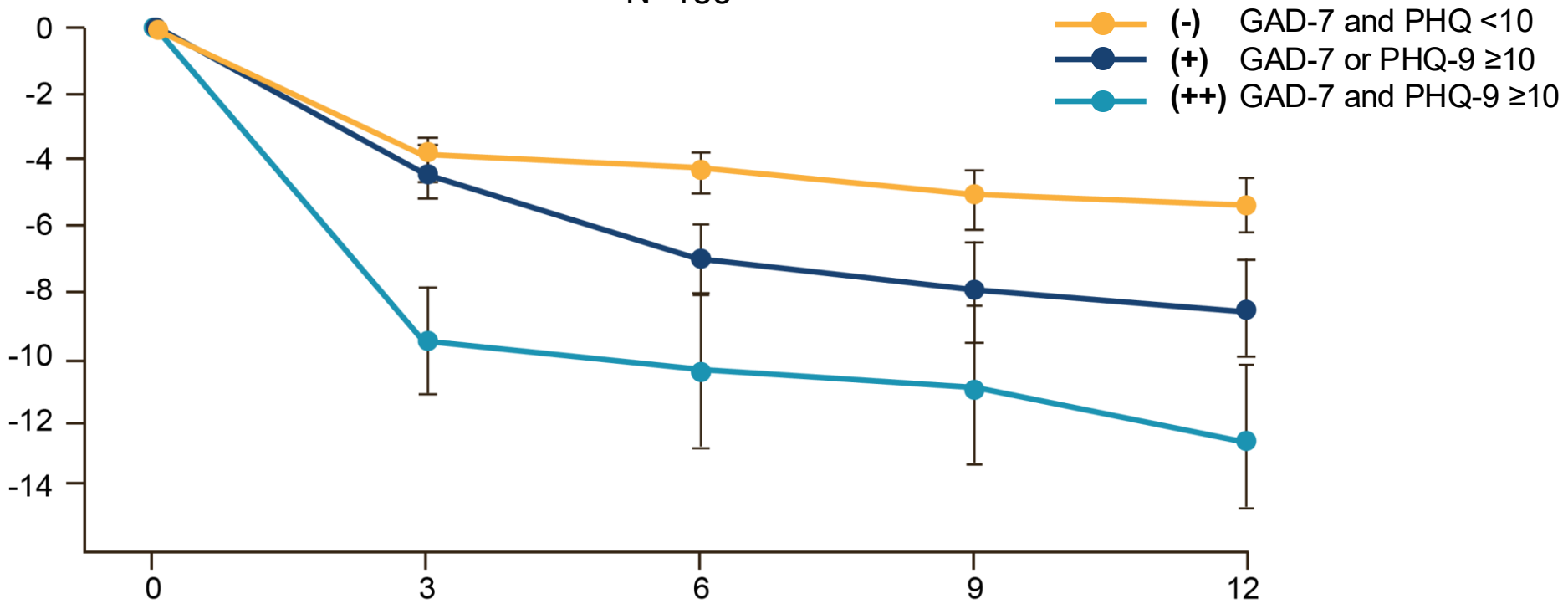
CTS, calories to satisfaction; GRS, genetic risk score; SC, subcutaneous.
[a]Number of participants with weight values/number of possible particiants.
Fansa S et al. Presented at ADA. 2024.

Emotional hunger phenotype questionnaires for clinical validity of naltrexone-bupropion ER

12-month weight loss outcomes in patients with high vs low depression/anxiety levels treated with naltrexone-bupropion ER

