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A Clinical Review of Adult Obesity and Weight Management in the United States

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Purpose Statement

Obesity is a global public health epidemic causally associated with an increased risk for developing a multitude of comorbidities. Pharmacotherapy is an option for individuals who are unable to achieve weight loss with lifestyle and dietary modifications alone. This clinical review will summarize the current standard of care for obesity management and review the newest options for drug therapy, recently approved by the United States Food and Drug Administration (FDA) for weight loss management in the United States.

Abstract

The standard of care for obesity has been lifestyle modifications, dietary changes and the use of some anti-obesity medications, however, given the increased rate of growth of obesity in not only the United States but globally, new drug therapies are needed. This paper aims to summarize and compare the current safety and efficacy evidence of new United States Food and Drug Administration (FDA) approved weight loss drugs and to discuss the availability, cost-effectiveness, and use of these drugs in combating the obesity epidemic.

Web of Science and PubMed searches of obesity revealed primary sources and review articles on the topic of obesity and weight management. The Web of Science database was queried with keywords such as “obesity,” “weight management,” “Liraglutide,” “Semaglutide” and “Tirzepatide” and the results were narrowed by indicating 2020 - present. Other articles were gathered using referenced articles from chosen review articles, and from UpToDate, inc. referenced sources.

Multiple review articles, randomized clinical trials, cohorts and the FDA drug databases were used to gather safety and efficacy data regarding these novel anti-obesity medications as well as supporting data towards the benefits of the addition of these anti-obesity medications with lifestyle and dietary modifications.

There are several new drugs when it comes to novel anti-obesity medications, with several showing great promise in phase III clinical trials. All these novel anti-obesity medications have shown to be safe and effective in significant weight loss in clinical trials. These novel anti-obesity medications are still lacking availability and are not cost-effective in the United States, making the widespread use of these drugs currently unrealistic.

Introduction

By 2030, it is estimated that close to 50% of the U.S. will be classified as obese based on Body Mass Index (BMI).[1] BMI can be further broken down into class I obesity - BMI 30-34.9; class II obesity - BMI 35-39.9 and class III obesity - BMI ≥ 40.[2] Obesity is associated with many weight related complications, comorbidities and significant disease progression such as prediabetes, type 2 diabetes (T2D), hypertension, cardiovascular disease, osteoarthritis, obstructive sleep apnea, cancer, irritable bowel disease, asthma, depression and more.[3] According to the 2011-2014 National Health and Nutrition Examination Survey, more than ⅓ of the U.S. population were classified as obese, with a BMI > 30 kg/m².[3] Even more concerning is the fact that childhood obesity is on the rise with 19.3% of children in the U.S. classified as obese.[4] Additional factors precipitated by the COVID-19 pandemic, meaning "work from home", "social distancing" and "virtual school" have only exacerbated obesity.[4] Obesity is not just an issue in the U.S., this is a global public health epidemic with 13% of adults globally considered obese based on BMI according to the World Health Organization (WHO).[5] According to the 2023 World Obesity Atlas, it is expected that the obese adult population will be 58% in the United States alone and 4 billion people worldwide (>50% of the world's population) by the year 2035.[6] This clinical review aims to understand the standard of care of obesity in the United States and to highlight the importance of pharmacotherapy use combined with lifestyle in sustainable weight management. Within the past few years, new drugs have been FDA-approved for weight loss and obesity in the United States with the potential for changing the trajectory of this obesity epidemic; these new drug options will be reviewed in depth. Lastly, the cost-effectiveness of these new drug options will be reviewed.

