Personalisation of pharmacotherapy for obesity

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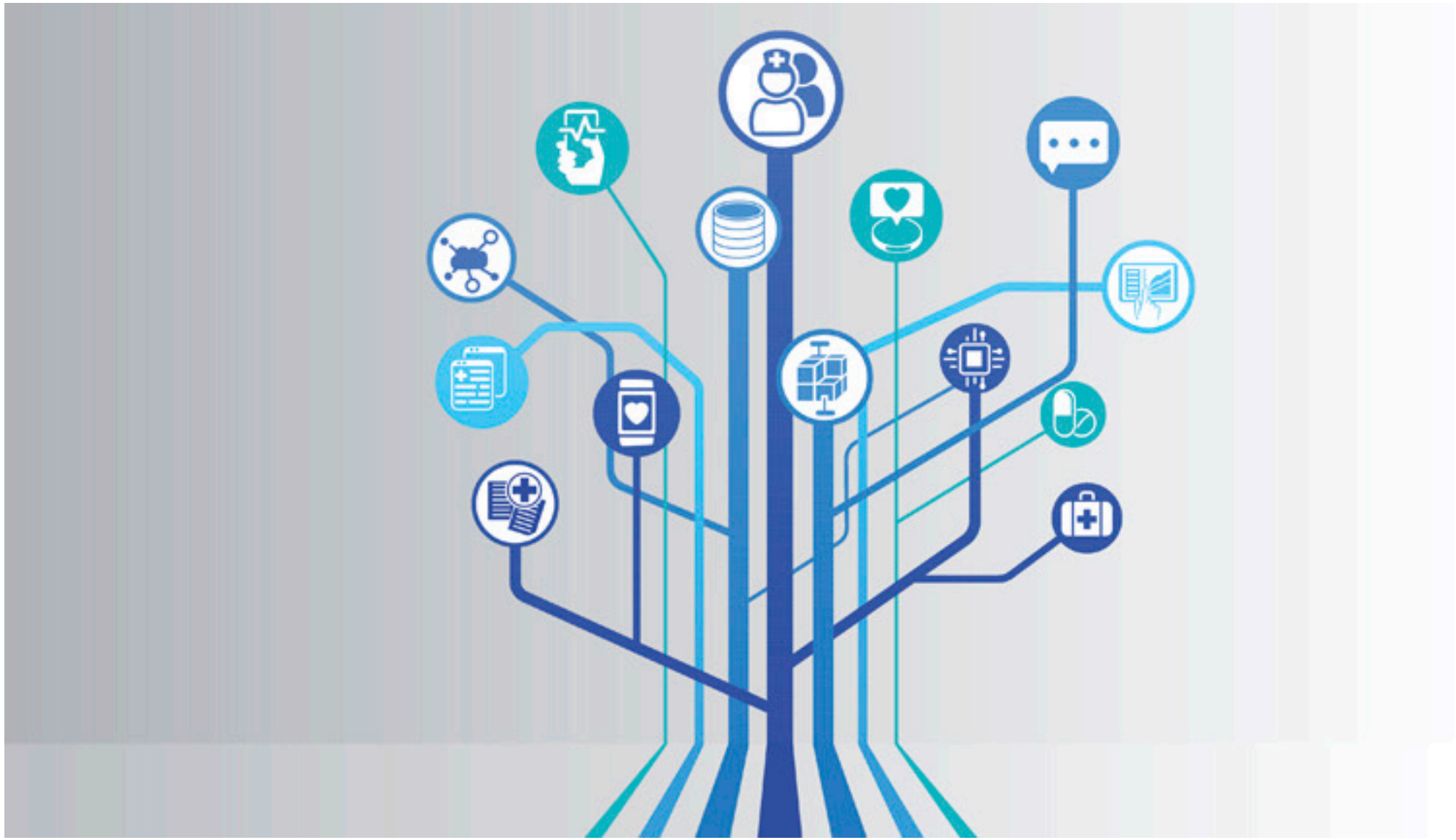
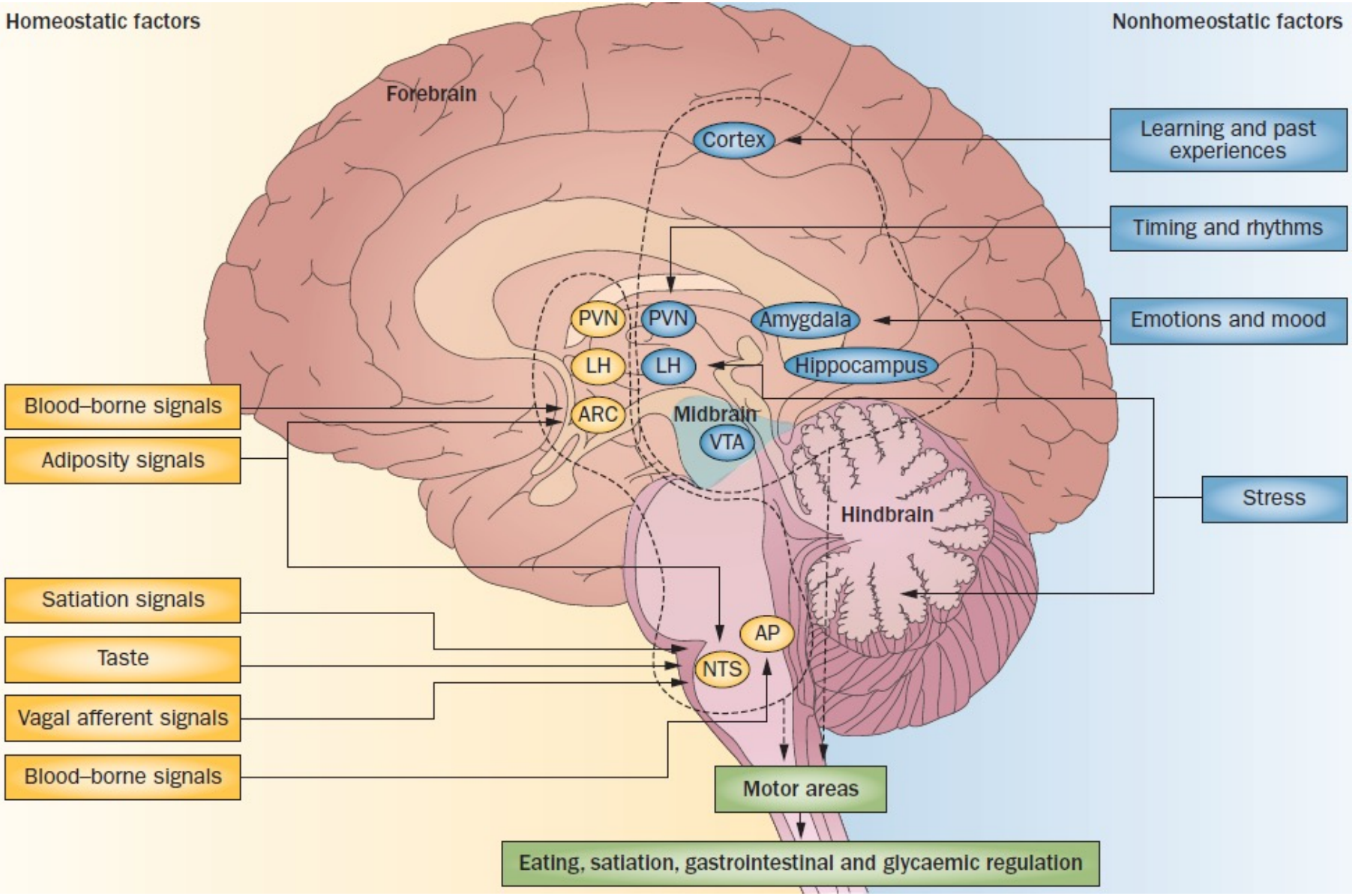
- Other Financial or Material Support/Honorarium: Novo Nordisk, GI Dynamics, AstraZeneca, Boehringer Ingelheim, Currax Pharmaceuticals



Obesity: a neurological disease of the appetite centres of the brain

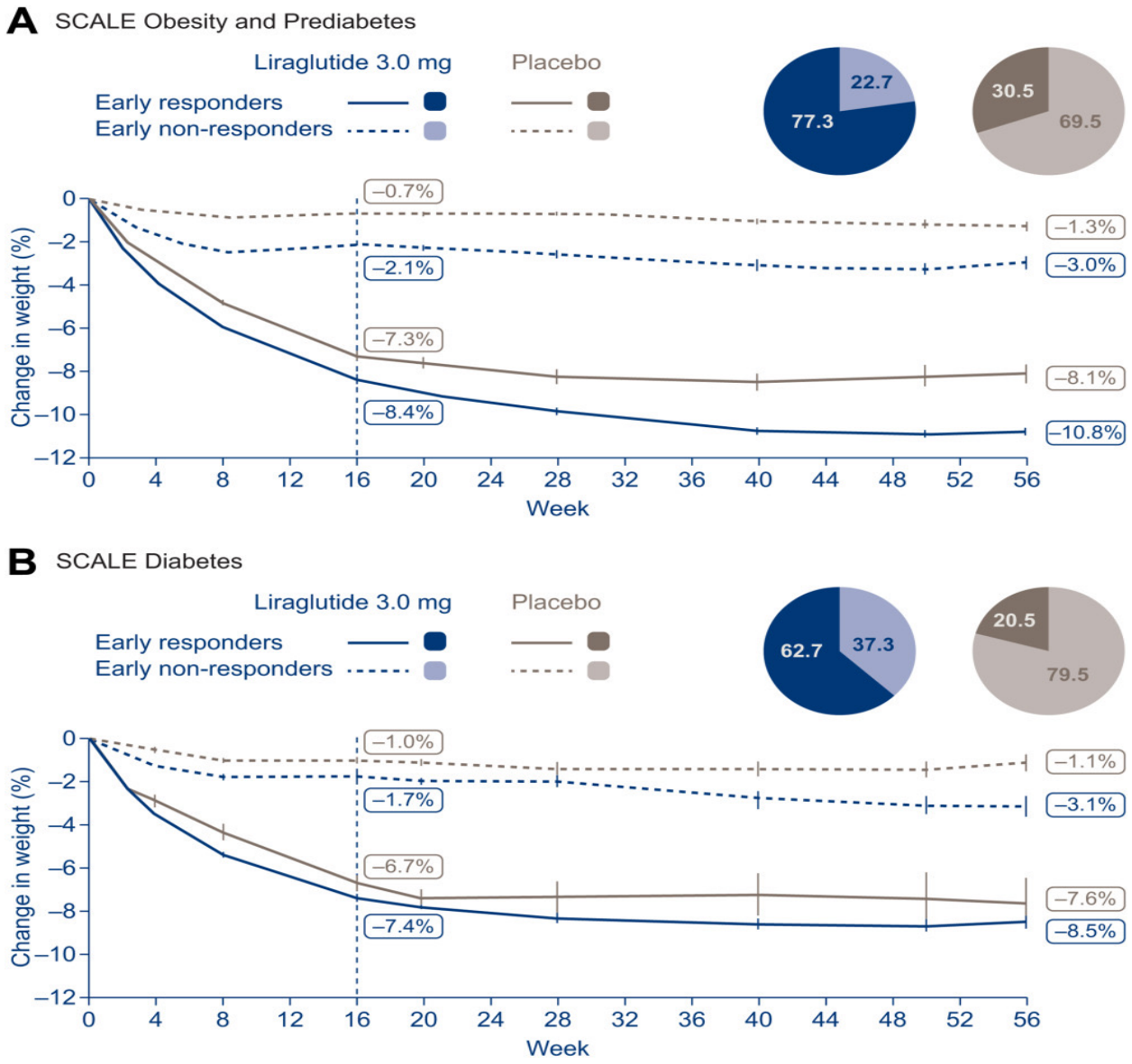


The Endocrinology of food intake, Begg DP, Nature Endocrinology, 2013 Oct;9(10):584-97

Benefits of Personalisation

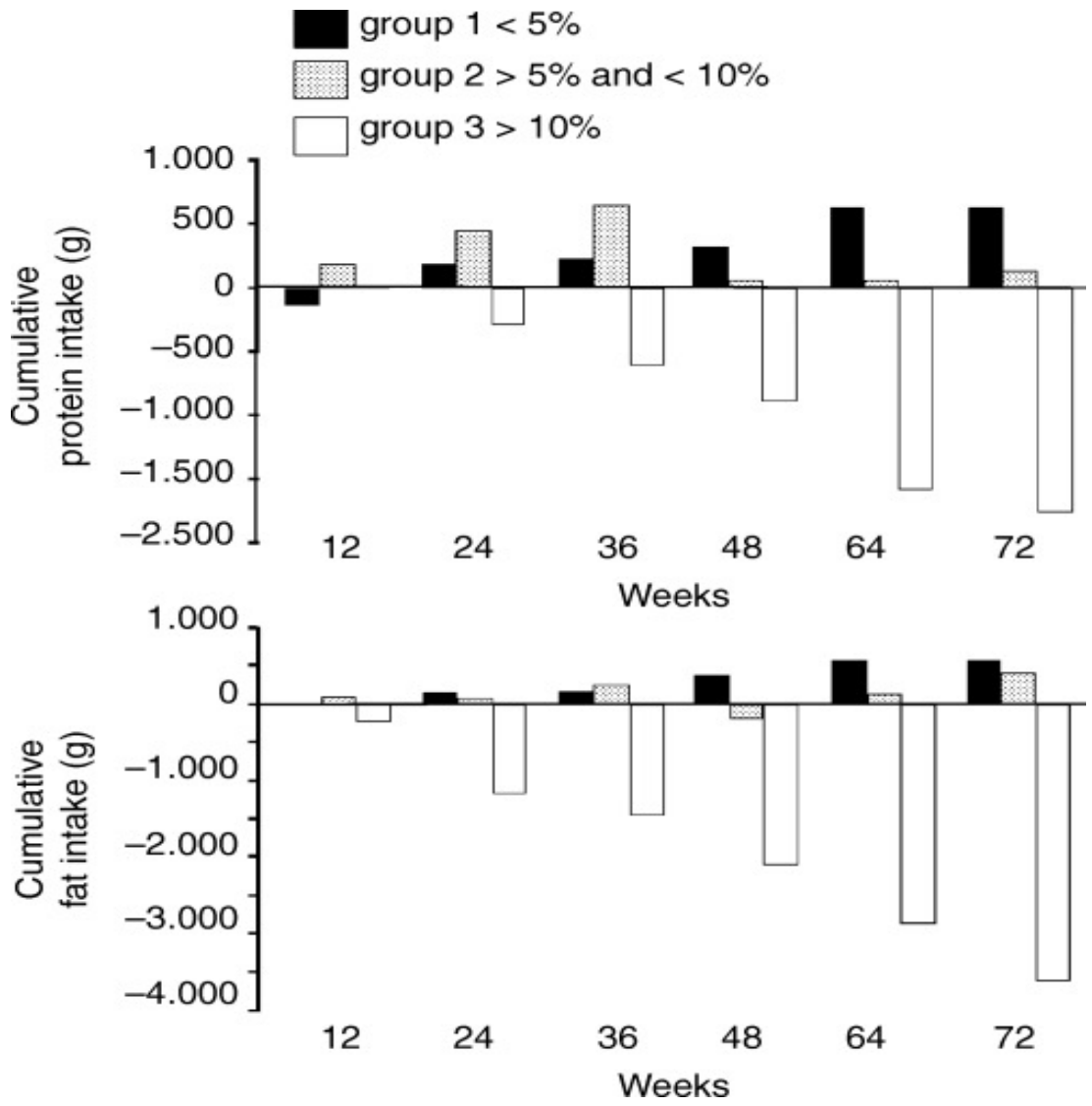
- Risk stratification and patient prioritisation
- Avoidance of exposure to side effects in non-responders
- Maximisation of effect size
- **Cost-effectiveness**
- Better, cheaper, faster clinical trials