Retrospective, 12-month, real-world evidence

N=185

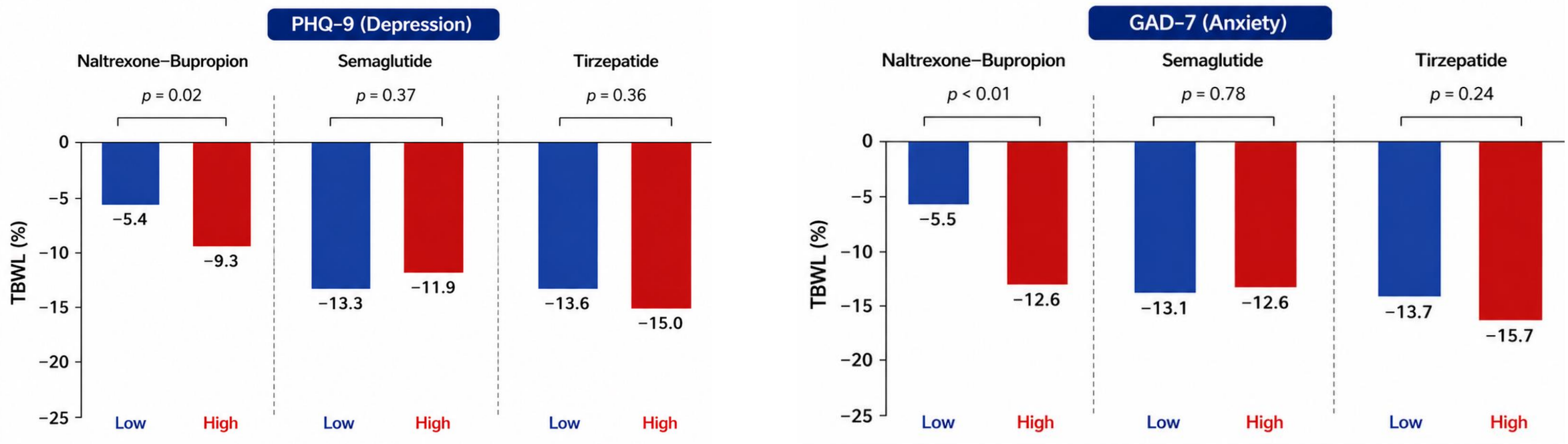


185 patients
Mean age 52.1 ±13.9 y
83% female
BMI 39.4 ± 7.5 kg/m^2

GAD-7, Generalized Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; TBWL, total body weight loss.
Villamarin J et al…Acosta A. Presented at *Obesity Week* 2025, manuscript under review.

Emotional hunger phenotype in naltrexone-bupropion ER, semaglutide and tirzepatide: Comparative analysis

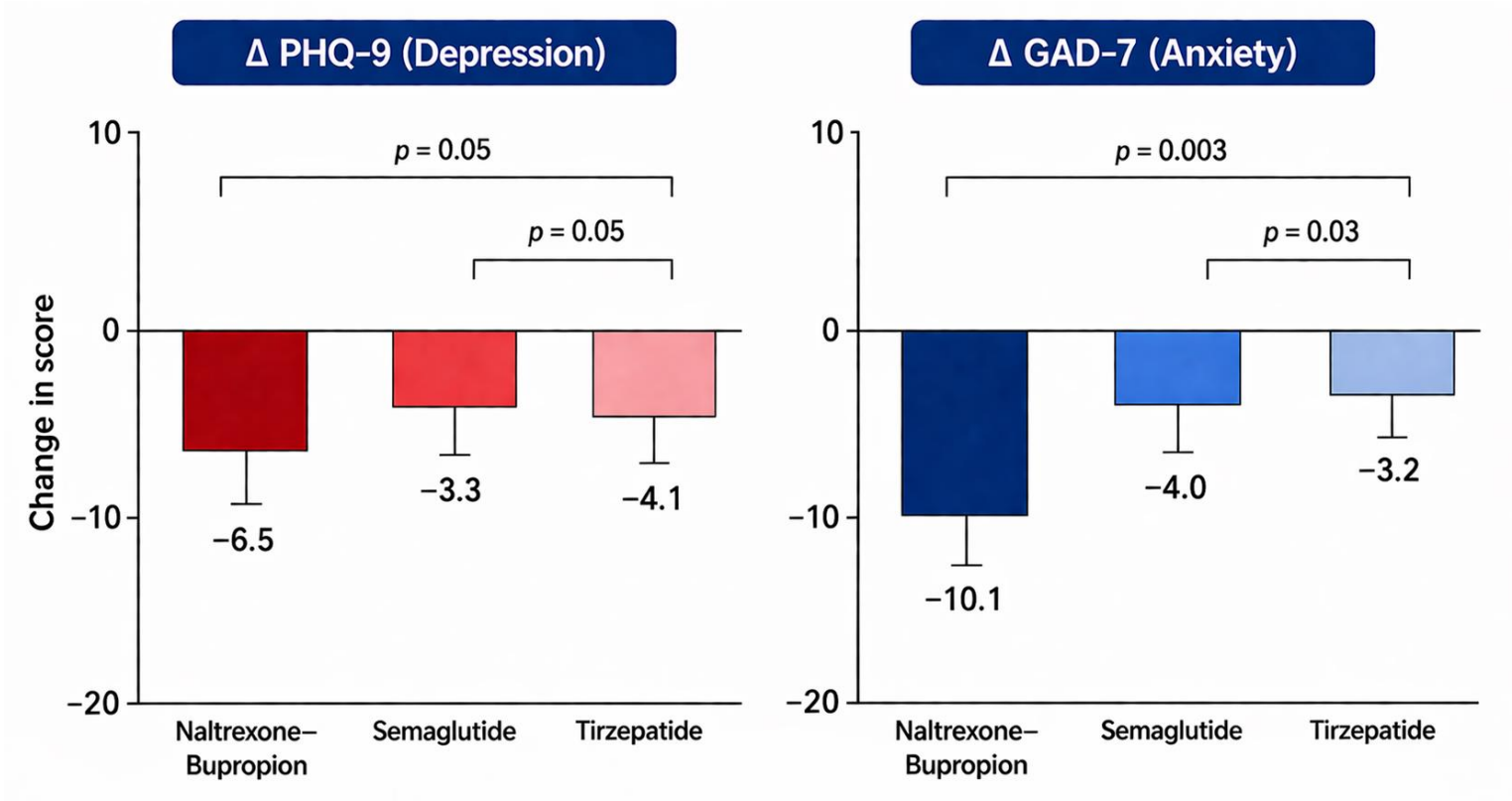
12-month total body weight loss by baseline depression and anxiety severity across obesity medications



