Combination Therapies: Where The Obesity Medications Fit 12m

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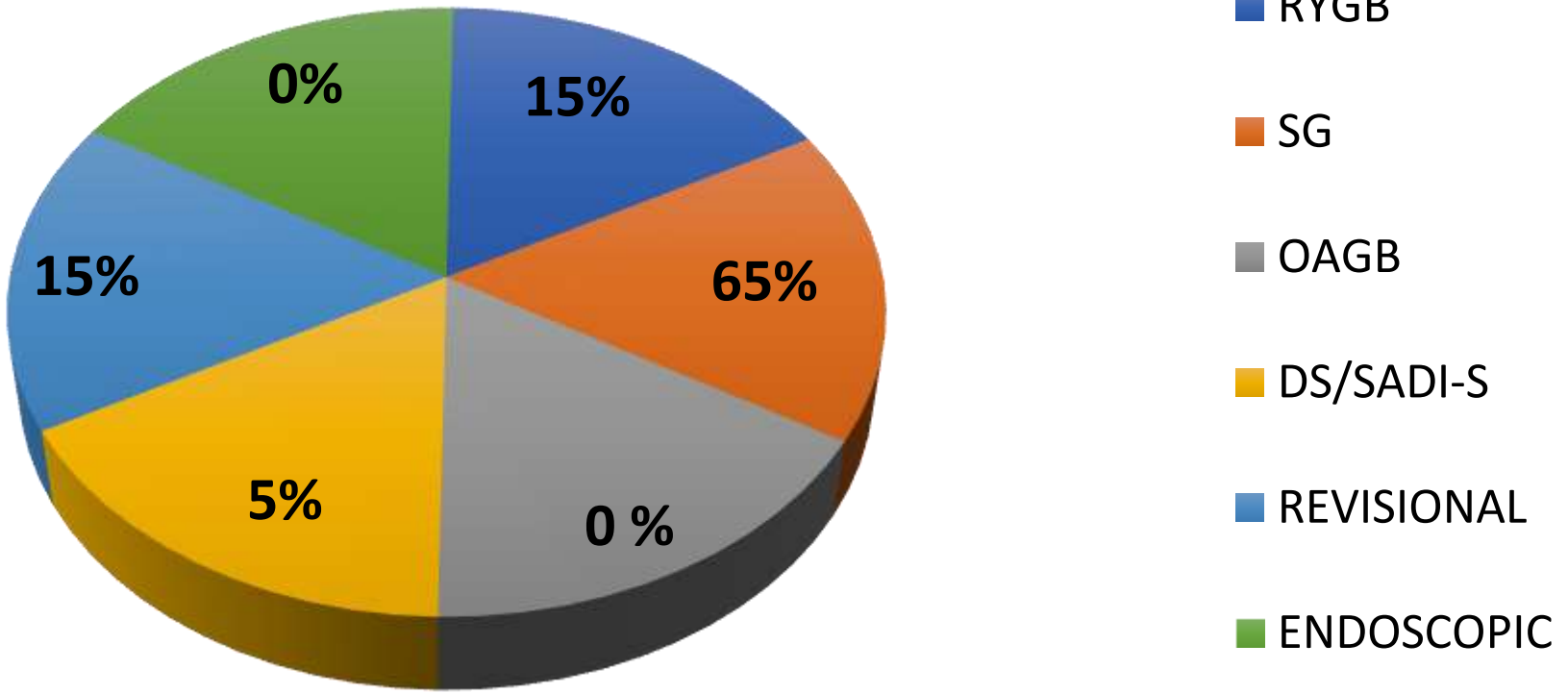
CONFLICT OF INTEREST DISCLOSURE

Honoraria for teaching:
WL Gore, Medtronic, Ethicon, Ezisurge, Stryker, Vivus

CASE MIX DISCLOSURE



CASE MIX DISCLOSURE

Total CASE Volume:

- RGB: 1800
- Sleeve: 1900
- Lap Band 2000
- Revisions: 1200

The Scope of the Problem

Obesity rates slowly climb

ASMBS/IFSO guidelines lowered BMI and special groups

More medications came out and are coming with >15% TBWL

Cost of injectables are ?too high

Medication Class	Weight Loss Mechanism	Food Intake	Expected Weight Loss
Phentermine	indirect sympathomimetic	↓	5% TBW
Qysmia (phentermine and topiramate)	indirect sympathomimetic and increased satiety	↓	5% TBW at low dose 10% TBW at high dose
Orlistat	decreased fat absorption	↔	>5% TBW
Contrave (naltrexone/bupropion)	affects hypothalamus and dopamine pathways of CNS	↓	10% TBW
GLP-1 Receptor Agonists (incretin hormones)	act on GLP-1 receptor to delay gastric emptying and reduce food intake	↓	4-15% TBW
Tirzepatide (GLP-1, GIP dual agonist)	Acts on GLP-1 receptor and GIP, delays gastric emptying and reduces food intake	↓	20% TBW

Review > Trends Endocrinol Metab. 2020 Jun;31(6):410-421. doi: 10.1016/j.tem.2020.02.006.
Epub 2020 Mar 16.

