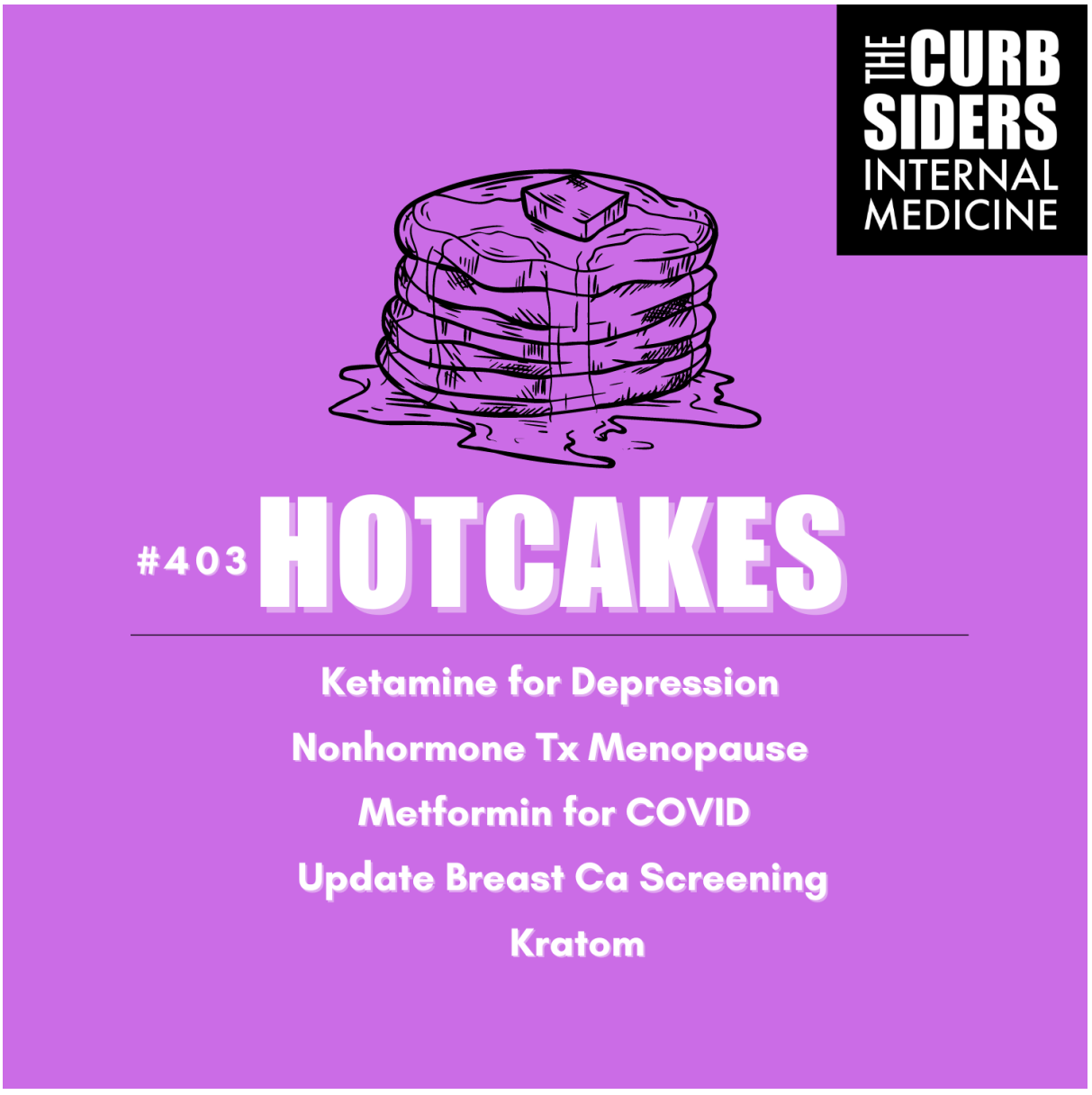
#403 Hotcakes: Ketamine, Kratom, Nonhormone therapy for menopause, Metformin for long COVID, and New Breast Cancer Screening Recs



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[The Curbsiders theme]

Matt: Welcome back to The Curbsiders. I'm Dr. Matthew Watto, here with some great friends. But first, I'll introduce America's primary care physician, Dr. Paul Nelson Williams. Paul, how are you doing tonight?

