#349 Hotcakes: Tirzepatide for weight loss, Personalized Antidepressants, Seasonal Edema, Nirmatrelvir for low-risk COVID-19

[Curbsiders theme music]

[disclaimer]

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Matt: All right, Paul, I'm getting the energy up.

Paul: [chuckles] I'm feeling.

Matt: Please keep this energy into the final. Welcome back to the Curbsiders. Paul, we're doing Hotcakes tonight. It's been like six months since we did Hotcakes. I'm very excited, so coming in hot tonight. And we have some great articles to talk about. But how are you doing?

Paul: It's so nice of you to ask. I'm doing great. I have been legitimately excited for this episode because it's been so long since we've done it. And I feel like these are little bit freer, looser, I get to learn from smart people, like a group of smart people who I also consider friends, it's nice. Good energy, Matt. I love where you're coming from, buddy.

Matt: So, before we introduce our two spectacular cohosts, by way of their picks of the week, Paul, would you tell people, what is it that we do on the Curbsiders?

Paul: Yep, happy to, Matt. We are The Internal Medicine Podcast. We use expert interviews to bring you clinical pearls and practice changing knowledge. Most times, but this is obviously a little bit different. This time, we are the sensible experts. But as you know, Matt, we have a couple of real experts and then also us to talk about some stuff.

Matt: Yeah, well, first I want to remind the audience that this and most episodes are available for CME through VCU Health at *curbsiders.vcuhealth.org*. And now before we get to the articles, let's go to the great Dr. Rahul Ganatra for his pick of the week. And, Rahul, we're going to you first. Just because I know you get a lot of anxiety that your pick isn't as good as other people's, even though my opinion, they're always excellent. So, great to see you and tell the audience what's your pick of the week.

Rahul: Hi, Matt, thank you for acknowledging how difficult it is to give a pick of the week after Paul.

[chuckles]

I just finished reading-- well, I shouldn't say finished. I'm almost done reading the second book in *The Expanse* series. I don't know if people are familiar with this. It is also a show on Amazon Prime.

Matt: Yes.

Rahul: This is a series by author James S. A. Corey. And it is kind of an EPIC space opera interplanetary geopolitical, spy craft. It is a thrilling ride. The first book I thought was a little slow but I'm almost done with the second book. And it's totally worth the ride. I hear the show is good. I've not seen it, but the books are fantastic. So, I highly recommend the expanse books by James S. A. Corey.

Matt: And I think the first book is *Leviathan Wakes*, right?

Rahul: That's it, yes.

Matt: And I read it. I haven't got to the second one. But now you are kind of pulling me back towards that. So maybe I'm going to have to check it now.

Rahul: Oh, you got to hang on. Yeah, I wasn't going to, but then a friend of mine said, "You got to read the second one and it really starts to pick up and get spicy."

Paul: So, I'm in the exact same boat, Matt. Like literally, I read the first one, I was like, "That was pretty good. But also, these are family Bible-sized [Matt chuckles] and I don't know if I have two more in."

Matt: Yeah.

Paul: But if they pick up, I will revisit.

Rahul: Oh, stick with it.

Matt: All right, we're going to give even more distance from your pick of the week to pause. Dr. Nora Taranto. We are now kind of neighbors, and you and Paul are really neighbors. You've moved to the city of Brotherly Love, welcome. And tell people how is it and what's your pick of the week?

Nora: Thank you so much, glad to be here. I haven't cited Paul yet, but I think he may actually be intentionally avoiding trying to see me in our neighborhood so.

Matt: He seen you 17 times already.

[laughter]

Paul: First of all, I don't-- [crosstalk] [chuckles] If we should not accidentally DOCSIS on air, that would be super-duper.

[chuckles]

Matt: I said this, Philly is a huge city, Paul. That's all I said.

Nora: So big. [laughs]

Matt: We can cut that. We can delete that if you want.

Paul: It's fine.

Nora: So, in my time, since moving, I have had a little bit of time to watch TV, and I actually just started *Cheers*. Which I know is a throwback, throwback, throwback, but I realized I had heard folks talking about it for a long time. And upon moving away from Boston, I decided that I should watch a show that was set in Boston and really good so far.

Matt: You are an old soul, Nora.

Rahul: Just wait for the spin-offs, Nora.

Nora: Really? What? Wait, *Frasier* is a spin-off of *Cheers*? Wow. Okay.

Rahul: Well, I feel like I just spoiled a major part of *Cheers.*

Matt: Paul, we are so old.

Nora: [laughs]

Matt: I've never felt older on this show then right at that moment, Paul.

[laughter]

Nora: You're welcome.

Matt: Enjoy your youth, Nora.

Nora: Thanks.

Matt: So, Paul, pick of the week?

