OZEMPIC: Stephan Guyenet, PhD: GLP-1, Semaglutide, and the Big Future of Weight Loss Therapies

Welcome to the External Medicine podcast My name is Daniel Balkin and I'm here with my co host and brother Mitch Balkin We're both medical students interested in non traditional ideas and innovation This podcast is our attempt to explore topics currently on the outskirts of medicine topics not widely accepted by the mainstream but that we believe merit a closer look is for educational and entertainment purposes only We do not endorse any health care providers or treatments Our views do not represent the views of any official organization or institution if you'd like to support us follow us on Twitter at E Med pod and sign up for our newsletter at external medicine podcast dot com forward slash subscribe Today we are interviewing doctor Stefan G A Doctor GN A received his phd in neurobiology and behavior from the University of Washington afterward He completed a postdoctoral fellowship in the Neuroscience of Obesity He is the author of the book The Hungry Brain and the founder and director of Red Pen Reviews He's also a senior researcher at give Well in this interview we discuss Anthony Sloane's experiments on food reinforcement and nutrient receptors in the small intestines we talk about glucagon like peptide one A KAG LP one We talk about its mechanisms of action with a focus on one G LP one agonist In particular semaglutide we go over semaglutide efficacy as a weight loss agent as well as some of its effects on mood and compulsive behavior Finally at the end we touch on some of the exciting new weight loss drugs that may not only replace the male but potentially even bariatric surgery as well Mitch why is that such a big deal Daniel this is huge news Bariatric surgery is the gold standard for weight loss Currently people can lose 25 to 33% of their body weight Now being able to take a drug that could have an equivalent level of weight loss is a total game changer So let's start off with a bit of background about some magnet tide We don't get into this in the interview So we wanna talk about the step one trial which was a landmark New England Journal of Medicine trial which came out in March of 2021 So why don't you tell us Daniel what is what does step one stand for some male treatment effect in people And it's it's one because it was the first they they just kept going So the step one is a randomized double blind placebo controlled trial that enrolled almost 2000 nondiabetic adults with either A BM I over 30 or A slightly lower BM I if they had weight related

comorbidities like hypertension dyslipidemia or obstructive sleep apnea then they randomly assigned the participants in a 2 to 1 ratio for 68 weeks of treatment and gave them either a once weekly subcutaneous injection of some magnet or placebo And then they also gave each group some lifestyle intervention because why not So um what were the results of the trial So people in the sub magnetite group lost 15% of their body weight and the people in the placebo group lost about 2.5% of their body weight And just for context this study defined success as a weight loss of 5% body weight or greater participants who received some magnet tide had greater improvement with respect to cardio metabolic risk factors like lower blood pressure reduced hemoglobin A one C and lipid levels So male also improved physical functioning as assessed by the SF 36 and the IWQOL Light CT Dude I don't know what those are Why why did you even mention that Well just that it was written in the study I just want people to know what was in the study So you're just gonna read off a string of letters and numbers because that's what it said in the study I'm not reading them Dude I memorized them Is that what we're doing here We're just memorizing stuff Yeah this is what medical school trains us to do Mitch why don't you tell us about the strengths and limitations of the trial So some of the strengths of this trial were that it was a relatively large sample size and had high rates of adherence to the treatment regimen Some of the limitations included that it was a predominantly white population About 75% of the participants were white and it also had a relatively large percentage of women It was 76% female So what that means is this data may not be as Generali to other populations It was also a relatively short trial at only 68 weeks And the trial excluded people with type two diabetes who represent a large percentage of people who are obese Furthermore the participants who actually were enrolled in this trial are likely more committed to weight loss efforts than the general population And now we bring you doctor Stefan Guana OK We're here with Doctor Stefan DNA Thank you so much for joining us on the External Medicine podcast Well OK My pleasure So before we get started do you have any financial disclosures I don't have anything to disclose related to this topic No Excellent So our first question is to somebody who's not familiar with your work Can you tell us a little bit about your background and how you got interested in your current research I received a BS in Biochemistry at the University of Virginia and always had the idea that I was going to um go into neuroscience and that's what I did for grad school I um got a phd in neurobiology and Behavior at the University of Washington At