Early Weight Loss with Liraglutide 3.0 mg Predicts 1-Year Weight Loss



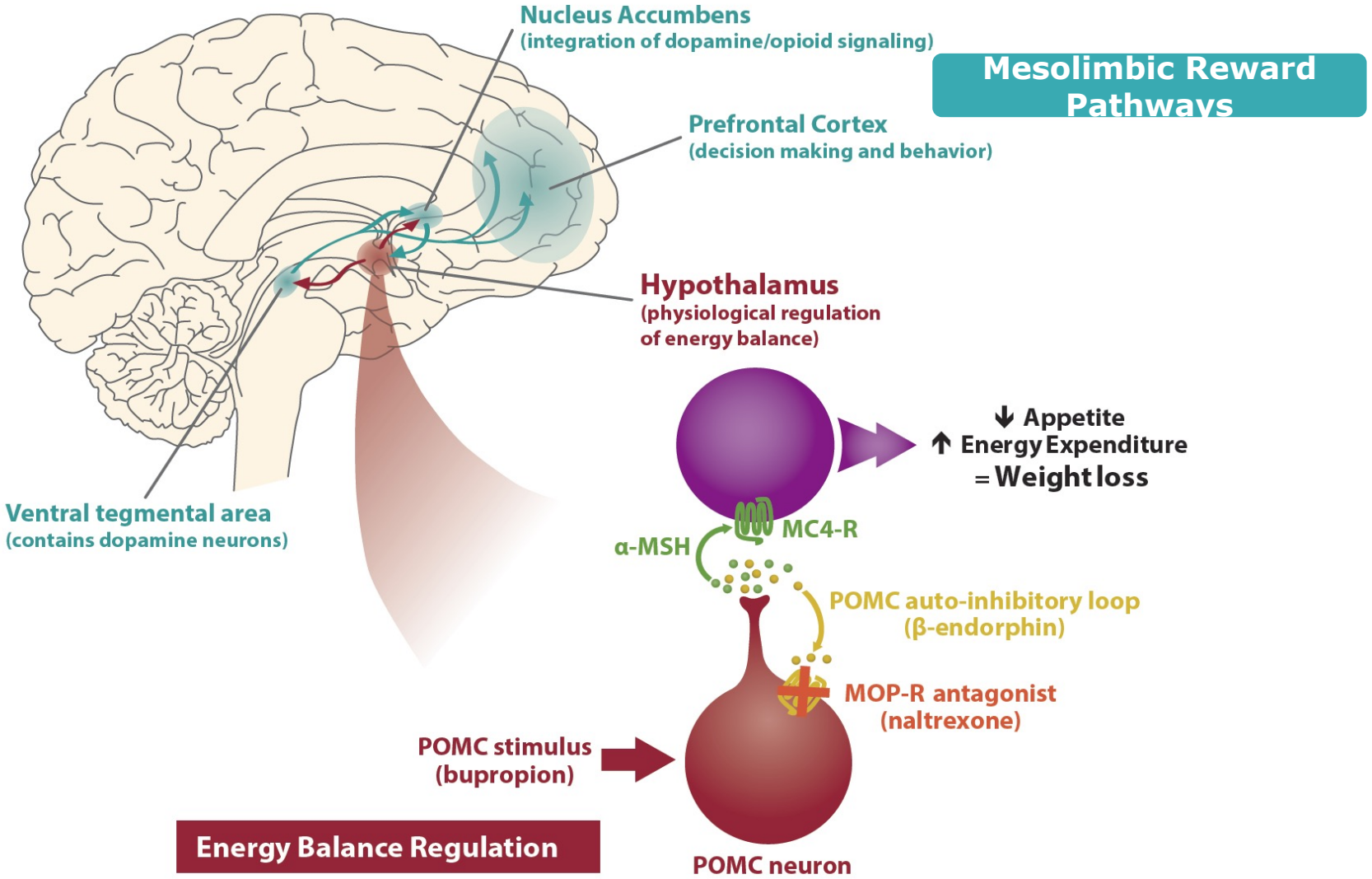
Fujioka et al, *Obesity*, 2016

Low Fat Consumption During Orlistat Treatment Predicts Weight Loss



Aliment Pharmacol Ther, 2003;17(8):1007-1013

Naltrexone/Bupropion Influences Energy Balance and Reward



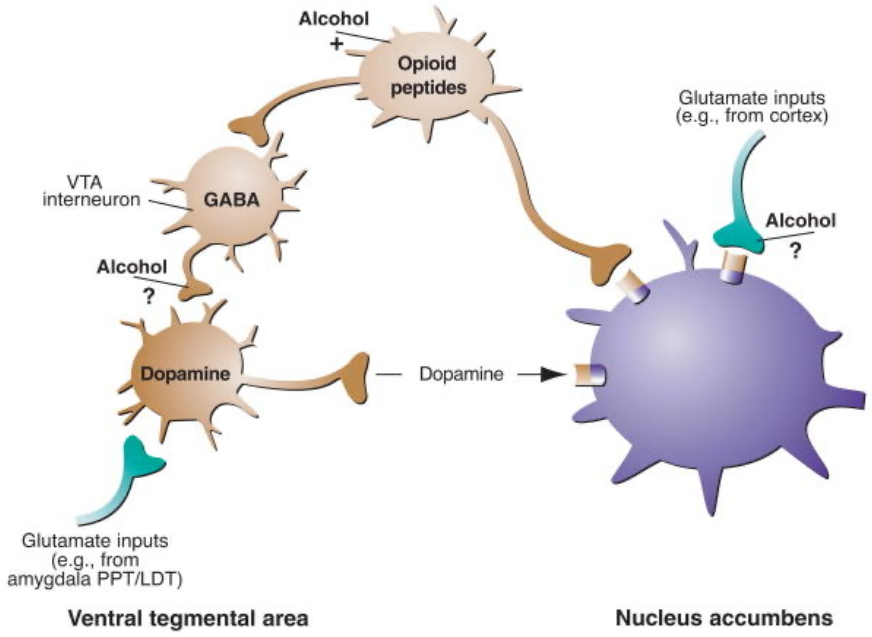
Adapted from: Billes, et al. *Pharmacol Res*. 2014;84:1-11.

Addictive Behaviours Share Common Mechanisms

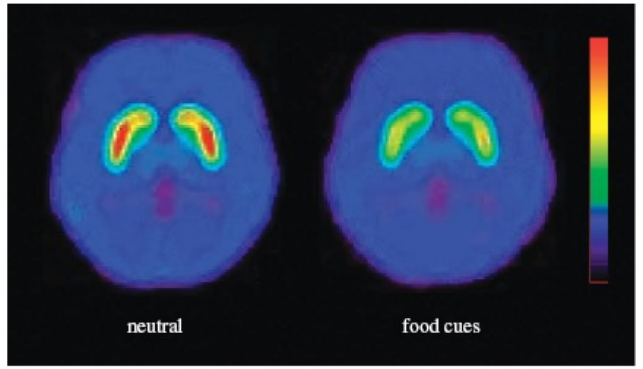
Dopamine, mu-opioid receptor (μOR) and mesolimbic reward center

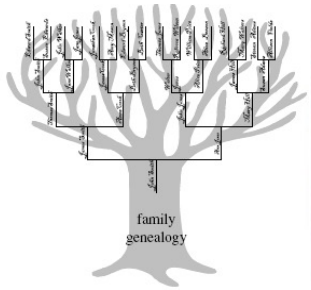
- Key link between a stimulus and behavioral response
- Common neurobehavioral mechanisms drive addictive behaviors, including over-eating (i.e., eating beyond energy needs)

Dopamine and μOR are central to Mesolimbic Reward Circuitry



Dopamine Changes in Response to Food Cues





Gilpin NW, et al. *Alcohol Res Health*. 2008;31(3):185-195.
Volkow ND, et al. Philos *Trans R Soc Lond B Biol Sci.* 2008 Oct 12;363(1507):3191-200.

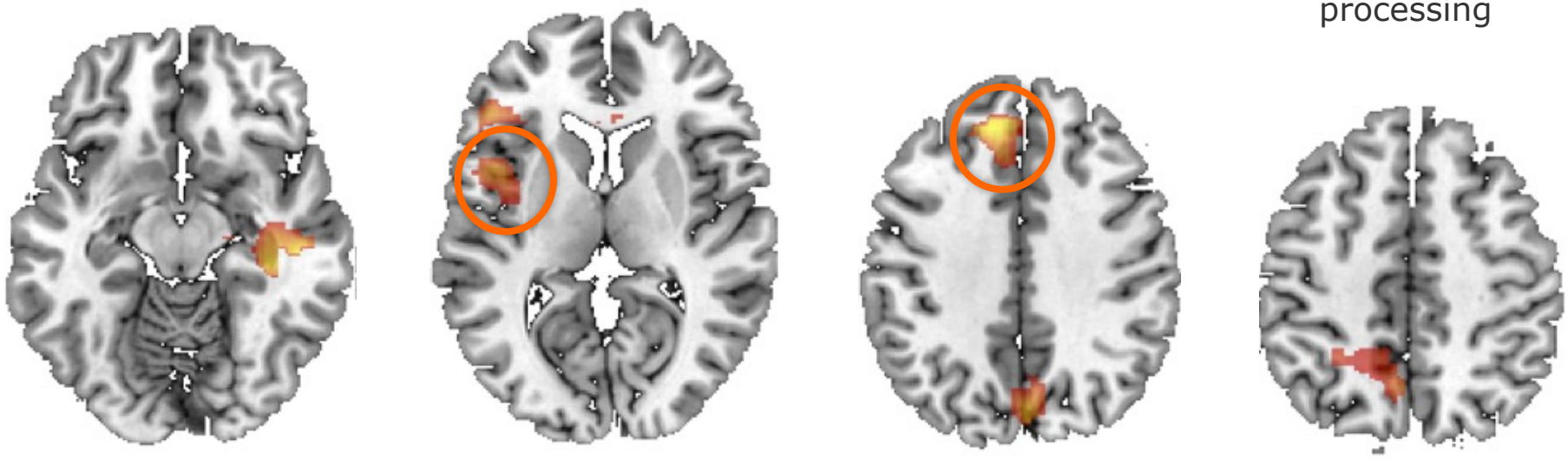
Naltrexone/Bupropion Enhances CNS Control Mechanisms

Hippocampus
memory / conditioning

Posterior Insula
internal awareness
(taste / fullness)

Anterior Cingulate
self-control

Superior parietal
cognition /
somatosensory
processing



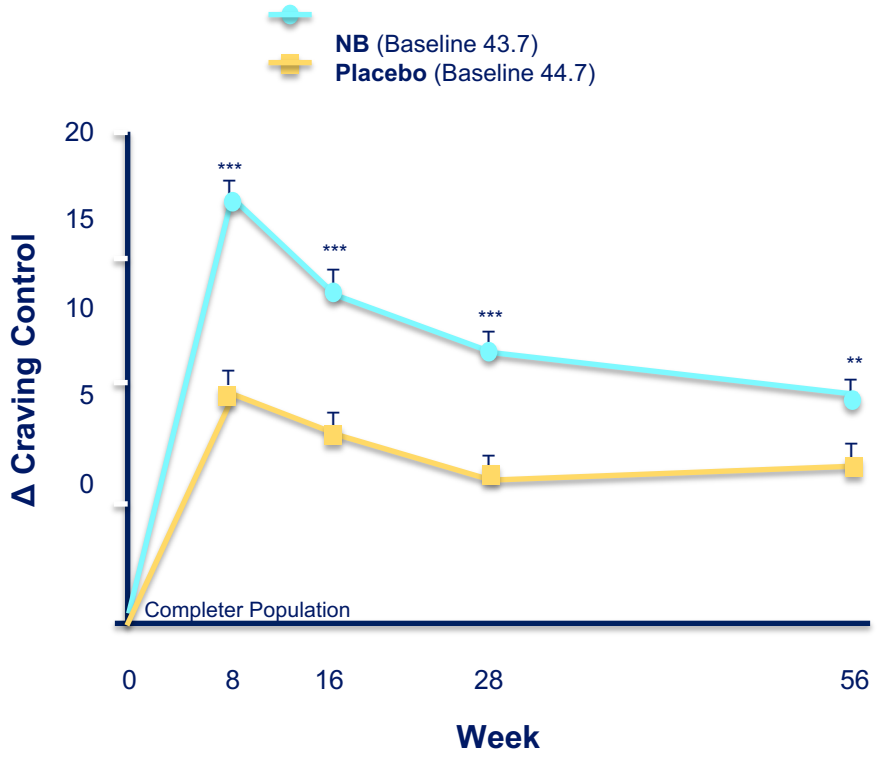
Colourings indicate regions of increased response to food cues of naltrexone/bupropion vs placebo

increasing response

Selected Safety Information (See SmPC for full details)
Suicide and suicidal behaviour: Closely supervise patients particularly those at high risk, especially in early treatment and following dose changes. Seizures: Bupropion is associated with a dose-related risk of seizures. Exercise caution when prescribing to patients with predisposing factors that may increase the risk of seizure.

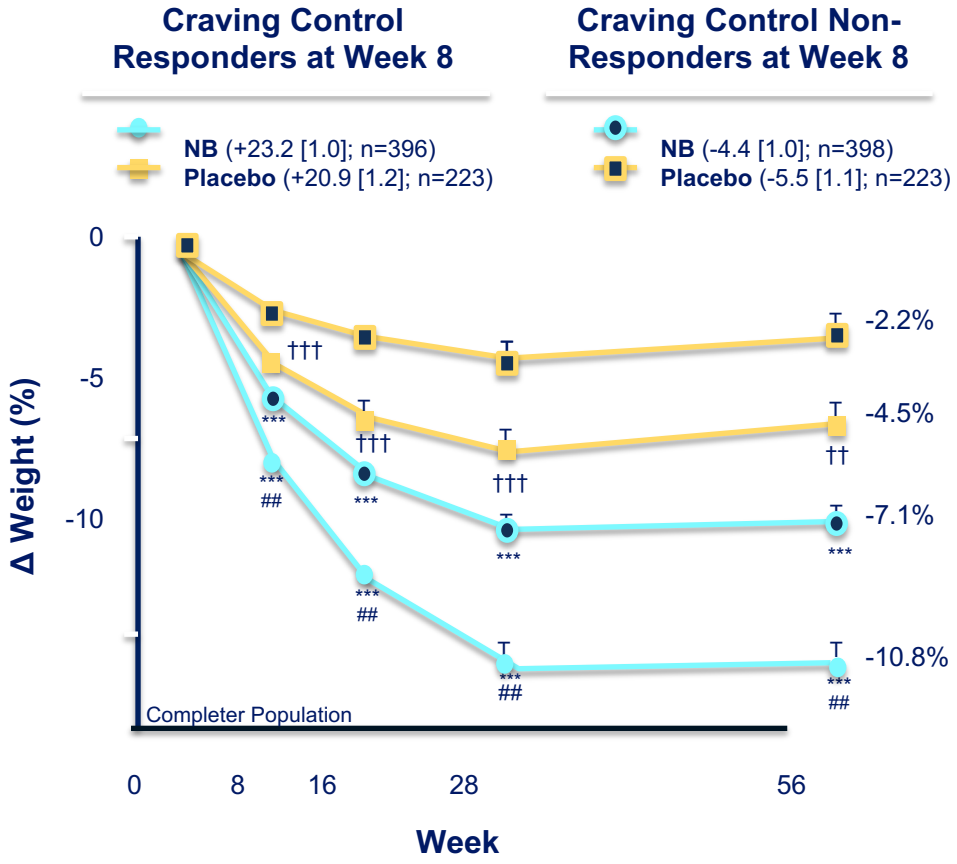
Adapted from: Wang et al. *Int J Obes (Lond).* 2013

Lower "Craving" at 8 Weeks with Naltrexone/Bupropion Predicts Weight Loss at 1 Year



Mean (SE)

*** = p<0.001, ** = p<0.01 vs Placebo



Mean (SE)
Responder = Upper tertile of response
Non-responder = Lower response

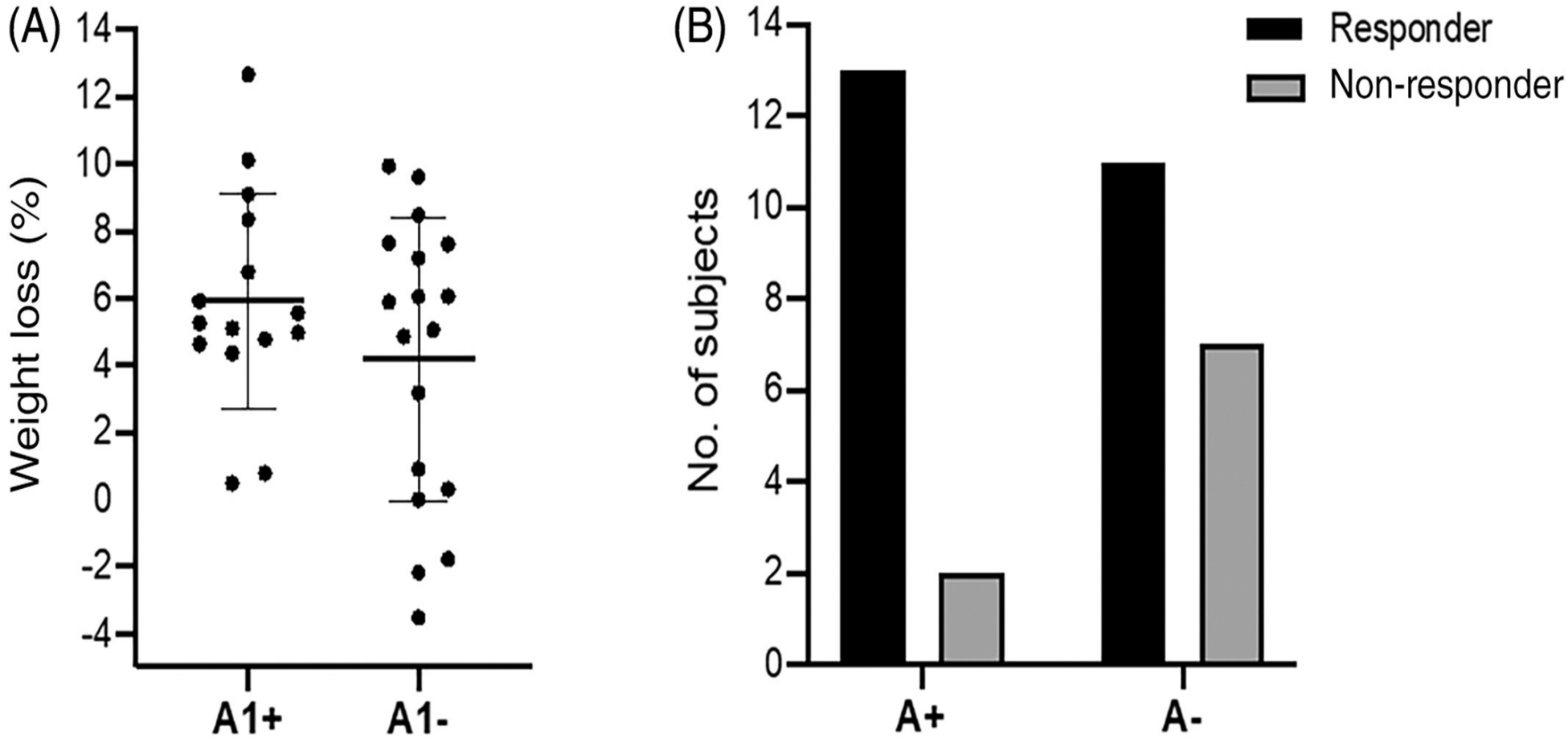
p<0.01 vs NB Non-responders
*** p<0.001 vs. both Placebo groups
†† p<0.01, ††† P,0.001 vs. Placebo non-responders

*Craving control is one of four principal components of the Control of Eating Questionnaire (CoEQ). Dalton et al. *Eur J Clin Nut* 2015

Selected Safety Information (See SmPC for full details)

Allergic reactions: Discontinue if experiencing allergic or anaphylactoid/anaphylactic reactions(e.g.skin rash, pruritus, hives, chest pain, oedema, and shortness of breath) during treatment.