Paul: Yeah, thanks. I'm going to recommend the movie *Men.* So, *Men* it's a 2022 movie that came out It's by Alex Garland, who is a director that I deeply love. He directed the movie *Annihilation*, which is a movie I'd probably recommend in the past. It is a movie, I think about all the time. It's one of my favorite movies of all time. So, he directed this movie called *Men* that just came out. And it's about this woman who is in an abusive relationship. It's exactly as grim as it sounds, by the way. And basically, witnesses her partner plunged to his death outside the window and goes away to a British countryside to regather herself and becomes menaced by a group of men sort of around. It's awfully hard to explain, but the men are all played by the same actor. And it's this really, like hypnotic, beautiful, fascinating interpretation and sort of meditation on the relationships between genders. But I also think, and I think I can say this without spoiling things, it's filtered through the myth of pan[?]. There's some stuff with echoes that are sort of weirdly important. I didn't realize this until after I came home. And it was a movie I couldn't stop thinking about. And the more I sort of researched the more I realized that that myth became applicable. And it doesn't give you any easy answers.

At the end, there's no sort of tiny resolution, but you just leave just stunned and thinking the entire time that what they were trying to accomplish and what they're trying to say. So, it's a beautiful, horrifying, deeply uncomfortable movie. So, if that sounds at all appealing to you, I would recommend the movie *Men*, which has to come out streaming sometime soon.

Matt: Paul, that sounds a little too heavy for me. I'm not going to lie. I still need to watch that, what's that movie *Everything All At Once*, whatever that--

Paul: *Everything Everywhere All At Once,* also terrific.

Matt: Yeah, I still need to get to that one. Well, thank you for the pick of the week. You know what, Paul? I'm going to save my other pick of the week for another time, because I was going to try to really annoy you with a pick of the week that wasn't really a pick of

the week. But I'll say I recently watched a movie *Free Guy*, it's predictable, but it's a fun movie. And not nearly as heavy as what Paul just recommended so. *Free Guy*, so it's a--

Paul: Goes down easy.

Matt: It was fun, [chuckles] goes down easy. Just like I like it, Paul, nice and stupid. Yeah. All right.

Paul: It rolls right off the brain, I could not remember a thing about it.

Matt: Okay. All right. Let's talk some medicine here. So, the first article which I will be presenting, this is exciting, Paul, this new weight loss drug tirzepatide, or is it a diabetes drug, Paul? I don't know. What are your thoughts? Weight loss drug or diabetes drug? [chuckles]

Paul: [crosstalk] I mean, it's peanut butter and jelly. You can't really have one without the other. So, but it's certainly the weight loss is the thing everyone's talking about.

Matt: Yes, so this is the SURMOUNT-1 study. It was published in the New England Journal in July. And this was asking the question, does the glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1, so let's just say GIP/GLP-1 agonist tirzepatide, lead to meaningful weight loss. And they were looking at patients who had obesity or who were overweight with comorbidities, but did not have diabetes, because we already know it does work for diabetes, and there was weight loss seen in patients with diabetes, but they're trying to get this approved as a weight loss drug as well. So, this was a phase three multicenter randomized placebo-controlled trial, lots of sites, almost 120 sites in nine countries and included just over 2500 patients. And they basically looked at three different doses of tirzepatide, there was the 5mg, 10mg or 15mg dose, or placebo, so there was four groups, and there was a 20-minute. Paul, this is one of those ones with Semaglutide which we talked about in the past, where you have to ramp the patient up first. So, there was about a 20-week run-in period. And then they continued to study for another 52 weeks, so it's 72 weeks total.

And this was a positive trial, they were looking for a percent change in weight from baseline and weight reduction of 5% or more. And my goodness, Paul, they had a huge weight. What were your feelings about the numbers that you were seeing here?

Paul: No. I mean, alarming is not the right word. But I think one of my favorite things about this study is even the authors seem shocked at the extent of weight loss that they had. I think they even comment, "This was more than what we expected." So, I think it's impressive. I think I can't imagine why we wouldn't be excited about this medication right now. I think you'll talk about potential

downsides, but, really deeply compelling. I think on par with what you're talking about offline with metabolic surgery to some extent, so it's impressive stuff.

Matt: So, I'll give the numbers, and then I want Rahul to talk to us a little bit about this because it's a positive trial so he's going to talk about potential sources of chance or bias. So, they had a dose-dependent weight loss, that the average weight loss in the lower dose group was somewhere around 15%, all the way up to almost 21% weight loss from baseline in the 15mg group of tirzepatide. And in the placebo group, there was only a 3% weight loss. So, that means that the absolute difference between groups was something like 12% to 18%. And just a huge number. I mean, patients lost like four to six inches on their waist circumference and about half the patients in a 10mg group and about 57% of patients in the 50mg group had over 20% weight reduction. So, that's just insane. Rahul, tell us, what did you think about the setup of this trial?

