"Unlocking the Potential of GLP-1 Receptor Agonists: What we've learned and its implications on lifestyle"

Webinar Questions Answered by Angela Manderfeld, MS, RD, CDCES, BC-ADM

Please note that these are brief answers to complex questions and are not meant as medical advice. Please seek medical advice from your personal healthcare professional for more complete information.

******THERE ARE SOME ADDED NOTES AT THE END THAT MANY OF YOU REQUESTED*******

- How does GLP-1 directly improve NAFLD? Or is it a result of the benefits of overall lowered excessive adiposity? **They may improve NAFLD through direct effects on liver metabolism and inflammation, not just from weight loss. Also see decrease hepatic steatosis and fibrosis, improve insulin sensitivity, and reduced oxidative stress.**
- How do you approach GLP 1 conversations with those who may be at risk for eating disorders? **Generally speaking, I would not even put GLP1 on the table if an eating disorder was suspected. I would recommend treating the ED first. BUT, would also look at risks vs benefits. Does this person with possible disordered eating have DM2 out of control, or morbid obesity? If so, then risk analysis would be important as well as looking at the individual.**
- Could you comment on GLP1 use during cancer treatment? I'm seeing so much of this in my clinic, including during H&N chemoradiation and other high-risk malnutrition-type diagnoses/treatment plans. **Use during cancer treatment would require careful consideration. While these drugs can assist with metabolic control, obviously they impact nutritional status and appetite, crucial for patients undergoing chemoradiation. Close monitoring and a tailored approach- such as, lower dosing or every other week dosing…. or maybe using a different diabetes med until they are in the clear.**
- Can somebody who had a total thyroidectomy use a GLP1? **Yes**
- Should GLP-1 be prescribed for T2DM patients with neuropathy, at higher risk for gastroparesis? **They can be used, just warn pt and monitor. We want to get blood sugar down to minimize complications, but do need to be aware of the possibility of gastroparesis, I would not say it's a hard no, just should be monitored.**
- Why is it not beneficial for someone who has IBS? What about someone who has Celiac Disease? **The only reason for not using in IBS is the possible exacerbation of GI Symptoms. IF you start at ultra low doses, like the "clicks" we discussed and titrate up slowly, they may tolerate better. No reason not to use with celiac disease.**
- Is there a range of time a person can use GLP1 without adverse side effects? **That's very individualized and depends on if you are talking about short term or long term. I will assume long term, for instance, the thyroid study said risk of developing thyroid cancer was being on GLP1 >1 year (overall risk still very low), but generally speaking most of the longer term side effects were correlated with being on GLP1 >1 year**
- For a person with BMI=27, who has had STROKE or TIA, without diabetes, is a GLP-1 recommended? (In absence of high BP, high Chol, pre-DM) **Yes, any CV condition could be a co-morbidity.**
- Why do we see so many adverse side effects in patients taking GLP1's if it is a miracle drug? **When it slows gastric emptying, a lot of gut stuff occurs. Like with ANY pharmaceutical, there is always a risk of side effects. I believe people call it a "miracle" drug because of how effective it is in weight loss, they are not looking at the drugs overall impact on daily life. Some patients will tell you it's a miracle, others will tell you it's a nightmare.**

- Why is it advised that those who have/had thyroid cancer should not be taking GLP1 medication? **Patients with a history medullary thyroid carcinoma, should avoid GLP-1 receptor agonists due to the potential risk of thyroid C-cell hyperplasia and neoplasia . There is a black box warning on GLP1 for medullary thyroid cancer and MEN2. This black box warning does not apply to ALL thyroid cancers.**
- Why is Vitamin B 12 added? **B12 may support GLP1 by boosting metabolism, energy levels, and lowering risk of B12 deficiency, which could aid in weight loss. GLP-1 can slow down gastric emptying and reduce stomach acid production, which may affect the absorption of B12.**