Weight-Loss to Naltrexone/Bupropion is Modulated by the Taq1A Genetic Variant Near DRD2

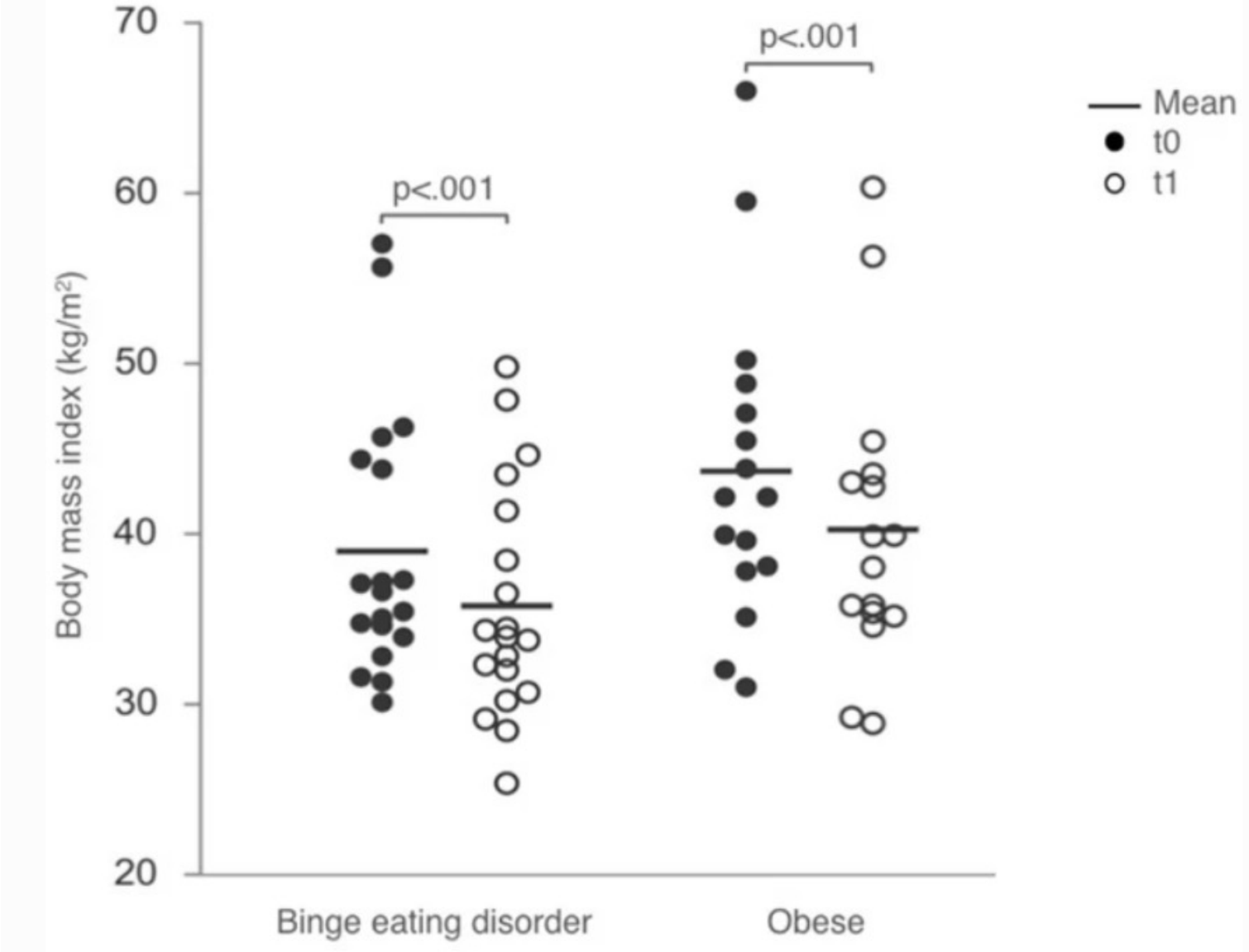


Diabetes Obesity Metabolism, 2020;23(3):850-853

Selected Safety Information (See SmPC for full details)

Patients receiving opioid analgesics: Do not administer to patients receiving chronic opiates. The attempt to overcome any naltrexone opioid blockade by administering large amounts of exogenous opioids is very dangerous and may lead to a fatal overdose or life endangering opioid intoxication (e.g. respiratory arrest, circulatory collapse).

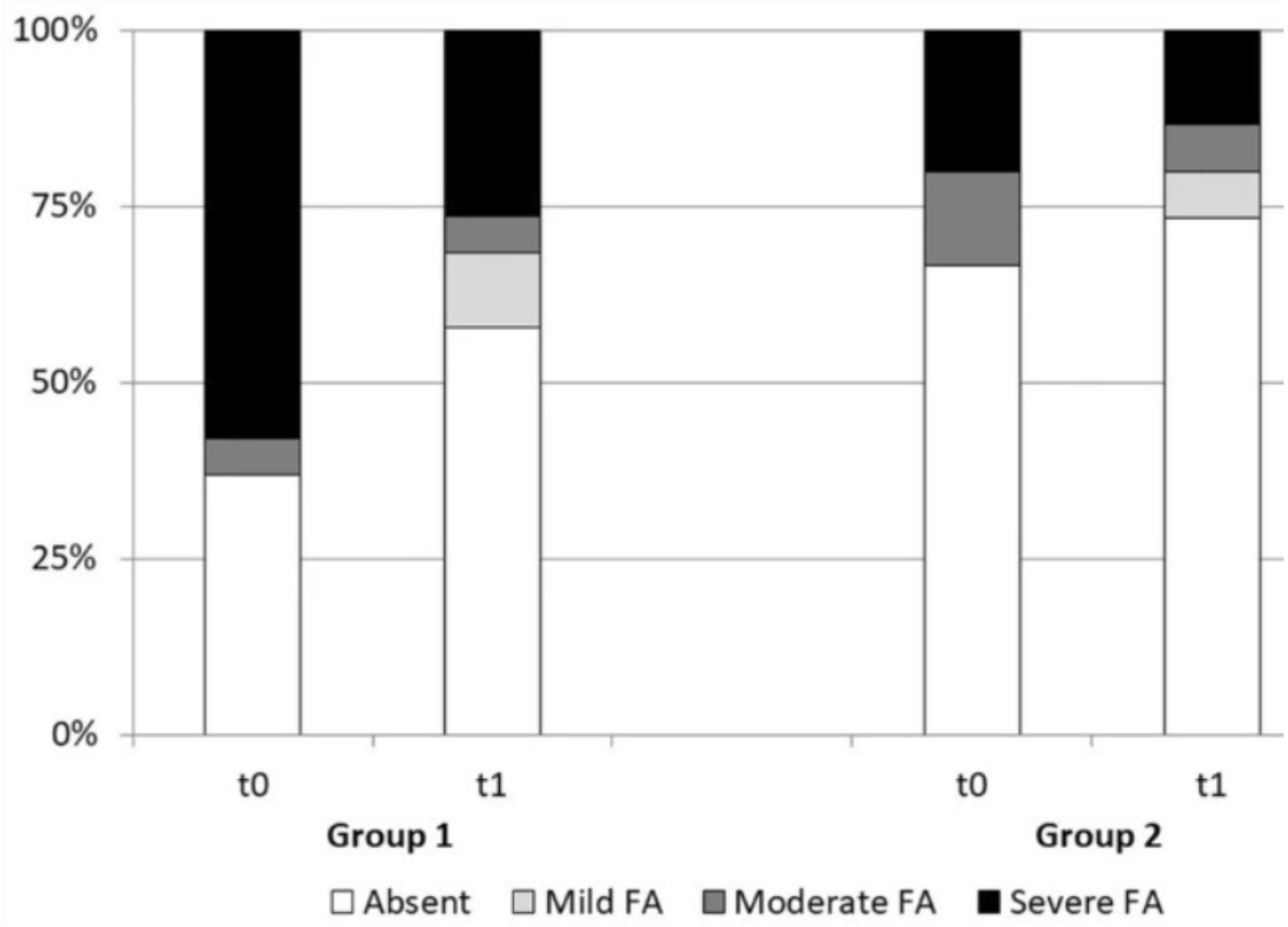
Naltrexone/Bupropion Works in Binge Eating Disorder



Carbone et al, Eat Weight Disord 2021

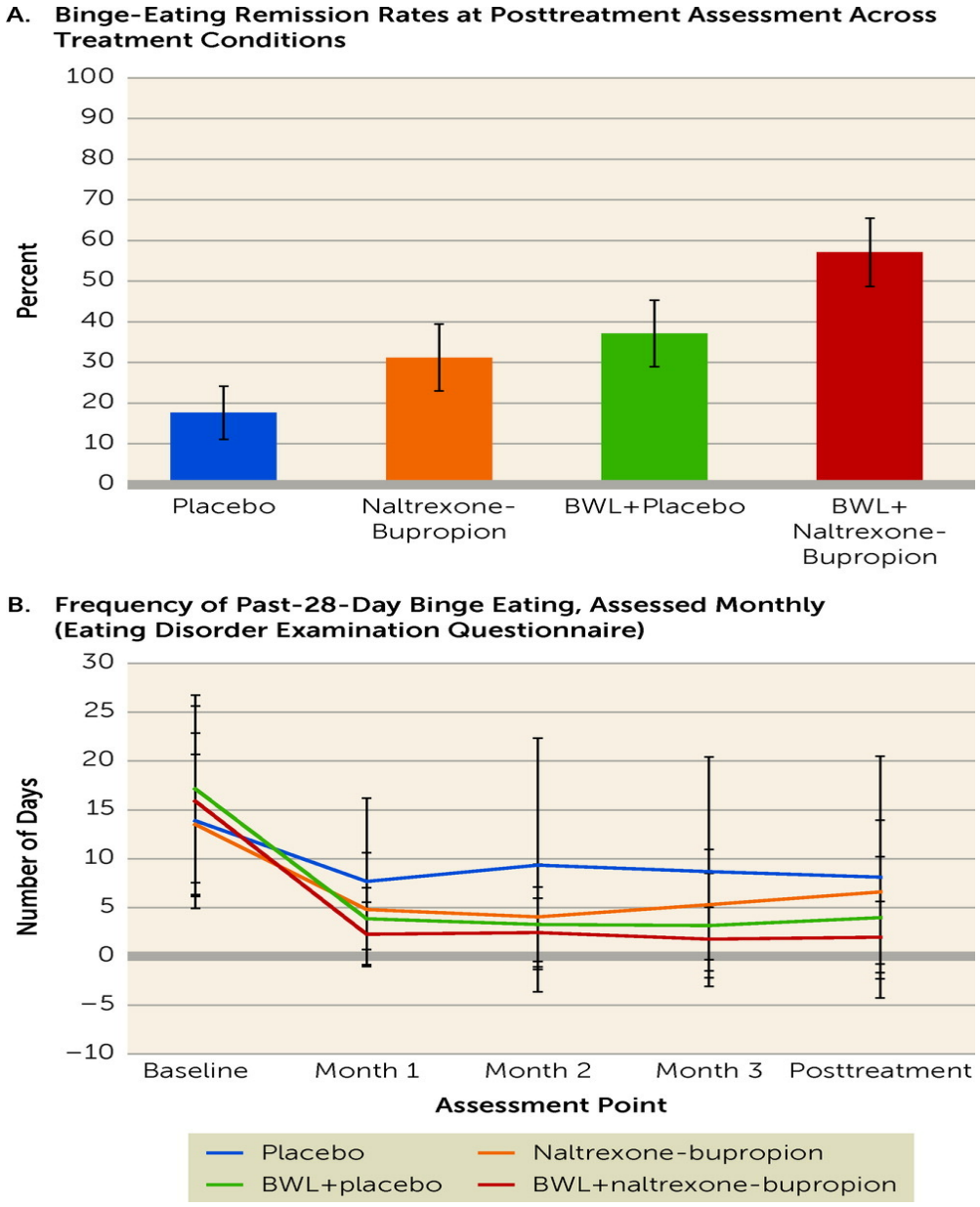
Naltrexone/Bupropion Works in Binge Eating Disorder