Rahul: Yeah. You chose the right statistics to report for the primary outcome. And you highlighted the absolute risk reduction, or excuse me, the absolute change in percent body weight from the end of the trial to baseline. And you also included the timeframe. So that's enough information for us to calculate the number needed to treat over the course of the study period. It's going to surprise nobody that with an effect size this large, the numbers needed to treat are like in the single digits. So, you do not need to treat a lot of patients to see a huge benefit with these drugs. So, I'm already my bias is that I'm very excited, this is a very kind of thrilling paper to read. And I need to sort of calm down and look for sources of chance and bias that could have made a positive result more likely. So, for any positive trial, I always start by thinking, "Okay, is the primary outcome in the paper, the same thing that was decided a priori?" And so, to verify that we look at the protocol on *clinicaltrials.gov*. You can just Google that number that's at the bottom of the abstract, primary outcome was unchanged from the beginning. So that's good.

And then other sources of chance and bias that could have made this a positive trial, you could envision selection bias, if this was a very, very highly selected population of patients, maybe this is the sort of goldilocks group of patients who is going to respond to the study drug. We don't have a lot of ways to decide if selection bias is a concern in a study apart from looking at the inclusion and exclusion criteria. And then another sort of cheap and dirty way that I like to do this is to look at the CONSORT diagram. And the ratio of patients who are screened ultimately, to the patients who are randomized is one very rough approximate measure. I feel a lot better about a study that included 90% of screened patients than I do about a study that included only 10% of patients. So that's not a hard and fast rule, you got to look at the reasons why patients were excluded and decide if you think that that matters.

Unfortunately, the CONSORT diagram, I couldn't find this in the paper or in the supplements. So that's one piece I was not able to evaluate. But apart from those two potential sources of bias, I'm not really seeing a lot to make me question the results of this study. And putting this in the context of another GLP-1 agonist, the effect size is really large. So, you have to wonder will this effect size remains to be the case when these drugs are used in the long term. That's a question that's not answered by this study of only a year

and duration. So, there's still some unanswered questions that remain. But I'm having a hard time identifying any sources of chance or bias to make me question this positive result.

Matt: When I was looking, the exclusion criteria are really pretty extensive. And there was some stuff in there that I was just a little surprised by, so anybody with either an active or untreated cancer, I mean, that makes sense to exclude them. But even if you had serious cancer in the past, and it was in remission, like let's say breast cancer or something, they would have excluded you from the trial. And then, Paul, anybody that has used cannabis in the past three months, or using cannabis and unwilling to stop for the duration of the study, it was excluded. And anybody with like psychiatric illness, like that was unstable, or history of suicide-attempt, they didn't have those patients in there. And I didn't find anything in a drug monograph that said it increases risk of mood disorder. So, I'm not really sure what that was about that any-- but it was just--

Paul: I thought concerns over treatment adherence, I thought was the justification I had rather--

Matt: Maybe.

Paul: Maybe I'm making that part up.

Matt: Yeah. They did say that the authors had some leeway to say if they thought a patient wasn't going to be able to adhere to the study regimen, then they could exclude those patients. So, I mean, I think, Rahul, that was to me a potential source, like this was a fairly well-selected group of patients and making sure that they didn't have any other major comorbidities that were uncontrolled at this time. But these patients did have obesity or they were overweight, they had other comorbidities. So, it was not so, so restrictive.

Rahul: Yeah. Those are important and that's in my view, exactly how we should be thinking about the inclusion and exclusion criteria. Not just from a generalizability standpoint, but also with the lens of could this bias towards a positive or negative result.

Matt: Yeah.

Rahul: So, I think that's great.

Matt: And this medicine, which I haven't used, but it seems like it comes, you start them out at 2.5mg weekly, and then you go up by 2.5mg every four weeks. So, it takes quite a while to get to the fifth 10, or the 15mg dose, which was speculating, that's probably what they're going to recommend, because there weren't many more side effects. And there was a little bit extra weight loss at that dose. So, I think, ultimately, that's what this will be. We were talking a little bit beforehand, how is this going to happen in practice, because with semaglutide, which we've talked about when there is some evidence that when patients stopped the study drug, they

do start to gain weight again. And people are like, "Oh, so that's a downside." But, Paul, tell me what you think about this, but I think we're moving to the point where this is just going to be like a blood pressure medicine that you take chronically, and if you stop your blood pressure meds, we know your blood pressure goes up. And I think with the weight loss drugs, it's going to be that sort of thing. We just haven't had weight loss drugs that were safe enough to take long-term. And we don't know that yet about tirzepatide, or really semaglutide, like can we put people on these things for decades, but I think we need drugs that do that.

Paul: Yeah. And this will sound, again, please edit this to make me sound smarter than what I am. But I would be curious to know the tempo of weight loss, which I imagine will be hard to estimate. So, at 72 weeks, were patients still losing weight? Is there a plateau that they reached on that medication?

