Clinical Review:

Pharmacotherapy of Weight Loss

Weight loss is an area of major concern in the United States. The National Institute of Diabetes and Digestive and Kidney Diseases estimates that nearly 1 in 3 adults may be classified as overweight, and 2 in 5 adults have obesity.[1,2] Obesity has a major impact on patient health and other disease states. Significant weight loss has the potential to produce overall mortality benefits and moderate weight loss (defined as loss of 5-10% of body weight) has been shown to significantly improve conditions such as type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease among other chronic conditions.[3] Weight loss may be achieved through a variety of avenues, lifestyle changes such as dietary changes and increased physical activity are key, surgical intervention such as bariatric surgery may also be indicated for patients and has demonstrated significant results for ongoing weight loss.[3] For patients who fail to achieve weight loss goals (at least 5% of total body weight in 3-6 months) despite lifestyle changes, pharmacotherapy in conjunction with these changes can be key.[5] This review will focus on pharmacological interventions for the management of weight loss.

Medications for diabetes including semaglutide (a long-acting glucagon-like peptide-1 receptor agonist (GLP-1)), liraglutide (a GLP-1 receptor agonist), and tirzepatide (a glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 receptor agonist) are all of major interest for weight loss. These medications are all available as subcutaneous injectable products, semaglutide is also available as an oral tablet. GLP-1 receptor agonists work by enhancing glucose-dependent insulin secretion and by slowing gastric emptying, increasing pancreatic beta-cell proliferation, and reducing glucagon release. All of these factors contribute to overall appetite reduction. Activation of GLP-1 receptors in the hypothalamus may also contribute to weight loss by decreasing sensations of hunger and alleviating food cravings.[4] Despite overlapping mechanisms of action, clinical trials have found differing levels of weight loss with these medications. Placebo-corrected weight loss reports from clinical trials suggest approximately 5% weight loss with liraglutide, 12% with semaglutide, and 18% with tirzepatide.[5] The SCALE (Satiety and Clinical Adiposity Liraglutide Evidence) clinical trial of liraglutide reported 8±6.7% weight loss at 56 weeks in the treatment group as compared to 2.6 ±5.7% in the placebo group. The STEP trial (Semaglutide Treatment Effect in People with Obesity) found semaglutide 2.4mg to produce mean weight loss of 14.9% as compared to 2.4% with the placebo group over a treatment period of 68 weeks.[6] The SURMOUNT-1 Trial found weight loss at all three doses of tirzepatide (5, 10, 15mg) with the most significant weight loss in the 15mg group with a reported 20.9% mean weight loss as compared to 3.1% for placebo over a 72 week trial.[7] Though data is difficult to compare directly due to differing treatment times, head to head clinical trials between semaglutide and tirzepatide have confirmed a greater percentage of patients achieve 5% or greater weight loss with tirzepatide as compared to semaglutide.[8] Semaglutide oral therapy has also been evaluated for weight loss. The OASIS-1 trial evaluated semaglutide oral tablets over 68 weeks. The dose was escalated starting with 3mg daily for 4 weeks and escalating to 7mg, 14mg, 25mg and then eventually 50mg daily in 4-week intervals. The study found 15.1% weight loss compared to just 2.4% with placebo.[61] Though the study did not include an injectable treatment arm, it should be noted that this weight loss is comparable to that reported with 2.4mg semaglutide subcutaneous injection.

Though tirzepatide has been demonstrated most effective for weight loss in clinical trials, among the GLP-1 receptor agonist medications it is associated with the highest risk of vomiting and gastroenteritis. Semaglutide represented the highest risk of abdominal pain, and liraglutide represented the highest risk for diarrhea and dyspepsia. One meta-analysis found that of these medications, tirzepatide was associated with the highest risk of discontinuation due to adverse events.[60]