Reduction of food addiction (FA) severity within the two groups



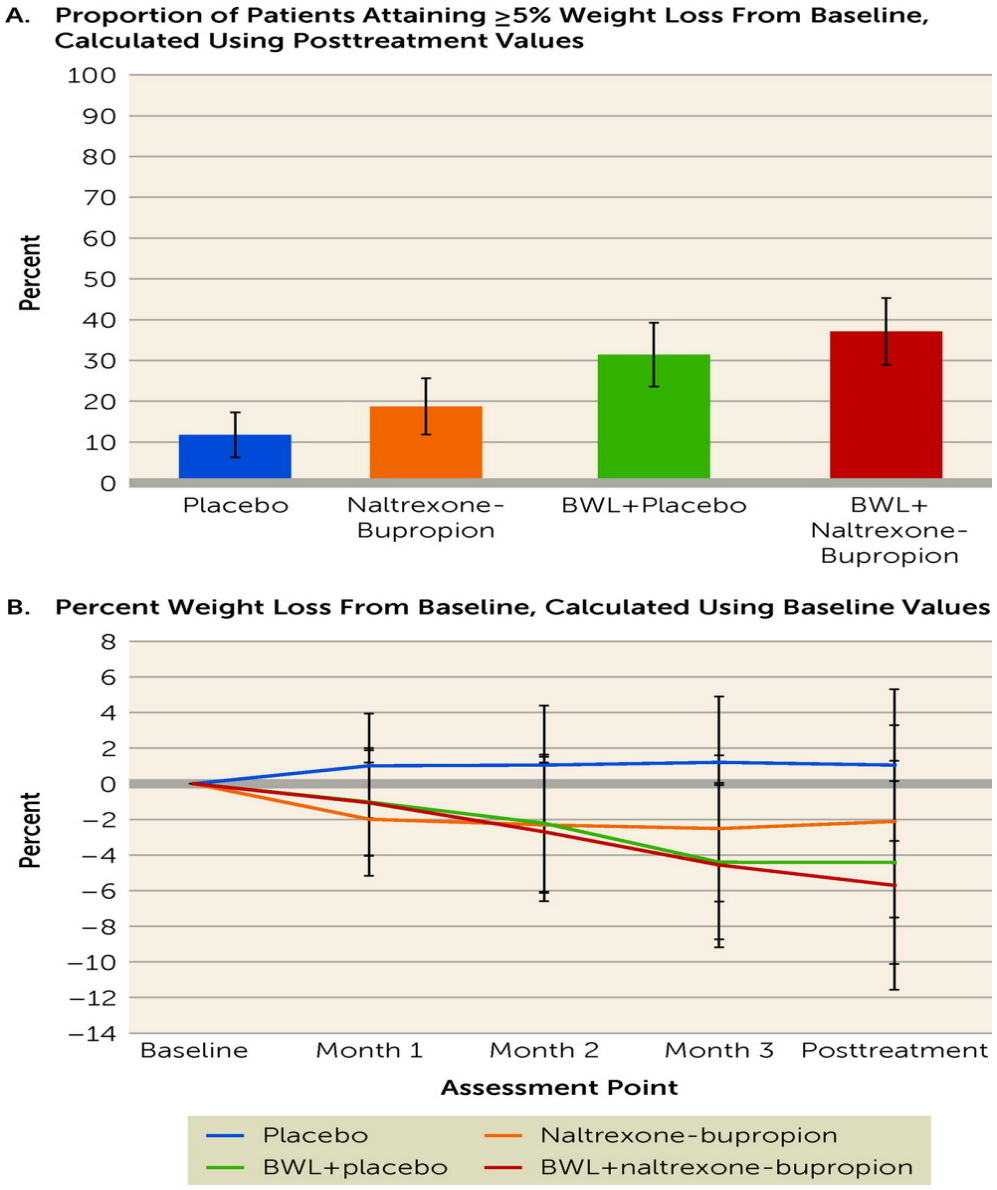
Carbone et al, Eat Weight Disord 2021

Mysimba for binge eating disorder



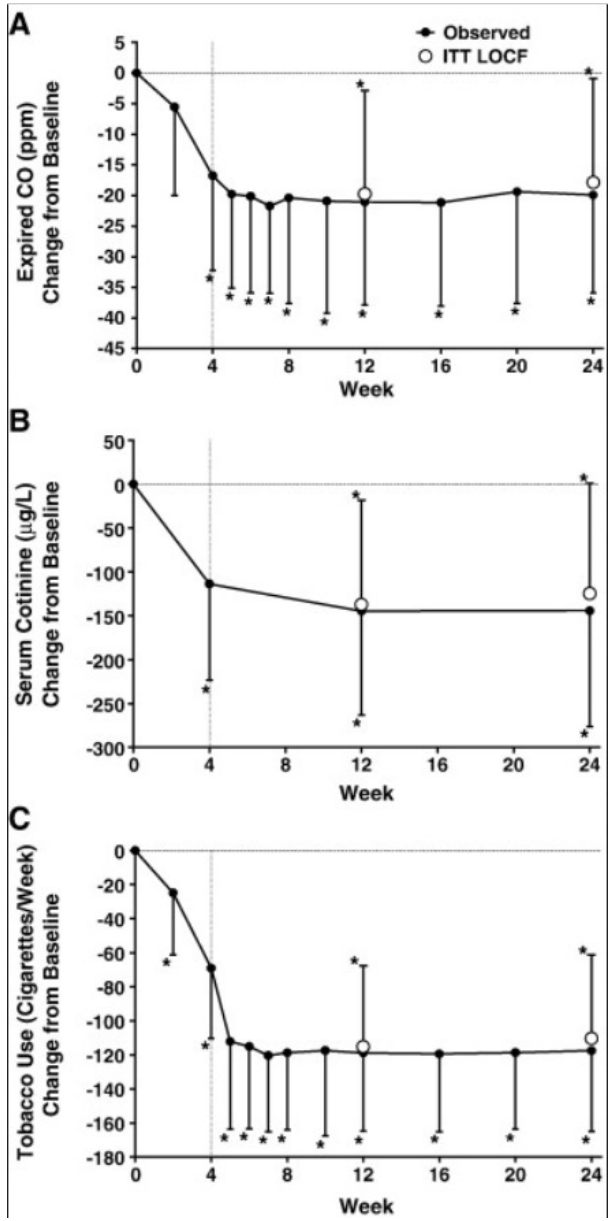
Grilo et al, Am J Psych, 2021

Mysimba for binge eating disorder



Grilo et al, Am J Psych, 2021

Naltrexone/Bupropion helps with smoking cessation and resists weight gain



N=30

No weight loss

Wilcox et al, *Addict Bheav*, 2010

Mysimba safety profile

Contra-indications:

- Unregulated hypertension
- Known history with seizures or tumors in the CNS
- Current or prior diagnosis of bulimia or anorexia nervosa
- Current dependence on chronic opioids, opioid agonists or continued treatment of alcohol-, benzodiazepines- or opioid dependency.
- Current treatment with bupropion or naltrexone
- A history with bipolar disorders
- Prior treatment with a MOAi the past 14 days
- Severe liver disorders or late-stage renal failure

Most common side effects:

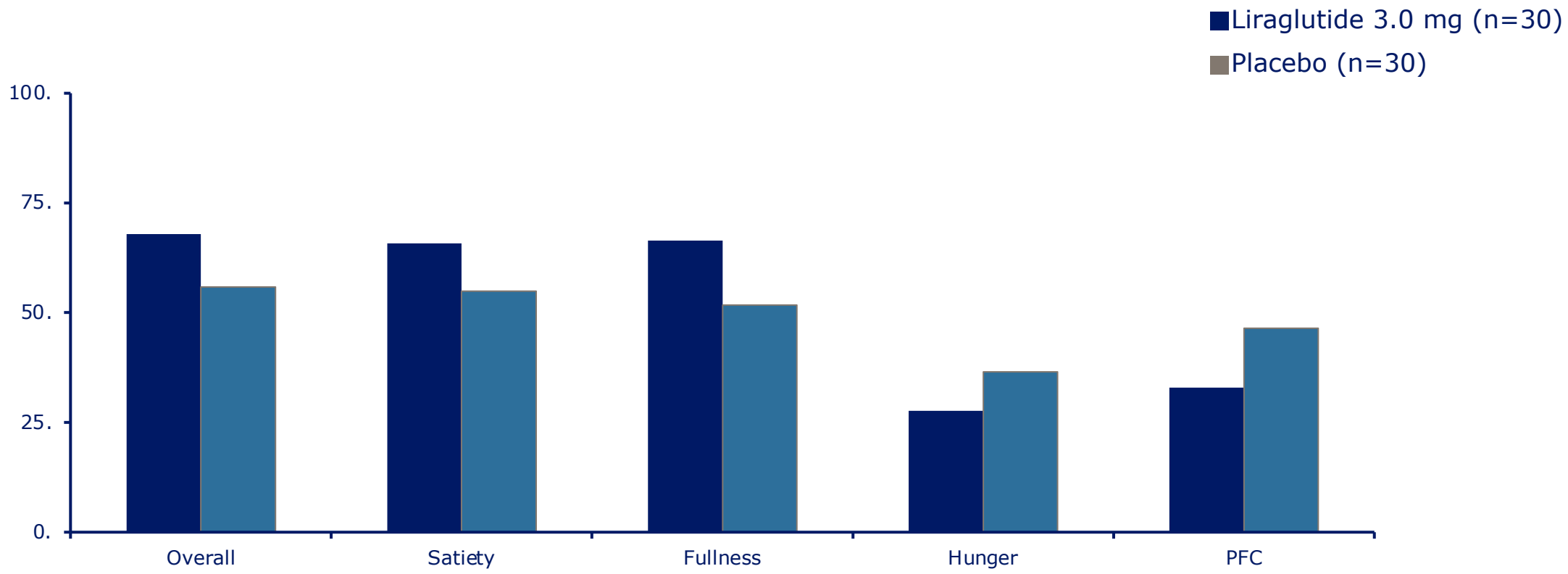
- Headache, nausea, obstipation. Mostly transient after the titration phase

Caution is advised if:

- The patient is already using other anti-depressants due to potential drug interactions with bupropion (liver enzyme interactions)

1: spc Mysimba®

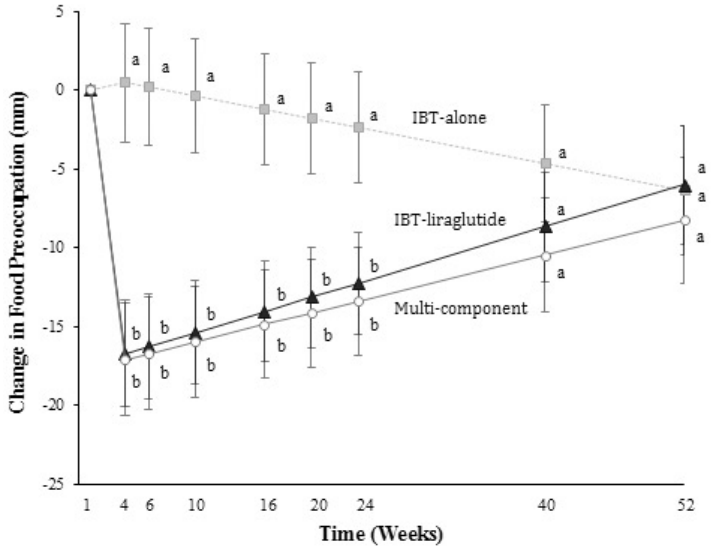
Liraglutide 3.0 mg reduces hunger and increases fullness

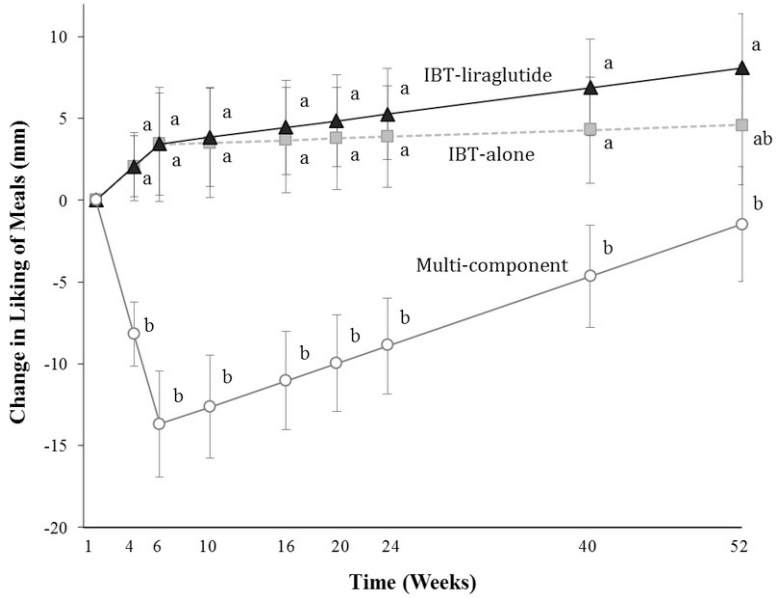


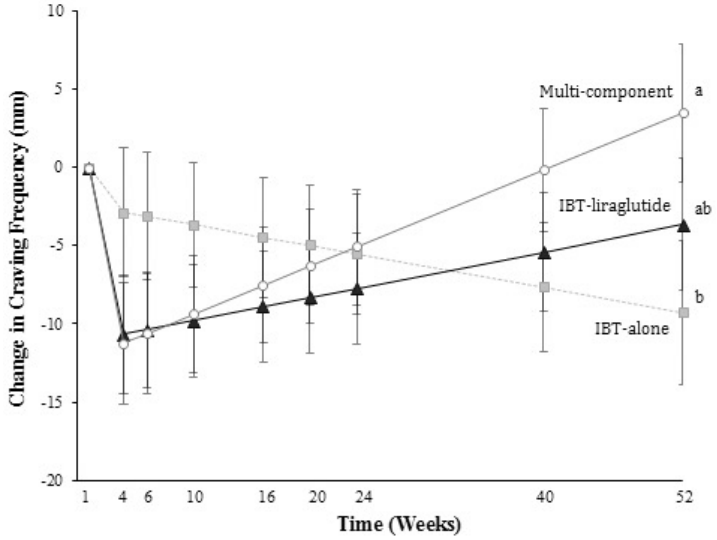
5 weeks treatment including 0.6 mg weekly dose escalation. Ratings are $AUC_{15\text{-}300\ min/285\ min}$ reported as FAS LS-means.
*Statistical significance $p \leq 0.01$ vs. placebo. Data for overall includes 100 minus scores for hunger and PFC.
AUC, area-under-the-curve; FAS, full analysis set; LS, least squares; PFC, prospective food consumption

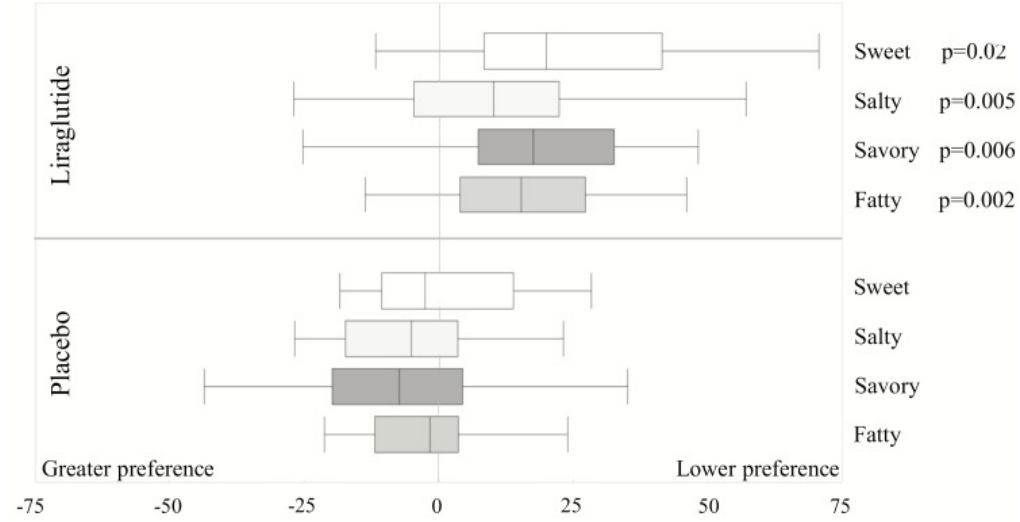
Adapted from: van Can *et al. Int J Obes* 2014;38:784–93