Villamarin J, Garcia Cordova JM, Romanos M, et al. PO4.133. *Obes Facts*. 2026;19:1:430

Emotional hunger phenotype in naltrexone-bupropion ER, semaglutide and tirzepatide: Comparative analysis

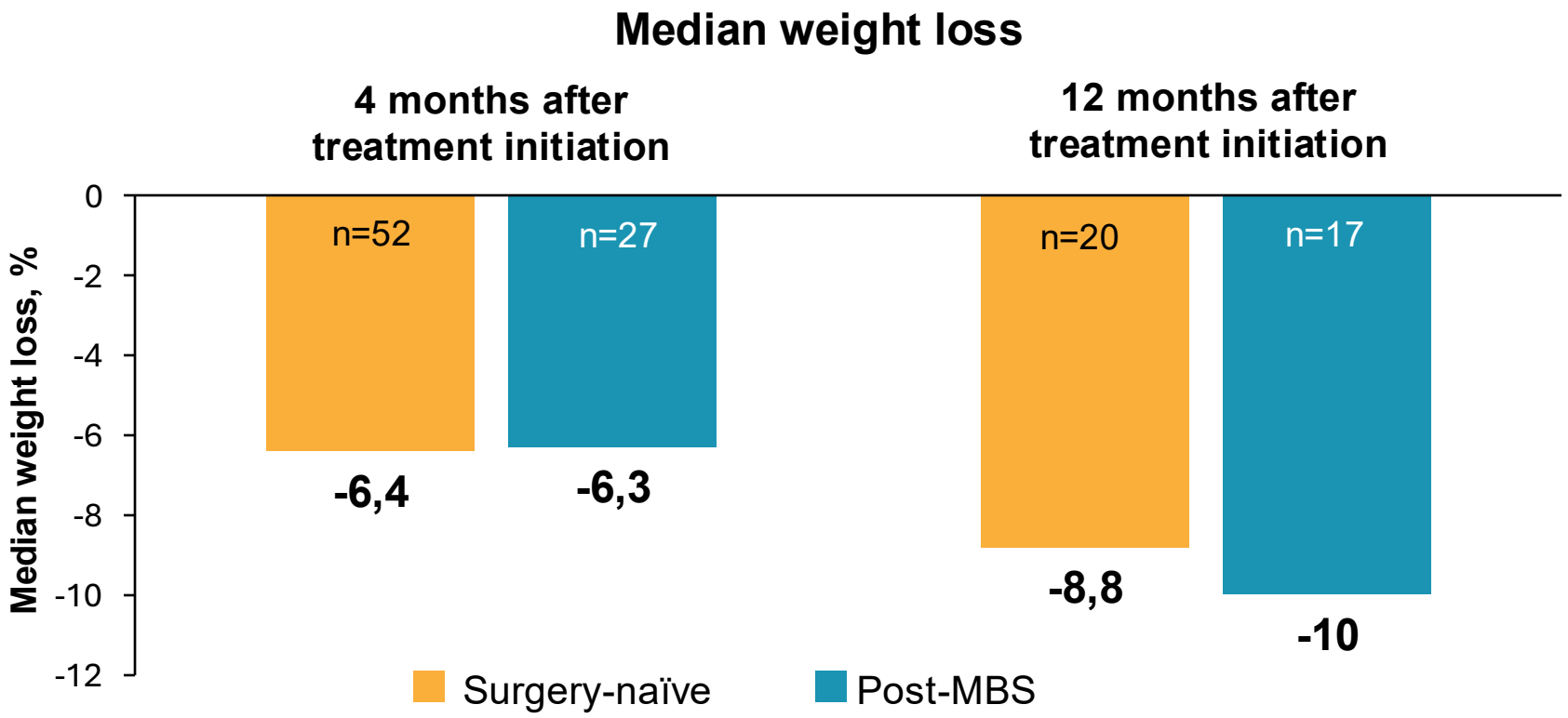
Changes in depression (PHQ-9) and anxiety (GAD-7) scores at follow-up by obesity medication