How May GIP Enhance the Therapeutic Efficacy of GLP-1?

- Dual GIP/GLP-1 receptor agonist therapy produces profound weight loss, glycemic control, and lipid lowering.

Clinical Trial > Diabetes Care. 2020 Jun;43(6):1352-1355. doi: 10.2337/dc19-1892.
Epub 2020 Apr 14.

Effects of Novel Dual GIP and GLP-1 Receptor Agonist Tirzepatide on Biomarkers of Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes

Mark L Hartman [1], Arun J Sanyal [2], Rohit Loomba [3 4], Jonathan M Wilson [5], Amir Nikooienejad [5], Ross Bray [5], Chrisanthi A Karanikas [5], Kevin L Duffin [5], Deborah A Robins [5], Axel Haupt [5]

Conclusions: In post hoc analyses, higher tirzepatide doses significantly decreased NASH-related biomarkers and increased adiponectin in patients with T2DM.

Randomized Controlled Trial > Lancet Diabetes Endocrinol. 2022 Jun;10(6):393-406.
doi: 10.1016/S2213-8587(22)00070-5. Epub 2022 Apr 22.

Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial

Amalia Gastaldelli [1], Kenneth Cusi [2], Laura Fernández Landó [3], Ross Bray [3], Bram Brouwers [3], Ángel Rodríguez [4]

Interpretation: Tirzepatide showed a significant reduction in LFC and VAT and ASAT volumes compared with insulin degludec in this subpopulation of patients with type 2 diabetes in the SURPASS-3 study. These data provide additional evidence on the metabolic effects of this novel dual GIP and GLP-1 receptor agonist.

> Expert Opin Investig Drugs. 2023 May;32(5):355-359. doi: 10.1080/13543784.2023.2206560. Epub 2023 Apr 24.

Is retatrutide (LY3437943), a GLP-1, GIP, and glucagon receptor agonist a step forward in the treatment of diabetes and obesity?

Sheila A Doggrell [1]

Review > Peptides. 2023 Mar;161:170939. doi: 10.1016/j.peptides.2023.170939.
Epub 2023 Jan 3.

An update on peptide-based therapies for type 2 diabetes and obesity

Clifford J Bailey [1], Peter R Flatt [2], J Michael Conlon [3]

- GLP-1R agonist semaglutide, available in oral and injectable formulations and in clinical trials combined with the long-acting amylin analogue, cagrilintide.
- High efficacy in both glucose- and weight lowering capacities with the GLP-1R/GIP-R unimolecular dual agonist, tirzepatide
- Long-acting unimolecular GLP-1R/GCGR dual agonist peptides and GLP-1R/GCGR/GIPR triagonist peptides have entered clinical trials
- human monoclonal antibody, bimagrumab which blocks activin type II receptors and is associated with growth of skeletal muscle
- an antibody blocking activation of GIPR to which are conjugated GLP-1R peptide agonists (AMG-133)
- melanocortin-4 receptor agonist, setmelanotide for use in certain inherited obesity conditions.

> Peptides. 2007 Feb;28(2):235-40. doi: 10.1016/j.peptides.2006.08.041. Epub 2007 Jan 3.

Neuropeptide Y (NPY) Y2 receptor-selective agonist inhibits food intake and promotes fat metabolism in mice: combined anorectic effects of Y2 and Y4 receptor-selective agonists

Ambikaipakan Balasubramaniam [1], Rashika Joshi, Chunhua Su, Lou Ann Friend, J Howard James