Paul: I'm great, Matt. Excited to be doing a hotcakes. I feel like it's been half a year since we've done one. So, it's nice to actually-

Matt: I think that's-

Paul: -go back to literature to catch up.

Matt: -pretty true.

Paul: Yeah.

Matt: At least a quarter of a year. And with us tonight, the great Dr. Rahul Ganatra. He is, I guess, our resident epidemiologist. Paul, is he a wiz kid?

Paul: Yeah, that's correct.

Matt: How do you describe Rahul?

Rahul: Oh, stop.

Paul: Well, it's not because we already have a hospitalist wiz kid, *Wonderkin.* Is that--? [crosstalk]

Matt: There we go.

Paul: Yeah.

Matt: Yeah, I think that's good.

Paul: Excellent.

Matt: Yeah.

Rahul: Although I don't want to be associated with Nate from *Ted Lasso*.

[laughter]

Paul: Don't know the reference. Never will.

Matt: [laughs] Paul refuses to ever watch *Ted Lasso*. Paul, before we get into it, can you remind people what is it that we do on The Curbsiders and what will we be doing this evening?

Paul: Sure. Happy to, as always, Matt. As a reminder, we are always *the* Internal Medicine podcast, and we typically use expert interviews to bring you clinical pearls and practice-changing knowledge. The beloved hotcakes episodes are a little bit different in that we each have reviewed an article that is exciting or interesting or potentially even practice-changing TBD and went through it and tried to apply some critical analysis to it and decide if it's how we feel about it and try to learn a little bit about how studies are done in the process.

Matt: Yeah, that's right. A reminder to the audience that this and most episodes are available for CME for all health professionals through VCU Health at *curbsiders.vcuhealth.org*. And we'll stick to a format. So, first up, we're going to have these hotcakes where we go a little bit more in depth, and then at the end, we have a couple more newsy items. So, we're going to

be talking about ketamine, we're going to be talking about a new nonhormonal therapy for menopause. Paul is going to be talking about metformin and whether or not it works to prevent long COVID.

Paul: Prevent long COVID just in the nick of time.

Matt: Yeah. [chuckles] Just in the nick of time. We'll talk about the new breast cancer screening recommendations and finally, kratom, which if you haven't heard of it, Paul's going to tell us about it. It's a new party drug? Not really, no, over the counter.

Paul: By new you mean centuries old and just Americans are misusing it? We'll talk about it.

Matt: Right. Okay. New to me, Paul, because I am [Paul laughs] not cool. All right. Rahul, so can you tell us the article you chose? What's the article, the authors, and let's get started?

Rahul: So, the paper that I'm going to be talking about is the eLeCT D study. And this was a paper by Anand and colleagues and this was published in a June 2023 issue of the New England Journal of Medicine. So, what was this paper all about? This was a study looking at the use of ketamine for severe treatment-resistant depression. So, what was the research question here? The question that the authors were asking was, is ketamine noninferior to electroconvulsive therapy or ECT in the treatment of moderate to severe resistant depression? So, why is this study important, particularly for generalists like us to know about? Well, about one in three patients with major depression have a suboptimal treatment response and that's even after two good trials of effective antidepressants.

ECT is something that generally works well for patients in this situation, but there are downsides. For example, it's not available everywhere. It requires general anesthesia. There is still some stigma and fear around the use of ECT. And there are adverse effects, mainly affecting patient's cognition and memory that are thought to persist for up to a few months. Ketamine is increasingly being used at sub-anesthetic doses for treatment resistant depression, but prior studies have not really been a slam dunk that this has high efficacy. So, this study aimed to clarify that. So, how is the study done? Well, this was a randomized, unblinded, pragmatic, non-inferiority trial, and this was done at five hospitals in the United States through 2017 to 2022, and this was funded by the nonprofit Patient Centered Outcomes Research Institute or PCORI.

Patients were randomized one to one to get either ECT done three times a week for three weeks or to receive IV ketamine, which was administered two times a week for the same duration, three weeks. Patients could continue their existing medications with their usual providers. These were not standardized. The primary outcome in this study was clinical response, which was measured as a 50% or greater reduction from baseline severity on a questionnaire, the QIDS-SR-16. And this was basically inventory that's a quantification of the SIGECAPS symptoms that you learn about in med school. So, the primary outcome was assessed at three weeks and then patients who had a response to either treatment were followed for a total of six months for assessment of secondary outcomes and durability.