the time I was studying neurodegenerative disease and um I was studying a rather rare neurodegenerative disease and I wanted to work on a topic that was more impactful and I've always been interested in health and nutrition And so it was a natural transition for me to move to do a post doc in the um neuroscience of obesity So working with Mike Schwartz and trying to understand how the regulatory systems in the brain that regulate body fatness and energy intake are altered in obesity And uh from there I uh decided not to pursue a career in academia but I've continued um I've continued following the literature in these areas and continued with public communication in these areas including writing my book The Hungry Brain which is about the Neuroscience of overeating and obesity and uh other various contributions that I've made including a recent article in works in progress on um the future of weight loss Yeah we read that we really liked it We'll talk about that in in a little bit but I I saw that you are a senior fellow at give Well is that correct Yeah that's correct The titles have changed around a little bit So now I'm a senior researcher But yeah that is correct Can you tell me a little bit about what you do for them I'm a huge give Well fan Ok Yeah Um I am a yeah I'm I'm kind of a general purpose researcher on the research team Currently I'm leading an investigation into water quality interventions in low income countries So building uh cost effectiveness analysis to figure out how much good it does to clean up water in places with unsafe water such as uh countries in sub-saharan Africa And I'm also working on building a cost effectiveness analysis for malnutrition treatment So Children who have severe acute malnutrition or moderate acute malnutrition in low income settings with high infectious disease burden and um suboptimal nutrition How much good does it do to come in and uh provide treatment to these Children And when I say how much good does it do Obviously these are very beneficial interventions Um But really what we try to do is determine how good is the cost effectiveness of these interventions relative to all the other places that you could put your money And so um yeah so those are two of the big things I'm working on for them right now So essentially I do a lot of uh research into what the interventions are what the evidence is that underlies their effectiveness and then build cost effectiveness models based on that and and other factors Very cool You also have a number of other projects going as including red pen reviews Can you tell us what is Red Pen Reviews And what is it that you're doing with that project Yeah So Red Pen Reviews is my response and our team's response to our perception that there is just a lot of low quality nutrition information in the public sphere So

essentially you have uh there's no disincentive there's very little disincentive to making wild claims about nutrition in the public sphere And and the reason for that is that there's no um there's no accountability for making those claims So the people judging that information aren't necessarily knowledgeable about it So there's no accountability And so what we do is we publish expert reviews of popular nutrition books And um in order to do that we developed a structured semi quantitative review method that um is totally unique and that allows us to numerically rate these books in in a a structured um consistent manner And so by doing that we can we create the most informative most consistent and uh most unbiased reviews of popular nutrition books that are available and you can go onto our website all the reviews are available for free and you can see the review score summarized at the top So literally in 10 seconds you can have a uh a very good idea of whether a book is worth reading and you can have a sense of how scientific it is how good the health information in it and it is and how uh accurately it uses citations and you can take those numbers and you can compare them across any book that we've reviewed So if you wanted to say what's the best book that's been reviewed on topic X you can look for the one that's received the best score Um So it's really a kind of a reimagining of what you can do with a book review and how you create an incentive structure for the nutrition publishing industry So what is the most accurate uh book out there on nutrition that you have reviewed so far Yeah So the one that has scored the best thus far is titled Eat Drink and Be Healthy by Walter Willett I guess I'll have to go check that out All right you mention Anthony Sloan frequently Uh He's not someone who I think most people are familiar with So why is he so important And uh if you could tell us a little bit about his interesting experiments Yeah So Anthony Anthony Scni is someone who he's he's a researcher a physiology researcher who has done a lot of the fundamental research identifying how food reward works So in other words how does food link up with the motivational processes in our brain that cause us to be motivated to eat certain types of food more than others And um there's a few different things that he's done in in this field that are notable But I would say the one that comes to mind first is that he developed this method for very cleanly assessing the rewarding properties of different food substances And so uh when I say rewarding I'm talking about reinforcing So the food substances that cause animals to develop uh that basically stimulate dopamine release and cause them to be motivated to seek foods that have those substances in them So like OK I'm I'm being kind of confusing here

but let me let me give you drugs as an as a cleaner simpler analogy So you take uh crack cocaine it causes dopamine to go up in your brain and that causes you to be more likely to uh seek cocaine and take it in the future And it increases the intensity of your behaviors related to seeking and taking cocaine that's called reinforcement So how does that work That's how does that work for food Because these circuits in your brain that cocaine acts on they didn't evolve for cocaine seeking they evolved for food seeking and sex seeking and and other natural rewards And so um he developed this really clean process for understanding how that works for different food substances And what he does is he infuses different substances directly into the stomach or the upper small intestine or different areas of the intestine and at the same time simultaneously infuses flavor into the mouth of the animal And so and then later on he determines whether the animal has uh developed a preference for that flavor above other potential flavors that that the animal is exposed to So they put bottles in their cages with different flavors And they say did this animal develop a preference for the flavor that was paired with this nutrient infusion directly into its gut And this is like you can think of this if you're familiar with Pavlov's dog experiments He found that the dogs when he rang a bell at the same time that he fed them they came to associate the sound of the bell with the receipt of food and they would salivate at the sound of the bell alone So this is called Pavlovian conditioning And it is where your brain basically makes a link between some previously neutral stimulus In this case the bell or the flavor and some innately rewarding substance the the food that Pavlov fed the dogs or the you know substance that Sloan infused into the gut And so basically he used this method that he developed to determine where this reinforcement occurs in the body and what substances cause it And what he determined is that most of this reinforce enfor excuse me most of this reinforcement occurs in the upper small intestine So there are receptors in the upper small intestine Now we know a lot more about how this works than uh because others have built on his work But we know that there are receptors in the upper small intestine that detect nutrients particularly they detect carbohydrates especially glucose they detect fatty acids they detect amino acids And then there may be other ones that detect things like uh salt and and glutamate which is that umami flavor And once they detect those things they send a signal up nerves that connect the uh small intestine to the brain particularly the vagus nerve is the one that's carrying the signal And those go to the brain stem and from the brain stem they are communicated to dopamine releasing cells in the brain in