This medication class represents a significant step forward in managing weight loss and weight related illnesses, however, benefits seen with these medications tend to diminish after discontinuation. An extension of the STEP trial on semaglutide found that participants gained back 2/3 of their prior weight loss in just one year after discontinuation of the drug.[9] Similarly, an extension of the SURMOUNT trial on tirzepatide noted that patients that discontinued treatment at week 36 regained 14% of their weight over the following 52 week monitoring period and those who remained on treatment lost an additional 5.5% of their body weight over that same period.[58]

Rebound weight loss is a major concern for patients who do not want to take an injectable medication indefinitely. This has resulted in interest in alternative routes of administration. Peptides are often limited in route of administration by issues with stability or metabolism. Semaglutide, the only of GLP-1 receptor agonist medications with an oral dosage form, has an amino acid substitution changing the penultimate alanine such that the drug is no longer a substrate for the protease dipeptdyl peptidase 4 (DPP4), a protease in the gut that breaks down peptides and proteins.[10,11] Even with this modification, commercially available semaglutide oral tablets contain a permeation enhancer, sodium N-(8-[2-hydroxybenzoyl]amino) caprylate (abbreviated SNAC), that greatly enhances the oral bioavailability. SNAC operates by raising the local pH and neutralizing the surrounding stomach acid and fluidizing the lipid membrane to increase permeability and allow for easier uptake via the transcellular route.[12] Tirzepatide shares this substitution, though data on oral bioavailability alone or in combination with permeation enhancers is not yet available. Liraglutide retains its penultimate alanine group similar to native GLP-1 and thus is likely not a candidate for an oral dosage form. Limited data is available on alternative routes of administration. Studies looking to evaluate sublingual liraglutide at 3, 12, and 30mg doses are currently recruiting with an expected end date in 2026.[13] Human trials on the administration of semaglutide, liraglutide, or tirzepatide via the nasal route are not currently available, but the parent molecule (glucagon-like peptide-1) has been studied in limited human trials via the nasal route. One double-blind placebo-controlled trial had patients administer 1.2mg of human GLP-1 via nasal spray before every meal for 2 weeks. The study found rapid absorption with a T_{max} of 8.1min and expected effects of GLP-1 including induced insulin secretion, inhibition of glucagon secretion, and improvement in intermediate-term markers of glycemic control.[14] Further data is needed on the safety and efficacy of GLP-1 or GLP-1 receptor agonist medications for long term use via alternative routes.

Commercially available pharmacotherapy options for weight loss include Contrave (Naltrexone/Bupropion extended release), and Qysmia (Phentermine/Topiramate extended release). Contrave combines bupropion and naltrexone, both of which have shown some limited weight loss in patients as solo agents and takes advantage of their synergistic effect. Bupropion stimulates pro-opiomelanocortin cells (POMC) to produce an anorexic effect, when paired with naltrexone HCl, a negative feedback loop that may reduce efficacy of bupropion is inhibited resulting in increased weight loss compared to monotherapy with either active pharmaceutical ingredient (API).[15,16] Naltrexone alone may result in weight loss due to its opioid blockade resulting in a decreased feeling of reward associated with food.[17,18] Phentermine is also available as a solo agent for weight loss. The main impact of phentermine on weight loss may be due to its impact on norepinephrine resulting in appetite suppression. The exact mechanism of action for topiramate with weight loss is not known, but it is thought to decrease appetite and

enhance satiety.[19,20] Combination therapies offer the potential for increased benefits for weight loss over monotherapy. Studies on combination phentermine/topiramate have demonstrated improved weight loss over treatment with the individual APIs, but also an increased risk of adverse events such as paresthesia, dry mouth, and headache among others.[21,22] Similarly, studies on naltrexone/bupropion combination therapy have demonstrated reduced food intake vs therapy with bupropion or naltrexone alone.[23] Patients on low dose phentermine/topiramate (3.75/23mg) reported 9.3% weight loss while patients on high dose phentermine/topiramate (15/92mg) reported 10.5% weight loss over 52 weeks.[53] Patients on low dose naltrexone/bupropion (8mg naltrexone/180mg bupropion twice daily) reported 5% weight loss while patients on high dose treatment (16mg naltrexone 180mg bupropion twice daily) reported 6.1% weight loss over 56 weeks.[53]