Standard of Care Background:

Guidelines developed for the management of obesity have remained relatively constant, in that lifestyle modifications and dietary changes are the first-line therapeutic recommendations.[2] Obesity is diagnosed by BMI and clinical assessment, in which a patient is screened for comorbidities or weight-related complications mentioned above.[2] Each individual will have different treatment and target plans based on the assessment, genetics, lifestyles, etc. so no one treatment fits all.[2]

It is recommended that there is a strong patient-provider relationship, regular check-ins and open communication while starting and during treatment.[2] The first line recommendation is to decrease caloric intake, to begin aerobic exercise and strength training, reduce sedentary time and behavioral therapies to keep themselves on track and accountable.[2] Behavioral therapies recommended include but are not limited to, social support groups or cognitive behavioral therapy (CBT).[2] The recommended amount of restriction and increased physical activity is to be tailored to the individual.[2] The recommended amount of weight loss is 2.5% within 1 month or 5%-10% over 6 months, with early weight loss a prime indicator for sustained weight loss long term.[2]

Lifestyle and dietary therapies have been the primary recommended therapeutic intervention for weight loss, however, most individuals do not benefit substantially from these methods alone.[7] Nonetheless, lifestyle and dietary modifications are essential to achieving long-term and sustainable weight loss.[3] Bariatric surgery is an option for adults who have a BMI > or = to 40 kg/m^2 which is considered severe obesity [7] or children with a BMI > 35 kg/m^2 with severe comorbid disease or BMI > 40 kg/m^2 without severe comorbid disease.[4] Although bariatric surgery is safe and effective [4], there are high costs associated with the surgery,

complications associated with the surgery, and follow-up needed which makes this an ineffective choice for many adults and children.[7]

Pharmacotherapy alongside lifestyle modifications are indicated in patients who have class II obesity or for any individual in any class of obesity who fails to continue weight loss with lifestyle modifications alone.[2] There are many drugs indicated for the use in management of weight in those with T2D, however more recently drugs have been FDA-approved for weight loss and obesity and known as anti-obesity medications.[2] This offers individuals at risk for the development of T2D to use pharmacotherapy alongside lifestyle modifications to be proactive. Many of the newly approved drugs have differing contraindications, warnings, adverse event (AE) profiles and dosing schedules, so pharmacotherapy should be individualized.[2]

Pharmacotherapy Then and Now:

Prior to 1975, it was assumed that anti-obesity medications would "cure" obesity so clinical trial data are short-term, with few long-term outcome data.[3] Then, in 1992, approval authority was transferred and drugs were required to show clinical trial data outcomes, and approved for short-term use, up to 3 months only.[7] What we now know is that anti-obesity drugs do not "cure" obesity and often need to be taken on a continuous basis to sustain the weight lost by the individual especially if the individual is not also taking steps to better their lifestyle and dietary choices.[3] Today there are only 4 drugs approved prior to 1992 that are still available today; phentermine (1959), diethylpropion (1959), phendimetrazine (1959) and benzphetamine (1960) with many others being stripped from the market due to long-term adverse events, showing just how important long term safety data is.[7]

In the past few years, drugs with different mechanisms of action compared to older drugs have been in development and FDA-approved specifically for weight management and obesity in the United States, making more options available to individuals struggling with weight management.[3] These new options that will be highlighted in this review are liraglutide (Saxenda), Semaglutide (Wegovy), Setmelanotide (Imcivree) and Tirzepatide (Lilly), however Tirzepatide is still in the pipeline and not yet FDA approved for use in the United States. Having a larger profile of available pharmacotherapy options enables providers to offer drug options that best fit the patient's needs, concomitant medications, lifestyle and past medical history.

Methods/Evidence Acquisition

Web of Science and PubMed searches of obesity revealed primary sources and review articles on the topic of obesity and weight management. The Web of Science database was queried with keywords such as “obesity,” “weight management,” “Liraglutide,” “Semaglutide” and “Tirzepatide” and the results were narrowed by indicating 2020 - present. Other articles were gathered using referenced articles from chosen review articles, and from UpToDate Inc. referenced sources.