Villamarin J, Garcia Cordova JM, Romanos M, et al. PO4.133. *Obes Facts*. 2026;19:1:430

Naltrexone-bupropion ER is equally effective in surgery-naïve and post-surgical patients

Single-center retrospective cohort study of patients who initiated ER-NB
(N=153)



There was no statistically significant difference in weight loss between the surgery-naive and post-MBS groups.

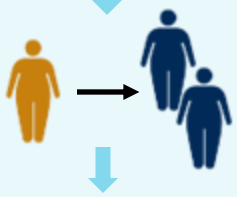
MBS, metabolic and bariatric surgery.
Yskout M et al. *Int J Obes.* 2025;49:2102-2109.

RYGB & genetics: leptin-melanocortin pathway

Methods

50,000 participants of the Mayo Clinic Biobank were assessed for patients with history of RYGB

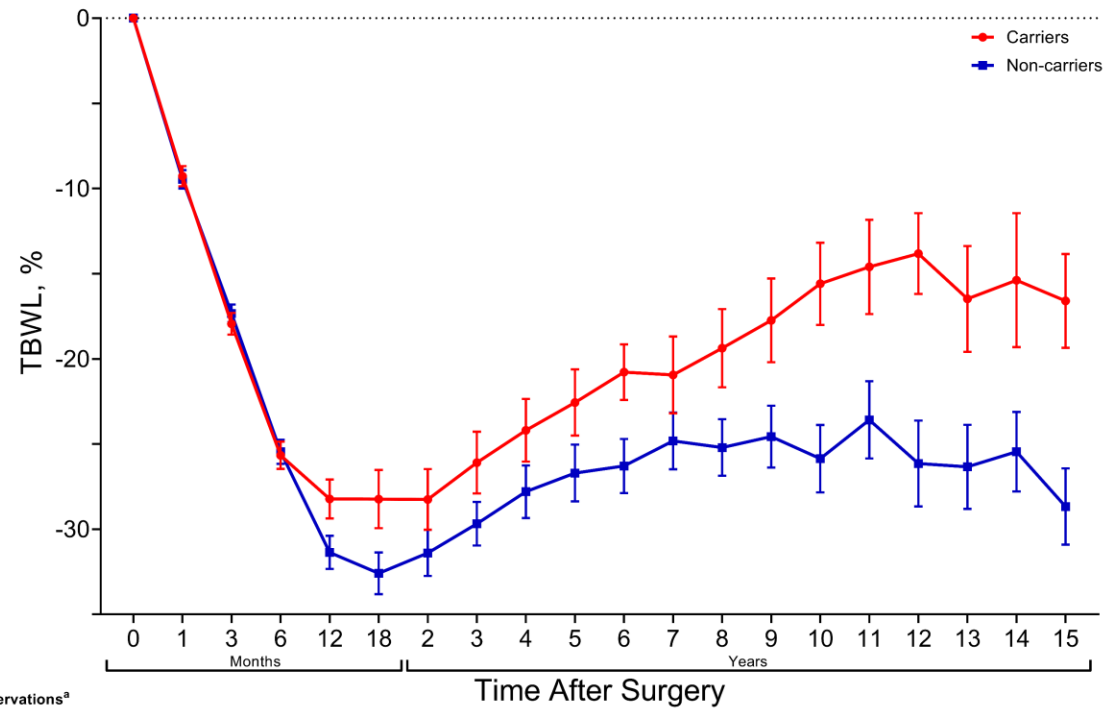
Eligible patients were genotyped for heterozygous variants in the leptin-melanocortin pathway