Trials on safety and efficacy for larger combinations of these agents are not yet available, though, individual case studies demonstrate some patients using metformin, phentermine, and topiramate combined for weight loss (the patient was also on bupropion, but not for potential weight loss benefit) in addition to semaglutide.[24,25,26] Though combination therapy may improve results, it also increases the likelihood for drug interactions and adverse effects. For example, phentermine and bupropion combined could potentially increase the risk of seizures. Though no combination product currently exists, some limited case studies have reported on the utility of combination metformin and topiramate as well. One small case study on 3 candidates for bariatric surgery evaluated combination therapy with metformin and topiramate (chosen in part due to potential cost benefits over other combinations). The study found that all patients achieved at least 8% total body weight loss with topiramate and/or metformin prior to surgery. The patient on combination metformin/topiramate therapy lost more weight than patients on topiramate alone.[25] Another placebo-controlled study of topiramate 96mg and 192mg per day added to metformin monotherapy in patients with type 2 diabetes lost 4.5% and 6.5%, respectively of their baseline body weight as compared to the placebo group that lost only 1.7% over a 24 week period.[29] Though little randomized controlled trial data exists, case studies and retrospective cohort studies of patients utilizing topiramate, phentermine, and/or metformin have found significant weight loss. One small retrospective study looking at these three medications vs surgery alone found that patients on weight loss medications had greater post bariatric surgical weight loss than those not on medications.[27] In summary, in addition to commercially available combinations of naltrexone/bupropion and phentermine/topiramate, there may be increased benefit with the addition of metformin or with combinations of these active ingredients beyond just the available double ingredient combinations. Further comparative data on safety and efficacy is needed.

Some studies have also evaluated the utility of medications traditionally used for type 2 diabetes in nondiabetic patients who are overweight or obese. Recently, sodium-glucose co-transporter 2 (SGLT2) inhibitors have been of interest for weight loss. Unlike many GLP-1 receptor agonist medications, these medications are commonly used orally. Their mechanism of action of increasing secretion of glucose in the urine can lead to significant caloric reduction. The impact of this effect, however, may be reduced by compensatory appetite increase. The addition of appetite suppressant drugs to SGLT2 inhibitors may result in a synergistic effect for weight loss.[36] One recent trial tested this theory and evaluated combination empagliflozin (an (SGLT2) inhibitor) 10mg and topiramate 25mg once daily for one week before escalating to empagliflozin 10mg once daily and topiramate 25mg twice daily starting at week 2 in patients who were overweight or obese in combination with a calorie restricted diet. Patients in the treatment group saw significantly increased weight loss at week 12 compared to the placebo group (− 8.92 ± 1.80 vs. − 4.93 ± 1.17kg).[36] Phentermine in combination with canagliflozin has also been evaluated for weight loss. One trial evaluated placebo vs canagliflozin 300mg vs phentermine 15mg, vs combination phentermine/canagliflozin in

obese and overweight patients without diabetes. The study found a statistically significant number of patients achieved weight loss with combination treatment as compared to placebo and more patients saw significant weight loss in the combination group as compared to treatment with either phentermine or canagliflozin alone. Combination therapy was well tolerated, though patients taking canagliflozin or combination canagliflozin/phentermine did note increased number of urinary tract infections (UTIs) compared to placebo.[37] Investigational SGLT2 drugs (such as DWP16001 a.k.a. enavogliflozin) are also being studied in combination with phentermine. A randomized, open-label crossover study of this investigational SGLT2 drug in combination with phentermine 37.5mg for a short 7-day period saw a trend to greater weight loss in the combination therapy group even over this limited duration.[54]