Interventions in Bariatric Surgery

- For weight recurrence
- For inadequate weight loss
- For weight loss plateaus

Weight Loss Trajectory

- 2918 RYGB patients from a comprehensive medical center used data up to year 7 post-surgery.
- Three weight change trajectories were identified (above average, average, and below average). Mean percentage weight change: **above average group was -42.85% compared with -31.57% in the average group and -22.74% in the below average group**
- Below average group was more likely to be male and have diabetes
- Lower initial weight loss post-surgery was associated with a greater chance of a poorer weight outcomes (OR = 1.64, P < .0001).
    - Surg Obes Relat Dis. 2018 Nov;14(11):1680-1685. Demographic, clinical, and behavioral determinants of 7-year weight change trajectories in Roux-en-Y gastric bypass patients. Lent MR

Obesogenic Medications and Weight Loss Trajectory

- 32 commonly prescribed medications that have weight gain as a side effect were identified.
- (%EWL) of patients divided into two groups based on post-LSG exposure to obesogenic medications
- 150 patients (Meds group) were prescribed obesogenic medications within the one-year post-LSG follow up period, whereas 173 patients (Control group) were not prescribed obesogenic medications.
- The Meds group lost significantly less weight compared to the Control group **(%EWL ± SEM at 12 months 53.8 ± 2.4 n = 78, 65.0 ± 2.6**, n = 84 respectively, P = 0.002).
- obesogenic medications were associated with worse weight loss outcomes post-LSG. Closer scrutiny of patient medications is needed

Meds that Can Cause Weight Gain

Antihistamines: Benadryl, allergy meds

Tricyclic AntiDepressants: Elavil, Pamelor

SSRI:Paxil>> Prozac/ Zoloft (wt gain over time)

- Remeron, Effexor and Cymbalta weight neutral but in some patients cause significant weight gain

Beta Blockers (Coreg and Bystolic less likely to cause weight gain)

Diabetes Medications: Glucotrol, Glipizide, Amaryl, Actos and Avandia

Seizure Medications: Valproic Acid, Neurontin, Tegretol, Lyrica

Antipsychotics: Lithium, Clozapine, Zyprexa, Risperidone, Seroquel

Abilify causes weight gain in some

Predictors of Inadequate Weight Loss

- 227 LRGB patients
- Preoperative factors that predict inadequate EWL at 12 months:
  - higher initial BMI
  - older age
  - presence of DM
  - preoperative weight gain
    - Al-Khyatt W, Obes Surg 2017

Weight Recurrence

- 1278 patients with adequate follow-up up to 7 years
- Postsurgery behaviors independently associated with **weight recurrence: sedentary time, eating fast food, eating when feeling full, eating continuously, binge eating and loss-of-control eating and weighing oneself <weekly**.
- Postsurgery characteristics independently associated with **greater weight recurrence** included: **younger age, venous edema, poorer physical function, and more depressive symptoms**
    - Ann Surg. 2019 Apr 4. Patient Behaviors and Characteristics Related to Weight Regain After Roux-en-Y Gastric Bypass: A Multicenter Prospective Cohort Study. King WC et al.

Technical Failure

- Pouch too big (58.9%)
- Stoma too big (28.8%)
- Both (12.3%)

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- Yimcharoen et al
- Duration of weight recurrence impacts on weight loss amount

The Stoma Fix

- 331 RYGB patients underwent 342 TORe procedures
- Mean body mass index was 40 ± 9 kg/m^2
- Pre-TORe GJA size was 23.4 ± 6.0 mm, which decreased to 8.4 ± 1.6 mm after TORe
- Patients experienced 8.5%, 6.9%, and 8.8% total weight loss (TWL) at 1, 3, and 5 months
- Some patients (39.3%) had additional weight loss therapy (pharmacotherapy or procedure), with 3.6% getting repeat TORe
    - Pichamol Jirapinyo , Gastrointest Endosc, 2020

Endoscopic Methods

- Injection w collagen
- Sclerotherapy
- Argon Plasma Coagulation
  - 3 sessions separated by 8 weeks
  - 67% reduction in stoma size
  - 79% reduction in regained weight

- Baretta GA(1), Alhinho HC, Matias JE, Marchesini JB, de Lima JH, Empinotti C, Campos JM. Argon plasma coagulation of gastrojejunal anastomosis for weight regain after gastric bypass. Obes Surg. 2015 Jan;25(1):72-9.

Weight Loss Nadir or Weight Regain?

- Young adults aged 21 to 30 following Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) between November 2000 and June 2014.
- Patients who used **topiramate, phentermine, and/or metformin** postoperatively
- 54.1% of study patients lost ≥5% of their postsurgical weight; 34.3% and 22.9% lost ≥10% and ≥15%, respectively. RYGB had higher median percent weight loss (-8.1%) than SG (-3.3%) (p = 0.0515).
- **No difference was found in median percent weight loss with medications started at weight plateau (-6.0%) versus after weight regain (-5.4%) (p = 0.5304).**

- Children (Basel). 2018 Aug 29;5(9). pii: E116. Weight Loss Medications in Young Adults after Bariatric Surgery for Weight Regain or Inadequate Weight Loss: A Multi-Center Study. Toth AT

Weight Loss Nadir or Weight Regain?