the uh VT A and the uh substantial Nigra that then produce dopamine that mediates reinforcement So basically when that dopamine hits your brain whatever sensory stimuli you're experiencing are going to get reinforced So in this case dopamine hits the rat's brain It at that same time it is experiencing this particular flavor in its mouth And so that flavor gets reinforced And so that's how we acquire a taste for foods And that's how we develop our motivation cravings to prefer certain types of foods over others And there's less research on this in humans but there has been some research done by Leanne Birch um that has successfully used both carbohydrate and fat to cause food reinforcement in humans Um And and you see this in surveys of the types of foods that are associated with cravings and addiction like behavior What you see is that the foods that are higher in dopamine stimulating nutrients especially combinations calorie dense combinations of refined carbohydrates and fats You find that those are the foods most commonly associated with cravings and uh addiction like eating behaviors People don't get addicted to celery They don't you know they don't crave plain lentils Um These are not those are not foods that have the properties that are strongly reinforcing to the brain and drive this elevated motivational state It's a very interesting design of an experiment to pair flavors orally with different nutrients because in terms of like the way natural selection would work the senses and the flavors that you're tasting in your mouth are presumably the same ones that would eventually end up in your small intestines So it's sort of it's sort of interesting I'm I'm curious if you have any thoughts on how you would essentially have taste receptors located in the small intestines Like it it's very strange Do you have any thoughts on how that could have come to be Yeah So essentially you have two levels of information gathering I mean there's many levels but you could break it down broadly into two levels One is the level of prediction of what the nutrient content of the food is and that's what your mouth is doing That's what your nose is doing That's what your eyes are doing when you're looking at food and smelling it and tasting it But by the time it gets into your small intestine what that's doing is measuring what the actual nutrient content is So it's not just predicting based on your past experience with that food So like you know when you see a slice of pizza your brain you've eaten pizza before your brain already knows what's in it And so you have a predictive uh you you can make a prediction about what that is that's very fast before you even consume it However once it actually gets in your small intestine and it's getting broken down then you have nutrient sensors that are saying OK

what's actually in this and did what we thought you know what we thought was in this food Is that actually what we got out of it And then you can get a what's called a reward prediction error that updates your brain on the value of that food Very interesting So we wanna talk for some time about silat specifically with respect to a number of recent trials on them But before we can talk about some Malott I guess we need to talk about G LP one what G LP one is and how G LP one agony work with respect to um these sorts of medications like Sam male Yeah absolutely So G LP one is a compound that is produced or it's a hormone that is produced by the intestine when you eat And um it is what's called an incretin hormone And what that means is that it signals to the pancreas to increase insulin secretion in a glucose dependent manner So when you eat a meal and you have uh glucose blood sugar increasing in your bloodstream and you have the secretion of G LP one G LP one prods your pancreas to secrete more insulin in in response to that um that glucose And so originally when this hormone was discovered the you know primary application that came to mind was as a diabetes drug because it increases insulin secretion around meals And that is when extra insulin is particularly useful for a person with diabetes Because you know the the problem is it's it's really tough to match insulin injection with insulin need So for someone who has diabetes you know the body is very good at secreting exactly as much insulin as you need to cover your your your glucose But it's a lot harder to do that by injecting bolus of insulin into your body And so having this hormone that is already tuned to only help you release insulin right when you need it uh was you know viewed as a as potentially a very helpful thing and that turned out to be the case It was developed initially as a diabetes medication Um I'm trying to remember what the uh what it was first marketed as let's see here Etta and by Duan which is those were the that was the first G LP one based drug and it was a synthetic version of the hormone that had a longer longer half life So essentially instead of having a super short lived hormone that degrades really fast in the blood you have this longer lived version of it that can um be injected less frequently and and be effective in a in a clinical setting Um However what they also discovered with G LP one is it suppressed food intake in animals And this effect is um really differs quite a lot across different um G LP one based drugs So some drugs suppress food and take a lot and cause a lot of weight loss Some do not cause very much weight loss and do not suppress food and take very much Um However what was discovered was really interesting is that the impact of these drugs on insulin secretion is mediated entirely by their effects on the