So, who are the patients in this study? Well, patients in this study had to have at least moderate depression and they had to have failed at least two antidepressants previously. Patients couldn't have had psychotic features because there's some worry that ketamine might worsen symptom control in patients with psychosis. So included patients were in their mid-40s, roughly equal proportions, men and women. Essentially everybody was non-Hispanic white and 90% were outpatients. These people all had pretty severe depression. The average duration was over 20 years with a median of five previous episodes. The majority of patients had a family history of depression and one in three

patients in this study had a history of attempting suicide. A lot of patients had concomitant anxiety, but comorbid substance use disorders were uncommon. So, what did the study show? What were the top line results before we get into discussing some cool things about it?

So, the top line findings were that at three weeks, 55% of patients who got ketamine had a clinical response, compared with only 41% of patients getting ECT. And the noninferiority margin in this study was 10% and the absolute difference in this study was positive well above the negative noninferiority margin. So 14% difference between groups and the confidence interval was nowhere near that noninferiority margin. So, the authors determined that ketamine was noninferior to ECT. A lot of the secondary endpoints really supported this. I will note though that both groups saw an improvement in quality of life at the end of this six-month follow-up period. So, before I open it to discussion, the last thing I'll just add is that in terms of adverse events, there were differences. Musculoskeletal problems were more common among people who got ECT, and as you might expect dissociative symptoms were more common with ketamine.

Matt: Yeah, and the ECT is basically inducing a seizure, I guess, as part of how it works, which is probably why people think it's scary. Rahul, I noticed because this was an open label trial that when they talked about how some patients after they found out which group they were randomized to, there were about 30 patients dropped out of the ECT group, maybe because of that scariness that were just talking about, and only eight patients dropped out of the ketamine group. So, I was just wondering, if this was kind of marketed as a ketamine study and that was the big draw, because at least I hear a lot about ketamine. Maybe it's just like the podcast I listen to people are talking about ketamine. I know-- [crosstalk]

Paul: Or the podcast that you actually run, because it was actually brought up with our substance use disorder episode that just came out this week.

Matt: Yeah, true. So, in my world, in general-- Thank you, Paul.

Paul: [laughs]

Matt: In my world, ketamine just seems to be a hot topic.

Paul: Everyone's getting ketamine. It's just willy-nilly out there.

Matt: Yeah, as do psychedelics. So, I just wonder, Rahul, do you think that that is a potential source of bias for this positive trial?

Rahul: Yeah. So, great question. I will say, it's not just you. Ketamine, I do think is really entering the zeitgeist for the treatment of resistant depression. As a generalist, I've had to do several pre-procedure evaluations for patients who are going to receive ketamine for severe depression. This is something that I think we'll start seeing more and more of. But yeah, ask your questions, so this, in the vernacular, is a positive study, because the primary endpoint of noninferiority was shown. One thing I'll just say that I put out there for listeners who I'm just inviting you to please tell me what I'm missing about this. But I think that the results are compatible with superiority of ketamine over ECT, because the confidence interval doesn't include zero for the absolute difference there. The authors are very cautious about this and they don't actually say superiority in the paper. I have tweeted about this and nobody is responding to me.

Paul: I've been watching. Yeah.

Rahul: Yeah. I was hoping somebody was going to have the answer, I'm wondering what I'm missing here. So, listeners, please help us solve this mystery.

Matt: With the noninferior margin of 10%, so it could be no more than 10% worse, but it was actually 14% better, but in absolute terms.

Rahul: That is correct. That is a perfect statement in words of what that means. I love it. So, listeners, help us learn, participate in this with us, what am I missing. So, at a minimum, the authors found that ketamine was noninferior to ECT. Matt, the point you raise about the people who didn't complete the assigned treatment, this is an important thing. This is called differential loss to follow up. 16% of patients randomized to ECT didn't do it. Only 3% of people assigned to ketamine didn't do it. So, this is a source of selection bias that occurs after randomization. And in this study, since we know that ECT is an effective therapy, I would expect this to bias towards ketamine looking better, because more people in the ECT group did not get an effective therapy. So, that's an important source of bias towards ketamine looking better there.

Matt: Paul, we talked a little bit about this. I don't know that I've seen a case of ketamine dependence, but I believe it's a condition that exists. The editorial that accompanied this in New England Journal, the editorialist was just like, "Remember we had this opioid epidemic because we were just prescribing people opioids." Do you have that kind of concern, Paul, as you're largely an addiction medicine physician these days, even though you like to be humble about it?

