Obesity and Weight Loss with Endocrinologist Rocio Salas-Whalen

David Puder, M.D., Rocio Salas-Whalen, M.D.

David Puder, M.D and Rocio Salas-Whalen, M.D. have no conflicts of interest to report.

In today's episode of the podcast, I interview Dr. Rocio Salas-Whalen, owner of New York Endocrinology on Park Avenue. Dr. Salas-Whalen has deep expertise in diabetes, metabolism, obesity, thyroid abnormalities and other endocrine disorders. She completed her internal medicine residency at Albert Einstein College of Medicine and her endocrinology fellowship at the University of Maryland School of Medicine in Baltimore. Additionally, she was a research fellow at Johns Hopkins University School of Medicine and is board certified in Obesity Medicine.

We will be discussing obesity and weight loss. The definition of obesity has changed significantly in the last few years. In 1942, WHO classified obesity as a chronic disease. In 2013, the American Medical Association accepted it as a chronic metabolic and multifactorial disease.

COVID and obesity

COVID brought to light, in multiple studies, that patients with high BMI had higher admissions to the ICU, had more severe effects from COVID, higher mortality, and higher need of mechanical ventilation.

Many studies were initially done in Europe and Asia, where obesity is not as prevalent as it is in America. After COVID came to the U.S., an NYU study showed a correlation between BMI and patient admittance into the ICU. Now, looking back at European cases, even though obesity levels are not as high, a correlation can be seen between more adverse effects to COVID and a higher BMI or obesity. The reason for this correlation is that obesity is chronic inflammation, which forces the immune system to be preoccupied with the chronic inflammation and there is not enough immunity to fight the virus.

Obesity and mental health

Obesity has a profound effect on mental health. The need for the individual to focus on food and weight starts at an early age. By the time they reach adulthood, most of their life's mental energy has been consumed by their weight and how food will affect their weight. It is deeply taxing and is an emotional, deeply personal journey for patients. The idea that these patients are lazy, could do better if they wanted, or that they have obesity due to their lifestyle is not the case. Patients, by adulthood, will have gone through varying combinations of weight loss camps, nutritionists, physical trainers, and multiple diets throughout their lifetime, many times truly having done the work and still having obesity.

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Having done all the work, knowing that it is not for lack of trying that they are not losing weight, can actually bring relief because it validates they are putting forth the effort and are not lazy. By having this pressure and guilt relieved, patients are more able to open their minds to other treatments.

Family history

When evaluating a patient seeking treatment for obesity, it is important to ask the right questions and obtain a detailed family history in order to capture the entire picture.

1. Family history: Plays a major role in obesity. Gather information from as far back as possible (At what age do they remember recognizing they had to think about food and weight?). Finding where the obesity genes come from can be helpful (Dr. Salas stated 98% of her cases can be traced to family history). There is a very strong familial link.
2. For females, ask about menstrual history, fertility and PCOS symptoms. For males, erectile dysfunction could be related to obesity.
3. Lifestyle/Environmental: Exercise, eating habits, relationship with food, sleeping habits, traveling a lot for job. Sleeping habits are very important. Majority of patients don't have proper sleep, which is an environmental factor that could cause obesity. Many patients also have sleep apnea, which raises cortisol, leading to weight gain and possibly obesity.
4. Medication: There are multiple medications that cause weight gain. Antidepressants, beta blockers, steroids. Diving deep into their medical history can help find additional causes for obesity.

Fault with BMI

BMI has limitations when it comes to determining the ratios of muscle mass to fat mass. Sometimes seeing a normal BMI has to do with a higher fat mass and lower muscle mass, which isn't healthy. Using MRIs, bone density/dexa scans, or impedance machines can differentiate between fat, water, and muscle, find visceral fat and make calculations that give a better picture than the BMI scale.

Obesity and metabolic function

The concept of metabolic health is for the ratio of your skeletal muscle mass to be higher than your body fat mass and for your visceral fat to be low. Diagnostic metabolic values include insulin resistance, A1C, blood pressure, and cholesterol.

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Most of Dr. Salas-Whalen patients exercise in some capacity but it is important to guide them towards the right exercise, especially on weight loss treatment. There's going to be caloric restriction and muscle loss, so guiding the patient to exercises that will result in the least amount of muscle loss in the weight loss phase is important.