- Who are the researchers determining who this medication is appropriate for? (i.e. some medications can be used in children as young as 10 with a BMI in the 95th percentile)? **The American Academy of Pediatrics urged the aggressive treatment. Semaglutide for Adolescents With Obesity. *AAP Grand Rounds* April 2023; 49 (4): 40. https://doi.org/10.1542/gr.49-4-40**
- What about long-term side effects/complications? Do patients need to stay on these drugs for the rest of their lives? **People with diabetes, benefiting from all the CV and renal improvements from GLP1 may be destined for longer term use of GLP1. I would like to think that those using it for weight reduction in the absence of DM2 would be able to titrate to a lower dose or possibly nothing and rely more on lifestyle. I think only time and more research will tell….**
- What if the patient no longer has a gallbladder? Is that a contraindication? **A person could still use a GLP1, again with monitoring. Without a gall bladder the less concentrated bile continuously drips into the intestine which can impact digestion and absorption - bile can have a laxative affect. So, a pt may need some supplements to support liver function and digestion, so seeking help from an RD may be beneficial here to help mitigate issues related to both gall bladder removal and tolerating the GLP1.**
- What are your thoughts about long-term safety studies? **We need them! Byetta (exanatide) has been around since 2005, so there are some people who technically could have been on this CLASS of med for the past 20 years. Four years is the longest study we have so far in people without diabetes, (SELECT study).**
- Can you tell me how GLP1 improves the microbiota? I am concerned that GLP1 would decrease bacterial diversity because of decreased caloric intake and slowed motility. **You are right to a point, but it also decreases the gut damage from high fat diets which impacts gut dysbiosis. As overall gut health in proves, it's a cyclical effect….GLP1 helps improve gut health by getting rid of less healthy food, good gut bacteria flourish which can improve gut barrier, immune function……BUT, like you said, if pt's aren't actually FEEDING the good gut bacteria by consuming fiber, healthy fats, polyphenols, then the gut microbiota can suffer.**
- Some doctors are prescribing microdoses of the pill form to reduce or negate the negative side effects of GLP1 medications while still having good treatment and patient outcomes. I've read in several places that it is the dose, not the peptide, that is the issue, and too many people are getting way too high a dose and then having negative side effects. Have you found this to be the case in your practice? **Agreed, that is why I made that slide with the "clicks" column. You can definitely micro dose and gradually increase. I have NOT seen any western providers stay with the small micro doses only though, they always titrate up. I am hopeful that the microdosing will help with long term weight maintenance as pts start to wean off GLP1.**
- Have you seen more severe side effects with patient taking Tirzepatide compared to Semaglutide? **Hard question because every person responds so different. Tirzepatide has lower GI than Semaglutide, but exanatide and dulaglutide have reported lower GI upset than the former, but not as effective. I had a pt who was violently ill with dulaglutide but tolerated tirzepatide and**

semaglutide just fine. I think the key is putting pts on the most effective med their insurance will cover and then slowly titrating (if possible), like microdosing, if the delivery device allows for it.