Results and Discussion/Evidence Synthesis

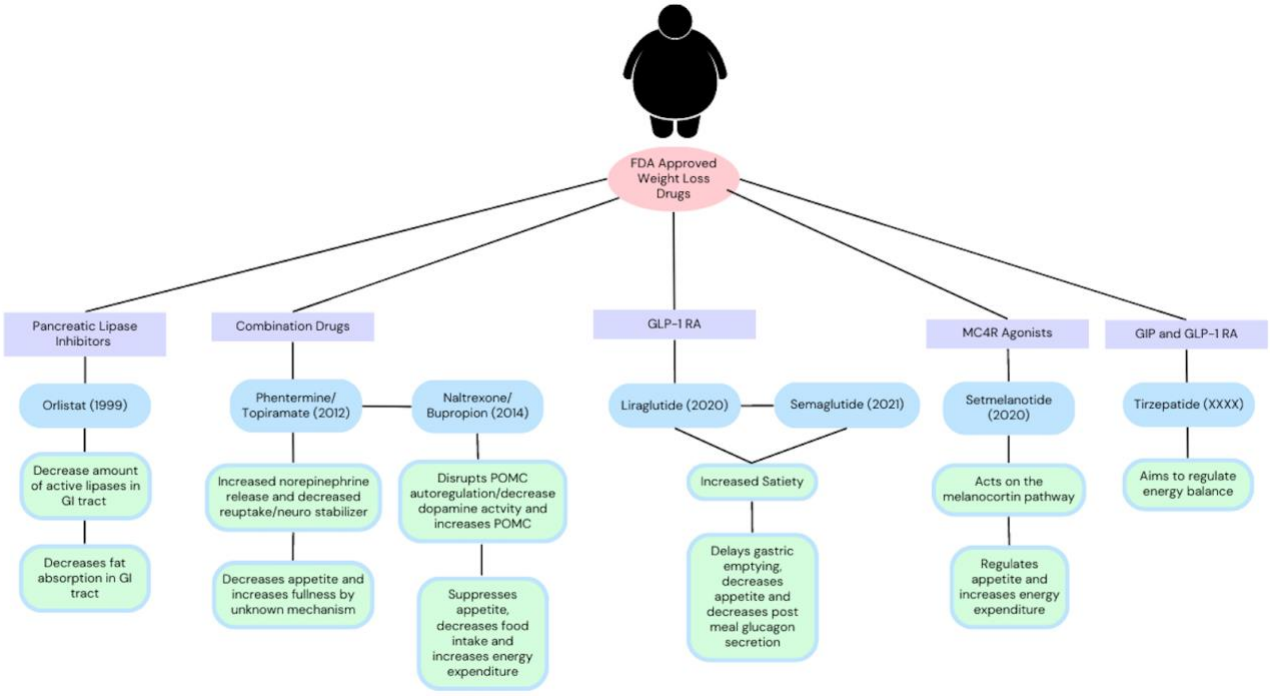

Figure 1: The FDA-approved weight loss drugs and their mechanisms of action.

Mechanism of Action and FDA Approval Year:

Pancreatic Lipase Inhibitors:

Orlistat (1999) is the only lipase inhibitor approved in the U.S. for weight loss and works by altering fat digestion by decreasing the number of active lipases in the gastrointestinal tract.[3]

Serotonin Agonists:

Lorcaserin (2012, Withdrawn 2020) selectively activates 5-HT(2c) which activates proopiomelanocortin (POMC) ultimately suppressing appetite, decreasing food intake and increasing overall satiety.[3]

Combination Drugs:

Phentermine/Topiramate "PHEN/TPM" (2012) is a combination drug in which phentermine is a sympathomimetic which increases the norepinephrine release and inhibiting reuptake and topiramate has an uncertain mechanism of action for weight loss but is a neuro stabilizer (GABA receptor modulator).[3]

Antidepressant/Opioid Antagonist:

Naltrexone/Bupropion (2014) is a combination drug in which naltrexone is an opioid receptor antagonist (μ) and acts by disrupting β-endorphin proopiomelanocortin (POMC) autoregulation and ultimately suppresses appetite. [4] Bupropion is a dopamine and norepinephrine reuptake inhibitor that works to decrease food intake and increase amount of energy used by means of increasing dopamine activity and increasing POMC.[4]

Glucagon-Like Peptides (GLP-1 Receptor Agonists (RA)):

GLP-1 RA's act to increase satiety by utilizing delaying gastric emptying, decreasing appetite and decreasing post meal glucagon secretion.[8] Drugs in this class include **Liraglutide (2020)** and **Semaglutide (2021)**.