Matt: Yeah, they do. A lot of the weight loss was upfront, and then it does start to plateau towards the end of it. But there are some graphs in there talking about that.

Nora: Yeah. I think that they said, maybe for the higher doses, they had almost reached the weight loss plateau point, and so they were interested in the two-year follow-up, as opposed to the 72-week follow-up.

Matt: Yeah. We'll get more data from this. I think this is really exciting. We talked about this at ACP. I wasn't in the room, Paul. I was on a cell phone on a stick in the room. [Paul laughs] But you guys talked about this at ACP, where the basic science lecture that there's the translational, I forget what they call it, Paul. But it's an endowed lecture that they have every year, this year was on obesity. And they were talking about trying to reset that hormone setpoint because when you start to lose weight, if you've ever been obese, if you've ever attained a high weight, your body reaches that as a setpoint. And we need ways to short circuit, try to reset that setpoint, work against the physiology that's causing this recidivism once when people lose weight. So, I think this is really exciting that we have these neuro[?] agents that were comfortable as internists using because we're using them for diabetes. And we can co-purpose this in a lot of cases. So, I'm still cautious, I'm not ready to start putting everybody on these, but I do think they will be used. And we'll just have to really watch out for safety signals as they start to get approved. I don't think this is officially approved for weight loss yet, at least as of the day we're recording this.

Rahul: Correct. And I think you bring up an important point about safety. It's worth reminding our listeners that clinical trials will generally tend to underestimate adverse events from treatments, especially if run-in period where the treatment is given to all patients was used, because patients who don't tolerate a treatment during the run-in period tend to drop out of the study. So, I don't think that all patients received the study drug in this study. I think the patients were just up-titrated in the therapeutic[?] arms. But it's something to look for in randomized controlled trials, reasons why adverse events might be underestimated. So, this is one reason why post-marketing surveillance for adverse events is really important.

Matt: Yeah. A trial that I remember that did that was Sacubitril/Valsartan. They really made sure they were selecting group patients that could tolerate that. This didn't seem to be the case. I was worried for that when I was initially looking through the protocol. But that didn't seem to be the case in this study. So, well, how many Hotcakes am I going to give this? You know, it's the summer, Paul, I don't know that there's any special type of Hotcakes we have in this summer. So, I'm going to give this four out of five. I think this was a very well-done study. I do believe that this has a potential to be a real game changer for us in primary care treating obesity. So, I'm excited to have this as a potential tool, and I thought it was well done.

Paul: Yeah, no, I think I agree with you. I think barring horrifying safety outcomes that are yet to be discerned, like this is going to be a landmark trial. I think this is going to be a really big deal for a really long time. So, it's exciting.

Matt: Well, next up, Nora, tell us what you've got in store for the audience.

Nora: So, today I'm bringing article from a recent issue of JAMA that we actually talked about a little bit in the digest already a couple of weeks ago. And this is data from the VA's Prime study, which looked at how we can harness pharmacogenomic testing in choosing antidepressants and in potentially choosing better antidepressants for our patients. And as we all know, having started patients on antidepressants and then switching them, with time, as we see that they're not working for one reason or another. Choosing that initial antidepressant can be really tough, and there are a lot of different options. And so, this study was a randomized control trial. It looked at about 2000 patients in the VA's system in the primary care setting. And they looked at comparing pharmacogenomic testing upfront upon initiating or switching a single antidepressant treatment with just standard[?] of care.

Interestingly, everyone got their DNA swabs done. And then the testing just came back to the pharmacogenomic group about 24 weeks before the other group. And so that 24 weeks were the weeks in which there were clinical decisions made based on it or just based on a standard[?] of care. And so, this trial was a pragmatic effectiveness study, which, Rahul, I'm not sure whether you can describe what exactly that means for us.

Rahul: I don't know that I have anything earth-shattering to say about this beyond what you've already said. But pragmatic is typically used to mean that it's kind of embedded into the flow of patient care. So, this is something that is overlaid onto existing clinical infrastructure. It's a powerful tool for research that needs to be done quickly and was used a lot during the COVID pandemic. And I should give full disclosure, some of the patients enrolled in this study were actually enrolled at my VA, so I know some of the investigators involved in this. And it's cool to see research happening alongside clinical care like that.

Matt: Nora, I'm sure the audience has the question, pharmacogenomic, I have a vague idea of what that means. What were they looking at here? My simplified understanding is something about the CYP enzymes, but can you tell us how did they think that would change things? Why did they think that was important to look at?

Nora: Yeah. Generally speaking for a bunch of different drugs, both in psychiatry, and you name it. Clopidogrel is one classic one. We know that they're metabolized differently by different people based on the different gene alleles that they have. And these tests, look at the alleles that they have for these different enzymes that metabolize drugs. And there are a bunch of different commercially available tests that look at what we call Pharmacogenomic Testing, which is looking at a panel of these genes, what alleles patients have, and whether they're likely to be poor metabolizers, intermediate metabolizers, or high metabolizers, in which case, they would be likely to have no response or less response or more response depending on where they fall in those buckets.