Impact of Liraglutide on Reward Behaviour and Taste



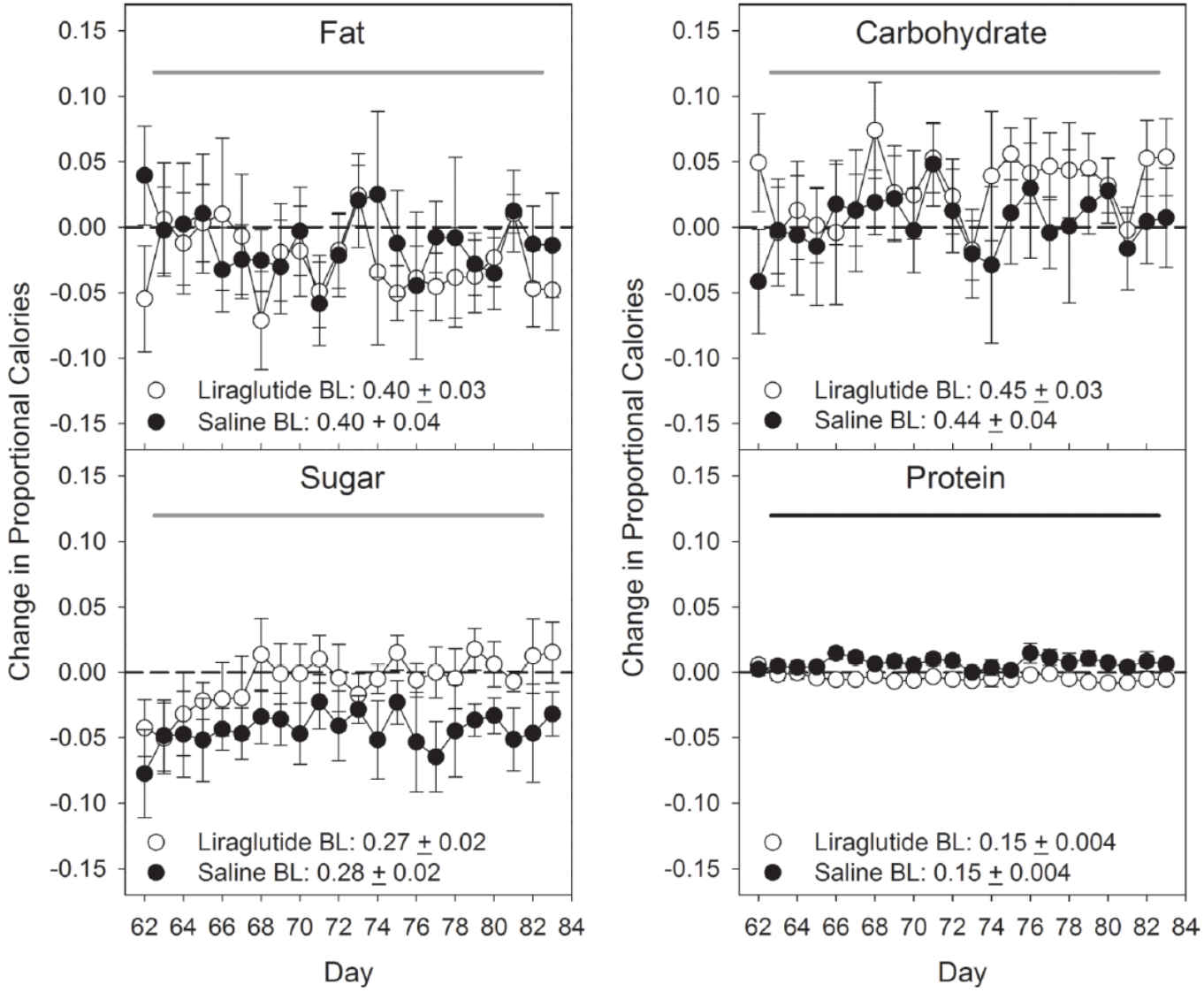






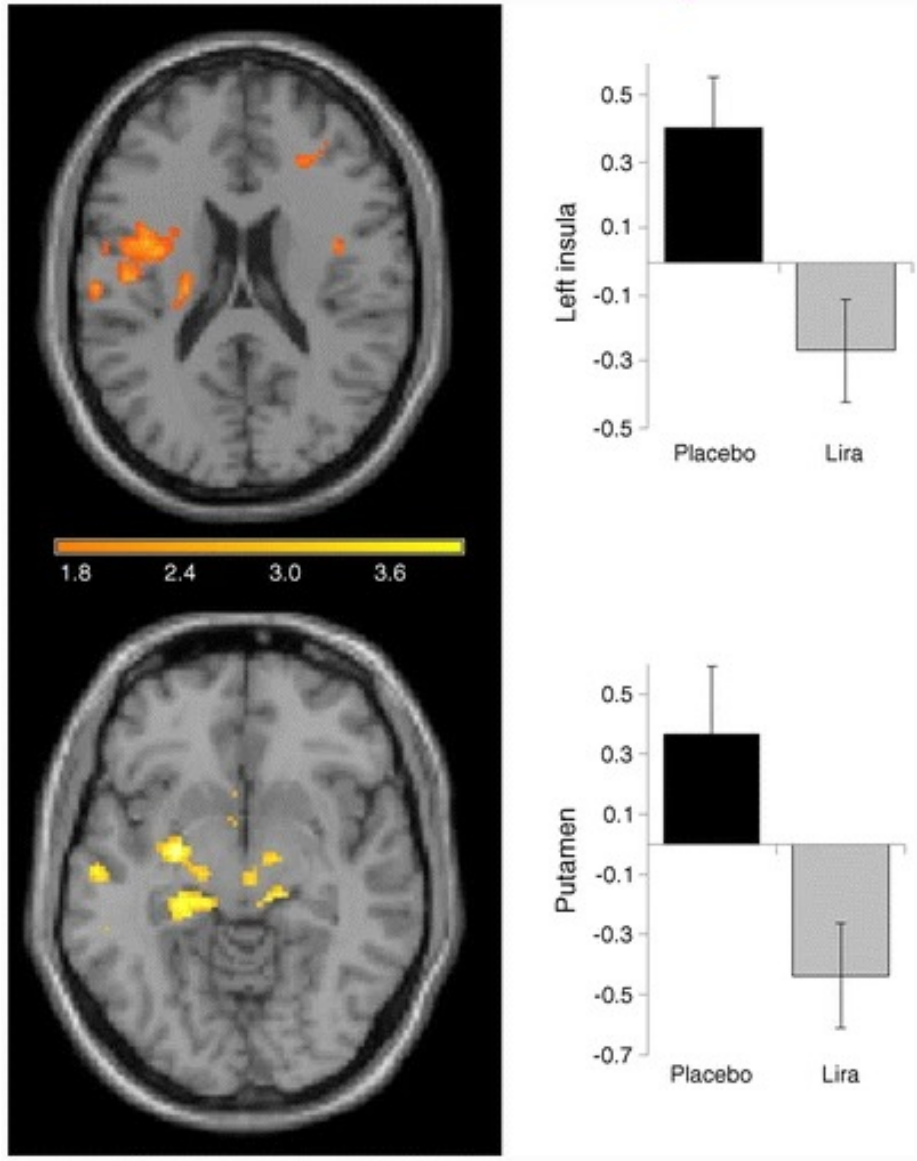
Tronieri et al, *Int J Obes* 2019

Impact of Liraglutide on Food Choices in Rats



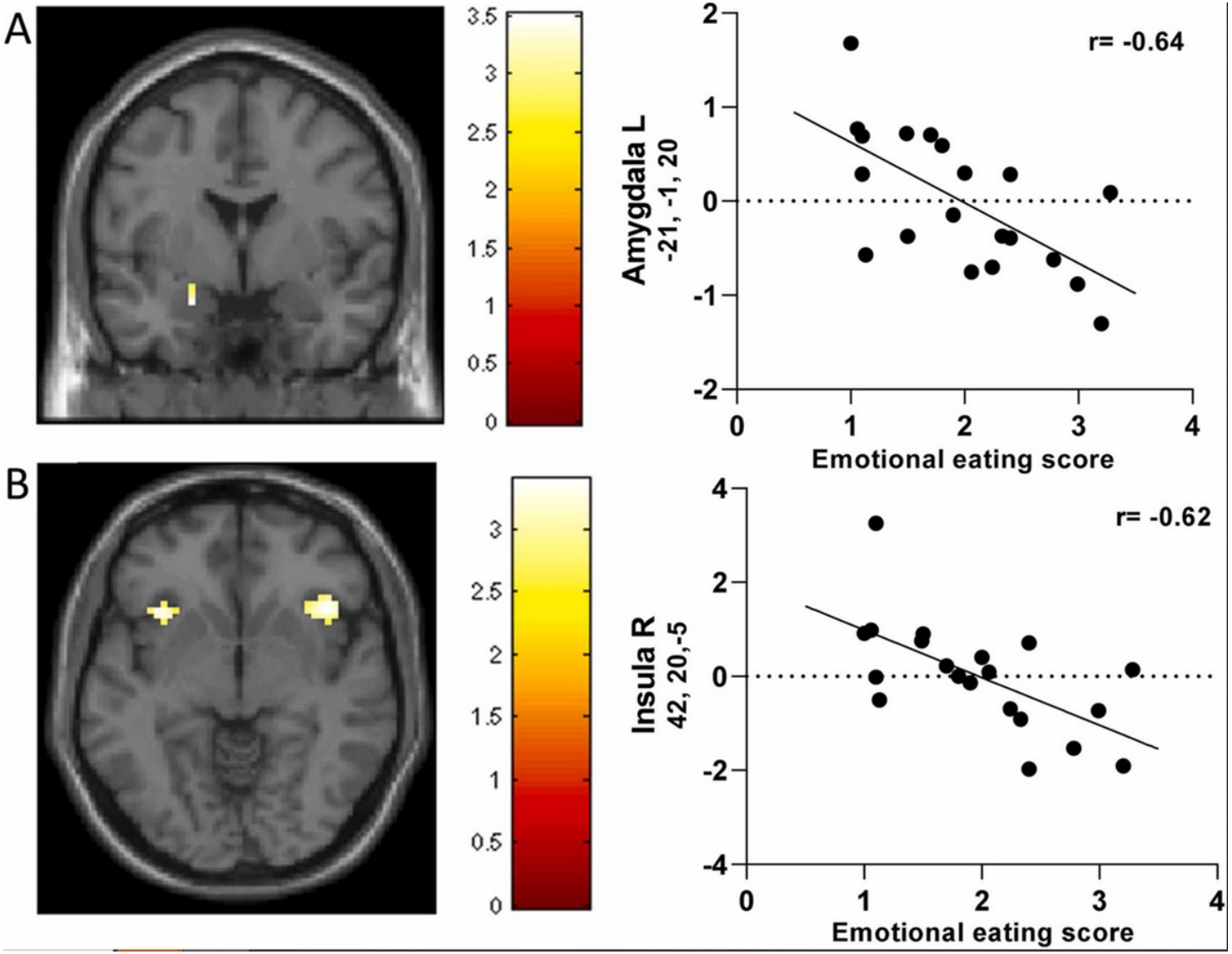
Hyde et al, *Physiology and behaviour* 2017

Liraglutide Decreased Activation in the Insula and Putamen in People with Type 2 Diabetes Mellitus (but not a consistent finding)



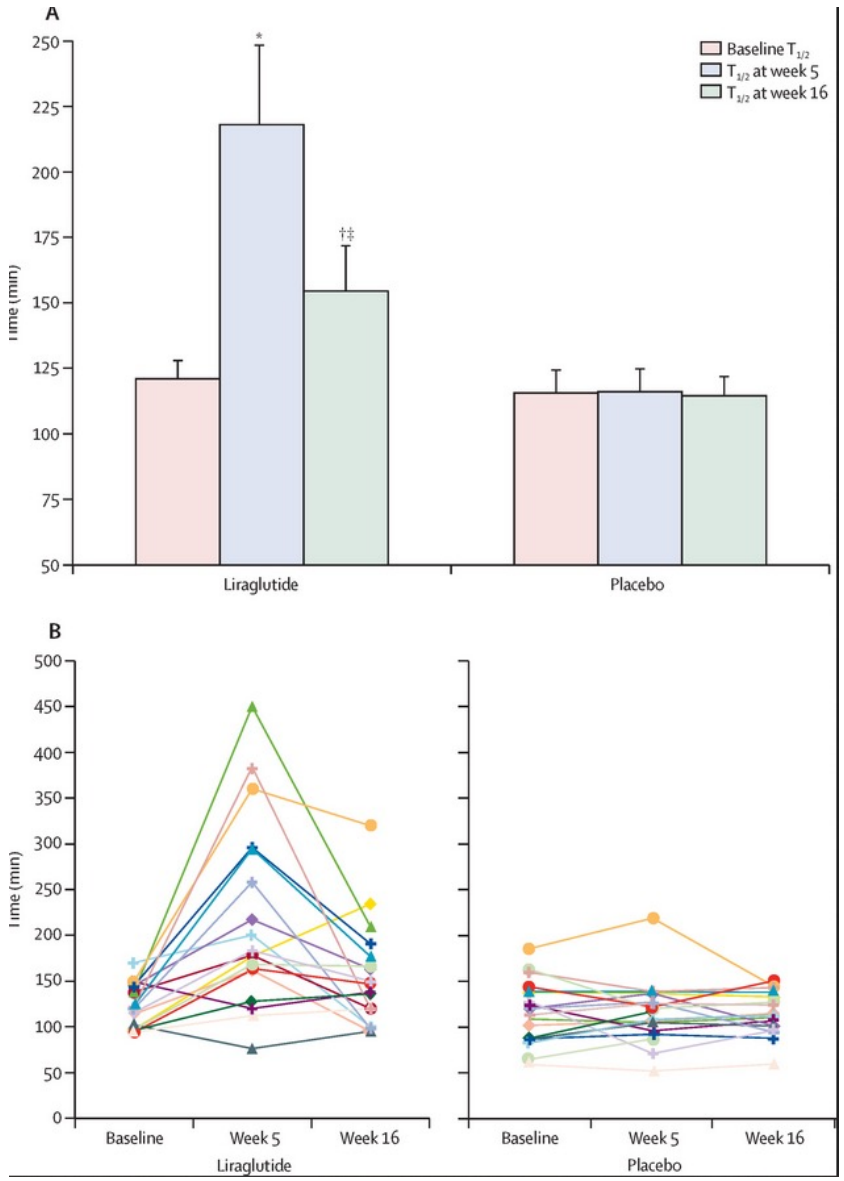
Farr OM et al, *Metabolism*, 2016

Higher Baseline Emotional Eating Scores are Less Sensitive to the Central Effect of Liraglutide



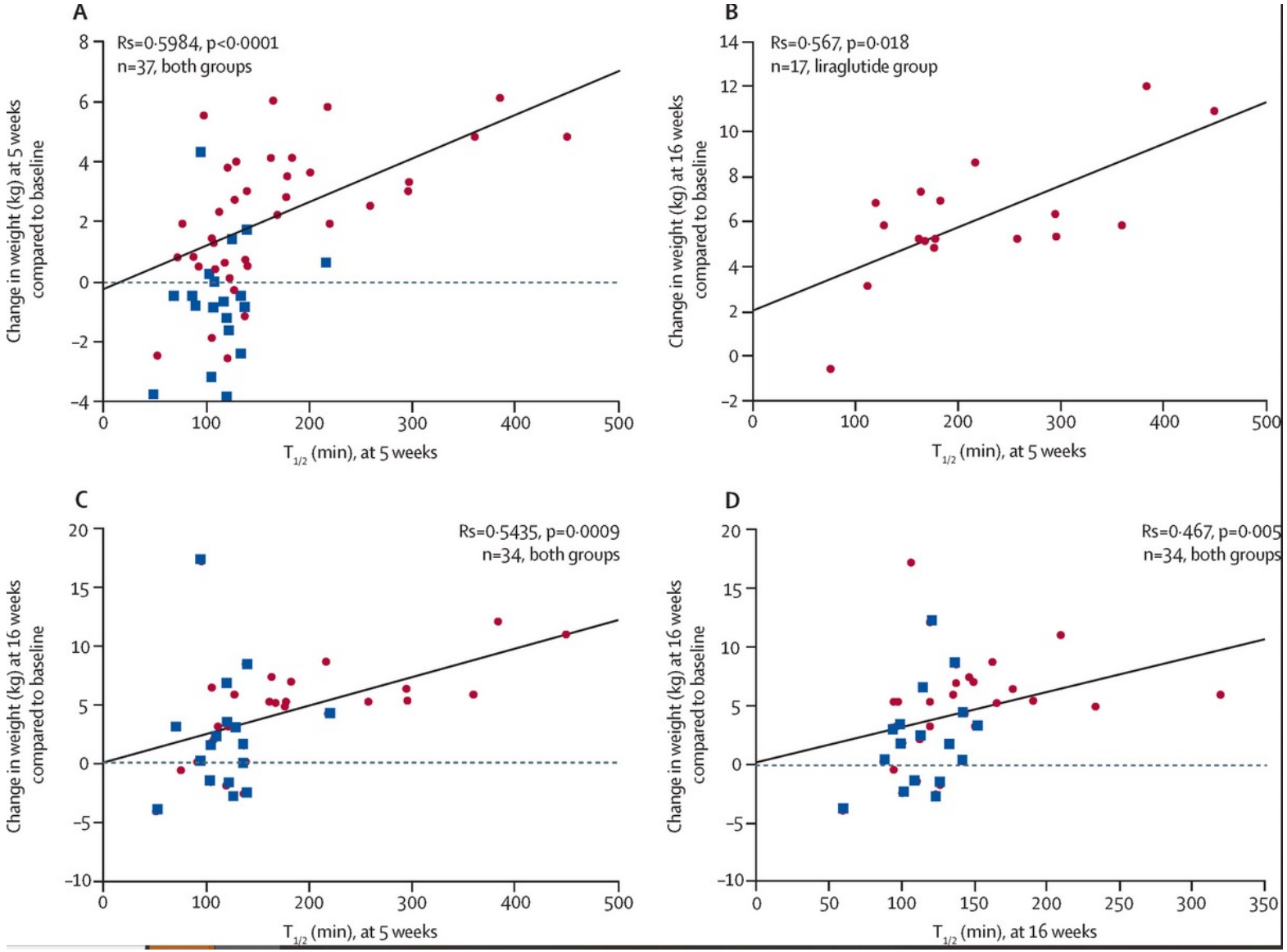
Van Ruiter et al, *Pyschoneuroendocrinology* 2022

Liraglutide 3.0mg Decreases Gastric Emptying



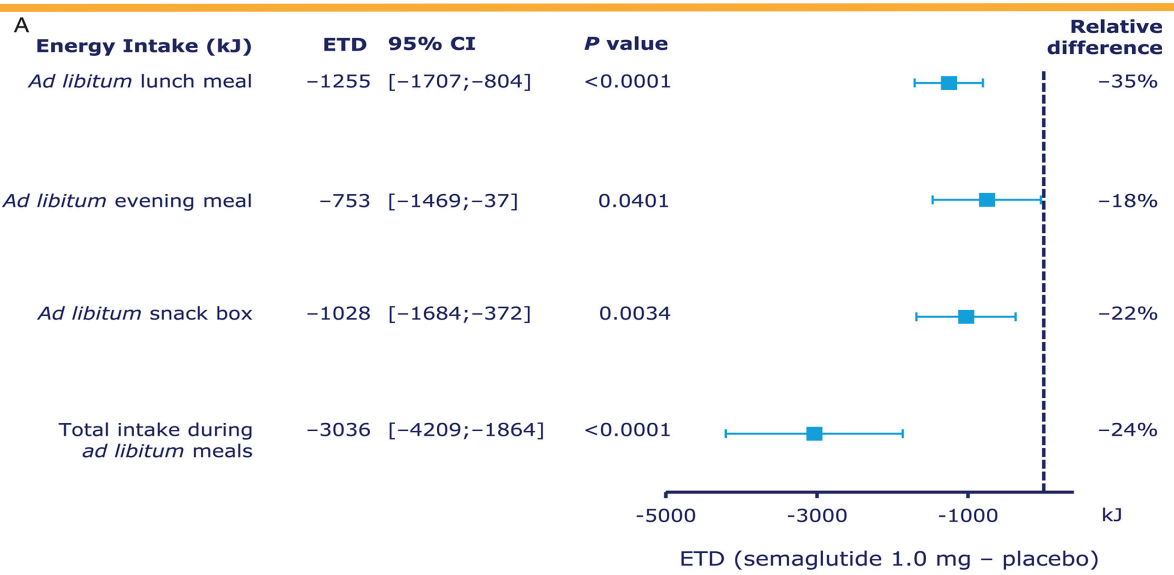
Halawi et al, *Lancet Gastroenterology* 2017