Paul: I've not seen enough of it to be concerned yet. It seems like it's on the uptick. I think that your point is well taken that there just seems, in general, to be out there in the [unintelligible [00:11:19] a sense of wild enthusiasm for ketamine as a use for almost anything like I remember for certain withdrawal syndromes. I've seen it thought forward for depression, for management of alcohol use disorder. It seems like we're just trying to look for reasons to use ketamine now. So, I think the wild enthusiasm is the thing that makes me probably a little bit more cautious. So, I've not seen it as a reason to be concerned in the patient populations that I've taken care of yet, but that doesn't mean it can't happen.

Rahul: I just want to say, there's one other source of bias that I could identify for ketamine looking better in this study, and that was something that the editorialist pointed out in the editorial. This is out of my area of subject matter expertise. So, this is an example of an area where having subject matter expertise can really enhance your critical appraisal. But the editorialist talks about how in this study, all of the ECT treatments started out as unilateral. From what I understand, as a layman, the intent of that is to try to reduce the incidence of side effects. But that's also less effective than bilateral ECT. And 40% of patients in this study had to be switched to bilateral ECT. If they started with a less effective version of ECT than what would be done for patients like this in the real world, that's another potential source of bias for ketamine looking better.

Matt: Rahul, so I think we should get hotcakes rating for this. What's your final take home? Do you think this is practice changing, not that you're prescribing either of these therapies?

Rahul: Yeah. From the outside looking in, I think this is a pretty well-designed study. There are a couple of sources of bias towards ketamine looking better. But what the study did persuade me of is that, at least in the short term, there don't seem to be obvious drawbacks to the use of ketamine. And looking at the primary outcome in different ways with different surveys and using different cutoffs, the results showed some consistency. So, this is encouraging, particularly for people who can't get ECT due to access or other

contraindications. I think ketamine could emerge as an important tool in the arsenal for these patients. So, I'm going to give this 4/5 hotcakes. I'm excited.

Matt: Yeah. I just think we've raised our concerns about dependence, so I think enough said about that. That should be with any substance you're introducing this kind of substance anyway. All right, so we'll move on [crosstalk] Paul?

Paul: Just real quick. I don't think I've ever had a patient that is identified as having been treated with ECT. So, in terms of having another possible option that is available to someone who has treatment resistance is also exciting of itself. So, you're right. We may not be doing it ourselves, but to have something in our arsenal is just at least nice to know about.

Matt: Yeah. So, I covered Paul, SKYLIGHT 1. This is a study of a new nonhormonal therapy for the vasomotor symptoms of menopause, which we talked about, Paul. I can't remember if it was SGIM or ACP, one of our conferences [crosstalk] that we attended this year. Yeah, maybe even both. So, this was a study by Lederman et al, and this was the use of fezolinetant for the treatment of moderate to severe vasomotor symptoms of menopause. It came out in The Lancet in 2023. And Paul, what do you think of the SKYLIGHT 1 as a title for this study, as a big trial head?

Paul: Yeah. No, I appreciate you asking, because I think I didn't have a whole lot editorial to add in terms of your review of this, but I don't think I understand the pun in terms of relation to vasomotor symptoms of menopause, if there even is one. How does SKYLIGHT relate to that? Because I feel like I'm missing something important here. And if it doesn't, then boo. I like it's just at-- [crosstalk]

Matt: You know what, Paul? I couldn't figure that out. Audience tweet at us if you know why it was titled that. They didn't cram in an acronym that I could find. So, I'm not sure, Paul. But they had SKYLIGHT 1 and SKYLIGHT 2. They had a SKYLIGHT 4. They've been using this name-- [crosstalk]

Paul: You are right, they really lean into it. So, it has to be something. I feel like I'm just missing something, so apologies to the trials.

Matt: So, the question here was does fezolinetant which is a neurokinin 3 receptor antagonist, does it reduce the frequency and severity of vasomotor symptoms and improve quality of life? They were also looking at safety. This is important because not everyone can receive hormonal therapies just because of contraindications. Some people don't want to take hormones. The 2023 NAMS, the North American Menopause Society has 2023 position statement on nonhormonal therapy. They actually included this as one of the highest levels of evidence in there. I'm used to using SSRIs, SNRIs, gabapentin, some of these for hot flashes, but this is now included in higher level of evidence within that guideline by NAMS. I was surprised to see that the guidelines came out in June and this study is from April, so they got it in there pretty quickly.

Paul: Yeah.