Each carrier of a heterozygous variant was randomly matched with 2 non-carrier controls based on: sex, age, BMI, & years since surgery.

Data was abstracted from the electronic medical record for up to 15 years after surgery

RYGB and carriers of leptin-melanocortin mutations



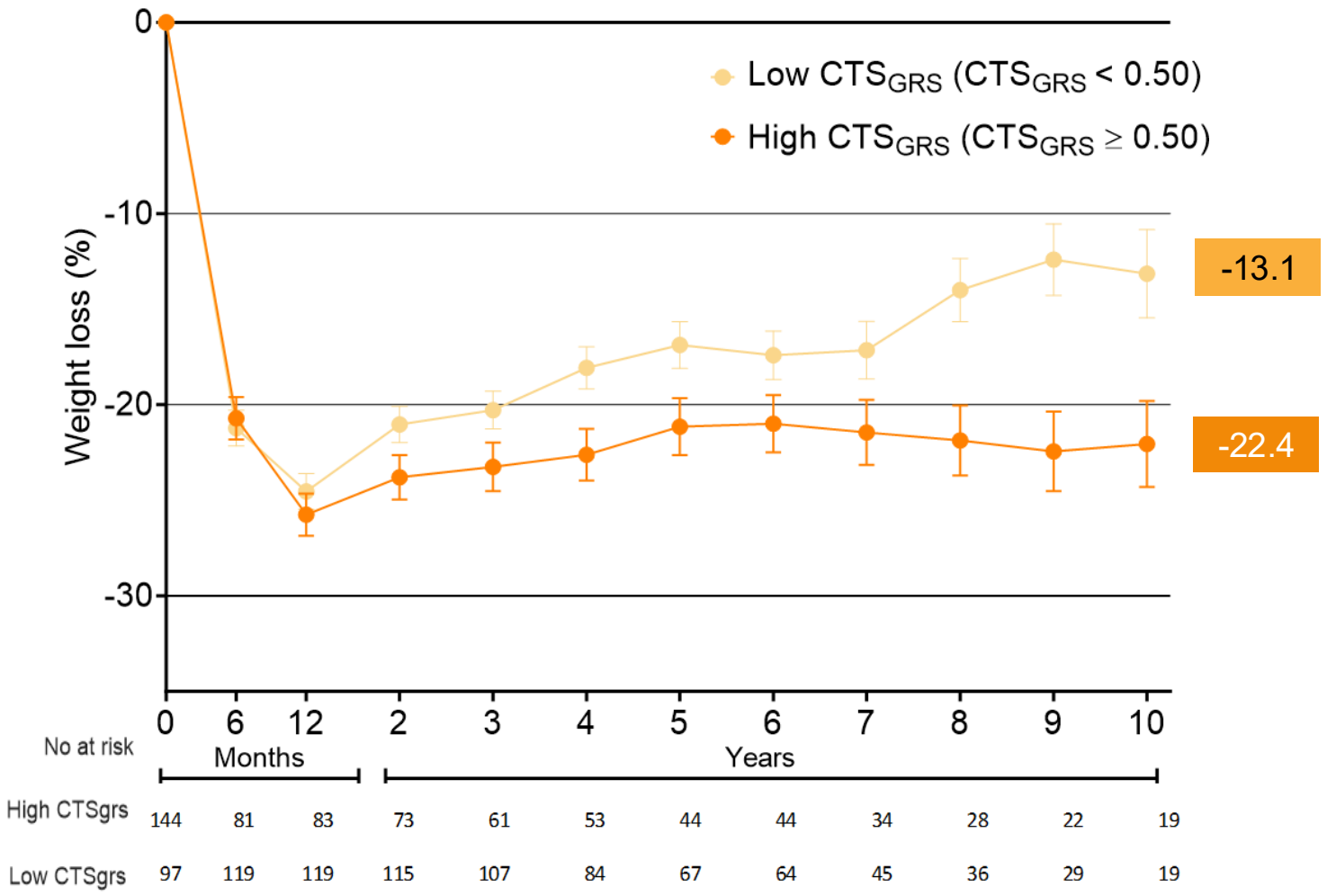
Observations[a] / Possible Observations[b]																				
Carriers	50	43	44	46	48	37	39	39	36	34	37	25	25	21	23	18	18	15	14	15
	50	50	50	50	50	49	48	46	46	45	40	35	32	27	26	23	22	19	18	16
Non-Carriers	100	78	88	94	93	80	83	86	82	73	68	66	65	59	50	49	40	39	36	33
	100	100	100	100	100	99	99	97	94	90	88	86	77	72	68	59	51	50	45	43