In addition to combinations of commercially available options, studies on alternative options such as oxytocin nasal spray are also under evaluation. Oxytocin is a hormone naturally found in the body. Oxytocin is thought to result in weight loss via reducing food intake, increasing energy expenditure, and inducing lipolysis.[30] High quality data on nasal oxytocin is conflicting. One double-blind, placebo-controlled crossover study evaluated 24IU of oxytocin delivered nasally prior to an offer of snacks. Participants who had recently been given oxytocin ate significantly less sweet and salty snacks as compared to placebo.[31] Another placebo-controlled study of oxytocin 24IU intranasal dose four times daily (once approximately 20 minutes before each meal and again before bed) found significant weight loss in patients at 4-week (average of 4.6±3.2kg weight loss) and 8-week (average of 8.9±5.4kg weight loss) time points. Researchers noted that the impact was larger in obese patients.[32] A follow up randomized double-blind placebo-controlled trial had patients use intranasal 24IU oxytocin or placebo four times daily for 8 weeks and did not note significant benefit between groups in terms of weight loss over this 8 week period, however, they did note that intranasal oxytocin was associated with reduced caloric intake at the test meal (an average of 152kcal difference) so a longer term study may note a statistically significant weight loss. Additionally, the study protocol did not specify that oxytocin should be taken immediately prior to a meal whereas the study that did note benefit had subjects use the product immediately before a meal. It is possible that oxytocin immediately before a meal may result in a more significant weight loss effect than simply taking it four times a day given oxytocin's short half-life.[33,34] Another evaluated oxytocin 16-24IU three times daily at mealtimes over an 8-week period in pediatric patients and young adults (age range 13.3-20.6 years) with hypothalamic obesity. Within an 8-week period they observed a minor change (-0.6kg) in the treatment group as compared to placebo and treatment was well tolerated. A longer trial or one with a set 24IU dose may observe a more significant benefit.[35] It should also be noted that weight loss studies typically last longer than 8 weeks and that the studies on GLP-1 receptor agonists for example spanned 56-72 weeks. The STEP 5 trial on semaglutide saw only minor benefits over placebo by the 8-week timepoint (approximately 2kg of placebo adjusted weight loss) so studies evaluating oxytocin over a longer study period may be beneficial.[55]

Methionine, inositol, and choline combination injectable products, sometimes combined with other vitamins such as B12, are purported to promote weight loss as well. These "lipotropic" injectable products are intended to facilitate increased fat burning and decreased lipid synthesis.[41,42] These injections are typically given once to twice weekly over a period of months to assist with weight loss. Though such injectable products are fairly common, little data exists on their safety and efficacy. B vitamins in general are also sometimes used as a weight loss option, but again data here is limited. One study found that vitamin b1, b2, b6, and b9 levels were inversely correlated with obesity, however this correlation does not prove that supplementation of these vitamins will result in weight loss.[43] One prospective study of young adults in the US found that serum concentrations of folate, vitamin b6, and vitamin

b12 were inversely associated with metabolic syndrome. Data suggests that low levels of B vitamins may be associated with adiposity, glucose intolerance, and insulin resistance among other negative factors.[44] Low levels of other vitamins, such as vitamin D has similarly been associated with insulin resistance, metabolic syndrome, and obesity among other chronic diseases.[45] Though correlational data is intriguing, further studies are needed to determine if supplementation of these vitamins can lead to significant weight loss.[44] Another active ingredient sometimes added to combination lipotropic injection products is L-carnitine. L-carnitine may contribute to weight loss given its role in transporting long-chain fatty acids allowing for the breakdown of fat reserves and the regulation of protein balance in muscle. Limited data suggests l-carnitine supplementation may provide a modest effect on reduction of body weight, BMI, and fat mass, though, most studies evaluate oral l-carnitine at high doses of 2000mg per day rather than an injectable product.[46] One meta-analysis of randomized controlled trials found a non-linear but modestly positive impact of l-carnitine supplementation on weight loss, this effect was only noted in overweight or obese subjects.[47] Taurine is sometimes also added to these injectable products. Data from animal trials suggests that taurine supplementation may contribute to weight loss via inhibition of adipogenesis in fat tissues.[48] Limited available information on combination vitamin injectable products sometimes report patients injecting once weekly for a period of time before decreasing to once monthly or every other week dosing, but protocols differ and scientific studies on dosing protocols for injectable vitamin combinations are not currently available. The specific utility of these vitamins in combination injectable products for weight loss has yet to be evaluated in high quality studies.