Matt: And there was some sort of guidance given to the clinicians, just like training how you might use these results.

Nora: Yeah. So that's one piece of this study, that is kind of interesting. I couldn't get a great sense. I'm not sure if anyone else could about the exact guidance that was given to providers about the testing. And so, they used in this study, they used one particular company's pharmacogenomic panel that looked at 12 genes. And you can actually look it up in the supplemental information in the paper. But the information and guidance about exactly what to do with that was a little bit unclear to me, it gave the gene and then what it was associated with from a drug perspective, just the names of the drugs that different alleles were associated with different responses too, but further steps from that weren't totally apparent to me.

Matt: I just found one line in the methods section where it said there was a substantial effort during the trial to educate clinicians and patients using educational videos, talks, written materials, and one-on-one consultation with local site investigators. So maybe there was someone on site that at least some of the time had understood what these were and you could bounce questions off of. I feel like I would need significant guidance to use something like this.

Nora: Yeah. I think that's one of the challenges with utilizing these tests in real practice that many providers, myself included, don't feel particularly comfortable with implementing them, in terms of interpreting exactly what the alleles translate to and where we land from a risk of adverse event perspective. And also, likelihood of success from choosing drug X versus drug Y.

Rahul: You can just Google the GeneSight report and see a sample. And they basically list all of these included antidepressants and then it's sort of green uses directed yellow, some caution red, a lot of interactions suspected. So, I think the design is meant for people like us who don't have a lot of content expertise in how to interpret that. So that was all I was going to say. I did not want to interrupt you, Paul.

Paul: No, absolutely was. But I think depression is such an interesting choice to sort of plant the pharmacogenomic flag, because its manifestations are so protean and I think it's a little bit of a frameshift in the way that we treat. I mean, you guys tell me, when I think about how to treat depression, the way I conceptualize it is that all the medications based on the study trial work about the same and

you choose based on sort of adverse effects and side effect profiles, not how affected the medication is. And even with this study, the outcome of the medication efficacy was sort of a-- I don't want to call it a throw-away, but it was not really the main thing that they were looking at. And in terms of the actual treatment effect on patients, did not seem all that impressive, nor have some of the previous trials that they cited, like the guy[?] did one. I think some chain[?] scene but nothing that blows you away. So it's such an interesting disease to sort of study using this framework when I think how you measure it, how it looks, and how patients respond to treatment. I think it's nuanced to interpret as opposed to something like blood pressure, we have these sorts of hard and fast numbers that are very easy to interpret.

Matt: Nora, I think we should get your take on this. Was this a positive or negative trial? Would this be practice-changing for you if you want to give it a Hotcakes rating?

Nora: Yeah. Just to very briefly summarize the results. So, they looked at the proportion of patients that had remission from depression symptoms over the 24 weeks of study. And they found at 12 weeks that there was a slightly higher proportion of patients in the pharmacogenomic testing group than in the standard of care group that had remission of symptoms, but that actually that difference did not persist at 24 weeks at the end of the trial. And then they also looked at the proportion of patients that had medication with a predicted drug-gene interaction. And similarly, in the pharmacogenomic group, there was a lower proportion of patients that had a likely drug-gene interaction that was predicted by the test. So, that part suggested me that the folks were following the instructions to some extent of the panel. In terms of whether or not this is a positive or negative trial, we were talking before air about how to interpret this. I think, nominally it's a positive trial. They met two different time points; they met their endpoints. But from a clinical relevance perspective, and clinically practice changing perspective, I don't know that this is ready for prime time right now for me.

Matt: I would agree. Rahul or Paul, any other final comments on this before we move on?

Rahul: Yeah. I like that you identified the primary outcome, as even though technically, the endpoint in this trial was met, patients were more likely to be free of drug-gene interactions. I almost consider that a surrogate outcome in that we don't really know if patients who got drugs with a high likelihood of drug-gene interactions ended up having more side effects or worse control of their depression. And the only patient centered outcome in the trial of remission at 24 weeks really did not show any difference. So, I agree with your interpretation that although this was technically a positive study, in the sense that the primary outcome showed a difference. The patient-centered component of that really was not persuasive to me that this is ready for widespread adoption.

Matt: Well, next up, Paul Williams, a favorite topic of his is Lower Extremity Edema. And, Paul, this was on the cutting room floor. So, I'm going to ask you to tell people, once you tell them about this study, I'm going to ask them to tell you about the study that you had conceived and suggested to me. So, tell us about this study about seasonal edema.