RYGB, Roux-en-Y gastric bypass.

Campos A et al. *Obesity Surgery*. 2022;32(8):2632-2640.

Obesity phenotypes and sleeve gastrectomy by CTS_{GRS}

N	241
Age	49 ±13
Gender	Female 80%
BMI	43.1 ± 7 kg/m^2
Race	White 90%
T2D	34%

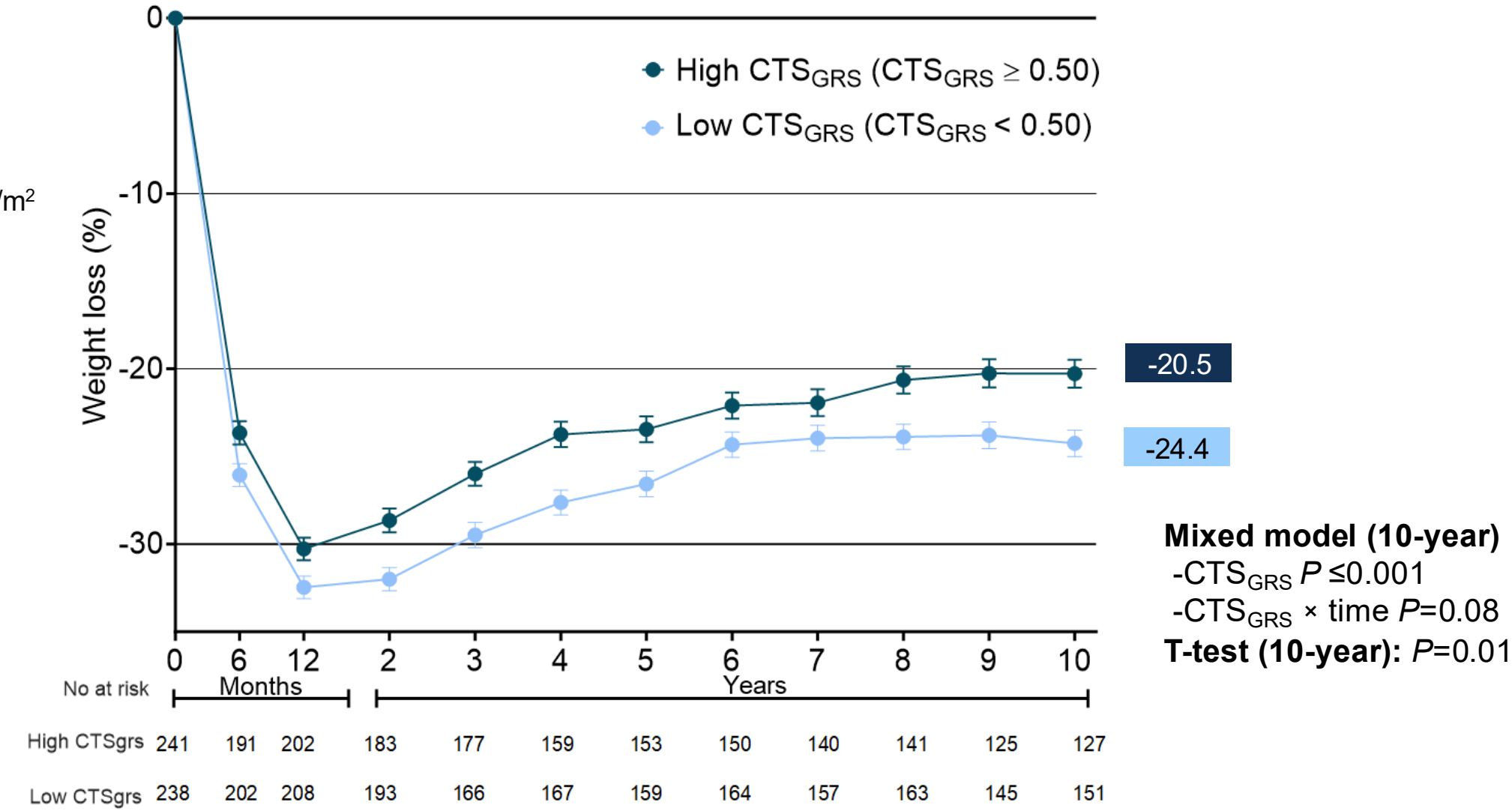


Mixed model (10-year)
-CTS_{GRS} $P \leq 0.001$
-CTS_{GRS} × time $P=0.007$