MC4R Agonists:

The melanocortin 4 receptor (MC4R) is part of the melanocortin pathway in which when activated acts to regulate appetite and increase energy expenditure.[9] This drug is called **Setmelanotide (2020)** and is highly useful in individuals with severe obesity related to leptin receptor (LEPR) or POMC deficiency.[9]

Dual Glucose-Dependent Insulinotropic Polypeptide (GIP) and GLP-1 Receptor Agonist:

Tirzepatide (XXXX) is a drug that enhances the mechanism of GLP-1 RA by the addition of GIP hormone which aims to regulate energy balance.[10]

Legacy Drugs:

Orlistat:

Orlistat is the oldest and one of the earliest FDA approved weight loss drugs, in which long term safety data is established.[3] However, long term use of this medication is often not tolerated well due to gastrointestinal side effects.[3] Several randomized clinical trials have shown Orlistat to be effective in weight loss when compared to placebo administration or lifestyle modifications alone.[3] The Adverse effects associated with the use of Orlistat include steatorrhea, fecal incontinence, urgent bowel movements and overall GI upset stemming from this drug's mechanism of action.[4] A recent study by Alanazi et al. aimed to understand the efficacy of Orlistat on managing BMI, systolic BP and hyperlipidemia and found that there was significant improvement in lipid profiles but no significant impact on BMI or systolic BP in which lifestyle

modifications would be necessary for achieving these goals.[11] The prescription dosage of Orlistat for adults and children 12+ is 120 mg orally 3 times daily after main meals, and a non-prescription dosage of 60 mg orally 3 times daily after main meals is approved for 18+.[4]

Lorcaserin:

Although Lorcaserin is mentioned above, this medication was actively withdrawn from the market by the FDA after possible risk associated with increased incidence of cancer was noted in the CAMELLIA-TIMI 61 trial, and will not be discussed further in this paper.[12] This risk of cancer will be further studied and followed, with a possibility we could see this drug in the future if no increased risk is found.[12]

Naltrexone/Bupropion:

The Contrave Obesity Research Trial (COR-I) was a large phase III (N =1742) randomized, placebo controlled clinical trial that took place over 56 weeks showing that the average weight loss of a participant assigned to the naltrexone/bupropion (NB) treatment arm had an average body weight decrease of 6% when compared to the placebo arm of 1%.[3] A number of clinical trials have been conducted on this combination therapy, however the LIGHT study was another phase III randomized trial of importance because the study aim was to determine long term cardiovascular outcomes.[5] This study was terminated early and the FDA allowed an interim analysis of the data at 25% and 50% and both failed to show cardiovascular benefit with the use of this drug when compared to placebo.[13] A post-hoc analysis conducted by le Roux et al. evaluated long term weight loss maintenance of NB + lifestyle versus placebo + lifestyle in those who originally lost ≥ 5% of body weight in 16 weeks on that regimen and

overall found that long term weight loss was maintained in the NB group at 208 weeks versus placebo.[5] Overall, naltrexone/bupropion combination drug is a good option for long term maintenance of weight loss in individuals who achieve ≥ 5% of weight loss at 16 weeks.[5] There is still a lack of safety data regarding cardiovascular risk and NB does carry a black box warning of suicidality given the combination medication includes the antidepressant bupropion.[3]

Phenteramine/Topiramate:

Two large 56-week randomized trials by the names of CONQUER and EQUIP found a dose-dependence for weight loss with the use of phentermine/topiramate (PHEN/TPM) combination drug when compared to placebo.[3] The CONQUER study found that daily low dose (7.5-46 mg) of the combination resulted in 7.8% weight loss while the daily high dose (15-92 mg) resulted in 9.8% weight loss which were both substantially higher than the placebo group with 1.2% weight loss.[3] Depression and anxiety were low in incidence as adverse effects (<5%) but occurred more frequently from use of the high dose.[3] An extension study to the CONQUER study, called SEQUEL aimed to evaluate long term safety and efficacy and found that there were reduced rates of adverse events between weeks 56-108 and that long term use reduced the rate of comorbidities and decreased the need for cardiovascular related concomitant medications.[14] Of highlight, "Specifically, 7.5% (n = 17) of subjects in the placebo group experienced a decrease in concomitant antihypertensive medication use compared with 13.1% (n = 20) in the 7.5/46 group and 15.6% (n = 46) in the 15/92 group."[14] Another highlight from the SEQUEL study is that participants in the PHEN/TPM had lower fasting glucose levels and lower fasting insulin levels along with 54% reduction in progression to type-2 diabetes for the low dose group and 76% reduction in progression to type-2 diabetes for the high dose group.[14]