Paul: And by the way, I have no memory of this conversation. So, my best idea is-- [crosstalk]

Matt: I have a tape of it, Paul, so.

Paul: [crosstalk] [chuckles] No, I believe you. This is from [unintelligible [00:29:52]. It's an older article. It's actually I want to say it's 2016 in the Annals of Family Medicine, looking at the seasonality of ankle swelling. I love it so much because it's just so smart. The way they did things was so clever. And I just think we have to give points for that. I think we've talked before, anecdotally; I had noticed that in the summertime when it's hotter outside, I see more patient's lower showing edema. And maybe that's because [unintelligible [00:29:52] dilated, a little bit leakier, and as a result, they have underlying dependent edema or any other condition that might cause edema. It just seems worse in the summer. And that's something that I've always noticed. I'm like, "Somebody should study that." And whenever I say that, I mean somebody who is not me. And it looks like these authors identified a kind of the same trend. And so, they actually did the work. And by the work, they looked at google searches, and they looked at the frequency and then trended against seasons. So, they looked at a google search for, I think it was ankle swelling or foot edema, or foot swelling or sort of similar phrases, and then plotted this over time on using Google Trends. So, the software that kind of evaluates google searches over a timeframe.

Sure enough, what they saw is that so their null hypothesis was that it wouldn't make any kind of differences, so season wouldn't matter. So, they compared to what they found to basically a straight line versus the sort of sinusoidal pattern that would peak in the summertime and trough in the wintertime. And sure enough, their model of seasonality actually matched what the google searches look like. So, people are looking, they're google searching ankle edema, that peaks in June, and it's probably at its lowest in December. And the other thing that they said in the article that I just I love that they even thought of this. Heart failure readmissions, by the way, the exact opposite trend. You see a much higher rate of heart failure readmissions in the wintertime, and then it's decreased in the summertime. So, you can't even chart it up to that. And they also note that anecdotally, the patients where they're like, "It's summertime, your legs are more swollen, don't tend to go on and actually develop like heart failure, or in stage renal disease." No one ever identifies myxedema from hypothyroidism for these patients they see in the summertime, most of the time.

And then just to prove their point, and this is the part that I love the most. They looked at Australia's Google Trends. And Australia seasons are reversed them from ours. And sure enough, in December, that's when it peaks. And in June, that's when a trough, so if you actually track it out, it's the exact opposite pattern of ours. So, it proves that the seasonality and not just the timing actually matters. It is so damn smart. And, yes, I recognize that they weren't actually looking at ankles or measuring things or doing chart reviews, but they use the data that already existed to prove a point that they knew. I thought it was so clever. I could not get over it. I shared it with my section, they're like, "That's nice, Paul, we're glad that you're happy." I shared it with Rahul, he was probably

excited about it, I put it on Twitter and no one cared. [Nora chuckles] So now I'm forcing all to listen to now because I just think it's such a smart study.

Matt: And, Paul, also what I was hinting at before, you had suggested the follow-up study to this, which would be to look at the ordering of echocardiograms, and is it seasonal as well, because patients are presenting with ankle edema. If anyone wants to do it, Paul doesn't want to do it. So, we're putting it out there. If someone wants to do the follow up.

Paul: The study is there, just give me an acknowledgment, please. That's all I ask, a thank you at the end.

Matt: Yeah.

Paul: That's all I want.

Matt: And then check out our edema episode, which I don't remember the number 315, 316, something like that. And it was a great one. Paul talks about Nicki Minaj. It's great.

Paul: [chuckles] Yeah.

Nora: I think to move on. Well, Paul, how many Hotcakes, did you want to give this, full stack?

Paul: Yeah, I mean, it's like a full stack of like the silver dollar pancakes, like it's a little study, but it's super cool. A modified score for them.

Nora: The Google Trends searches is also fascinating and something that I got deeply into after reading this paper.

Paul: Same, yep.

Nora: Yes. I played with it the last couple of days.

Rahul: Yeah, has any never played with Google Trends?

Paul: Nora is barely paying attention to us right now.

[laughter]

Matt: t's very useful.

Rahul: If you Google Trends search for the Curbsiders, you see, basically nothing until our first episode in 2016. And then an abrupt in meteoric rise, which I predict will just continue.

Matt: Fantastic.

Nora: Oh, look at that.

[laughter]

Matt: So, Rahul, your turn here. So, there is antiviral medication for COVID-19 that has been, which I can't pronounce, which you will tell us how to pronounce, which has been prescribed quite a bit lately. So, the question is, does it work for standard risk patients? It was approved for high-risk patients for emergency use. So, tell us about this.