body other than the brain So the effects in the pancreas but their effects on food intake and body weight are media mediated entirely by the brain So you have these two different effects that are that have completely different physiological mechanisms And it turns out that there are a bunch of G LP one receptors in the brain and probably they mostly are not actually responding to hormonally secreted G LP one in in the typical state So when you're eating food and secreting G LP one it's probably not doing much to your brain However G LP one is also a neurotransmitter in the brain So it's used by neurons to communicate independently of its incretin hormone effect And basically when you inject the right type of G LP one analog into the bloodstream you start stimulating those cells that naturally respond to G LP one particularly in the brain stem but also maybe in the um in the hypothalamus And that is the effect that mediates the um reduction in food intake and the weight loss that's caused by these drugs There's there's also the slowing of gastric emptying That's a result I mean these incretins also slow gastric emptying Does that also contribute to decreases in food intake Or is the neural mechanism really the predominant effect It's it's really the neural mechanism because the gastric emptying effect doesn't last it's transient whereas the weight loss and reductions in food intake are durable So could it contribute in the first couple of weeks Maybe Uh that's possible but most of the weight is not lost in the first couple of weeks So um I think that if it's playing a role it's it's got to be pretty minor and transient relative to the neurobiological mechanisms Could you go into just a a bit more detail So with the actual G LP one agonist is in the blood stream is crossing the blood brain barrier it's getting into the brain stem it's going into the hypothalamus like this What is it signaling Is it also through the ventral uh the VT A and the um sort of dopamine neurons in the striatum or is it a different mechanism that's actually leading to reduction in appetite Yeah that's a good that's a good question Um I wish I remembered more clearly This actually has been this question has been answered by studies that were conducted by Nova Nordisk Um what they did was they injected fluorescently labeled Um I think it was Lara or some Malott one of those G LP one receptor agonists And the first thing they did was they saw where does it go in the brain And the second thing they did was they looked at what cell types were activated in response to it And that includes cell types that are directly activated as well as second cell types that are secondarily activated So they didn't necessarily themselves see some malay but they were activated by the cells that that did see some male And so they've they've mapped this stuff out in

pretty pretty good detail and they see activation in the brain stem They see activation in the hypothalamus which are two areas that are intimately involved in uh regulation of eating behavior and body fatness Um I don't remember whether they saw activation in the in the sort of dopamine secreting and dopamine responsive circuits But it's a good question So now let's talk a little bit more in detail about semi glut Is it semi glut Is it some male I say it's the male I I think I think it's the mag all right All right We're gonna go with the male then So what what makes the magnet special and why is it possibly a new chapter in the treatment of obesity Yeah The thing that makes it special is that it causes a ton of weight loss And uh so if you look at the trials and it these are really rigorous trials you know these are large uh phase three randomized controlled placebo controlled trials published in uh you know high quality journals So this is this is a really high level of evidence we're talking about And what what they show is that in people assigned to take some male over 68 weeks you see anywhere between 15 to 18% loss of body weight and just to put that into perspective So first of all that's intent to treat So not all those people necessarily not all the people included in that figure were necessarily even on some male by the end of it there is that includes dropouts Um I think if you exclude dropouts it's more like 18 to 20% weight loss Um And that's what we're seeing in the clinic People like David Macklin who have been treated treating a lot you know over 1000 people over the last couple of years they report 18 to 20% average weight loss Um Yeah and and these drugs have a really good safety profile too at least as far as we currently know So they cause some unpleasant gastrointestinal side effects particularly early on when you're just starting and just ramping up dosage Those usually go away And um most people end up having a really good experience with it As far as I can tell like they lose a lot of weight they feel like they're gaining control of their eating behavior and they are not experiencing ongoing uncomfortable side effects And then in in terms of the more serious side effects there are a number of large randomized controlled trials that have reported data for some male and there were some early concerns about pancreatic cancer about thyroid cancer In in animal models none of those have really been borne out by the human data particularly from randomized controlled trials And there are tens of thousands of of people now that we have that have gone through those trials Um the evidence is not perfect You know these trials you could argue they had they didn't last long enough to see um outcomes that might take a long time to manifest like certain types of cancer outcomes Um You could say