- I recently saw a patient who was placed on a GLP-1 for intracranial pressure related to a benign brain tumor. This is something I'd never seen done before. Any information/guidance on this topic? **I think it's still considered a novel use of this drug, but I certainly wouldn't discount it. I personally have not had experience with this. Mitchell JL, Lyons HS, Walker JK, Yiangou A, Grech O, Alimajstorovic Z, Greig NH, Li Y, Tsermoulas G, Brock K, Mollan SP, Sinclair AJ. The effect of GLP-1RA exenatide on idiopathic intracranial hypertension: a randomized clinical trial. Brain. 2023 May 2;146(5):1821-1830. doi: 10.1093/brain/awad003. PMID: 36907221; PMCID: PMC10151178.**
- How are you avoiding muscle loss with such rapid weight loss (regarding 15% weight loss with the Case Study on insulin adjustments)? **Muscle loss is 100% unavoidable at this point, even in people losing weight without a GLP1. They are currently looking at combining GLP1 with a muscle preserver/builder (pemvidutide), not FDA approved yet I tell pt to *aim for* 1 gram protein per pound of IDEAL body weight. If they want to weigh 130#, then aim for 130g per day of protein. It's a lot, so you can always start lower and work up, much of it depends on their activity level as well. I recommend .55g-1g per pound as a good place to start.**
- Why does the medications effectiveness wear off over time? **Much of it has to do with the set point theory. Pt's need to be focusing on lifestyle when they hit that plateau and it feels like the effectiveness is no longer there. Some people may also need to go up on their dosage if they haven't hit the max dose.**
- Is there an age gap in the population of individuals who are eligible to use GLP1s for weight loss? I have patients who are around 60+ years old who have asked. **I have a 77yr old on 5mg Tirzepatide, just reduced from 7.5mg because she felt she was losing too much weight, she has been on a GLP1 for over 10 yr. Recently we have been focusing on using heavier weights, grip strength, and increasing her protein intake. Once 60yr hits, muscle mass starts dropping very rapidly, so again it's a risk vs benefits analysis in these patients. My case study pt was also in her late 60's and benefits definitely outweighed risks.**
- I'm a huge fiber advocate, but I understand circumstances where it's contraindicated. What are your fiber recommendations for those on a GLP-1 RA since it delays gastric emptying? **Treat to tolerance. I like sunfiber in my diabetes pt, its tolerated well and is great for gut health. Pt's may need to keep food logs for a bit to raise awareness in regards to how they tolerate different foods.**
- If someone has class 3 obesity and weighs 350 lbs - what are your fluid recommendations? **Usually their ideal body weight cut in half = daily amount in ounces. IF someone weighs 350 and wants to weigh 175# (175/2) = ~87ounces a day is a good starting point.**
- Can you provide a range for how much protein (g/kg) per day for a patient trying to lose weight on a GLP-1, including resistance training? **Easiest calculation is .55g to 1g protein per POUND (not kg) of IDEAL body weight, for active people, which we should be encouraging in all of our patients.** Carbone JW, Pasiakos SM. Dietary protein and muscle mass: translating science to application and health benefit. *Nutrients*. 2019;11(5):1136. doi:10.3390/nu11051136
- Is there a GLP-1 medication that is least associated with gastroparesis risk? **No, it would be more related to the dose/duration of use.**
- What is your recommendation for a health watch to monitor diseases and hypertension? **I know there are some watches that monitor blood pressure but not sure of accuracy. I think the typical fitness watch that tells you VO2 max, heart rate variability, resting heart rate, etc, are fine, as long as the patients knows how to interpret these things- so some education would be necessary. I like the apple watch for VO2 max and heart rate zone, and my Oura ring for everything else.**