Some studies have also evaluated branched chain amino acid (BCAA, this includes valine, leucine, and isoleucine) supplementation for weight loss. Data for the use of BCAA and its impact on weight and measures implicated in weight loss such as satiety are mixed. One study evaluated BCAA supplementation in overweight and obese adults in combination with a hypocaloric diet. The study found that patients in the BCAA supplementation group experienced an increase in postprandial fat oxidation.[49] Further data is needed to establish appropriate dosing and verify the benefits of BCAA supplementation.

Lipolysis:

In addition to systemic weight loss therapy, options exist for local lipolysis for management of subcutaneous fat as well. These options are sometimes utilized in patients with specific areas, especially around the jawline where local fat destruction is desired. One common combination for induction of lipolysis is phosphatidylcholine and deoxycholate combinations. Deoxycholic acid is commercially available on its own as an injectable FDA approved product for the improvement of appearance of moderate to severe submental fat. Despite how common combinations of phosphatidylcholine and deoxycholic acid are, controversy exists around the mechanism of action of phosphatidylcholine and whether or not it offers additional utility compared to deoxycholic acid alone.[38] A review of various trials suggests that deoxycholic acid acts as a detergent to induce necrosis while phosphatidylcholine works via induction of tumor necrosis factor alpha release resulting in apoptosis and lipolysis. Some studies suggest that a combination of deoxycholic acid and phosphatidyl choline could have a synergistic effect while others suggest limited or no benefit with the addition of phosphatidylcholine to deoxycholic acid.[38] Though the additive benefits may be unclear, a phase 1 clinical trial on soybean derived phosphatidylcholine alone for management of submental fat has evaluated phosphatidylcholine at 250mg and 500mg doses vs placebo. This study used a 25 and 50mg/mL phosphatidylcholine injectable product and concluded that doses of up to 500mg (given in a series of small volume injections) appear to be safe.[39] Follow-up studies on this product to evaluate efficacy for reduction of submental fat in the chin area are currently recruiting.[40] Though lipolysis treatments are

mainly injectable products, limited data has evaluated topical aminophylline and/or caffeine for local fat reduction as well. One systematic review of topical aminophylline concluded that 0.5% aminophylline applied 5 times weekly for 5 weeks is a helpful alternative to injections or liposuction for localized fat reduction.[50] Authors of the review propose that xanthene drugs such as aminophylline may cause localized fat reduction via stimulation of cyclic adenosine monophosphate (cAMP) in fat cells resulting in lipolysis.[50] One of the studies evaluated in this review was a double-blind, placebo-controlled study of 3.93mL of a combination product containing approximately aminophylline 1%, caffeine 5%, vitamin E 1%, glycolic acid 1%, yohimbe 1.9%, L-carnitine 1%, and gotu-kola 1% applied twice daily for 28 days and the impact on reducing thigh circumference, thigh skinfold thickness, and thigh fat mass. The combination product reduced all these measures compared to placebo.[51] Another study evaluating 3.5% caffeine in combination with an undisclosed concentration of xanthenes found that twice daily application to the upper arms and thighs for 6 weeks decreased thigh and arm circumference. Patients reported some itching and transient flushing, but overall, the therapy was well tolerated.[57]

Choosing a Therapy/Combination Therapy:

Given the wide variety of options, choosing a therapy can be a challenge. Factors that influence which therapy may be best for a patient include patient characteristics (such as age or comorbidities), adverse effects, route of administration, any contraindications, and cost of therapy. Studies consistently demonstrate GLP-1 agonist medications, especially tirzepatide, to be most effective for weight loss. Weight loss trials have shown weight loss with phentermine (7.5-15mg)/topiramate (46-92mg) to be 10.9% at 56 weeks compared to 14.9% after 68 weeks of semaglutide 2.4mg and 20.9% after 72 weeks with tirzepatide 15mg.[59] However, given studies show that weight tends to rebound upon discontinuation the high cost of these medications for long term weight loss can be prohibitive. In the United States, economic evaluations of pharmacotherapy for weight loss in terms of cost and quality of life adjusted years suggest that oral treatments such as phentermine may be superior compared to semaglutide by these measures.[52] Additionally, though further long term data is needed, oral SGLT2 combinations represent a potentially highly effective oral option for weight loss, as one study of topiramate and empagliflozin combination therapy saw an 8.8% change in body weight over just 12 weeks of treatment.[36]