that they didn't have enough power to identify um low frequency outcomes like like thyroid cancer Um So you know it's not it's not like there is 100% certainty of zero risk However I think it does look pretty good And also um you have data suggesting that this drug class reduces cardiovascular risk quite substantially It's on par with statins you reduce the risk of major cardiovascular events by about a quarter So that is really good because one of the issues with previous weight loss drugs that ended up failing like Fen Fen is that they increased cardiovascular risk Um So that's a really important piece of evidence And then if you look at all cause mortality in people with type two diabetes there's a meta analysis showing that it's reduced by 12% So I think so far the safety data are looking really good And you know I I don't wanna like come across with complete confidence about this There's of course you know we're still learning and I can't say it for certain that there you know it will I can't say for certain that there aren't gonna be risks that we don't know about yet I think it seems pretty unlikely that they're gonna be large enough that it's gonna get the drug withdrawn but you never know what could happen Um And just to put these weight losses in into context losing 5% of body weight was considered like the threshold to reach using behavioral weight loss interventions like diet and lifestyle like you have these really intensive interventions like the diabetes prevention program that hit like 7% weight loss which was viewed as really good And then by three years into the intervention it was down to 4% And that again that's good Like by the standards of diet and weight loss or diet and lifestyle interventions that is effective Um And you know you look at the other drugs and most of them are achieving that something in that range of weight loss as well The drugs that came prior to some male and then now you have some Malott that's causing in in RCTS 15 to 18% loss of body weight So I mean for me this is a huge breakthrough and it's you know I just can't overemphasize how effective this is relative to other options that we have right now The one exception being bariatric surgery of course which is incredibly effective Um and it's just the beginning So so male is is just the first one in this wave of new therapies that are that are headed toward us You mentioned that some male had positive cardiovascular effects Is that through its effect on diabetes or is that separate Yeah it's it's a good question It um I don't know whether it's related to effects on diabetes However it is independent of the effect on weight loss Surprisingly or at least it's not dependent on that I should say So there are drugs in this class of G LP one receptor agonists that do not cause significant weight loss and yet they still have a cardiovascular benefit So it

seems to be via mechanisms that are not entirely dependent on weight loss Interesting And you mentioned bariatric surgery is also one of the most effective ways to lose weight Uh do you remember what percent weight loss you get when you do that Is it like 20% more than that typical would be you would get somewhere between a third and a quarter loss of body weight So somewhere in the 30 25 to 33% range if you look at studies where they do the surgery and then follow people up for a few years It's usually in the in the range of a quarter and and I'm I'm referring specifically to the more common surgery types like ruin y and vertical sleeve gas gastrectomy because there are other versions that are that are less effective or are more effective in terms of weight loss But those are like the most common really effective uh versions prior to sale You mentioned that there were other weight loss options that existed that were not nearly as effective as this appears to be What were some of the other options that previously were used I know we don't need to get into like uh dinitrophenol or anything like that but more recent than that So you mean uh drugs that have regulatory approval Mhm All right I'm gonna look up the list here to make sure I don't leave anything off that's important Um but you know you have uh probably the best one that was approved previously was Lara which was another G LP one receptor agonists Lara Causes about 7% weight loss which is kind of on the upper end of what you would see with drugs prior to some male Um So you have basically two types of drugs You have drugs that act in the brain like uh Contrave which is naltrexone bro SIA which is ventra to pram And then the other class is oral which uh Zenne is the the commercial name for it and that basically blocks a portion of fat absorption in the gut So it inhibits an enzyme that uh that helps you break down and absorb fat causing you to fail to absorb about a third of the dietary fat that you eat And it's not a very effective drug I mean it it does cause weight loss It actually reduces diabetes Um it reduces progression from prediabetes to diabetes quite substantially uh in randomized controlled trials But the weight loss effect is is pretty modest I mean most people are not going to achieve 5% loss of weight on that drug Um and so yeah I mean that's kind of what the landscape looked like prior to some male and all of those drugs except for Lara really had side effects that most people would consider not to be worth the amount of weight loss that they caused So a number of the drugs are or I should say the majority of drugs used for weight loss have central effects and only the uh or is is that a li li pace in um lipase what it inhibits Ok In terms of drugs having activity in the brain and sort of on similar reward circuits Are there any effects on say

