

Incretin Therapy for Obstructive Sleep Apnea

GLP-1 receptor agonists and dual GLP-1/GIP agonists: what the data show

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Agenda

1. Why OSA needs new options
2. Incretin mechanisms
3. The evidence: SURMOUNT-OSA and other trials
4. PAP and broader effects

Background and mechanisms

Why a drug for OSA?

Common and undertreated

Up to 1 billion people worldwide have OSA

- Many remain undiagnosed and untreated
- Major neurocognitive and cardiometabolic consequences

PAP has limits

PAP remains the gold standard

- Tolerance and adherence are challenging for some patients
- PAP does not generally improve weight regulation

Obesity is a reversible risk factor

Also linked to diabetes and MASLD

- Treating OSA may be critical for cardiometabolic risk
- Hence interest in agents that treat obesity

How obesity drives OSA

1 Upper airway anatomy

Excess adiposity around the airway, including tongue and soft tissue; craniofacial structure also contributes

2 Dilator muscle function

Robust upper airway dilator activity protects some people with obesity from OSA

3 Ventilatory control

Unstable control of breathing contributes; weight loss may stabilize it, at least in theory

4 Lung volume (EELV)

Obesity lowers EELV, reducing caudal traction on the airway; weight loss should raise EELV and improve patency

Incretin mechanisms

GLP-1 receptor agonists

- Glucose-dependent insulin secretion up; glucagon down
- Delayed gastric emptying, satiety, less intake
- Central appetite effects, including premeal satiety
- Dopamine reward pathways: suppressed hedonic eating

Dual GLP-1 + GIP (tirzepatide)

- GIP also potentiates glucose-dependent insulin secretion
- Central GIP effects reduce hunger, appetite, hedonic feeding
- Effects thought to be mediated more by GIP than GLP-1
- Vs semaglutide: may be superior for HbA1c, waist, weight

Beyond weight loss?

Anti-inflammatory

Reduced pro-inflammatory cytokines, independent of changes in adiposity

Carotid body

Attenuates hyperglycemia-driven sympathoexcitation; may help explain SBP reduction

Central actions

Appetite regulation, plus effects on sleep and wakefulness

Key caveat: weight loss is purported to be the primary mechanism. Meta-analyses suggest the magnitude of weight loss is likely a major driver of AHI improvement, regardless of the intervention.