Novel Drugs:

Liraglutide (Saxenda):

Liraglutide is a GLP-1 RA subcutaneous injectable administered to the thigh, arm or abdomen and has received FDA approval as a weight loss medication for 3.0 mg once daily.[4] A 56-week double-blind randomized clinical trial known as SCALE was conducted and results indicated beneficial weight loss with 63% of the treatment group losing 5% body weight, a decrease in systolic blood pressure of 6-9 mmHg and a decrease in the apnea-hypoxia index of participants with OSA.[3] The study also showed an increase in heart rate of the treatment group when compared to placebo as well as adverse effects of nausea and vomiting especially at higher dosages.[3] A population-based cohort study conducted by Leventhal-Perek et al. looked at weight loss of individuals who started Liraglutide 3.0 mg, Orlistat or Lorcaserin between 2018 and 2020, and found clinically significant weight loss associated with the use of Liraglutide 3.0 mg.[15] They also found that use of Liraglutide correlated with a high rate of persistence and progressive weight loss over the course of 9 months, meaning the adverse effects profile is favorable.[15] The effectiveness and tolerability of Liriglutide 3.0 mg was much more stable and favored over Orlistat or Lorcaserin.[15]

Semaglutide (Wegovy):

On the other hand, Semaglutide, similar to Liraglutide, is also a GLP-1 RA that is a subcutaneous injection of 2.4 mg except this is a once-weekly dosing regimen compared to daily dosing like Liraglutide.[16] A double-blind placebo-controlled randomized study of 1961 adults

with BMI > 30 for 68 weeks was conducted by Wilding et al. in which the mean change in body weight from baseline to 68 weeks in treatment versus placebo arms had a p-value <0.0001 with -14.9% in the treatment arm and -2.4% in the placebo arm.[16] Eighty-six percent (86.4%) of participants in the treatment arm achieved ≥ 5% reduction in weight, along with a reported increase in physical function, and an improvement in cardiometabolic risk factors.[16] Adverse effects associated with this trial were relatively similar in both treatment and placebo arms (89.7% and 86.4%) with the most frequently reported adverse effects being GI upset, nausea, vomit, diarrhea and constipation and 7% of the treatment group discontinued the study due to adverse effects.[16] The STEP 8 randomized trial by Rubino et al. compared once daily liraglutide versus once weekly Semaglutide and found that once weekly Semaglutide added to lifestyle modifications had a more significant effect of weight loss after 68 weeks versus once daily liraglutide added to lifestyle modifications.[17] Once weekly subcutaneous injection may be more favorable for individuals versus daily dosing, which may give reason to the fact that in the STEP 8 study, of 67 participants that discontinued altogether, 27.6% were in the Liraglutide arm, 17.6% in the placebo arm and lastly 13.5% in the Semaglutide arm.[17] One major conclusion of this study was that the variability in response between the drugs suggests that tolerability and sensitivity does play a role and that having multiple treatment options can only benefit patients.[17]

Setmelanotide (Imcivree):

Early onset obesity, could be due to POMC deficiency, LEPR (leptin receptor) deficiency, or PCSK1 (proprotein convertase subtilisin/kexin type 1) and often present in childhood as severe early onset obesity and can often be under recognized or underdiagnosed.[4] FDA approval for Setmelanotide is approved for ages 6 and up and has shown to be well

tolerated.[4] Two multicenter open label single armed phase 3 trials for the use of Setmelanotide in individuals with POMC and LEPR deficiency are two of the largest trials to date obtained the safety and efficacy profile for this drug.[8] Weight loss of 10% was observed in 80% of participants in the POMC study and 45% in the LEPR study and the only adverse effects associated with treatment were injection site reactions and hyperpigmentation. Additionally, no cardiovascular events were reported during either study.[8]