alcohol consumption or compulsive behaviors that you find in patients that are using any of these medications Yeah absolutely You know with the exception of oral which has a completely different mechanism it is actually typical for anti obesity medications to also have effects on drug use recreational or drugs of abuse And uh so you see that also with the G LP one receptor agonists particularly in uh animal models but they're starting to do human studies on this as well You see that these drugs reduce the consumption of alcohol they reduce the consumption of drugs Um like I can't remember which drugs that have been tested but some of the you know harder drugs harder illegal drugs of abuse And yeah so you know and and what you see with the SIM male tide anecdotally as well is that people report that they engage in fewer dopamine fueled behaviors across the board So they're not as interested in drinking alcohol they're not as interested in taking drugs they're not as interested in smoking cigarettes they're not as interested in shopping which is a pretty interesting one So I think these you know I think this highlights the fact that there's a lot of commonality in the the mechanisms of uh you know the mechanisms that drive us to eat food and overconsume food in the modern environment and the mechanisms that make us attracted to other highly rewarding stimuli like drugs or you know shopping So since these medications are changing behavior decreasing drive for alcohol decreasing shopping behavior and other sorts of dopaminergic reward behaviors Uh do patients who take these medications ever have psychiatric problems such as suicidal ideation or depression depressive type symptoms Yeah this is a very pertinent question because this is precisely what sunk Ramana Ban which is a uh a weight loss drug that was briefly approved in the European Union never quite got approved by the FDA Um And the issue was yeah precisely it increased the risk of psychiatric conditions and suicidal ideation and I don't think it was statistically significant but there was certainly a trend toward increase in completed suicides as well in the in the trials Um Yeah And so you know if you look at how Hermana Band works it is an inverse agonist at the cannabinoid type one receptor and that is the receptor that marijuana activates So it's basically the opposite of marijuana And you know marijuana is something that people take to feel good right And so what happens when you do the reverse of that People don't feel good Um But essentially you know it's I think it can be challenging I would speculate I would speculate that it can be challenging to target reward driven eating behavior which is one of the primary drivers of overconsumption without targeting other reward driven behaviors and

without targeting reward more broadly And so Hermana Ban was not able to thread that needle And I'm hoping that some male can thread that needle right now there's no evidence that it is causing adverse psychiatric effects Um And that is obviously something that has been examined with interest due to the history of Ramana Band And you can bet the FDA was very cute into that Um When they were reviewing the application by Nova Nordisk for uh for which is the um some male preparation that's used for for weight loss So right now there's not any evidence of that but it's something that I'd like to keep my eye on and you know even if it's subclinical like will these drugs you know if they reduce shopping behavior are they going to start cutting into natural reward behavior that we want to keep Like I think most people probably aren't gonna be sad to you know have less of a drive to shop compulsively or drink alcohol But you know what if people you know just don't enjoy eating or don't enjoy like catching a fish or having sex or you know whatever other like natural rewards that we consider to be positive and constructive I don't know the answer to that question and that that's something that I think I'm interested to know more about But but I will say right now you know what I find reassuring is if you talk to doctors about it they will tell you that their patients really like being on this drug they get a really good weight loss effect They feel like they have more control over their food They feel like they're not having significant negative side effects for the most part And so like I feel like if there was a really big problem here it probably would already be quite apparent But again I'm I'm open to you know further evidence on that I like that Your list of activities that people really enjoy doing was eating and then catching a fish and then having sex Now that's a good day Yeah So what from your point of view having done a lot of research on this what is does the future seem to be for weight loss medications The future looks awesome So we have some male tide which by the way is very expensive right now in the US wholesale cost of $1300 a month Um and you know to be determined how well it's gonna be covered by various insurance programs Um now it's a lot less expensive in other countries It's about a quarter of the cost and that's how it goes uh for many drugs which is pretty crazy but perhaps a topic for another day and but you have all these other drugs that are nipping at its heel right now and that promises to potentially yield more effective options and also bring the price down on on So the one that is closest to gaining FDA approval is topi that one is um currently under review for diabetes type two diabetes treatment But this is how these drugs have gone first They have get them approved for