- **BUT!!!** Patients taking **medications at weight loss plateau lost 41.2% of total body weight from before surgery versus 27.1% after weight regain** (p = 0.076).
- Median percent weight change on metformin was -2.9% compared to the rest of the cohort at -7.7% (p = 0.0241)
- RYGB patients achieve more weight loss on medications but both RYGB and SG benefit.
- **Median total body weight loss from pre-surgical weight may be higher in patients that start medication at postsurgical nadir weight.**

- Children (Basel). 2018 Aug 29;5(9). pii: E116. Weight Loss Medications in Young Adults after Bariatric Surgery for Weight Regain or Inadequate Weight Loss: A Multi-Center Study. Toth AT

Adding Medications to Endoscopic Procedures: ?Match Surgical Weight Loss

Balloon and

- Phentermine/Topiramate
- Phentermine
- GLP1

ESG and

- Phentermine/Topiramate
- Phentermine
- GLP1

ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Research Article

Endoscopic Sleesve Gastroplasty Plus Semaglutide Versus Endoscopic Sleeve Gastroplasty Alone for Weight Loss: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study

Anna Carolina Hoff[1]*, Zadid Haq[2], Abdellah Hedjoudje[2], Manoel Galvao Neto[3], Luiz Gustavo de Quadros[4], Sergio Alexandre Barrichello[5], Gabriel Cairo Nunes[5] and Dilhana Badurdeen[6]

Results: Comparisons between the two groups showed that patients who received injectable semaglutide within one month of ESG had a superior mean% TBWL at 12 m compared to those who received placebo, 25.21% (SD 2.14%) versus 18.65% (SD 1.44%) ($p < 0.001$). Additionally, the ESG-S group had a significantly greater reduction in percent body fat mass, 12.69% (SD 4.84%) vs. 9.04% (SD 6.38%), $p < 0.001$), and lower mean hemoglobin A1c, (4.93 [SD 0.45] vs. 5.33 [SD 0.60]), compared to the ESG group at 12 M.

Conclusions

- Indications for initial medical weight loss, as well as maintenance of surgical weight loss and/or further weight loss
- History and medication history as well as cost of meds impact patient options
- Intervene early
- Increase frequency of visits
- Don’t be afraid to layer therapies
  - I got my Diplomate American Board of Obesity Medicine

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Conclusions

Medications can result in good weight loss

Maybe prevent some revisions

Large pouch can be fixed

Stoma can be made smaller

Surgery is not always the problem or the answer

Medication	Route	%TBWL- average	$Cost- self pay
Lomaira	Oral, TID	variable	$50/month
Phentermine	Oral Daily	Variable	<$50/month
Qsymia	Oral Daily	>10%	$110-140/month
Contrave	Oral BID- ish	>10%	$90/month
Saxenda/Liraglutide	Daily Inj	>10%	$1100/month
Ozempic/Semaglutide Wegovy	Weekly Inj or daily pill	>>10% 15%	$800/month $1400/month
Mounjaro/Tirzepatide	Weekly Inj	>22%	$1000/month

The Future is a Pill

- centrally acting agents (setmelanotide, neuropeptide Y antagonist [velneperit], zonisamide-bupropion [Empatic], cannabinoid type-1 receptor blockers),
- gut hormones and incretin targets (new glucagon-like-peptide-1 [GLP-1] analogues [semaglutide and oral equivalents],
- amylin mimetics [davalintide, dual amylin and calcitonin receptor agonists],
- dual action GLP-1/glucagon receptor agonists [oxyntomodulin],
- triple agonists [tri-agonist 1706], peptide YY, leptin analogues [combination pramlintide-metreleptin]),
- other novel targets (methionine aminopeptidase 2 inhibitor [beloranib], lipase inhibitor [cetilistat], triple monoamine reuptake inhibitor [tesofensine], fibroblast growth factor 21
- anti-obesity vaccines (ghrelin, somatostatin, adenovirus36).
    - Curr Obes Rep. 2018 Jun;7(2):147-161. Future Pharmacotherapy for Obesity: New Anti-obesity Drugs on the Horizon. Srivastava G(1), Apovian C(2).