Tirzepatide (Mounjaro):

Lastly, the newest weight loss drug Tirzepatide (not yet FDA approved) is a once-weekly subcutaneous injection that was studied at 5 mg, 10 mg, and 15 mg dosages, for 72 weeks and a 20-week dose escalation period in a phase 3 double-blind placebo-controlled trial of 2539 participants.[9] At 72 weeks, all treatment groups had a reduction in weight loss statistically significant ($P<0.0001$) when compared to the placebo groups.[9] The most frequent adverse effects with Tirzepatide were nausea, diarrhea and constipation and occurred most frequently during the dose escalation phase of the study.[9] Overall the study concluded a substantial weight loss in the 10 mg and 15 mg groups (19.5% and 20.9% weight reductions) when compared to placebo (3.1% weight reduction).[9] Lastly, Tirzepatide was found to have a favorable effect on systolic BP, fasting insulin levels, lipid levels and >95% of participants who started the study as prediabetic converted to normoglycemia which shows a reduced risk in cardiometabolic comorbidities.[9]

OBESITY PHARMACOTHERAPY OPTIONS

FDA Approved Treatment for Obese Patients without T2D (2020 and Beyond)

DRUG	INDICATION	DOSING	CONTRAINDICATIONS	MOST COMMON SIDE EFFECTS
LIRAGLUTIDE (2020) **BRAND NAME: SAXENDA**	Indicated for use in overweight or obese individuals to achieve weight loss.	Initial Dose - 0.6mg SQ daily for one week. Dose escalation every week (as tolerated) 1.2, 1.8, 2.4, 3 mg with 3mg recommended highest dose.	Pregnancy, hx of pancreatitis, hx or fam hx of medullary thyroid cancer, MEN 2A/2B. Individuals also taking insulin should have dose reduction and blood glucose monitored.	GI side effects - nausea, vomit and diarrhea. Low blood sugar, anorexia, pancreatitis, gall bladder disease or renal impairment.
SETMELANOTIDE (2020) **BRAND NAME: IMCIVREE**	Indicated for use in adult and pediatric patients 6 years or older for obesity from POMC, LEPR or PCSK1 deficiency (genetic testing confirmation required).	Pediatric Initial dose (6-<12yo) is 1mg SQ daily for 2 weeks and if tolderated increase the dose to 2mg SQ daily. Adult initial dose (12yo +) is 2mg SQ daily for 2 weeks and if tolerated increase dose to 3mg SQ daily.	There are no contraindications, however there are warnings for spontaneous penile erections, depression and suicidal ideation, and skin pigmentation changes.	Injection site reactions, nausea, diarrhea, abdominal pain, back pain, fatigue and vomiting.
SEMAGLUTIDE (2021) **BRAND NAME: WEGOVY**	Indicated for use in overweight or obese individuals to achieve weight loss.	Initial Dose - 0.25mg SQ once weekly for 4 weeks. Dose escalation every 4 weeks (as tolerated) 0.5, 1, 1.7, 2.4 mg, with 2.4mg the recommended highest dose.	Pregnancy, hx of pancreatitis, hx or fam hx of medullary thyroid cancer, MEN 2A/2B. Individuals also taking insulin should have dose reduction and blood glucose monitored.	GI side effects - nausea, vomit, diarrhea, abdominal pain, gas, fatigue, headache and heartburn.
TIRZEPATIDE (XXXX) **BRAND NAME: XXXX**	Waiting on FDA approval	Waiting on FDA approval	Waiting on FDA approval	Waiting on FDA approval

Table 1: Newest (2020 and beyond) FDA approved drugs for weight management and obesity approved for use in the United States. Generic and brand names, indication for use, dosing regimen, contraindications and the most common side effects. Information in the table collected from: Liraglutide[18]; Setmelanotide[19]; Semaglutide[20]; Tirzepatide[21].