Studies show that when muscle mass drops, percentage body fat goes up. Muscle loss could be due to aging, severe caloric restriction or low protein intake. Likewise, when muscle percentage goes up, body fat percentage goes down. Anytime there's muscle gain there is automatically fat percentage loss even without medication. Guiding patients to gain muscle will build what was lost and gaining muscle will be part of the maintenance of body fat percentage.

Determining Treatment

There are a few FDA-approved medications available for weight loss:

- GLP-1 Wegovy (semaglutide) (weekly injection)
- GLP-1 Saxenda (liraglutide) (daily injection)
- GLP-1 & GIP, Mounjaro (tirzepatide) (weekly injection) (only FDA approved for diabetes)
- Qsymia (a combination of phentermine/topiramate)

Orlistat, which is one of the oldest medications approved, but its side effects can cause diarrhea/soiling and it doesn't produce the weight loss that we see in newer medications. A significant difference in weight loss is seen from weekly shots rather than daily shots.

While bariatric surgery is a treatment option, a downside is that, mechanically, it shuts down the ability to overeat but does not shut down the psychiatry emotional feedback which often leads to eventual weight gain. Whereas, the use of the GLP-1 and GIP agonists work in your brain, as well as mechanically.

Mounjaro (tirzepatide)

Tirzepatide, which came out this year, is the first combination drug, having GLP-1 and GIP. All the other versions were only GLP-1.

A study of tirzepatide by Jastreboff et al., followed 2539 participants who were given either 5 mg, 10 mg, or 15 mg of tirzepatide. At baseline, the mean body weight was 104.8 kg, the mean BMI was 38.0, and 94.5% of participants had a BMI of 30 or higher. The mean percentage change in weight at week 72 was −15.0% (95% confidence interval [CI], −15.9 to −14.2) with 5-mg weekly doses of tirzepatide, −19.5% (95% CI, −20.4 to −18.5) with 10-mg doses, and −20.9% (95% CI, −21.8 to −19.9). After one year, participants experienced an average change in waist circumference of 7.28 inches in the 15 mg group and -4.8 decrease in diastolic blood pressure.

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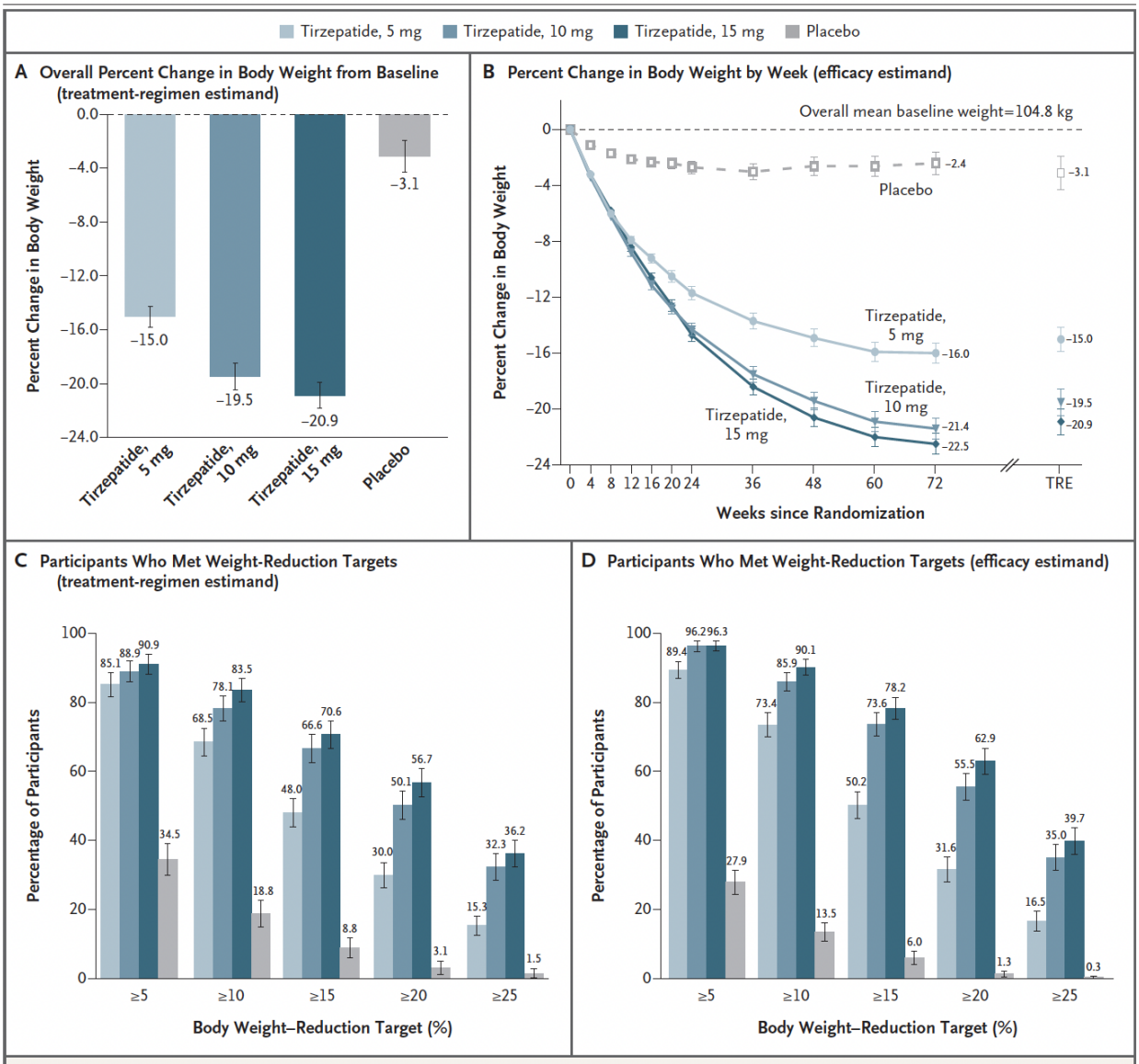