Matt: Let me tell you the topline results. So, this was another positive study and they looked at two different doses, the 30 mg and the 45 mg dose of fezolinetant, and they found that it is efficacious for reducing one of the coprimary endpoint, which was frequency and severity of symptoms. And the women had to have at least seven hot flashes a day. Actually, at baseline, all the groups had something like 10 or 11 hot flashes. And both of the fezolinetant groups by the end of 12 weeks had decreased to five hot flashes or less on average per day. In the placebo group, they decreased to seven hot flashes or so per day. So, both groups

decreased, but two less hot flashes per day with the treatment. The severity was a little harder to interpret because they were looking at a scale of one to three mild, moderate, or severe. And they said that it decreased by 0.25 points on a scale of 3. So, I don't really know what to make of that, but it was statistically significant.

They tried to look at sleep and it did not improve sleep disturbance based on the scale they were looking at. It seemed like there was some improvement in quality of life. I tried to look at this Menopause Quality of Life questionnaire they use, Paul, and it was a little bit hard for me to interpret the least mean square change in that.

Paul: This was actually a question I had for Rahul in terms of this lease mean squared comparison. When would you use that? Why would you use that? I tried to parse out the graphs and the figures in the study, and I was like, "Well, those lines look bigger than those lines." But other than that, [chuckles] I couldn't quite figure it out. So, would you mind talking me through that concept specifically?

Rahul: Yeah. Boy, this is an area that with regard to how it's done in this study, I'm not sure I understand well enough to be able to explain. But I do think that the use of this measure really what Matt was describing with the ordinal scale of mild, moderate, severe, and then showing a quantitative difference between those two. The way that they've reported this is not easy to interpret. That's in and of itself an important learning point in my view, because if results are not easily interpretable, then it's hard to know what to do with them.

Matt: Yeah.

Rahul: To me the 0.25 suggests that that's like less than one category improvement as the average treatment effect for this medication. What might be more informative is what percentage of women went from severe to moderate or moderate to mild. And that data might be available in the supplemental data. So, when I encounter an outcome measure that I don't really understand, I just think to myself, what would be the way that I would want to use this or how would I operationalize this? And then I look for that expression of the results in the supplement.

Paul: That's great.

Matt: Yeah, I like that. I didn't think to do that to look for how many women went from severe to mild or at least decrease their category fully. I just think that in general-- Let me make a complaint to both of you about research. I know we have this patient-centered outcomes are being coming more and more, but they put it in terms that you have to be a statistician to understand. Why not say, we use this scale. A meaningful change on this scale is this many points. We saw this many points. I feel like sometimes they don't want to give that information, because they just want to have the positive headline of, we had a P value that was significant, but really that doesn't translate always or often doesn't translate to something that I care about or the patient cares about.

Rahul: Yeah. I'll just put myself out there. I theoretically am the person in the room who's supposed to be the most interested and know about this stuff. But I encounter stuff all the time that I don't know how to interpret. So, I do a lot of googling. I do a lot of scouring Twitter to see what the discussion has been on some of the stuff. So, yeah, after we're done recording, I'll spend some time looking into this and I'll report back.

Matt: Maybe not tonight. Go to sleep. [Rahul laughs] Maybe another day.

Rahul: Yeah, not tonight. [crosstalk]

Paul: I feel like this is a [crosstalk] snapshot of our different personalities, by the way. So, Matt is like, "I think it might be obfuscation for holes like, this is a chance to learn." And me, I'm like, "I must be a dummy." I think this sums us up perfectly.

[laughter]

Matt: All right. Well, let me just [crosstalk] wrap up one or two more points about this study. So, there were two groups. They got a 30 mg dose, a 45 mg dose of the study drug fezolinetant or an exact match placebo. They had to screen 2,200 patients, Rahul, just to get about 175 patients in each group. And so, we both calculated, this is about 25%. Only 25% of the patients' screen made it into the study. Does that seem like a source of bias for you as far as the results go, this being a positive trial?

Rahul: Yeah, there's not that many tools we have available to decide how highly selected is a study population. One of the only tools that I think is routinely reported is in the concert diagram, the number of patients who are screened and the number of patients who are ultimately enrolled. So, I feel the best about studies that enroll a high proportion of patients who are screened. To me that suggests that the population is not highly selected or cherry picked.

Matt: Yeah.

Rahul: You feel great about a study. It's 95%, you may worry a little bit about a study that's 5% to 10% and ask why. That's not by just de facto a source of concern. It's just a signal that's a question we should ask.