Cost-effectiveness:

The backbone of weight loss as previously indicated is lifestyle and dietary modifications. However, long-term weight management is often not covered by health insurance and rigorous modifications over long periods of time by professionals is often necessary (ex. nutritionist, trainer etc.), making it hard for individuals to access or commit to.[7] This indicates a necessary need for pharmacotherapy options that individuals can add to lifestyle and dietary

modifications, while also creating cost-effective and accessible options to patients. This section will compare the cost-effectiveness of the novel weight loss medications discussed.

Levi et al. compared the cost of these different drugs in different countries around the world and was able to calculate the estimated minimum price (EMP) for a 30-day course of the approved and recommended dosages.[22] The price of the drug itself was calculated using a number of databases including pharmacy and insurance prices and used the lowest price they found.[22] Semaglutide, Liraglutide and Tirzepatide are liquid injectables that come in a pre-filled syringe with a needle and packaging, so researchers calculated the EMP for these drugs using price estimates for medications similarly administered such as heparin.[22] Levi et al. found that the highest national price across the board for these injectables were in the United States; Liraglutide: $1418 and EMP $50; Semaglutide: $804 and EMP $40; Tirzepatide: $1100.70 and EMP not available.[22] In conclusion, this study indicates that these drugs are produced and manufactured in other countries at a much lower cost than in the United States.[22] Another factor is that these injectable drugs that have shown impact in clinical trials are highly inaccessible globally and overpriced.[22] One long term key success factor for global and country specific impact will be improving access to these drugs, but also providing them to patients at a reasonable and cost-effective price.[22]

The costs associated with these novel drug therapies could cost upwards of $1000 per month, leaving these not an option for the majority.[23] Some companies have started programs for these drugs, offering them at a low cost (~$25) for the first three months as a sample period, however, many who wish to stay on the drug cannot afford the hefty price per month.[23] Another barrier is that many insurance companies refuse to cover anti-obesity medications because they believe they will be used in the wrong ways, and the insurance companies do not have a clear

understanding of the use.[23] Cost and access to these novel therapies creates a large barrier to the success that these anti-obesity medications have the potential to provide on a global scale.

Conclusion

Overall, all these novel anti-obesity medications have been found to be safe and efficacious for use in overweight and obese individuals. All have slight differences in mechanism of action, weight loss percentage outcomes, adverse effect profiles and dosing but have all shown >5% weight reductions in phase III clinical trials. A 5% or more weight reduction is the standard for continuation on an anti-obesity medication as well as the basis for seeing a meaningful effect.[10] Of the novel anti-obesity medications, Tirzepazide showed the largest percentage of weight loss with 19.5% in the 10mg group and 20.9% in the 15 mg group which is substantially larger than the standard of 5% weight reduction.[10] Nonetheless, treatment with the addition of an anti-obesity medication should be individualized, taking into consideration the patient's life as a whole, and no one treatment will "fit all". Taking into consideration dosing schedules, the most favorable among patients is the once-weekly injectables; Semaglutide and Tirzepatide.[10],[17] When combined with diet and exercise regimens, these novel anti-obesity medications have the potential to aid in sustainable weight loss.[2] One of the major unknowns with these new drug mechanisms is whether they will or will not need lifelong treatments, in which future research is needed. Lastly, the largest barriers for the use of these anti-obesity medications in the United States is access to and cost. These anti-obesity medications could have all the potential in the world to help in the United States alone, but also on a global scale, but if individuals are unable to afford or access these drugs, we will never see their potential to impact. The current cost is upwards of $1000 a month for these injectable anti-obesity medications with the potential estimated minimum cost calculated to be <$100 per month.[22] There are programs currently available in which patients could receive "sample" use of these drugs at a low cost for 3 months, however if they do see substantial benefit, they will either have to pay the high cost per month,

or stop altogether.[22] One of the problems with cost not explored in this paper is the fact that insurance companies do not see obesity as a disease, so they do not cover many of these anti-obesity medications on plans. These novel anti-obesity medications work on biological mechanisms supporting the fact that obesity is in fact a biologic disease.[23] Because there is no "one fit" for drug therapy, having a diverse range of available anti-obesity medications aids in the diversity of individuals, and these novel anti-obesity medications may just be the beginning.

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