T-test (10-year): $P=0.02$

CTS, calories to satisfaction; GRS, genetic risk score; T2D, type 2 diabetes.
Villamarin J et al. DDW 2026.

Obesity phenotypes and Roux-en-Y gastric bypass by CTS_{GRS}

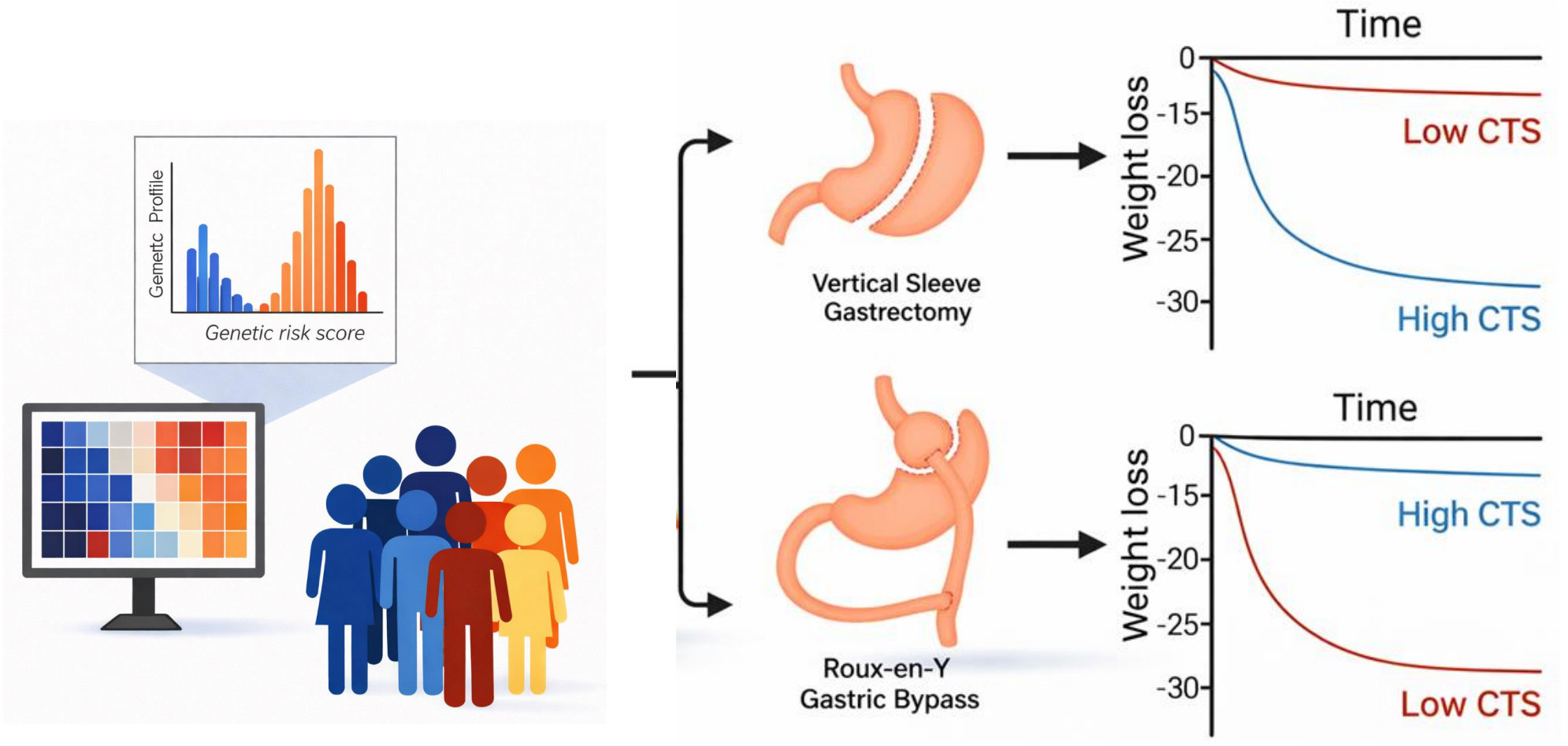
N	479
Age	51 ±11
Gender	Female 86%
BMI	45.4 ± 6.8 kg/m^2
Race	White 96%
T2D	37%