Figure 1. Effect of Once-Weekly Tirzepatide, as Compared with Placebo, on Body Weight.

Least-squares means are presented, unless otherwise noted. Panel A shows the percent change in body weight from baseline to week 72, derived from an analysis of covariance model for the treatment-regimen estimand (TRE). Panel B shows the percent change in body weight according to weeks since randomization, derived from a mixed model for repeated measures (MMRM) analysis for the efficacy estimand; week 72 estimates for the treatment-regimen estimand are also shown. Panels C and D show the percentages of participants who had weight reductions of at least 5%, 10%, 15%, 20%, and 25% from baseline to week 72. For Panel C, the percentage was calculated with the use of Rubin's rules by combining the percentages of participants who met the target in imputed data sets. Missing values at week 72 were imputed with MMRM if the missingness was due solely to Covid-19 and with multiple imputation if the missingness was not due to Covid-19. For Panel D, the percentage of participants who met weight-reduction targets was obtained by dividing the number of participants reaching respective goals at week 72 by the number of participants with a baseline value and at least one nonmissing postbaseline value. Missing values at week 72 were imputed from MMRM analysis. I bars indicate 95% confidence intervals.

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Table 4. Adverse Events and Safety.

Variable	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)
	number (percent)			
Participants with ≥1 adverse event during treatment period	510 (81.0)	520 (81.8)	497 (78.9)	463 (72.0)
Serious adverse events	40 (6.3)	44 (6.9)	32 (5.1)	44 (6.8)
Death*	4 (0.6)	2 (0.3)	1 (0.2)	4 (0.6)
Adverse events leading to discontinuation of trial drug or placebo†	27 (4.3)	45 (7.1)	39 (6.2)	17 (2.6)
Nausea	6 (1.0)	7 (1.1)	12 (1.9)	2 (0.3)
Diarrhea	2 (0.3)	5 (0.8)	3 (0.5)	0
Abdominal pain	0	2 (0.3)	3 (0.5)	0
Vomiting	0	4 (0.6)	0	0
Adverse events occurring in at least 5% of participants in any treatment group†				
Nausea	155 (24.6)	212 (33.3)	195 (31.0)	61 (9.5)
Diarrhea	118 (18.7)	135 (21.2)	145 (23.0)	47 (7.3)
Covid-19	94 (14.9)	98 (15.4)	82 (13.0)	90 (14.0)
Constipation	106 (16.8)	109 (17.1)	74 (11.7)	37 (5.8)
Dyspepsia	56 (8.9)	62 (9.7)	71 (11.3)	27 (4.2)
Vomiting	52 (8.3)	68 (10.7)	77 (12.2)	11 (1.7)
Decreased appetite	59 (9.4)	73 (11.5)	54 (8.6)	21 (3.3)
Headache	41 (6.5)	43 (6.8)	41 (6.5)	42 (6.5)
Abdominal pain	31 (4.9)	34 (5.3)	31 (4.9)	21 (3.3)
Alopecia	32 (5.1)	31 (4.9)	36 (5.7)	6 (0.9)
Dizziness	26 (4.1)	35 (5.5)	26 (4.1)	15 (2.3)
Eructation	24 (3.8)	33 (5.2)	35 (5.6)	4 (0.6)
Injection-site reaction‡	18 (2.9)	36 (5.7)	29 (4.6)	2 (0.3)
Adverse events of special interest				
Hepatic events§	2 (0.3)	2 (0.3)	0	0
Cancer	9 (1.4)	3 (0.5)	5 (0.8)	7 (1.1)
Pancreatitis (adjudication-confirmed)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Major adverse cardiovascular events (adjudication-confirmed)	4 (0.6)	5 (0.8)	0	5 (0.8)
Cardiac disorders¶	0	1 (0.2)	2 (0.3)	1 (0.2)
Severe or serious gastrointestinal events	11 (1.7)	20 (3.1)	21 (3.3)	7 (1.1)
Gallbladder disease§	5 (0.8)	11 (1.7)	6 (1.0)	5 (0.8)
Renal events§	2 (0.3)	2 (0.3)	2 (0.3)	1 (0.2)
Major depressive disorder or suicidal ideation§	1 (0.2)	2 (0.3)	2 (0.3)	0
Hypersensitivity‖	0	1 (0.2)	1 (0.2)	0
Hypoglycemia (blood glucose <54 mg/dl)	9 (1.4)	10 (1.6)	10 (1.6)	1 (0.2)
Other adverse events of interest that emerged during treatment period†				
Cholelithiasis	7 (1.1)	9 (1.4)	4 (0.6)	6 (0.9)

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Ozempic (semaglutide)

In a study of once-weekly semaglutide by Wilding et al., 1,961 participants (18 and older, average age 47) with one unsuccessful dietary effort and a BMI of 30 or greater or BMI of 27 and one untreated issue, were started with 0.25mg per week for 4 weeks and titrated up every 4 weeks to a dose of 2.4mg by week 16. Participants received individual counseling sessions every 4 weeks to help them adhere to a reduced-calorie diet (-500 kcal deficit per day relative to the energy expenditure estimated at the time they underwent randomization) and increased physical activity (with 150 minutes per week of physical activity such as walking, encouraged).

Table 2. Change in Efficacy Outcomes From Baseline to Week 68 (Treatment Policy Estimand; Full Analysis Set)[a,b]