The evidence

SURMOUNT-OSA: design

Population

Moderate to severe OSA
with obesity

Two trials

Trial 1: not on PAP
Trial 2: on PAP

Randomization

Tirzepatide vs placebo
for 52 weeks, double-
blind

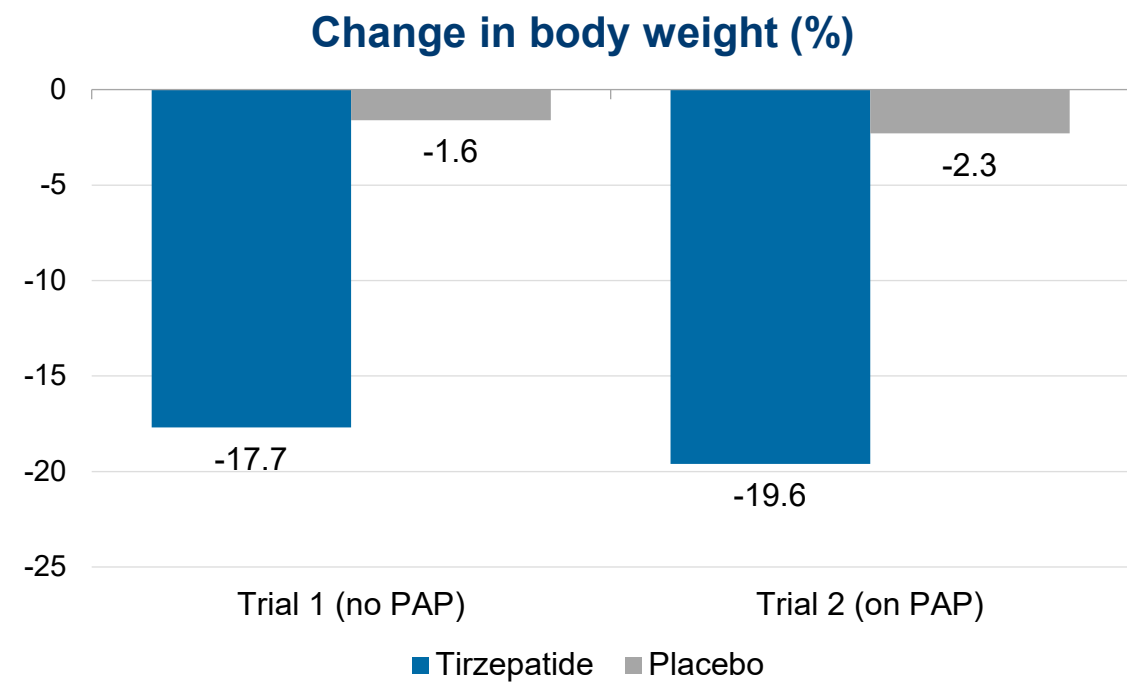
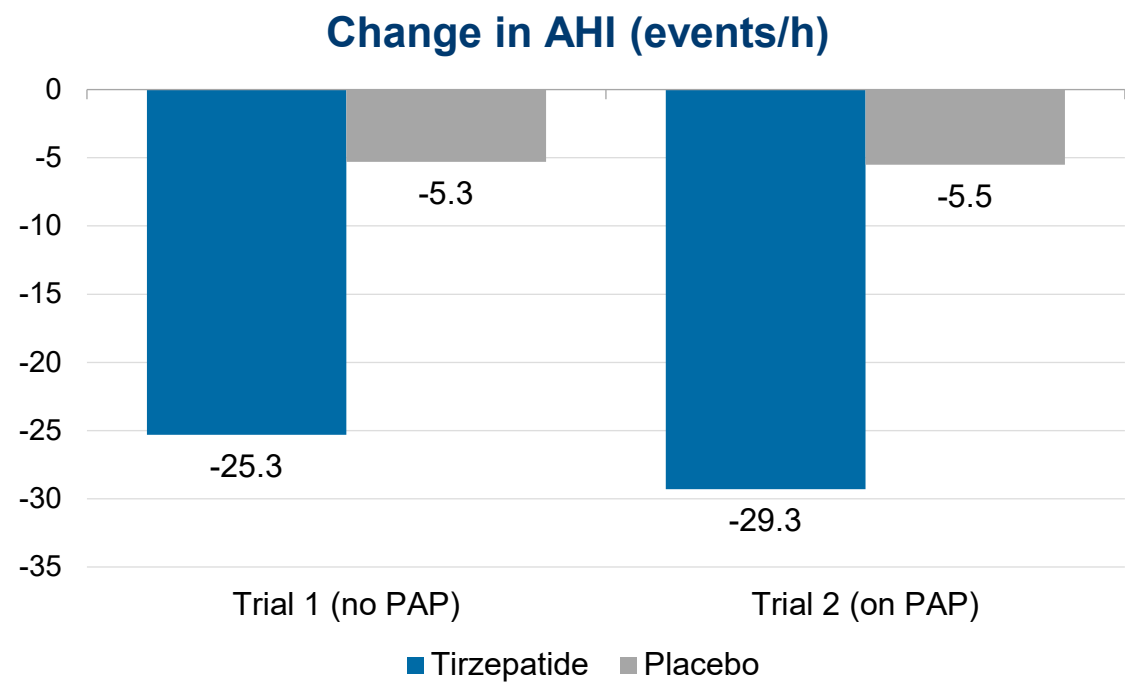
Primary outcome

Change in AHI at 1 year

Prespecified secondary outcomes (controlled for multiple comparisons)

Systolic blood pressure • hsCRP • Sleep apnea-specific hypoxic burden • Body weight • Patient-reported daytime and nighttime symptoms

SURMOUNT-OA: results



Also improved: SBP (reduced by up to 9.5 mmHg), hsCRP, hypoxic burden, patient-reported outcomes. FDA approved for OSA in Dec 2024.

Other GLP-1RA trials in OSA

Study	Population / design	Result
SCALE Sleep Apnea (liraglutide)	Obesity + moderate-severe OSA; 32 weeks vs placebo	AHI -12.2 vs -6.1 events/h; weight -5.7%; HbA1c and SBP lower
Jiang et al. (liraglutide + CPAP)	T2DM + severe OSA; CPAP with or without liraglutide, 3 months	AHI -4.9 vs +1.5; BMI -2.1 vs -0.1 kg/m ² ; SBP lower
ROMANCE (ongoing)	Obesity, T2DM, new OSA; n=132; control, CPAP, liraglutide, or both; 26 weeks	Primary outcome: change in AHI