type two diabetes then they get them approved for obesity That's how it went for Lara and some Magnotta And that's what uh Eli Lily is doing for TPI But from what I can tell looks like it might cause more weight loss than some Magli tide It might be actually a little more effective than some male tide both in terms of its effects on diabetes management and its effects on body weight So there are um trials I can't remember if they have um been initiated yet or not but there there are gonna be trials published on uh obesity specifically And then um Eli Lily will presumably apply to the FDA for approval for treatment of obesity as well Um But probably even before that people will be using it off label that's what happened with Sam malot So essentially with Sam malot you use a higher dose of it for treatment of obesity than you would normally use for treatment of diabetes And so people were using it off label at the obesity dose for for several years before its approval for obesity this year So I think that's probably gonna happen at least to some degree with teret And and again so male reet they both look really good If Teret causes a little bit more weight loss they're both still gonna be great options And the main benefit that I see is that it will force competition in the market and the prices will hopefully go down Um And then there's a lot of other stuff happening too So there was a trial published recently by Nova Nordisk showing This was a phase two trial showing that when you combine um some male tide with what is this stuff called I'm forgetting the name all these This is this Aly ridiculous sounding names Yeah Aly Um the Amy and analog Grill So OK collide It's it's an Amylin analog Uh So amylin is another one of these gut hormones You have a lot of this innovation in obesity pharmacology is coming from gut brain axis So grit Amylin analog that's a hormone produced by the pancreas That is also part of this kind of digestive tract brain axis And um when you combine slot and grill tide over a let's see what was it It was a 20 week trial and oh sorry this was a phase one trial apologies I said phase 2/20 weeks it almost doubled the weight loss of Sam malot tide So when you add this additional drug to Sagal Tide it almost doubled the effect size which is crazy because Magnotta is already causing 18 to 20% weight loss or I should say 15 to 20 So when I saw this it just blew me away because this was the first time I ever saw the results of a weight loss trial And I was like whoa are these people gonna lose too much weight Is this like gonna be unhealthy amount of weight loss This is just crazy So we don't know exactly where their weight would would stabilize because it was only a 20 week trial and they were still very much in freefall Um but you know given the rate of loss you would expect it to stabilize

significantly below where some Malott alone would leave somebody So you know we're probably looking at maybe 25% loss of body weight and that puts you on par with bariatric surgery So this drug combination it and it the side effects look fairly similar to some male alone You get some more severe gastrointestinal issues but they haven't seen any serious problems I don't know whether this drug will gain FDA approval or not Um but it seems like it might and you know even if it doesn't this is very significant that we're seeing the result of a randomized controlled trial of you know evidently safe pharmacology that's causing as much weight loss as bariatric surgery So even if this or that I should say that I think will cause as much weight loss of bariatric surgery if you extrapolate the weight loss curves out into the future and we'll see more from them on that Um but I mean this is a very very significant in my view and again that you know I'm I'm just getting started here There there's all these other ones Um one that I'm really excited about that I actually didn't write about in the works in progress Um article is so all of these all of these G LP one based drugs that I've been talking about so far they're all proteins So they are literally modified versions of the actual protein hormones that your body endogenously secretes So they've got some amino acid differences they've got extra side chains but it's at its base it's a protein and a protein creates some pretty significant challenges because proteins are hard to produce they require special facilities they're expensive to synthesize and they also in their native state they don't survive the trip down your gastrointestinal tract They get chopped up just like protein from cheese or tofu And so Novonortis has technology that allows these drugs to be uh absorbed through the G I tract So there actually is an oral version of some male but it's still you know it's still a major a major hurdle So what would be better is to have a drug that does the same thing but that's not a protein It's a small molecule So small molecule more like something like ibuprofen or Tylenol It's not a it's not composed of amino acids It's just its own molecular thing that goes into your body and hits the G LP one receptors And there actually is a small molecule G LP one receptor agony that's been developed by uh pfizer The drug is called PF 06882961 So that's uh an elegant name But uh they they recently published some results from that in people with type two diabetes and it looks really good They treat they treated them for 28 days Um and it caused depending on dose body weight loss of 2 to 9% and improved their blood glucose control substantially So um small molecule the advantages would be it could potentially be a lot cheaper it could be more shelf stable and it could be more readily orally bioavailable

So you could produce something that's more like a standard pill that would have the same in theory the same kind of effects that s male has So we're we're still in you know the early stages of this That was a phase one trial but it is a proof of principle that that type of pharmacology is is possible And so um that's another exciting development in that sphere Before we go on to our rapid fire questions I just wanted to pause on your concerns about people having too much weight loss Obviously a drug that can cause people to have reductions of 2025% of their body weight could take somebody that is obese and potentially bring them down to being normal weight And if you're taking somebody that's normal weight you could push them into anorexic territory So have you done much thinking on the potentials for abuse of these substances or is that something that people are actively thinking about Yeah I mean it's an interesting question It it is like totally foreign to me to think that there could be an obesity therapy that would be too effective Um given that you know by far the main problem is the opposite lack of effectiveness Um So you know honestly it's no it's not something I've given a whole lot of thought to Um it never you know it barely even crossed my mind before seeing this trial And yeah I mean if a drug is approved that has the potential to cause an unhealthy degree of excessive weight loss I think that is something that will have to be monitored Uh you know that's something that will have to be monitored medically And it makes me think though you know the the impact of some male tide is is quite variable between individuals So you know I gave you the average but it actually can vary quite a bit between individuals So it would be interesting to know if even with Sam Malot if there's a you know small subset of people who lose too much weight I actually don't know the answer to that question So uh now we just have a few rapid fire questions for you in the last 20 or 30 years What are one or two studies in the field of nutrition or obesity neuroscience that you think more people should be aware of I think the diabetes prevention program trial was extremely important Very large rigorous randomized controlled trial showing that a diet and lifestyle intervention could reduce uh progression from prediabetes to type two diabetes by 58% And it wasn't even that you know the weight loss wasn't that large The amount of physical activity they did wasn't that large but even that relatively modest change greatly reduced the progression to type two diabetes And so you know it does a couple of things One it gives us a a highly effective tool for preventing type two diabetes and two it tells us how type two diabetes works It gives us an idea of what the mechanism is So I think that trial is is really

