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Spital Männedorf

SMOB SWISS MULTIDISCIPLINARY OBESITY SOCIETY

Universität Zürich[UZH]

Potential Complications Of Combined Therapies

GI - INTOLERANCE

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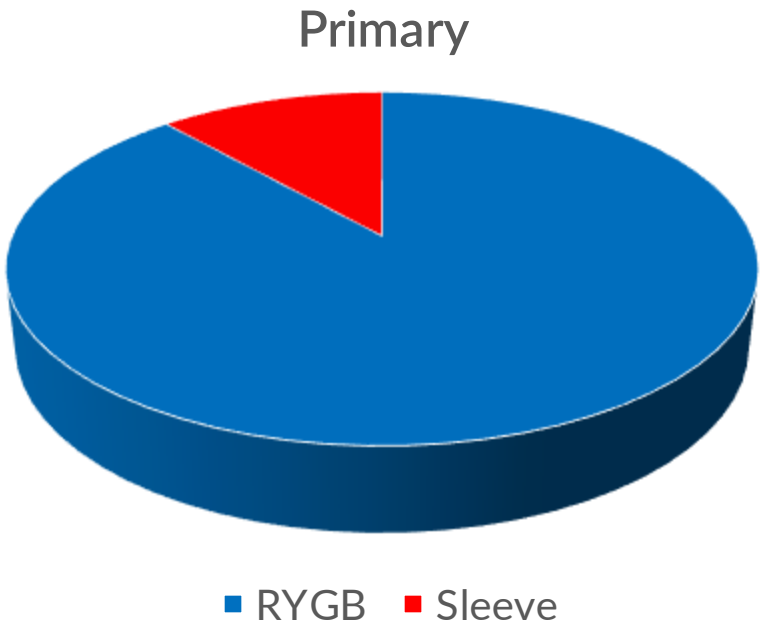
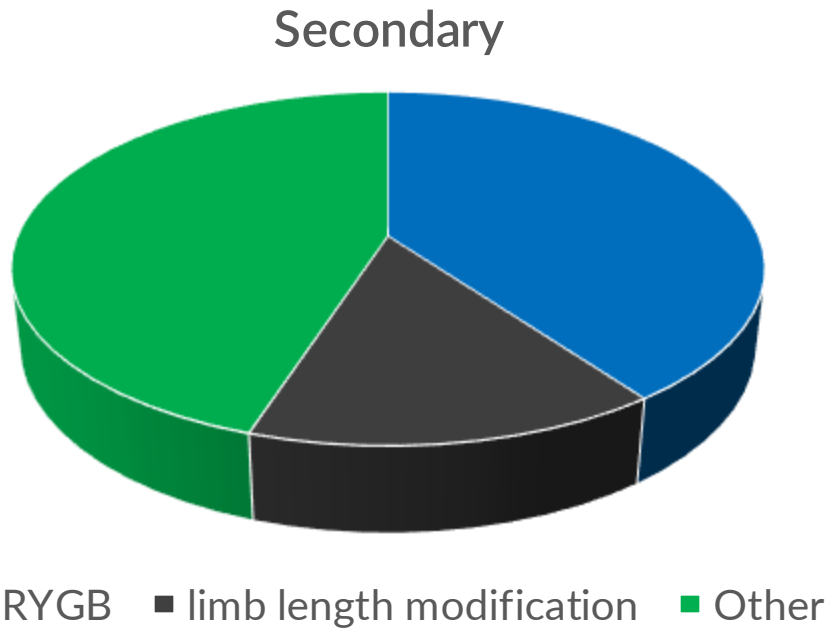
Disclosures

Research grants: Swiss National Science Foundation, Johnson & Johnson, Uniscientia Foundation, UZH - Hartmann-Müller Foundation

Lecture/consulting fees: Johnson & Johnson

Case mix:





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GI Intolerance: addition or interaction?

MBS + obesity pharmacotherapy

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1 + 1 = 2 ?

1 + 1 = > 2 ?

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MBS + obesity pharmacotherapy

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1 + 1 = > 2 ?

