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Obesity has a major impact on patient health and other disease states. The National Institute of Diabetes and Digestive and Kidney Diseases estimates that nearly 1 in 3 adults in the US may be classified as overweight, and 2 in 5 adults have obesity.[1,2] However, significant weight loss has the potential to produce overall mortality benefits. Even 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]

Fortunately, for patients who fail to achieve weight loss goals (at least 5% of total body weight in 3-6 months), pharmacotherapy (in conjunction with lifestyle changes) can make a key difference.[5]

Glucagon-Like Peptide-1 Receptor Agonist Medications

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.

Mechanism of Action

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.[4]

Impact on Weight

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]

Pros and Cons

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] Though highly efficacious, GLP-1 medications tend to be very expensive, which can be an issue for long term maintenance of weight loss. Evidence suggests that weight loss may be more significant in patients without diabetes. Those with diabetes may need additional intervention to achieve weight loss goals.

Commercially Available Oral Options

Commercially available pharmacotherapy options for weight loss include Contrave (Naltrexone/Bupropion extended release), and Qysmia (Phentermine/Topiramate extended release).

Bupropion and Naltrexone, Mechanism of Action

Both naltrexone and bupropion have shown some limited weight loss in patients as solo agents. Contrave takes advantage of their synergistic effect. Bupropion stimulates pro-opiomelanocortin cells (POMC) to produce an anorexic effect, and when paired with naltrexone HCl, inhibits a negative feedback loop that may reduce efficacy of bupropion. This results in increased weight loss compared to monotherapy with either active pharmaceutical ingredient (API).[12,13] Naltrexone alone may result in weight loss due to its opioid blockade resulting in a decreased feeling of reward associated with food.[14,15]

Phentermine and Topiramate, Mechanism of Action

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.[16,17]

Impact on Weight

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.[21]

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.[21]

Pros and Cons

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.[18,19] Similarly, studies on naltrexone/bupropion combination therapy have demonstrated reduced food intake vs therapy with bupropion or naltrexone alone, though adverse effects like nausea may be more significant with combination therapy.[20] Phentermine/topiramate combinations may be more effective in patients without type 2 diabetes.[21]

Sodium-glucose co-transporter 2 (SGLT2) inhibitors in combination

Mechanism of Action

SGLT2 inhibitors increase secretion of glucose in the urine, which 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.[28]

Impact on Weight Loss

One recent trial tested this theory and evaluated patients who were overweight or obese in combination with a calorie restricted diet. The trial tested a 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. 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).[28] 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. Additionally, more patients saw significant weight loss in the combination group as compared to treatment with either phentermine or canagliflozin alone.

Pros and Cons

SGLT-2s offer an alternative to GLP-1 receptor agonists that may be used orally and may be more affordable for long term use for patients. Long term data is needed to determine the efficacy of these combinations compared to GLP-1 receptor agonists. Combination therapy was well tolerated in these small studies, though patients taking canagliflozin or combination canagliflozin/phentermine did note increased number of urinary tract infections (UTIs) compared to placebo.[29]

Oxytocin

Mechanism of Action

Oxytocin is thought to result in weight loss via reducing food intake, increasing energy expenditure, and inducing lipolysis.[22]

Impact on Weight Loss

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.[23] 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.[24] A follow up randomized double-blind placebo-controlled trial had patients use intranasal 24IU oxytocin or placebo four times daily for 8 weeks. The researchers did not note significant benefits 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). 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. However, 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.[25,26]

Pros and Cons

Though well tolerated, trials report an inconsistent impact of oxytocin on weight loss. 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. Studies evaluating oxytocin over a longer study period may be beneficial.

Choosing a Therapy

Determining which therapy may be best for a patient includes consideration of 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.

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, indicating a need for lower cost options. 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 8.92% change in body weight over just 12 weeks of treatment.[28]

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.[21]

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 as well as mood or sleep disorders.[21] Further expanding these combinations to include additional medications may increase weight loss but may also worsen or increase the risk of certain adverse events.

For a more in-depth review of pharmacotherapy for weight loss, a list of related formulas, plus resources such as API comparison tables, head to fagronacademy.us and check out our resources section!

For further information or questions, please feel free to reach out to us by heading to www.fagronacademy.us!

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