	Estimated mean change (95% CI) [No.]		Difference for semaglutide, 2.4 mg, vs liraglutide, 3.0 mg (95% CI)[c]	*P* value
	Semaglutide, 2.4 mg (n = 126)	Liraglutide, 3.0 mg (n = 127)		
Primary end point				
Body weight, % change	-15.8 (-17.6 to -13.9) [117]	-6.4 (-8.2 to -4.6) [117]	-9.4 (-12.0 to -6.8)	<.001
Confirmatory secondary end points				
Weight loss at week 68, No. (%)[d]				
Participants with ≥10%	83/117 (70.9)	30/117 (25.6)	Odds ratio: 6.3 (3.5 to 11.2)	<.001
Participants with ≥15%	65/117 (55.6)	14/117 (12.0)	Odds ratio: 7.9 (4.1 to 15.4)	<.001
Participants with ≥20%	45/117 (38.5)	7/117 (6.0)	Odds ratio: 8.2 (3.5 to 19.1)	<.001
Supportive secondary end points				
Body weight, kg	-15.3 (-17.3 to -13.4) [117]	-6.8 (-8.8 to -4.9) [117]	-8.5 (-11.2 to -5.7)	
Waist circumference, cm	-13.2 (-15.0 to -11.5) [114]	-6.6 (-8.3 to -4.9) [113]	-6.6 (-9.1 to -4.2)	
Blood pressure, mm Hg				
Systolic	-5.7 (-8.1 to -3.3) [114]	-2.9 (-5.3 to -0.5) [112]	-2.8 (-6.1 to 0.6)	
Diastolic	-5.0 (-7.0 to -3.1) [114]	-0.5 (-2.3 to 1.3) [112]	-4.5 (-7.1 to -1.9)	
Fasting lipid profile, % change[e]				
Cholesterol				
Total	-7.1 (-10.7 to -3.3) [113]	-0.1 (-3.3 to 3.2) [107]	-7.0 (-11.7 to -2.1)	
HDL	-0.3 (-3.6 to 3.0) [112]	1.9 (-1.0 to 5.0) [107]	-2.2 (-6.5 to 2.2)	
LDL	-6.5 (-12.4 to -0.1) [112]	0.9 (-4.4 to 6.5) [107]	-7.3 (-14.9 to 1.0)	
VLDL	-20.7 (-25.1 to -16.0) [112]	-10.9 (-16.7 to -4.8) [107]	-11.0 (-18.5 to -2.7)	
Free fatty acids	-12.6 (-22.1 to -2.0) [108]	-8.8 (-19.0 to 2.7) [110]	-4.2 (-18.8 to 13.1)	
Triglycerides	-20.7 (-25.6 to -15.6) [112]	-11.0 (-16.9 to -4.7) [107]	-11.0 (-18.9 to -2.2)	
CRP, % change[e]	-52.6 (-61.3 to -42.0) [113]	-24.5 (-36.1 to -10.9) [110]	-37.2 (-51.7 to -18.5)	
HbA_{1c}, %	-0.2 (-0.3 to -0.2) [113]	-0.1 (-0.1 to 0.0) [107]	-0.2 (-0.2 to -0.1)	
Fasting plasma glucose, mg/dL	-8.3 (-10.4 to -6.1) [112]	-4.3 (-6.7 to -1.9) [106]	-3.9 (-7.2 to -0.7)	
Fasting serum insulin, % change[e]	-27.8 (-36.5 to -17.9) [108]	-15.4 (-23.1 to -7.0) [110]	-14.6 (-27.3 to 0.3)	
Exploratory end point				
Participants with ≥5% weight loss at week 68, No./total (%)[d]	102/117 (87.2)	68/117 (58.1)	NA	
Prespecified sensitivity analysis (J2R)				