- How much protein is recommended for pts on GLP-1 and is it based on Adj BW for obese patients? **See answer above, .55-1g per pound of IBW or adjusted body weight(depending on how overweight the pt is), not actual weight.**
- Are there any recommendations related to if patients on GLP1s should take Pro/Prebiotics? **I think a probiotic and fiber supplement are a great addition for people on GLP1 as they are likely not getting enough fiber and I really like Sunfiber because it is less likely to cause bloating or gut issues and is great for reducing post prandial blood sugar spikes. The probiotic should be individualized to the pt, Pendulum makes a metabolic daily that has several good strains of bacteria for people with diabetes.**
- What vitamins are good for people taking GLP-1's? **Definitely a multi-vitamin. I like Pure Encapsulations O.N.E - because it's just one pill a day, but there are many out there and again, should be individualized to the pt.**
- For the supplements - do you suggest taking them while taking the medication or for when weaning off? I work with peds and just had a mom asking me about the pendulum product and I would love to know more on this connection. **Pt's could start supplements while on the GLP1, as they start to wean off. Go to the end and I will list the supplements I mentioned.**
- Do you have a recommended protein intake amount for patients on GLP-1 RAs to help prevent muscle loss? **See 2 previous answers above.**
- Can you take Tirzepatide for life? You mentioned you are able to inject Tirzapetide every other week - Is that recommended? **Maybe? We don't have any long- term studies yet. The every other week or once monthly is an idea that I think they should research. At this point, providers are just trying different things to see what works in patients as we don't have a lot of research on how to wean people off the meds. Much of this depends on the pts co-morbidities. Once a pt is on a statin, it's usually for life, same with blood pressure meds. So, unless a pt really has their lifestyle locked in and has seen a reversal in their compromised metabolic state, I would think the pt may need to stay on the med long term to mitigate possible complications related to DM, heart disease, etc.**
- I had a patient with a history of IBS that she stated was stable for years until she took Ozempic. After taking it - it caused severe diarrhea 8-10 times per day and she had to discontinue. Have you seen this before? **Yes, both diarrhea and constipation are common with slowing gastric mobility. She would be one that I would try a small amount of "clicks" and titrate slower. Would also look at root cause of IBS and get that taken care of.**
- Are there apps you recommend to track carbs intake? This would require taking pictures rather than entering foods. **I use the Healthie app with my clients and they do a photo food log that goes directly into my EHR. FoodView is another free app pt's can use and then share with provider.**
- If no weight loss on Wegovy 0.5 mg for 4 week but slowing gastric motility, and nutrition is in line and weight training is in line, would it still be advised to increase dose up to 1? **Yes, keep going up as tolerated, as the max dose of Wegovy is 2.4mg**
- Have GLP1s been remarketed /updated by Byetta? How are they different from the previous Byetta? I see it listed as a weight loss. **I don't understand this question completely, but I'll give it my best shot. Byetta(exenatide) helps with weight loss but is indicated for diabetes only, Byetta is designed to be taken twice daily. The company came out out with Bydureon which is once a week. There are only 3 GLP1's indicated for weight loss, meaning insurance will *possibly* cover, those are Wegovy, Zepbound, Saxenda. There are several GLP1's on the market now, not just exenatide, other companies have made semaglutide, dulaglutide, tirzepatide, liraglutide.**

*******BONUS NOTES*********

Here are some things that WERE NOT on the slides that you might find helpful:

TITRATING DOWN on GLP1's

1. **First option is to just gradually decrease dose month to month until you get to a dose where you see weight maintenance and the patient still feels the dose is effective. Or maybe the patient wants to try and get off completely, that is a personal decision. The only issue I could see there is, if they stop completely, will insurance let them restart if they don't meet the BMI criteria anymore- I don't know the answer to that yet.**
2. **Another possible option to look at is dosing it every other week or monthly. This can certainly make ongoing costs more manageable. We are going to need more studies to see what approach works best, but these are some starting points.**

Side note: when people are not at their target weight OR if they have hit a plateau, this is where you could look at adding other weight loss meds such as phentermine/topiramate(qsymia) or bupropion/ naltrexone(contrave). This is the same approach we use in managing cholesterol, blood pressure, and diabetes…so why would it be any different for obesity.

I like to think of GLP1 as a tool that supercharges your ability to make behavior change. This tool, takes the hunger and crazy appetite out of the picture as you start on the weight loss journey. It makes it easier to make the healthy food choices without all the background noise of emotional eating, overeating, feeling guilty, increased appetite and cravings. Not to say that people won't still get cravings, as many of my clients do, but they will be less likely to act or over react to those cravings.

SUPPLEMENTS & TECH

Everyone is trying to say they have "nature's ozempic" or GLP1 in a bottle, and while none of those things are exactly true, there are some promising supplements, that MAY be helpful in tranisitioning off GLP1.

Amarasate/Calocurb - released in 2018 as a plant based appetite suppressant. NZ govt provided 20 million dollar grant for research. The bitter hops stimulate the bitter taste receptors that trigger the release of GLP1. Main side effect is diarrhea, don't take on an empty stomach .