Rahul: Of course, and I will just alert everybody the brand name of what we're talking about is Paxlovid, everybody is familiar with that. The generic name is Nirmatrelvir/Ritonavir. And this is a medication that has FDA authorization for emergency use. And there is a persnickety distinction between authorization and approval that I don't think really matters to any frontline clinicians, I could be wrong. But this medicine has FDA authorization for use, for outpatients who are at high risk for hospitalization and death from COVID-19. Ever since FDA granted the authorization to Ritonavir boosted Nirmatrelvir, there have been a lot of questions raised about who and who doesn't benefit from this and what the true downsides are. Thanks to a press release from Pfizer, the manufacturer of the drug last month. We finally have a little more information to guide practice. So, I'm going to take you through some of that information.

We know with a high degree of confidence from the EPIC-HR study, which was published in in April issue of The New England Journal of Medicine that Nirmatrelvir/Ritonavir, or Paxlovid is highly effective at reducing hospitalization and death. Among high-risk unvaccinated outpatients with COVID. And NIH in response to that currently recommends this as the first line treatment in this group. That is pretty uncontroversial, but increasingly vaccinated and boosted and generally, low-risk people with COVID-19 are asking me, having gotten COVID unexpectedly experiencing what's basically a mild cold, should they take Nirmatrelvir/Ritonavir? I'm curious if any of you have had this experience of either patients or friends and family asking you about Paxlovid.

Matt: Dr. Williams, I know you have thoughts.

Paul: No, my experience that have been the majority of patients, they ask for it. And even the ones that I've seen prescribed it are patients that have at least been vaccinated and tend to be sort of in the lower risk. And I think that there's a lot of reasons for that. But I have the same experience, Rahul.

Rahul: Yeah, so people have had a lot of legitimate questions in my mind about what is the effect of Nirmatrelvir/Ritonavir on symptoms, not just morbidity and mortality. So, the EPIC SR Study, which, even though the manuscript is not available yet, this is what this press release describes. So, the question that the EPIC-SR Study was designed to assess was whether Paxlovid shortens the time to resolution of symptoms in a low-risk population. And this was basically people who had none of the high-risk conditions that would have qualified them for EPIC-HR. So, those are advanced age, cardiovascular disease, obesity, immunosuppression, a variety of other things. So, the people included in EPIC-SR were all low-risk outpatients with COVID-19. This included vaccinated people, early on vaccinated, adults were not enrolled, but as vaccination became more widely available, vaccinated adults were enrolled.

Pfizer reported that in this study, enrollment has been ceased because of failure to reach its primary endpoint. And the primary outcome in this study was the time to sustained resolution of symptoms among the patients in the study. So, this was a negative study, enrollment was stopped. And, even though the manuscript is not yet available, we know that Nirmatrelvir/Ritonavir in low-risk patients did not hasten the time to resolution of symptoms.

There were two clues early on that this would be a negative study. And I'll tell you about them just briefly, because they're interesting. One was that Pfizer announced that they were increasing the sample size of enrollment in the study. And this is something you see done when investigators are worried that a trial is underpowered to detect a rare event. And that was exactly the case in this study. It turns out low-risk vaccinated people tend to do pretty well from COVID. So, there were not a lot of outcome events. So, the sample size was increased from 1100 to 1400 patients. But despite that, we still didn't see a difference in the interim analysis. So, it was announced that further enrollment was going to be closed as of this month.

And another clue comes from the EPIC-HR study in The New England Journal of Medicine, which is that the subset of patients who were seropositive, they had a markedly attenuated benefit from Nirmatrelvir/Ritonavir. In comparison with patients who had not yet mounted an antibody response. And this is probably reflection to the fact that by the time you've mounted an immune response and produced your own antibodies, you have limited viral replication, lower viral loads, you probably stand to benefit less from an antiviral compared with people who haven't started mounting an immune response. So, that's just a hypothesis. It's not definitive, but those two things led me to wonder that EPIC-SR might be a negative study, and lo and behold, now we have this information that it was. So, unfortunately, symptom relief was not reported in EPIC-HR. And we know from EPIC-SR, that Nirmatrelvir/ritonavir did not alleviate symptoms in low-risk patients with COVID-19.

It's worth noting that this drug is not totally benign dysgeusia, or an altered sense of taste seems to be happening fairly commonly. I'm curious, Paul, you in your practice have had patients that have been asking about this had been complaining about the altered taste?

Paul: Yeah, that should probably the most bothersome adverse effect that I've heard about it. It really seems to drive the patient's experience [unintelligible [00:39:39].