Body weight, % change[f]	-15.3 (-17.0 to -13.6) [117]	-6.0 (-7.7 to -4.3) [117]	-9.2 (-11.6 to -6.8)	
Post hoc sensitivity analysis				
Body weight, % change[g]	-15.8 (-17.7 to -13.8) [117]	-6.4 (-8.2 to -4.5) [117]	-9.4 (-12.0 to -6.7)	

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Table 3. Adverse Event and Tolerability Profile (Safety Analysis Set)[a]

	Semaglutide, 2.4 mg (n = 126)		Liraglutide, 3.0 mg (n = 127)		Placebo (n = 85)[b]	
	Participants, No. (%)	Events, No.	Participants, No. (%)	Events, No.	Participants, No. (%)	Events, No.
Fatal AEs[c]	0		0		0	
SAEs	10 (7.9)	14	14 (11.0)	18	6 (7.1)	9
AEs leading to trial product discontinuation	4 (3.2)	4	16 (12.6)	21	3 (3.5)	3
GI disorders	1 (0.8)	1	8 (6.3)	10	1 (1.2)	1
Any AEs	120 (95.2)	904	122 (96.1)	823	81 (95.3)	522
AEs in ≥10% of participants in any treatment group by MedDRA-preferred term						
Nausea	77 (61.1)	130	75 (59.1)	102	19 (22.4)	24
Constipation	49 (38.9)	80	40 (31.5)	52	20 (23.5)	24
Diarrhea	35 (27.8)	51	23 (18.1)	37	22 (25.9)	26
Vomiting	32 (25.4)	50	26 (20.5)	34	5 (5.9)	6
Headache	20 (15.9)	46	18 (14.2)	20	10 (11.8)	12
Eructation	17 (13.5)	20	5 (3.9)	5	4 (4.7)	4
Decreased appetite	15 (11.9)	15	16 (12.6)	18	3 (3.5)	3
Fatigue	12 (9.5)	12	14 (11.0)	17	4 (4.7)	4
Dyspepsia	11 (8.7)	14	15 (11.8)	16	5 (5.9)	7
Nasopharyngitis	10 (7.9)	10	11 (8.7)	13	9 (10.6)	11
Upper respiratory tract infection	9 (7.1)	11	19 (15.0)	26	18 (21.2)	23
Arthralgia	8 (6.3)	8	14 (11.0)	15	7 (8.2)	7
Sinusitis	8 (6.3)	9	8 (6.3)	8	13 (15.3)	14
Back pain	6 (4.8)	6	9 (7.1)	10	9 (10.6)	10
Influenza	5 (4.0)	5	14 (11.0)	14	6 (7.1)	6
Safety areas of interest[d]						
GI disorders	106 (84.1)	440	105 (82.7)	313	47 (55.3)	130
Cardiovascular disorders[c]	16 (12.7)	20	18 (14.2)	21	9 (10.6)	23
Allergic reactions	9 (7.1)	13	11 (8.7)	12	10 (11.8)	13
Psychiatric disorders	7 (5.6)	10	19 (15.0)	27	9 (10.6)	10
Injection site reactions	0		14 (11.0)	16	5 (5.9)	7
Malignant neoplasms[c]	3 (2.4)	3	3 (2.4)	3	1 (1.2)	1
Hepatic disorders	2 (1.6)	2	1 (0.8)	1	3 (3.5)	4
Gallbladder-related disorders	1 (0.8)	2	4 (3.1)	5	1 (1.2)	1
Cholelithiasis	1 (0.8)	1	2 (1.6)	2	1 (1.2)	1
Hypoglycemia	0		1 (0.8)	1	0	
Acute pancreatitis	0		1 (0.8)	1	0	
Acute kidney failure	1 (0.8)	1	0		1 (1.2)	1