Mixed model (10-year)
-CTS_{GRS} *P* ≤0.001
-CTS_{GRS} × time *P*=0.08
T-test (10-year): *P*=0.01

CTS, calories to satisfaction; GRS, genetic risk score; T2D, type 2 diabetes.
Espinosa MA et al. DDW 2025.

Obesity phenotypes and **Bariatric surgery** : Working Hypothesis

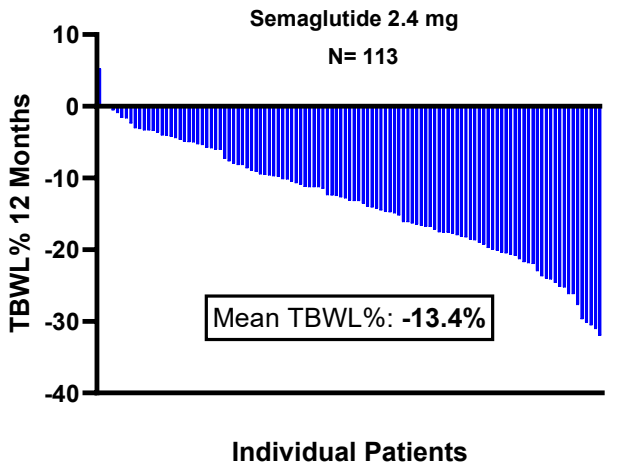


Key take-away points

- “One-treatment-fits-all” is not working
- Obesity is a complex and heterogenous disease with multiple phenotypes
- Phenotype-guided classification and interventions double weight loss
- Biomarker predicts phenotypes and identifies best responders to obesity interventions

Opportunities to tackle ~~Obstacles~~ In the obesity pandemic

HETEROGENEOUS OUTCOMES[1]



HIGH COST[2]

LIMITED PATIENT ACCESS[3]

Better outcomes with MyPhenome Test (CTS_{GRS}) → **Obesity Rx cost-effective?** → **Increase access and reduce stigma?**

1. Modified from Abu Dayyeh BK et al. Lancet. 2022;400(10350:441-451. **2.** Trujillo JM et al. *Ther Adv Endocrinol Metab*. 2021;12:2042018821997320. **3.** Ard J et al. *Adv Ther*. 2021;38(6):2821-2839.

Questions and Answers

azurity pharmaceuticals