Matt: Yeah, and I'll say that my practice has been to the older and sicker or anyone who's immunosuppressed is really who I'm recommending this for patients who are younger and really don't have comorbidities or doing well, I'm less likely to prescribe it. It can be a little bit challenging to prescribe because the all the drug interactions you have to look everything up. And sometimes you're having to alter the dose or hold doses of medications for eight days while they're on it. So, it's not the most user-friendly med, but it's great that we have it for the patients that are at highest risk and need it. But this will probably help me. I look forward to the full trial being published eventually. But this will probably help me just sort of talk some patients out of it who are lower-risk and might not need the medication. That's probably the tact that I'll take

Rahul: Yeah, I think that's the right interpretation of these data. Not to be a nihilist about the utility of this drug. It's worth remembering that Nirmatrelvir/Ritonavir, absolutely a game changer among patients at high-risk with COVID-19. And NIH recommends using vaccination status, advanced age in the presence of immunocompromised, the strongest risk factors for severe outcomes. For the average vaccinated boosted low-risk person with COVID-19, to date, we really have no compelling evidence that Nirmatrelvir/Ritonavir hastens resolution of symptoms. So, I agree with your interpretation, Matt, that most young healthy vaccinated boosted people are unlikely to see any benefit.

Matt: Yeah. Any more comments before we wrap it up here? I have a quick article, and this was The Society for Hospital Medicine, put out some new choosing wisely recommendations. There was 11 recommendations. And the bottom line here, I felt these were just like common sense and common decency, Paul. What do you think about that? We need some of that in medicine, right?

Paul: That sounds nice, Matt. [laughs] Then why does it feel like an attack? Why are you--[crosstalk]

Matt: No, I thought you would appreciate it because you're very common--

Paul: I do.

Matt: When you see things that don't make sense that are not good for patients, you don't like it. So, I think you will like these recommendations. That's why I was saying.

Paul: Okay, that's a nice framing. All right, I like that. Thank you.

Matt: These are low-cost and patient-centered ones, the ones that I want to highlight. I am not going to go through all of them for the interest of time. So, we've talked about this many times in the show, please don't just turn up the oxygen and think 100% is better. Don't artificially raise the oxygen saturation to above 96% on Peripheral capillary oxygen sets. We talked about that before, it's good to say it again. In the hospital, let the patient sleep, especially if the patient is doing well. Just let them sleep. Don't wake them up for routine vitals. Further, don't just automatically order a CBC and a chemistry every day, especially if the patient's stable, and you're not really looking for anything. I see this both of these things, patients woken up in the middle of the night for labs, and we're planning on discharging them. And we don't expect the vitals to be abnormal and we don't expect the labs to be abnormal, nor do we want them to because the patient's ready to go and they're not complaining of anything. And then finally, urinary catheters for convenience. Paul, let's not do that. Okay.

Paul: Great, yeah, agreed.

Matt: Yeah.

Paul: It seems bad.

Matt: Yeah, for convenience or incontinence. I know sometimes patients ask, but it's dangerous, it's not recommended, and we shouldn't be putting them in. So those are some ones that I wanted to highlight. But look at the full list. There's some other good stuff on there. Rahul, you practice primarily as a hospitalist. Are you seeing these things done routinely? Can you get on board? [chuckles]

Rahul: Oh, I see it all the time. As you're talking, I'm trying to decide in my brain how I'm going to, in the most persuasive way possible relay these recommendations to my house staff. I'm on service right now. And I think the fact that Matt Watto brought it up on the show will be compelling enough, because my efforts to cut down on daily lab orderings have not been successful.

Matt: Yeah, it's hard. And I think these are good, like quips projects to enact some of these things. But I think they're things we should be thinking about, especially letting patients sleep in the hospital. That's really been in literature a lot lately. I haven't yet seen a great implementation of it. But I'm working on only one place, and it's easier said than done. I think we have to change expectations of multiple team members, and the patients as well. But we should move towards trying to do some of these things because they are low cost, and they would be good for patients and good for outcomes. So that's that. And I think, Paul, we're ready for an outro.

Paul: All right, smoothly transitioned. This has been another episode of the Curbsiders, bringing you a little knowledge food for your brain hole.

Matt: Yummy.

Nora: Yummy.

[laughter]

Paul: A plus. Get your show notes at *thecurbsiders.com*, and while you're there, sign up for our mailing list to get our weekly show notes in your inbox, plus twice each month you'll get the Curbsiders digest, recapping you the latest practice-changing articles, guidelines, and news in internal medicine.

Matt: We're committed to high-value practice changing knowledge and we want your feedback, so please subscribe, rate and review the show on Apple Podcast or on Spotify or you can contact us at the *thecurbsiders@gmail.com*. Reminder that this and most episodes are available for CME through VCU Health at *curbsiders.vcuhealth.org*. I wanted to thank my cohost for this episode for helping to write and produce this episode. Our show is produced and edited by the team at PodPaste, Elizabeth Proto runs our social media and our theme music was composed by the great Dr. Stuart Brigham. So, with all that until next time, I've been Dr. Matthew Frank Watto.

Nora: I've been Dr. Nora [unintelligible [00:45:53] Taranto.

Rahul: I've been Dr. Rahul [unintelligible [00:45:56] Ganatra.

Paul: And as always remain Dr. Paul Nelson Williams. Thank you and goodbye.

[theme music]

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