What is a GLP-1?

GLP-1 drugs are not new. They were originally used for diabetes management. The first incretin, a gut hormone that regulates glucose, was discovered in 2005. The first GLP-1 was Byetta (exenatide). It regulates glucose control in type 2 diabetes by helping the pancreas make more insulin, decreasing insulin sensitivity and increasing insulin production. (The effect on the pancreas is glucose dependent—you must have hypoglycemia or type 2 diabetes for this drug

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to work on the pancreas. That is why it can be used independent of hypoglycemia and diabetes, because you do not develop hypoglycemia (exceptions being if the patient is on insulin or a sulfonylurea, in which case those medicines need to be titrated down).

As GLP-1s started being used, patients had better glucose control, better A1C, and better weight loss, which is rarely seen with any diabetes drug. In fact, many diabetes drugs actually cause weight gain. Then, due to these observations, we branched out off-label and began to use GLP-1 for weight loss. Soon after, studies were performed and these drugs were approved to treat weight loss and obesity.

Emotional component of obesity

Many patients who struggle with weight have emotional positive reinforcement with food. The GLP1 and GIP work really well because it works on the amygdala receptors which dissociates any positive reinforcement from food or alcohol for those who struggle with snacking, cravings, or drinking. These medications rewire the brain's connection to food and take away the element of emotional or social positive reinforcement. Patients will still enjoy and savor food, but they won't feel the intense anticipation or emotional response from food/alcohol.

Issues with medication

Medications can be very expensive and insurance may not cover them. Some patients order from Canada. Currently, terzepatide is offering patients with commercial insurance a coupon that, with no prior authorization required, for $25/month for one year.

Wegovy, the FDA-approved semaglutide, runs out of stock constantly because companies didn't anticipate the demand for it. Due to this, production was shut down, causing patients to switch to Ozempic which resulted in more shortages.

Additionally, upon renewal of health insurance, patients should add weight loss medications to their coverage benefits.

Side effects

Side effects of GLP-1s can include nausea, vomiting, medullary thyroid carcinoma, which is very rare and since the inclusion of incretin in 2005, there hasn't been a single case reported in its nearly 20 years of use. Cancer history is an important question to ask in family history because if there is a history of medullary thyroid carcinoma in a first-degree relative, the patient is not a candidate to use a GLP-1 or GIP.

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Pancreatitis is another rare (Dr. Salas-Whalen has only seen 2 cases in 12 years), and only seen in patients with type 2 diabetes. If you do not have diabetes, these medications do not touch your pancreas.

Dehydration is a more common side effect that isn't discussed as much as it needs to be. They can cause severe dehydration, possibly resulting in kidney stones or lightheadedness/loss of consciousness. As these medications take away hunger, they also take away thirst. However, patients may not feel thirsty even if they are dehydrated. The consistent ingestion of fluids is paramount.

GLP-1s and GIP work well and are relatively safe. The experience of the provider giving it is key. While it is possible in some places in the world to obtain these drugs without a prescription, this is highly discouraged because patients need to be closely supervised by medical professionals for the potential side effects and lack of results if the medication isn't being used properly.

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