really important and I guess I would site also the step trials which are the sale and obesity trials that were done by Nova Nok Those were the trials that demonstrated the effectiveness of uh sam male for weight loss and and obesity And I think those were also really landmark trials What important medical truths do Very few of your colleagues agree with you on I'm gonna go real controversial on this one I think that trans fats are probably not as unhealthy as they've been made out to be Whoa that's too controversial for our podcast Yeah Yeah I did a deep dive on this for uh open philanthropy project and give well it's not it hasn't been published but essentially I went as deep as as I could into all the evidence that's cited to indict trans fat And uh essentially you know one of the biggest things that stood out to me is in these review papers talking about how bad trans fat is that have been extremely influential Nobody ever talks about the animal research There's this whole world of animal research on trans fat that almost uniformly shows that it doesn't have any negative effects It doesn't cause atherosclerosis It doesn't you know contribute at least the evidence is not strong that it contributes to the metabolic syndrome It doesn't really seem to do much of anything relative to other fats in animal models You can look in rodents you can look in pigs you can look in uh primate nonhuman primates The the big claim of cardiovascular disease is totally unsupported in animal models of cardiovascular disease And uh so that that's really the biggest thing that stands out to me But also if you look at what it does to blood lipids um that was that's a major part of the argument is that it uh increases LDL and decreases HDL And it was kind of the combination of those two that was supposed to be the the the really bad thing the LDL thing I don't I don't have any issue with that argument I think LDL is just so tightly causally linked to atherosclerosis and coronary heart disease that I think that's a good argument But the HD LP S has really kind of crumbled over the years So you have these um HDL cholesterol in increasing drugs that totally failed cardiovascular trials And you know they either didn't change risk or they even increased risk showing that HDL cholesterol is just not a causal it doesn't have the kind of causal effects that people thought it did HDL particle itself might still But HDL cholesterol itself is just an epi phenomenon It's not causal And so when you're modifying it via trans fat what does that mean II I don't I don't think it's easy to interpret that in light of what we know about HDL cholesterol So if you're not if you don't care about the HDL cholesterol piece then all you're looking at is LDL cholesterol and it has an effect that's similar to saturated fat for LDL but you

eat a lot less of it in the diet So you know you're talking about a couple percent a few percent in the diet in in you know before we started getting alarmed about it that was kind of like what we were eating in the US So it's quantitatively not very large in the diet and the quantitative impact on blood level is is not very large So is it good for you No it's it probably is not good for you And I you know personally avoid it But I just I I'm not convinced that it is disproportionately harmful Like more than any natural type of fat is I could be wrong about that You know these are not high certainty conclusions But um I just think the evidence is not as strong as as it's been made out to be Ok Uh Last question what do you think about fasting and its utility and diabetes or obesity And lots of people make claims about its utility when it comes to longevity Yeah What do you think about fasting Yeah we've actually reviewed these claims pretty extensively in some of our reviews on red pen reviews Um So we reviewed Walter Longo's book was it called the Longevity Diet I think And uh also um Jason Fong's book The Obesity Code And those both talk a lot about fasting and and basically it it reduces weight it improves metabolic health but it doesn't have the cut doesn't live up to the hype So if you compare it head to head with standard old fashioned portion control type calorie restriction it's about the same So um that is to say it's helpful but it's it's not like this you know game changing home run of a of a method seems to have very similar effects to just standard calorie restriction Doctor Stefan Guenna thank you so much for joining us once again Um Do you want to leave your web website We're gonna put your website and Twitter handle in the show notes But do you want to save them here for our audience That's just listening Yeah sure My website is Stephan GN A dot com Um And my Twitter handle is at wh source is that White House source Wh No my blog used to be called Whole Health Source back in the day And it's unfortunate that that's my still my Twitter handle but it's uh better than losing 40,000 followers Well thank you Once again Stefan I really appreciate it Ok Thank you Yeah Thank you so much If you'd like to support us here are some ways you can help subscribe to this podcast wherever you get your podcasts Leave us a review preferably a phenomenal review visit us at external medicine podcast dot com and tell your friends