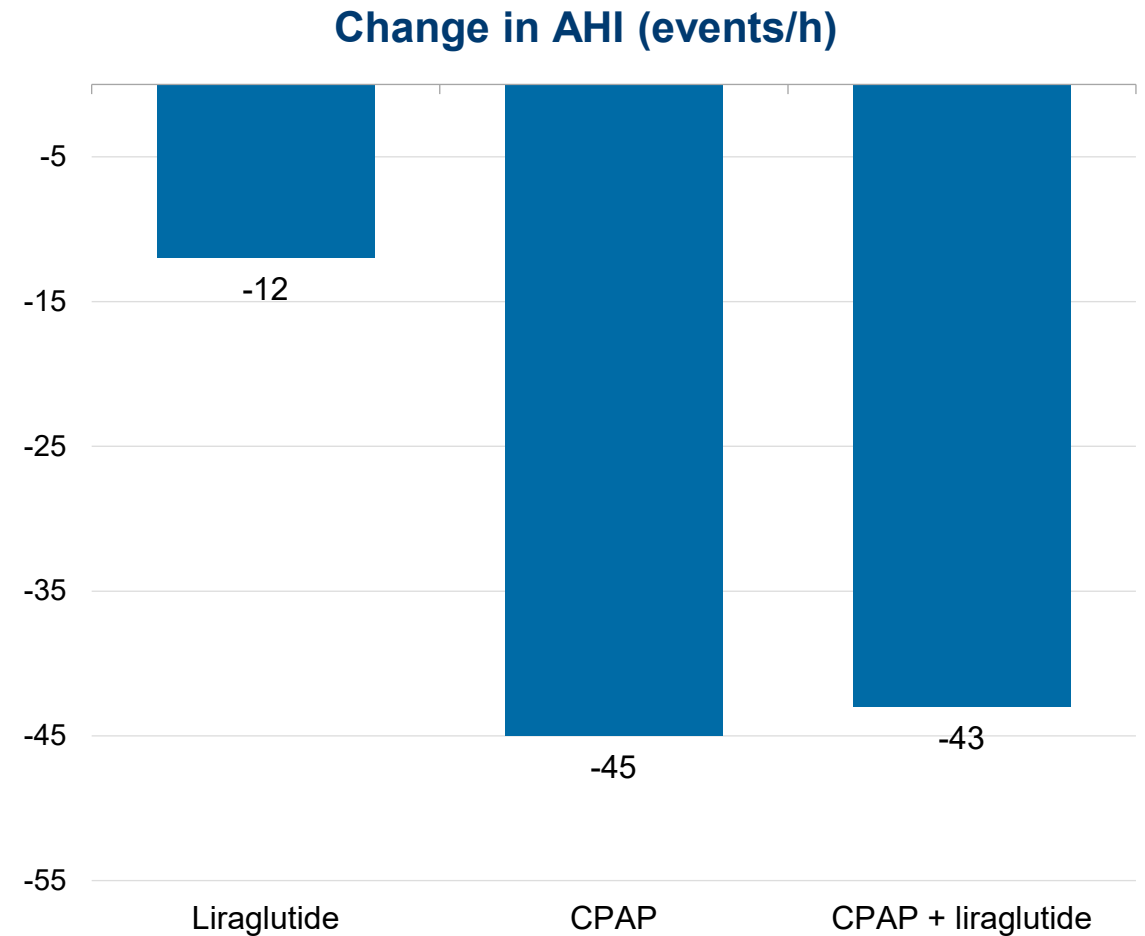
PAP still matters

O'Donnell 2024: 24-week RCT

- CPAP alone and CPAP + liraglutide reduced AHI more than liraglutide alone
- Only CPAP improved vascular inflammation and unstable coronary plaque volume
- Weight: liraglutide -6.17 kg, CPAP +2.73 kg, combined -3.67 kg

Chirinos, NEJM 2014

- Treating OSA plus obesity improved BP, triglycerides, and insulin sensitivity more than either alone



Broader effects

1

Cardiometabolic

Meta-analyses: improved hsCRP, glucose, and blood pressure with GLP-1RA

2

CV, renal, mortality

Emerging benefit in cardiovascular disease, diabetic CKD, and mortality; mechanisms under study

3

Cognition (preclinical)

Liraglutide attenuated chronic intermittent hypoxia-induced cognitive deficits via antioxidant and anti-inflammatory pathways. Cell and animal data only

Discussion

Take-home points

- 1 Tirzepatide reduced AHI and weight vs placebo in moderate-severe OSA with obesity, with or without PAP; FDA-approved Dec 2024
- 2 Weight loss is likely the major driver; direct effects remain unproven
- 3 PAP remains standard of care; no head-to-head data vs incretins
- 4 Treat OSA and obesity together, with lifestyle support and long-term follow-up

Key references

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Thank you