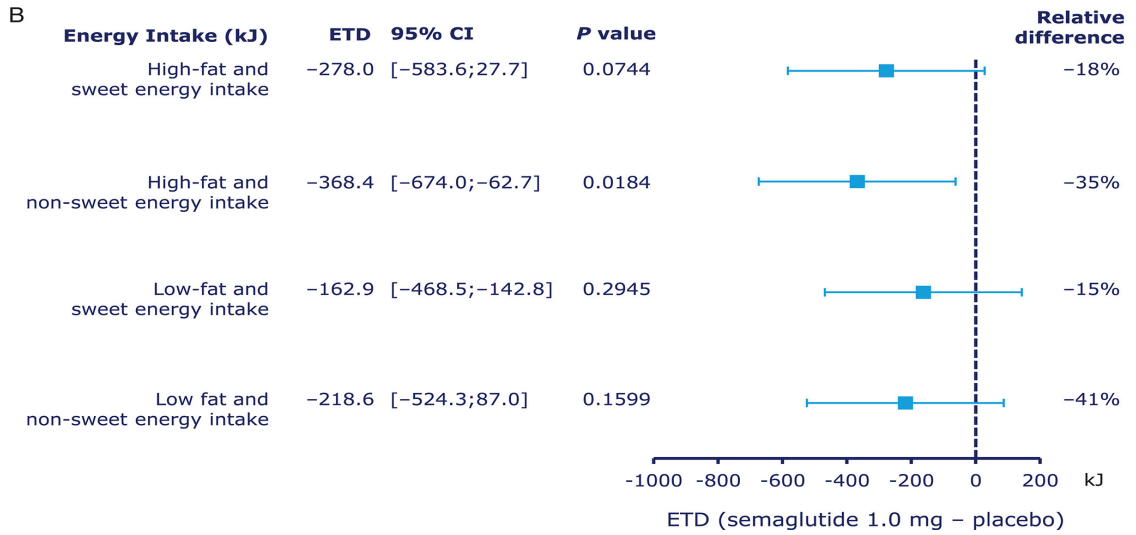
Gastric Emptying at 5 Weeks Correlated with Weight Loss at Week 16 with Liraglutide



Halawi et al, *Lancet Gastroenterology* 2017

Ozempic® (semaglutide 1mg) and Eating Behaviour in People with Obesity

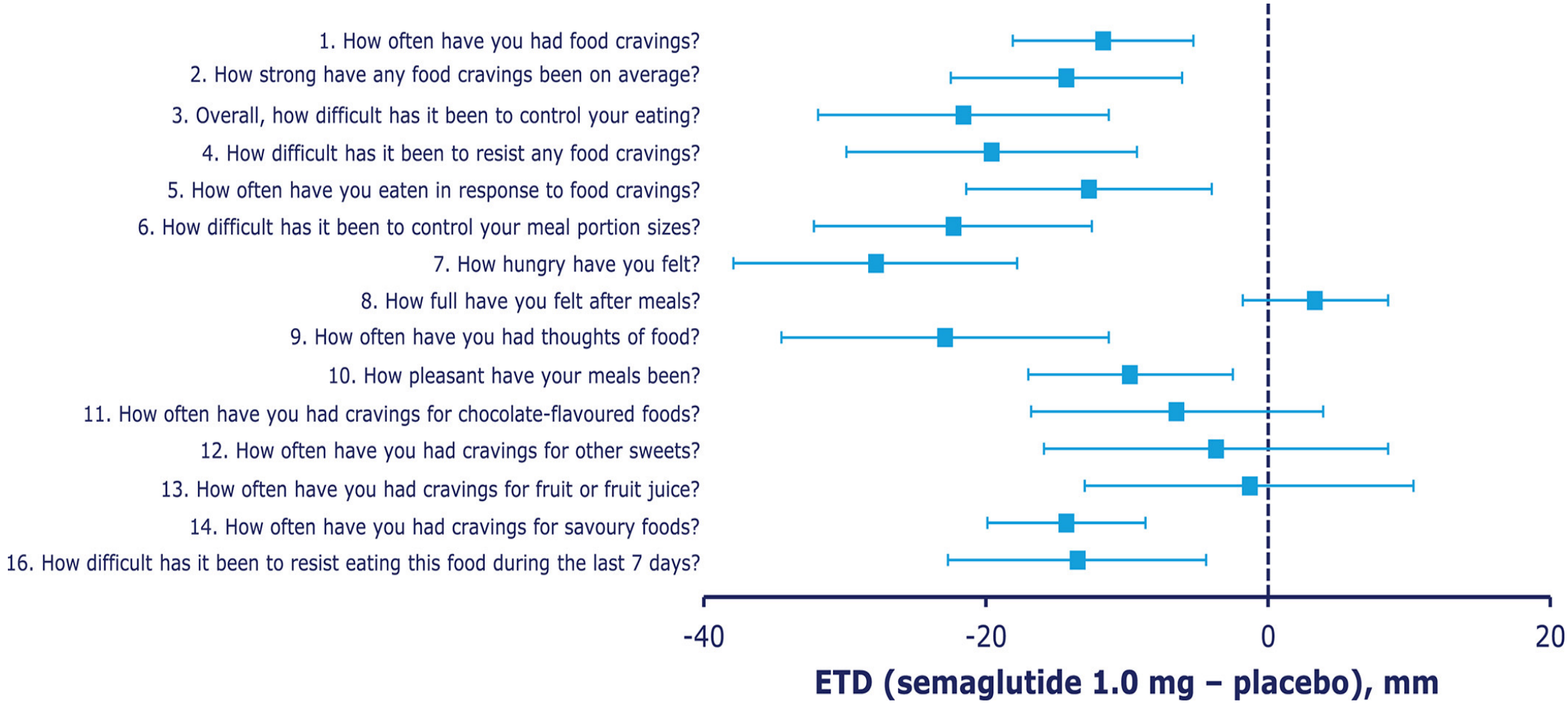




Diabetes Obesity Metabolism, Volume: 19, Issue: 9, 2017

Ozempic is not licensed for the treatment of obesity

Ozempic® (semaglutide 1mg) and Eating Behaviour in People with Obesity



Ozempic is not licensed for the treatment of obesity

ETD: estimated treatment difference

Diabetes Obesity Metabolism, Volume: 19, Issue: 9, 2017

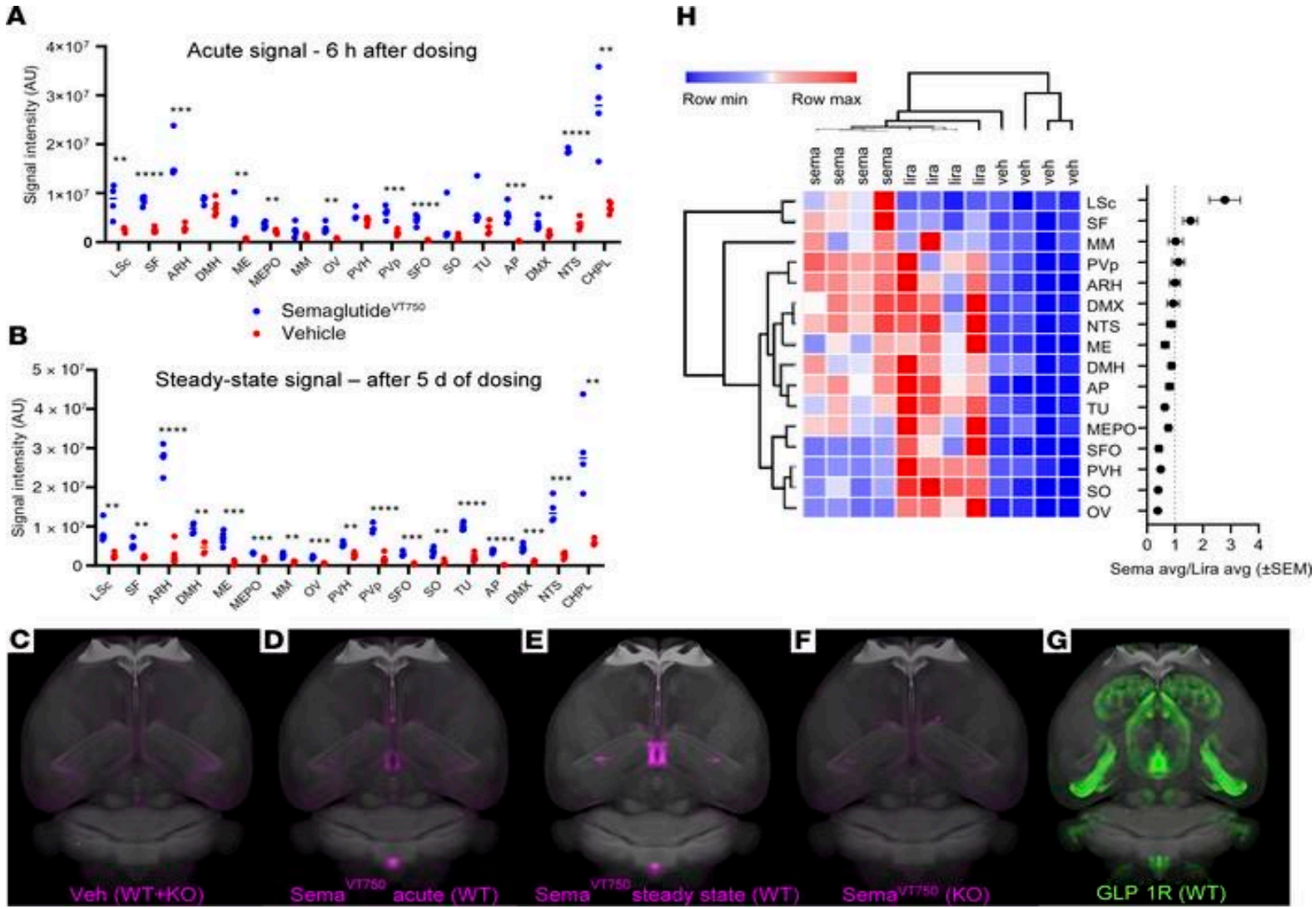
Wegovy™ (Semaglutide 2.4mg) and Eating Behaviour in People with Obesity

- Exploratory analysis from STEP 5
- RCT with 2 year follow up
- USA and Canada
- Semaglutide 2.4mg (n=88) vs. Placebo (n=86)
- Control of eating questionnaire (Scores on an 11-point graded response scale)

- Craving control: initial reduction with dissipation over time
- Craving for savoury: consistent reduction
- Craving for sweet: initial reduction with dissipation over time

Wharton S, et al. Presented at the 39 th Annual Meeting of The Obesity Society, November 1 5, 2021.

Brain Distribution of Semaglutide vs Liraglutide



Lateral septal nucleus
Septofimbrial nucleus
Medial mammillary nucleus
Hypothalamus; PVp, posterior part

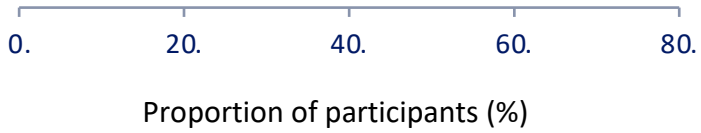
Tuberal nucleus
Lamina terminalis
Supraoptic nucleus
Paraventricular nucleus of the hypothalamus
Subfornical organ

Gaberi et al, *JCI Insight*, 2020

Adverse events reported in ≥10% of participants

STEP 1

Preferred term	Semaglutide 2.4 mg (N=1306)				Placebo (N=655)			
	N	(%)	E	R	N	(%)	E	R
Nausea	577	44.2	1068	62.6	114	17.4	146	17.6
Diarrhoea	412	31.5	766	44.9	104	15.9	138	16.6
Vomiting	324	24.8	636	37.3	43	6.6	52	6.3
Constipation	306	23.4	390	22.9	62	9.5	73	8.8
Nasopharyngitis	281	21.5	480	28.1	133	20.3	216	26.0
Headache	198	15.2	387	22.7	80	12.2	104	12.5
Dyspepsia	135	10.3	179	10.5	23	3.5	30	3.6
Abdominal pain	130	10.0	175	10.3	36	5.5	41	4.9
Upper respiratory tract infection	114	8.7	158	9.3	80	12.2	116	14.0



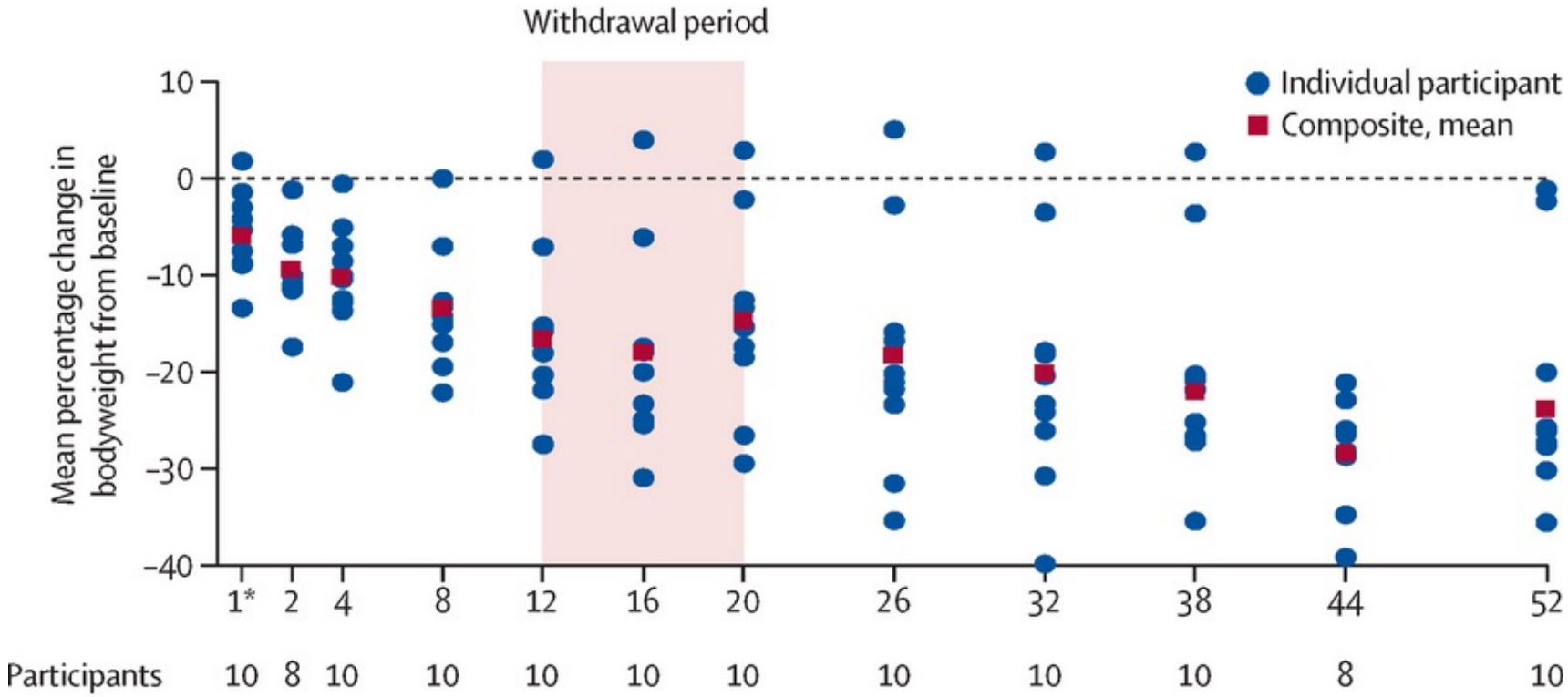
Proportion of participants (%)