We don't really know

The GI background noise is already substantial

Metabolic-Bariatric Surgery	GLP-1/ GIP Therapy
nausea/vomiting	nausea/vomiting
reflux	reflux/ dyspepsia
dumping	altered gastric emptying
abdominal pain	abdominal pain
diarrhoea	Diarrhoea
constipation	constipation
gallstones	gallstones
dehydration	reduced intake
nutritional deficiencies	reduced nutritional intake

Similar symptoms – very different causes

What do we actually mean by “combined therapy”?

Most evidence is about rescue therapy – not true combination therapy

MBS → suboptimal weight loss after years → GLP-1 RA

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Less Evidence

- GLP-1 RA → MBS
- MBS + early postoperative GLP-1 RA
- planned lifelong combination therapy

What trials do we have?

Randomized controlled trials of GLP-1 receptor agonists after metabolic bariatric surgery

Study	Population	Intervention	Treatment start after MBS	Duration	Main outcome
GRAVITAS – Miras et al., 2019	n=80; RYGB/SG; persistent or recurrent T2D	Liraglutide 1.8 mg vs placebo	**≥12 months; mean ~3.8 years**	26 weeks	HbA1c significantly improved; weight treatment difference **−4.2 kg**
BARI-OPTIMISE – Mok et al., 2023	n=70; RYGB/SG; poor WL + blunted meal-stimulated GLP-1 response	Liraglutide 3.0 mg vs placebo	**≥12 months; mean 52 months (~4.3 years)**	24 weeks	**−8.8% vs −0.5%** body weight; treatment difference **−8.0 %-points**
Lofton et al., 2025	n=132; RYGB; ≥10% weight recurrence after initially successful WL	Liraglutide 3.0 mg vs placebo	**18–120 months after RYGB**	56 weeks	**−8.8% vs +1.1% TBWL**
Brown et al., 2025	n=48; AGB/SG; suboptimal WL / weight recurrence	Liraglutide up to 3.0 mg vs placebo	**12–36 months; mean ~1.6 years**	12 months*	**−5.7 kg vs +1.4 kg**; difference **−7.1 kg**
BARI-STEP – Stanley et al., 2026	n=70; SG/GB; <20% WL after MBS	Semaglutide 2.4 mg vs placebo	**≥12 months; mean 84 months (~7.0 years)**	68 weeks	**−18.0% vs +0.4%** body weight; adjusted difference **−19.1 %-points**

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What do the combination trials actually tell us?

nature medicine

Article

https://doi.org/10.1038/s41591-026-04416-4

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

Received: 18 November 2025

Accepted: 20 April 2026

A list of authors and their affiliations appears at the end of the paper

Stanley C et al., Nat Med (2026) Jul;32(7):2662-2672

What do the combination trials actually tell us?

nature medicine

Article

https://doi.org/10.1038/s41591-026-04416-4

Semaglutide versus placebo in individuals with poor weight loss after bariatric

Study design: Double-blind, randomized, placebo-controlled, 2-arm trial
FU / treatment duration: 68 weeks of treatment, plus 6-week off-drug follow-up
Primary endpoint: %WL at 68 weeks
Cohort: 35 semaglutide, 35 placebo; 63 included in the primary analysis (no ITT!)
Operations: SG 78.6% (55/70), RYGB 21.4% (15/70)

Accepted: 20 April 2026

Stanley C et al., Nat Med (2026) Jul;32(7):2662-2672

What do the combination trials actually tell us?