Contraindications must also be considered. For example, phentermine/topiramate combination treatment is contraindicated in patients with glaucoma or hyperthyroidism and tirzepatide and semaglutide are contraindicated in those with or with a family history of medullary thyroid carcinoma. Naltrexone/bupropion combinations must not be used in patients on opioids or those with uncontrolled hypertension.[53] Adverse effects can also result in a therapy not being suitable for a patient. For example, GLP-1 medications are associated with nausea, vomiting, abdominal pain, and diarrhea whereas naltrexone/bupropion combinations can cause sleep disorders as well as gastrointestinal effects. Phentermine/topiramate combinations can cause elevated heart rate, paresthesia, as well as mood or sleep disorders.[53,60] Further expanding these combinations to include additional medications may increase weight loss but may also worsen or increase the risk of certain adverse events.

Multiple studies suggest that combination weight loss therapy, which can take advantage of multiple and potentially synergistic mechanisms of action, may be more beneficial than monotherapy. Some commercially available combinations such as phentermine/topiramate or naltrexone/bupropion already exist and have demonstrated efficacy over their respective monotherapies, but data is emerging on other combinations as well that add additional APIs such as metformin to these therapies. Studies on SGLT2 inhibitor medications have found increased weight loss when combined with topiramate or phentermine over monotherapy. Combination therapy

can allow for synergistic impact on weight loss for those who do not note benefit with commercially available products or monotherapies.

Patients more concerned with fat in specific locations, such as submental fat deposits or the appearance of cellulite in specific areas such as the thighs may benefit from local injectable or topical lipolysis therapy to minimize systemic adverse effects that may be associated with other general weight loss therapies. For a summary of some common weight loss therapies, head to www.fagronacademy.us and check out *Active Ingredient Summary Table: Weight Loss* in our resources section!

Formula ID	Formula Name
FA-23229	Phentermine 3.75 mg - Topiramate 48 mg - Metformin HCl 250 mg Altered Release Capsules (#0)
FA-23205	Phentermine 15 mg - Topiramate 96 mg - Metformin HCl 250 mg Altered Release Capsules (#0)
FA-21176	Topiramate 20 mg - Bupropion HCl 65 mg - Naltrexone HCl 8 mg - 5-Methyltetrahydrofolate Calcium 5 mg Capsules (#1)
FA-23998	Bupropion HCl 65mg - Phentermine 7.5 mg - Topiramate 15 mg - Naltrexone HCl 8mg - Methylcobalamin 1mg Altered Release Capsules (#1)
FA-23999	Bupropion HCl 65mg - Phentermine 3.75 mg - Topiramate 15 mg - Naltrexone HCl 8mg - Methylcobalamin 1mg Altered Release Capsules (#1)
FA-23206	Oxytocin 40 U/mL Lingual Spray
FA-23197	Oxytocin 60 IU/mL (6 IU/0.1 mL) Nasal Spray Solution
FA-23996	Aminophylline 1% - Caffeine 5% - Vitamin E 1% - Glycolic Acid 1% - L-Carnitine 1% Cream (Versatile)
FA-22793	Aminophylline 3% - Caffeine 3.5% Cream (Versatile™)
FA-23518	Methionine 25mg - Inositol 50mg - Choline Chloride 50mg - Methylcobalamin 1mg/mL Sterile Solution for Injection
FA-23547	Methionine 25mg - Inositol 50mg - Choline Chloride 50mg - Pyridoxine HCl 2mg/mL Sterile Solution for Injection
FA-23521	Phosphatidylcholine 5% - Deoxycholic Acid 2% Sterile Solution for Injection