Semaglutide 2.4 mg

Placebo

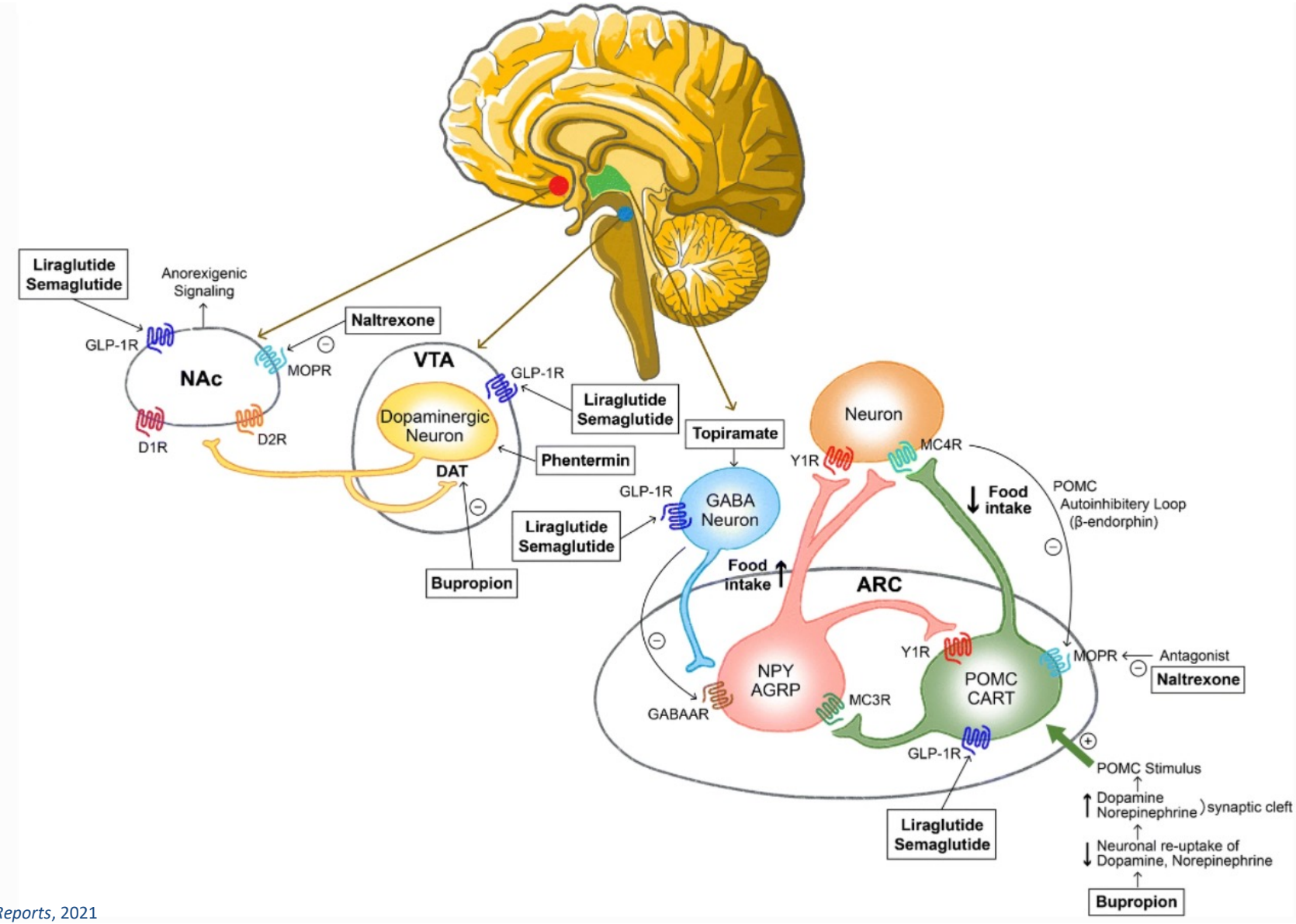
Data are for the on-treatment observation period.
E, number of events; N, number of participants with event(s); R, events per 100 patient years of exposure; %, proportion of participants with event(s).
Wilding et al. *N Engl J Med* 2021;384:989-1002.

Setmelanotide - MC4R agonist for POMC or LEPR deficiency



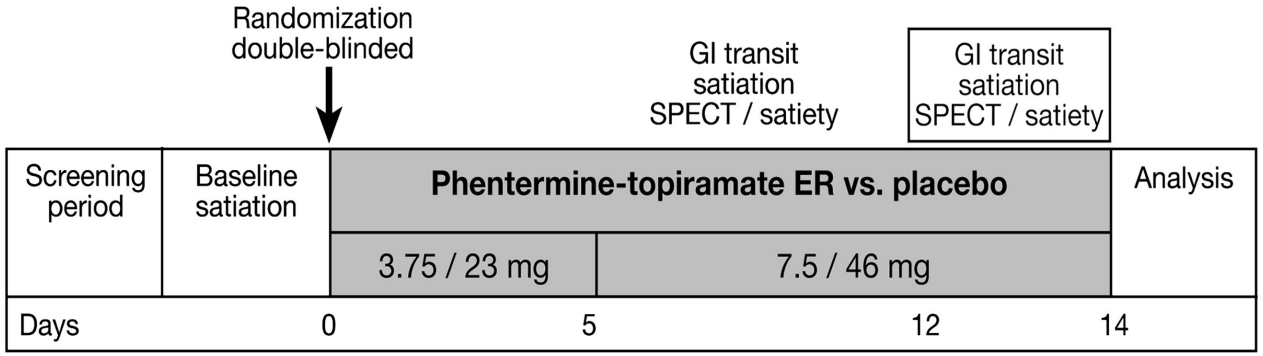
Clément et al, Lancet 2020

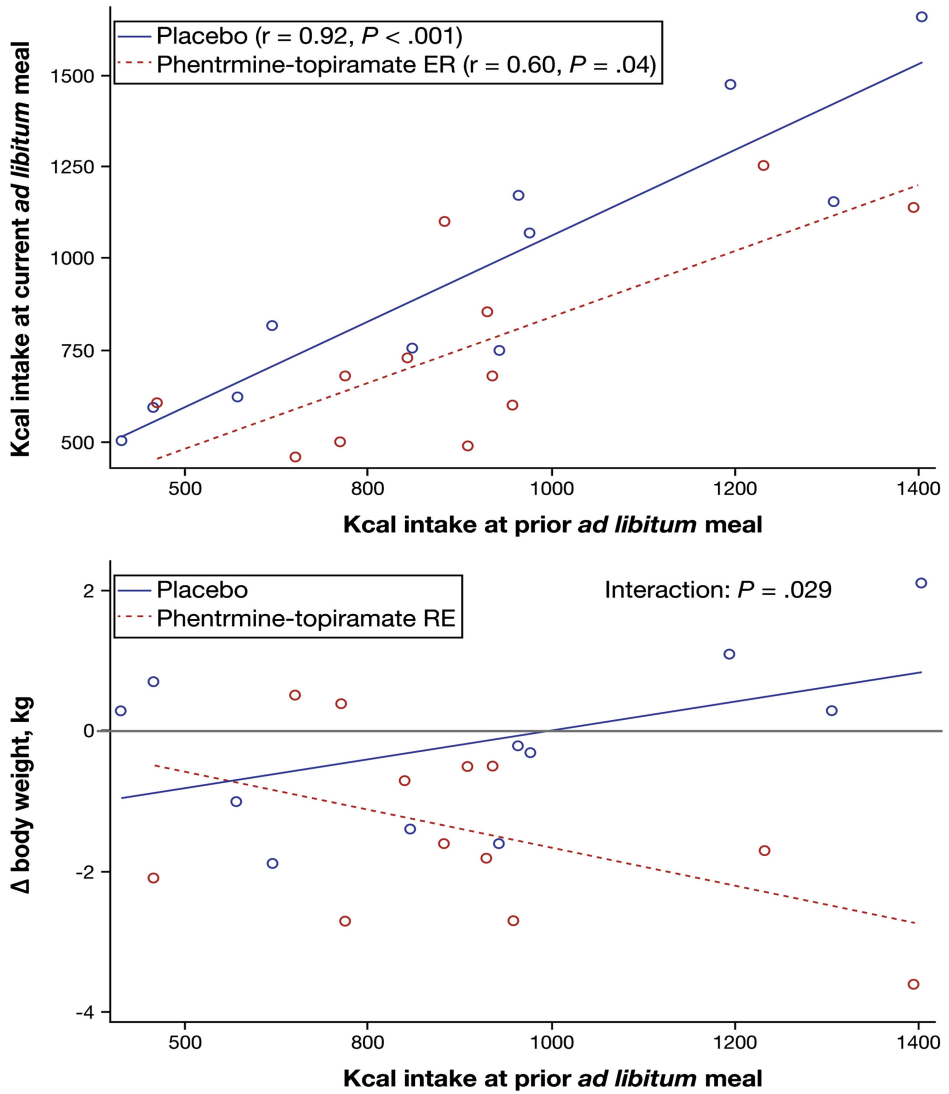
Phentermine and Topiramate Mode of Action



Tak & Lee, *Current Obesity Reports*, 2021

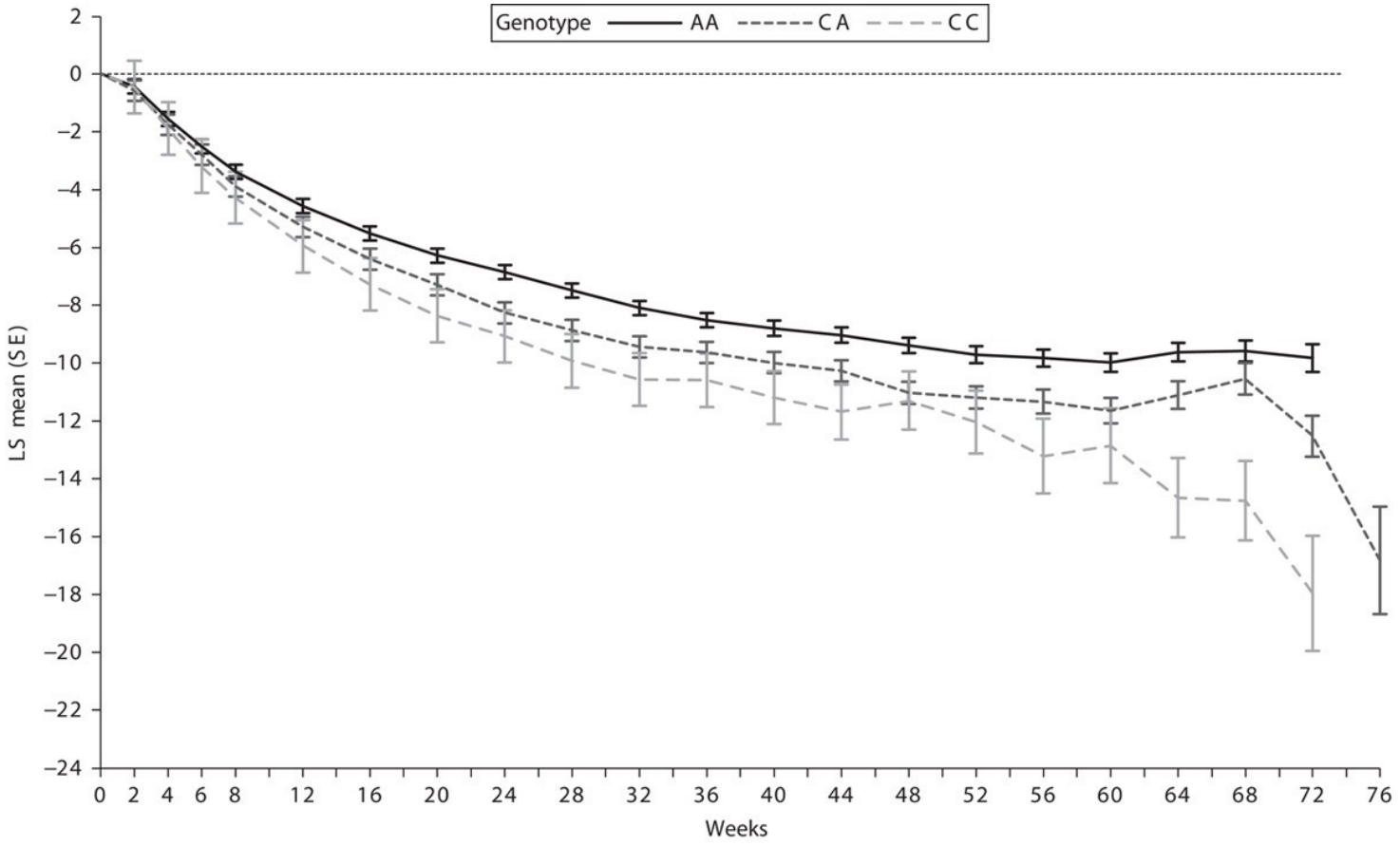
Phentermine and Topiramate - Prediction of Response





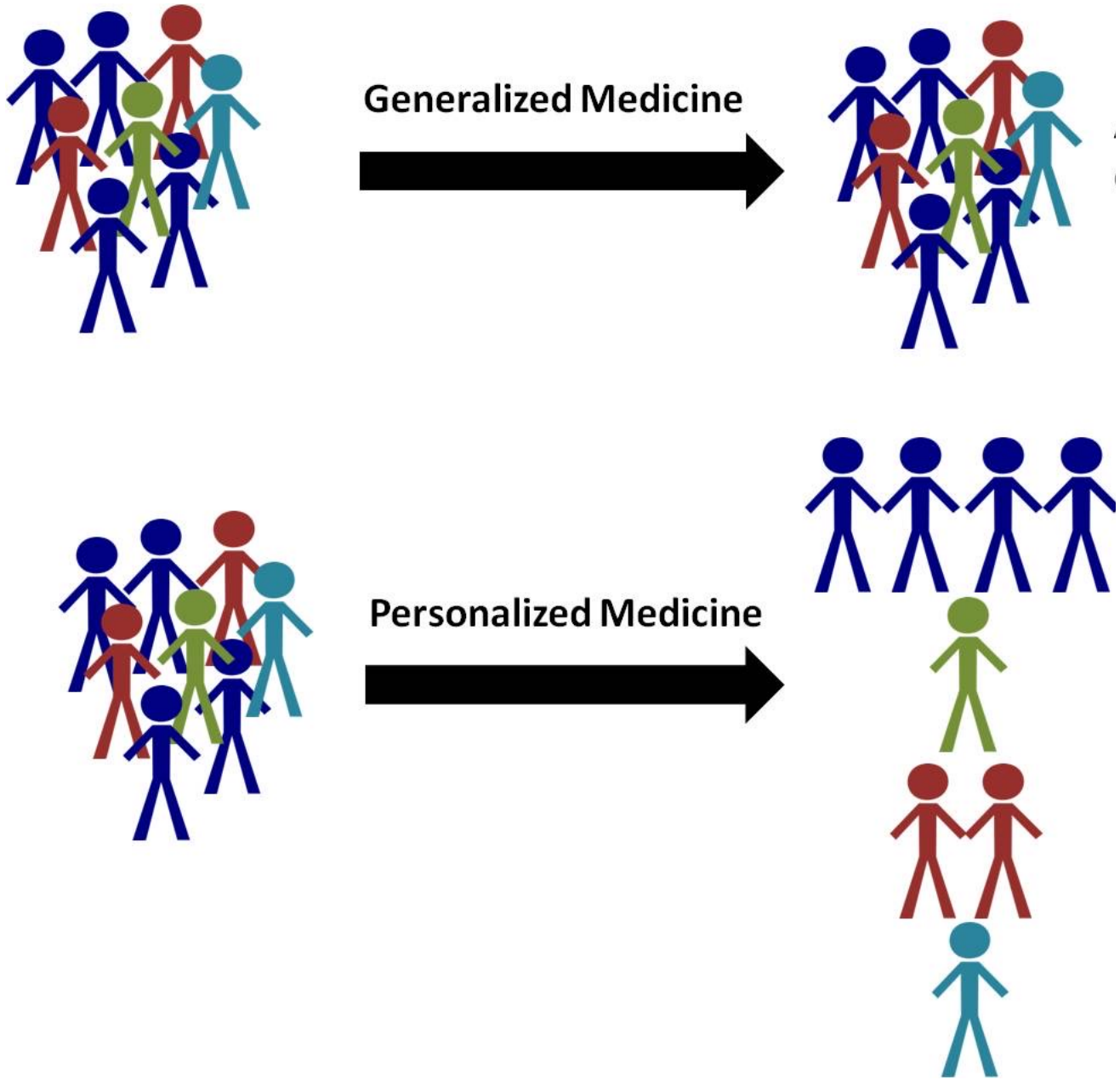
Acosta et al, *Gastroenterology*, 2015

Topiramate - Prediction of Response



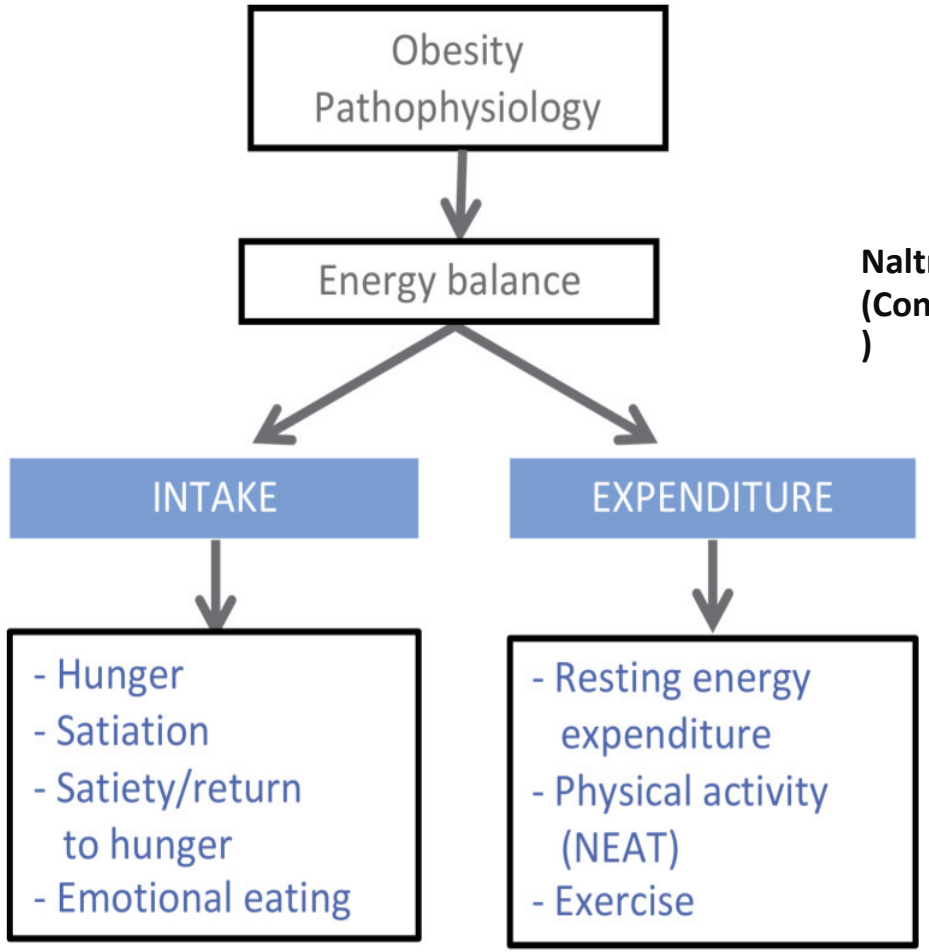
N	2	4	6	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76
AA	387	387	391	390	391	392	384	393	379	369	348	341	332	244	199	162	135	109	72	38	–
CA	163	164	163	162	164	163	163	165	156	160	151	149	142	117	107	79	64	50	33	16	2
CC	24	24	24	24	24	24	23	24	21	23	22	22	19	14	11	6	6	5	5	2	–