	Placebo (*n*=35)		Semaglutide 2.4 mg (*n*=35)		Total (*n*=70)			
	No. of events	No. of patients, *n* (%)	No. of events	No. of patients, *n* (%)	No. of events	No. of patients, *n* (%)	RR (95% CI)	*P*
Total AEs	231	33 (94.3)	310	34 (97.1)	541	67 (95.7)	1.03 (0.93 to 1.14)[a]	0.903
Gastrointestinal								
Diarrhea	17	14 (40)	29	21 (60)	46	35 (50)	1.5 (0.9 to 2.6)	0.103
Nausea	10	8 (22.9)	27	24 (68.6)	37	32 (45.7)	3.0 (1.7 to 6.3)	<0.001
Decreased appetite	4	4 (11.4)	15	15 (42.9)	19	19 (27.1)	3.8 (1.5 to 12.2)	0.009
Vomiting	7	6 (17.1)	15	10 (28.6)	22	16 (22.9)	1.7 (0.7 to 4.5)	0.264
Constipation	8	8 (22.9)	14	13 (37.1)	22	21 (30)	1.6 (0.8 to 3.7)	0.202
Abdominal pain	5	5 (14.3)	8	8 (22.9)	13	13 (18.6)	1.6 (0.6 to 4.9)	0.364
Upper abdominal pain	0	0 (0)	2	2 (5.7)	2	2 (2.9)	NA	–
Dyspepsia	5	5 (14.3)	9	9 (25.7)	14	14 (20)	1.8 (0.7 to 5.4)	0.243
Abdominal bloating	6	6 (17.1)	4	4 (11.4)	10	10 (14.3)	0.7 (0.2 to 2.1)	0.499
Gastritis	0	0 (0)	1	1 (2.9)	1	1 (1.4)	NA	–
Cardiovascular events								
Dizziness	5	5 (14.3)	13	12 (34.3)	18	17 (24.3)	2.4 (1.0 to 6.9)	0.066
Palpitations	1	1 (2.9)	3	3 (8.6)	4	4 (5.7)	3.0 (0.4 to 59.1)	0.331
Chest pain	1	1 (2.9)	1	1 (2.9)	2	2 (2.9)	1.0 (0.04 to 24.6)	1.000
Hepatobiliary								
Cholelithiasis	0	0 (0)	2	2 (5.7)	2	2 (2.9)	NA	–
Infections								
Upper respiratory tract	11	10 (28.6)	20	14 (40)	31	24 (34.3)	1.4 (0.7 to 2.8)	0.320

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What do the combination trials actually tell us?

		Placebo (n=35)		Semaglutide 2.4 mg (n=35)			RR (95% CI)	P
To	231	any AE	94.3%	310	34 (9	95.7%	67 (95.7)	n.s.	0.903
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any AE

Nausea

Diarrhoea

n.s.

P<0.001.

n.s.

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	0		1		1	1 (1.4)		–
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Trial was not powered for safety outcomes !!!

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There is evidence for an additive drug effect

There is little evidence for a surgery–drug interaction

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ıl;32(7):2662-2672

The complications we actually need to worry about

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Dehydration and nutritional compromise

Reduced hunger in combination with nausea, early satiety & vomiting
→ less fluid intake
→ hypoproteinemia
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Gallbladder disease

→ Gallbladder/biliary disease after GLP-1 RA (RR 1.37), with weight-loss-dosages RR 2.29

Delayed gastric emptying

→ Differences after Sleeve? RYGB? OAGB? SADI-S?

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Masking a surgical complication

Not every patient on semaglutide with nausea has semaglutide-induced nausea

What we DON'T know

1. Are post-MBS patients more susceptible to GLP-1/GIP GI toxicity than non-operated patients
2. Does the type of surgery matter (SG *vs.* RYGB *vs.* OAGB *vs.* SADI-S) ?

What we DON'T know

1. Are post-MBS patients more susceptible to GLP-1/GIP GI toxicity than non-operated patients
2. Does the type of surgery matter (SG *vs.* RYGB *vs.* OAGB *vs.* SADI-S) ?
3. What is best time to start adjuvant therapy?
4. How to titrate optimally after MBS?

What we DON'T know

1. Are post-MBS patients more susceptible to GLP-1/GIP GI toxicity than non-operated patients
2. Does the type of surgery matter (SG *vs.* RYGB *vs.* OAGB *vs.* SADI-S) ?
3. What is best time to start adjuvant Tx?
4. How to titrate optimally after MBS?
5. What are the nutritional consequences of long-term combined treatment?
6. Is the biliary risk additive?
7. How safe are the newer dual/triple agonists (no RCT on Tirzepatide post-MBS)

Summary

Summary

1. Is GI-Intolerance common with combined therapy? — YES!

2. Is there more than expected from the drug alone? — We don't know!

3. Is there evidence for serious synergistic GI toxicity? — Not so far!

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1. Is GI-Intolerance common with combined therapy? — YES!

2. Is there more than expected from the drug alone? — We don't know!

3. Is there evidence for serious synergistic GI toxicity? — Not so far!

The greatest current risk may not be GI intolerance itself, but attributing a surgical symptom to the drug

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