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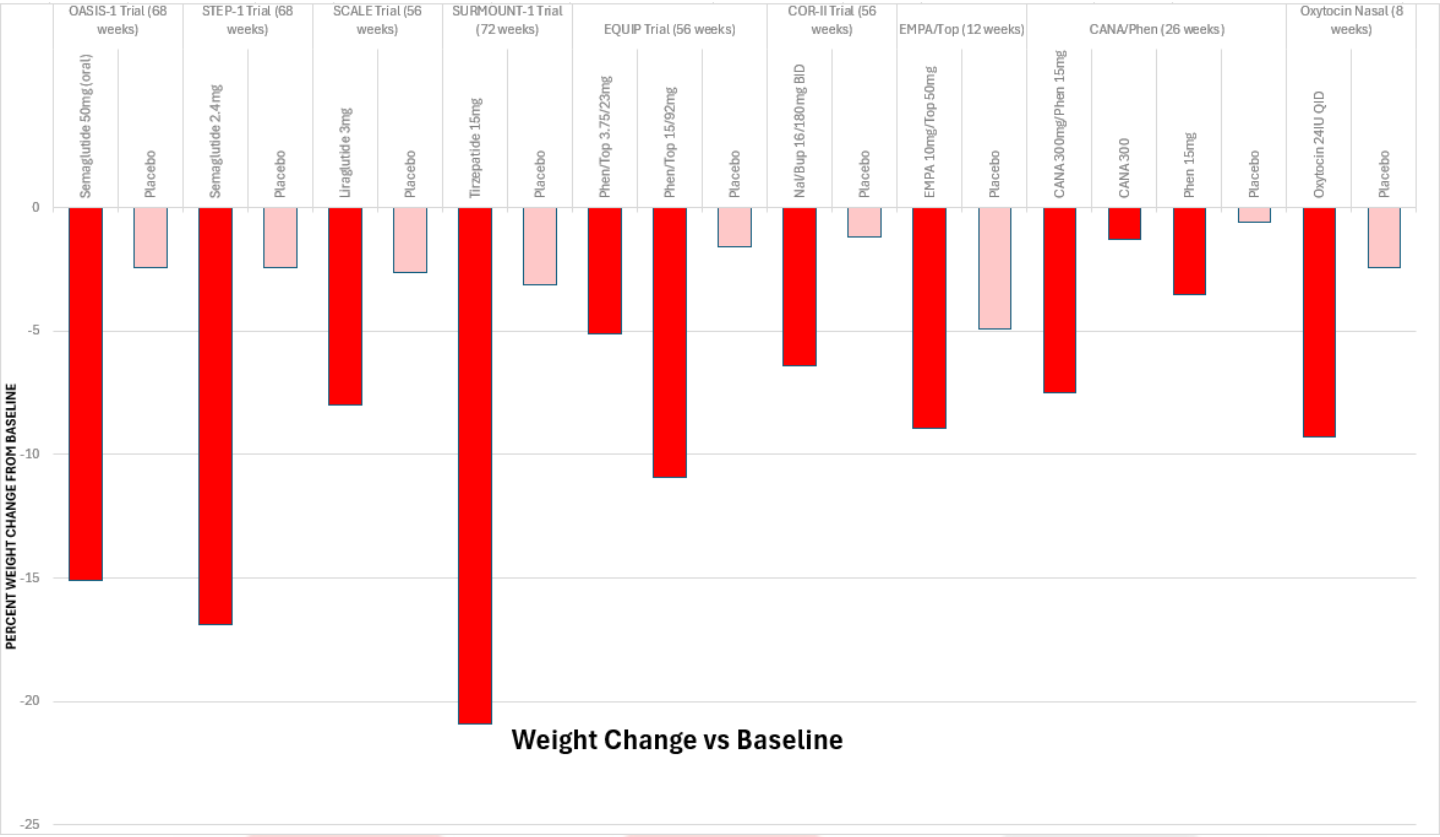

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