L- Phenylalanine /Diucaps- given in therapeutic doses to help release higher levels of cholecystokinin (CCK) the food satiety hormone

Akkermansia Muciniphila/Clostridium Butyricum/ Bifidobacterium infantis - there is a company out there called Pendulum that makes these supplements: Akkermansia and Clostridium Butyricum both have been shown to increase GLP1. And Bifidobacterium Infantis helps increase butyrate production in the gut which is a stimulator of GLP1

Berberine induces GLP-1 secretion in the intestine by altering the bacterial profile and increases SCFA production, which causes GLP-1 secretion from the L-Cell. I should mention the long standing drug for diabetes Metformin also increases akkermansia in the gut. Berberine and metformin have similar mechanisms of action

Tech - covered by FSA/HSA
People love monitoring their health, or at least I do, so I assume everyone else does as well. It's faschinating. There are bioelectrical impedance scales, like Hume health body pod, I'm sure there are many others, that one looked cool that's why I put it on here. There are now CGM like the Dexcom Stelo or freestyle libre. I mention stelo because it was made for people who don't have diabetes, less bells and whistles, literally - it won't be waking you up in the night telling you your sugar is 60. But it can give good feedback on meals and stress and other things that can cause blood sugar spikes. and yes, people who don't have diabetes can absolutely make their blood sugar spike.
Oura Ring - measure sleep quality, heart rate variability, stress, and so much more.

WT TRAINING/FOOD RECOMMENDATIONS:

Weight Training:
Muscle mass decreases approximately 3–8% per decade after the age of 30 and this rate of decline is even higher after the age of 60 , so to be perfectly honest, whether people are on GLP1's or not, they need to be doing some kind of resistance training we know it's good for metabolic health as well as longevity.
I tell my diabetes clients, that cardio works like rapid acting insulin lowering blood sugar now, and weight training works more like long acting insulin, lowering blood sugar over time for extended periods. When people drastically reduce their daily caloric intake, it would be great if it was just fat loss, but unfortunately up to 40% of the weight lost on GLP1 is lean mass (you can read more about this in the STEP 1 and SUSTAIN 8 trials). That sounds horrible, **but the proportion of lean body mass to overall body mass increased.**
FAVE YOUTUBE CHANNELS for at home weight training: Caroline Girvan, Donovan Green, and Popsugar are all youtube channels to help people. Donovan Green does seated chair exercises, Caroline Girvan is more advanced but can still be good for beginners and pop sugar has a variety of options as well. All of this can be done at home. **If pts have access to a trainer or a gym with weight training classes, that might be even better, it really just depends on the person**

Protein: Several studies in both humans and animal models have shown that protein and amino acid ingestion can lead to increased levels of GLP-1. For instance, a meal rich in protein can result in a significant rise in GLP-1 secretion compared to a low-protein meal.
Certain amino acids, such as glutamine, arginine, leucine and branched-chain amino acids (BCAAs), have been particularly noted for their ability to stimulate GLP-1 release.

Fiber: High-fiber vegetables support gut health by nourishing the gut microbiome, reducing inflammation, and curbing cravings. These bacteria help in digesting fiber and producing short-chain fatty acids (SCFAs) like butyrate, which nourish the gut lining and reduce inflammation. So you can see why helping pts get onboard with fiber, sooner than later, could be helpful. Occasionally higher fiber may give the patient some trouble or they may have some issues with vegetables. They could try bitters or digestive enzymes to see if that helps. But honestly, chewing food longer and being in a calm state to eat can work wonders for digestion.

Hydration: Stress the importance of staying hydrated to support overall health and help manage potential medication side effects like nausea/vomiting/ dehydration. 64 oz or half ideal body weight in pounds 150#= 75 oz water per day

Mindfulness and Stress Management: the more stress you have the more it impacts digestion, and GLP1 production is reduced, part of this is related to the release of cortisol which reduces GLP1 production. this is why exercise, sleep and mindful eating/ chewing your food and slowing down is so important, especially if you are dealing with a lot of stress. I will say that once GLP1's are added into the mix, mindful eating in terms of using hunger/fullness as a cue get thrown off a bit.
If people only ate when they were hungry on GLP1's I think that malnourishment would become a big cause for concern. So a 4 small meal a day approach may benefit many of your patients. Using a small volume, high nutrient value smoothie to get protein and other vitamins and nutrients in can be very helpful. Putting them in touch with a dietitian can certainly help them not only with managing possible side effects, but helping them get the most bang for their buck with each meal since volume is a big challenge.

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