Li, Qingqin et al, *Pharmacogenetics and Genomics*, February 2016



Selection of Obesity Medications Based on Phenotypes

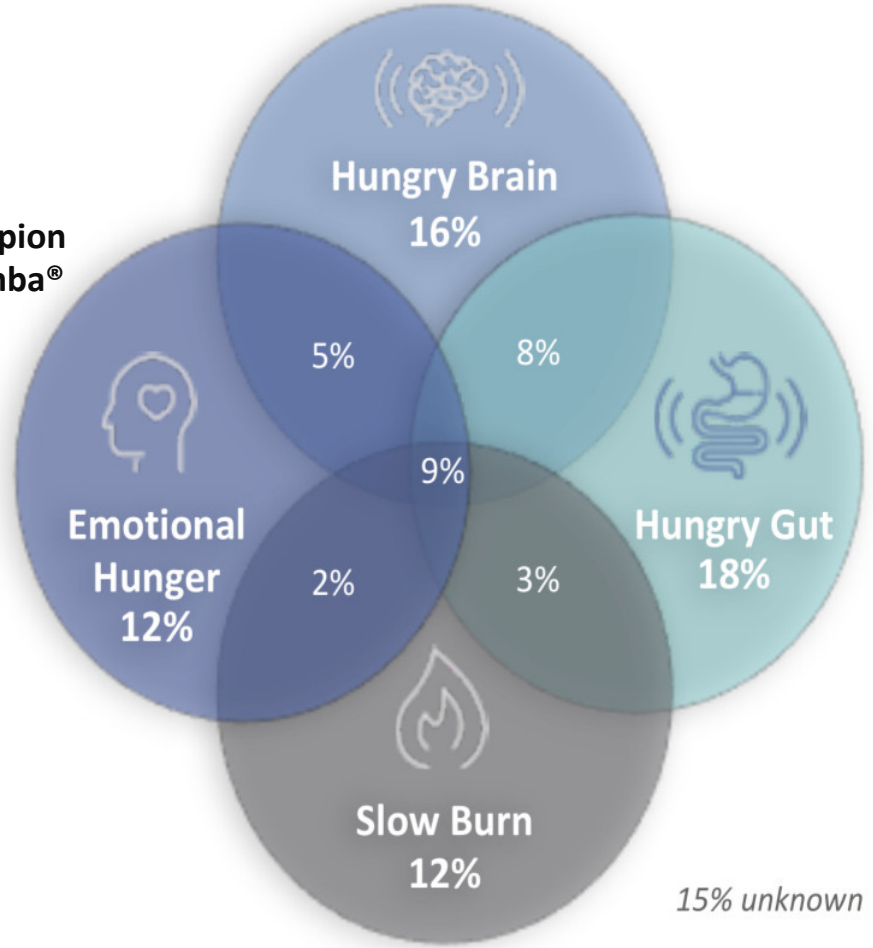
A



B

Phentermine-topiramate (Qsymia®)
Lorcaserin (Belviq®)

Naltrexone/bupropion (Contrave®/Mysimba®)



Liraglutide (Saxenda®)

Phentermine

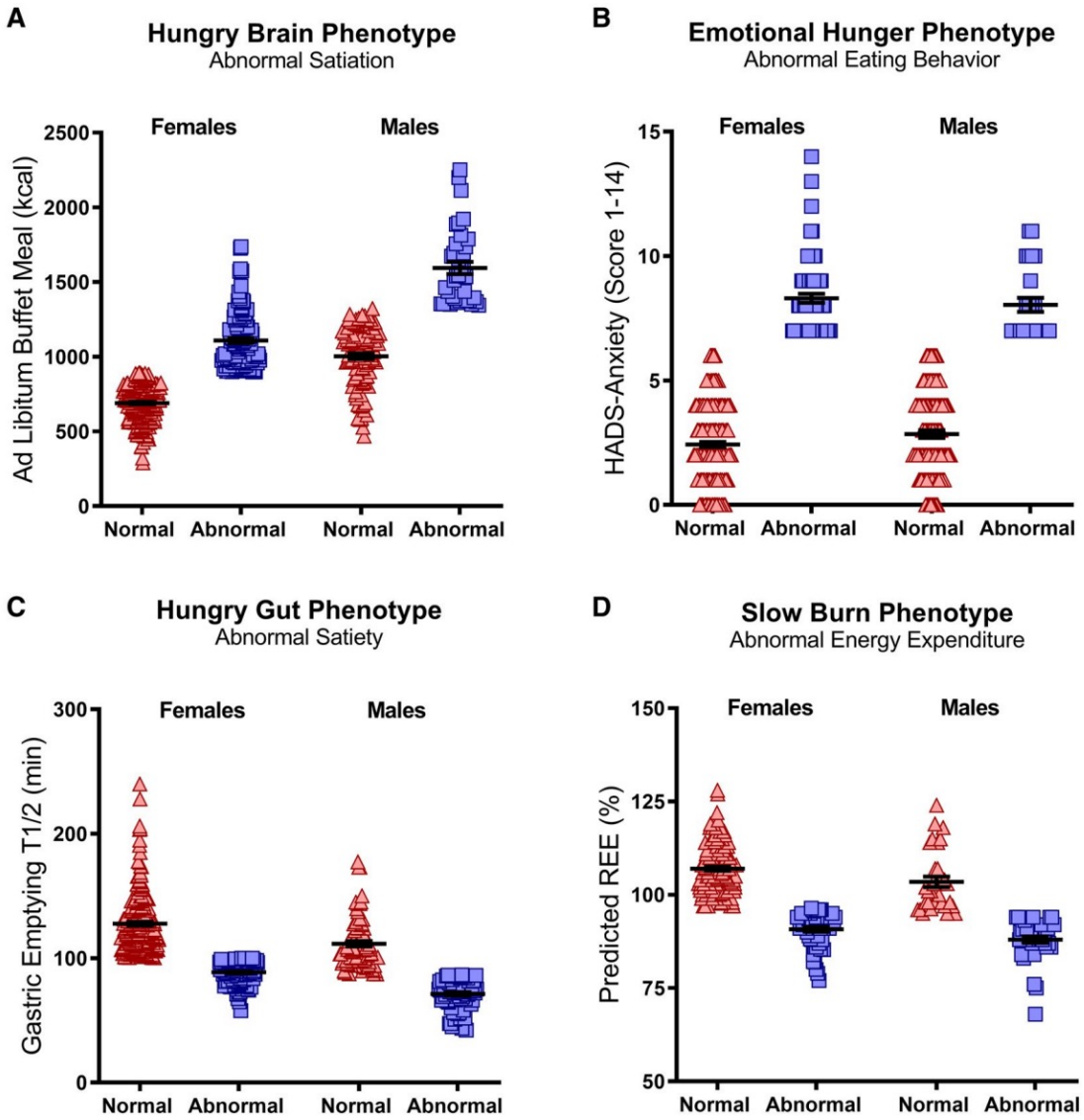
Contrave® is a registered trademarks of Currax Pharmaceuticals LLC
Mysimba® is a registered trademarks of Nalpropion Pharmaceuticals LLC
Qsymia® is a registered trademark of Vivus LLC

Belviq® is a registered trademark of Eisai Inc
Saxenda® is a registered trademark of Novo Nordisk S/A

Obesity, 2021;29(4):662-671

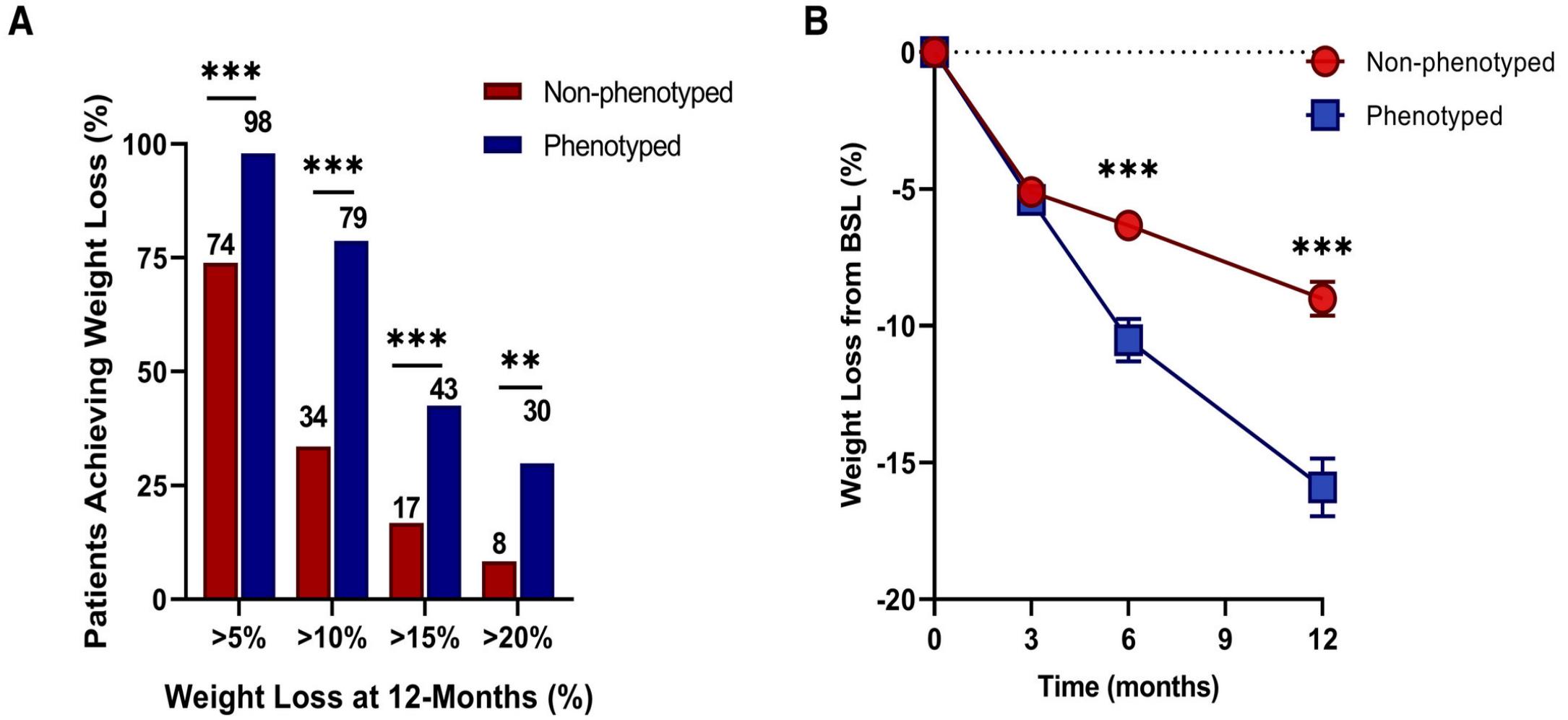
Belviq® was withdrawn from the US marketplace in February 2020

Selection of Obesity Medications Based on Phenotypes



Obesity 2021; 29: 662-671

Selection of Obesity Medications Based on Phenotypes

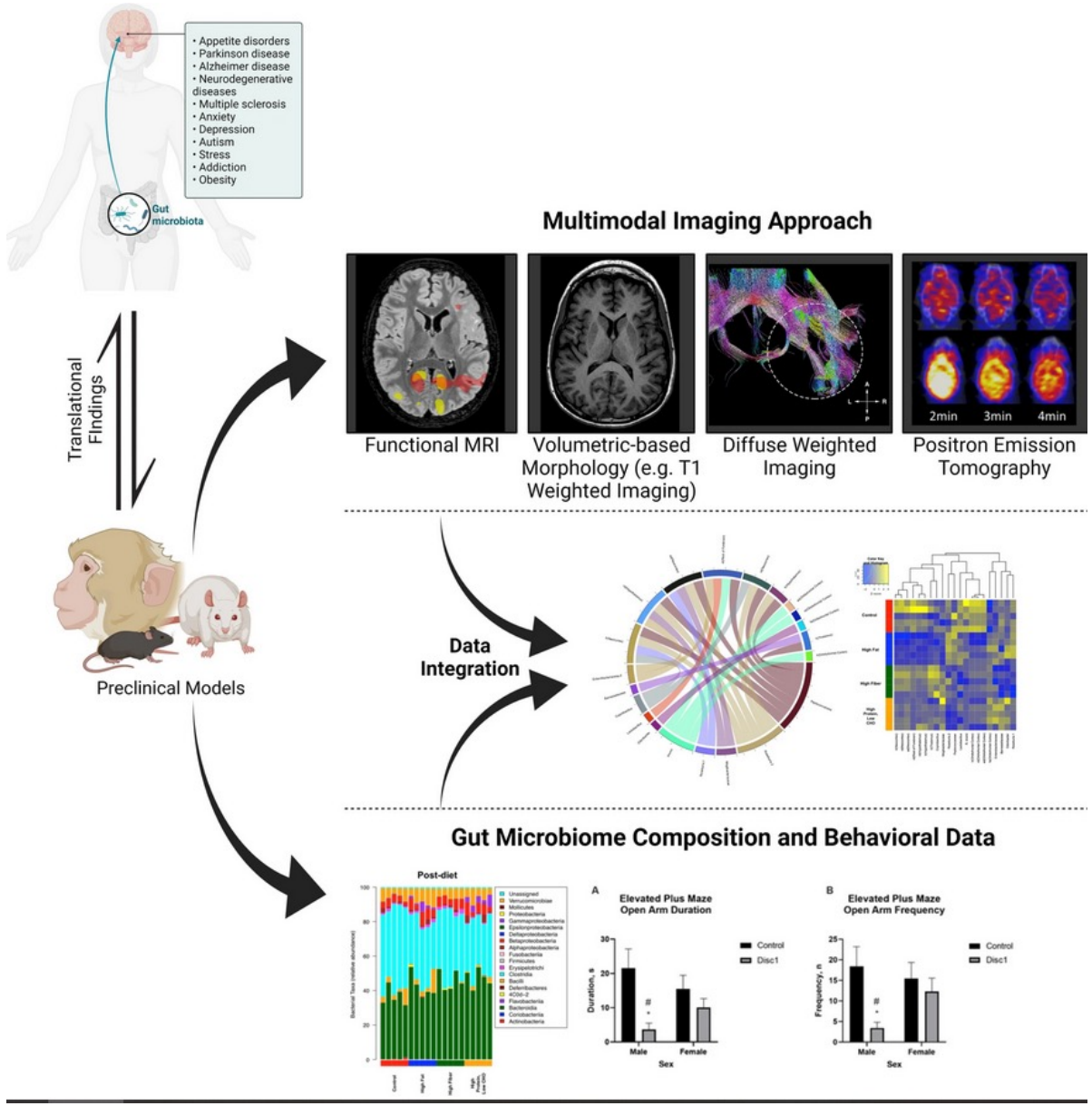


Obesity 2021; 29: 662-671

Potential Framework for Individualising Treatment

Phenotype	Medication	Measurement
High cravings Binge/reward-based eating Smoking	Naltrexone/Bupropion	Psychological questionnaires Genetics
High hunger	Phentermine/Topiramate	Ad libitum meal
Low fullness	Liraglutide Semaglutide	Gastric emptying
Preference for energy dense food Reward-based eating	? Semaglutide	Food choices
High fat diet	Orlistat	Food choices

Work in Progress



Montoro et al, *European Radiology* (2022)

Conclusions

- Field still in its infancy
- Phenotyping patients / assessing eating behaviour is challenging
- Some data already available to guide treatment
- Increase in medication choice will fuel research in this field
- Mechanistic studies with important clinical implications

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