Matt: Right.

Rahul: In this study, the biggest category of patients who are excluded was listed as other. So, no specific reason given there. So, that does raise my concern a little bit for selection bias in terms of the study population.

Matt: But the exclusion criteria couldn't have a cancer, either current or previous unless it was like a basal cell skin cancer, any chronic kidney or liver disease, even blood pressure above 130 systolic was like a no go. Or, if you were treated then it sounded like there was a little wiggle room there for the authors for this trial list to include you. But this was really a healthy group of women between the ages of 40 and 65, and they were from mostly US, Canada, and some European countries. I do think there were some sources of bias. Safety outcome wise, they were keyed in on some liver stuff because there were some other agents in this family of-- Paul, there're these things called the KNDy neurons. K-N-D-Y.

Paul: Sure.

Matt: It's an acronym.

Paul: Or, I know that, right?

Matt: This neurokinin, let me make sure I'm saying the right name now, yes. Neurokinin 3 receptor antagonists is one of a couple of different agents that they're trying to use to target these neurons, which are involved in thermoregulation and hot flashes essentially. One of these drugs previously had some signal for liver damage. That's why they're really keyed in on the liver. And practically speaking, for listeners, this has been FDA approved at a dose of 45 mg once a day for vasomotor symptoms of menopause based on this trial and some of the other ones. They want you to check liver enzymes at baseline, three months, six months, nine months for the first year, so basically, every three months for the first year that they're on the drug. In this study, about one patient in the placebo group, two patients in the 30 mg

fezolinetant group, and zero patients in the 45 mg group had liver enzymes above three times upper limit of normal, but no one had catastrophic liver issues.

Paul: There's no fulminant failure. Yeah.

Matt: Yes. So, it seems like it was okay. Rahul, before I give my hotcakes rating and whether or not this will be practice changing for me, did you want to give any other points about this one?

Rahul: Yeah. The only other thing that stuck out to me about this was a phenomenon that we've talked about on prior hotcakes episodes and that's the idea of regression to the mean. This is something that you have to look out for anytime enrollment in a study is contingent on a patient having some extreme value of something.

Matt: Yeah, the seven hot flashes.

Rahul: Exactly. Yeah. Not being a person who's ever experienced menopause. I don't know if that's a lot. It sounds like a lot. The patients, I think, in all the groups ended up having a mean of 10 or so, 10 to 11 per day. As you mentioned, we saw that even the placebo group declined down to six to seven or something and figure two shows that nicely. So, that is something that could be explained by a beneficial placebo effect or that could be this phenomenon of regression to the mean just by when you select a group of people based on an extreme value, over time they tend to regress to the mean. So, if you didn't have a placebo group in this study, you wouldn't know if that's why patients who got the study drug improved or not. So, this is another illustration of why placebo groups are really critical.

Matt: Yeah. So, I will give this hotcakes rating maybe a 3.5. I'm always a little skeptical of these fancy new medications, industry funded. Four of the authors of this trial were employed by the Astellas Pharma who makes the medication. So, I'm still going to wait a little bit. I think maybe if this starts getting rolled out to more and more patients, will some of these liver issues become more prominent? I think, in practice, it's hard to get a group of patients this healthy. So, I'm going to give it 3.5 because a lot of my patients in the 40 to 65 have been excluded from this. So, I'm not going to be rushing to start prescribing it for patients, but I do think overall, otherwise well-done trials. 3.5 hotcakes out of 5.

Paul: It's fair, I'm with you. It's so new and we have nonhormonal medications, even though they're not necessarily FDA approved. I was trying to look this up before we started doing this. The venlafaxine seems to reduce symptoms by 40%. So, not too far away from what's being reported here, especially since I don't fully understand the results here. I will probably lean on the ones where I know that venlafaxine is certainly an imperfect drug and has its own issues, but at least I know what those issues are, because it's been around for a while. So, I might just stall a little bit and see what else shakes out before I have too much wild enthusiasm for this class.

Matt: There's a special Paxil salt that's 7.5 mg daily that is FDA approved and has evidence. Yeah. So, anyway. I think we need to hear more on this, but I do think the audience needs to be aware of it, because patients are going to be asking about it. I'm sure they're going to be advertising. It's included in some guidelines with a high recommendation. So, I think we're going to start seeing this out there. Paul, you want to get to your article?

Paul: Sure. Yeah. No, timely. I'm going to tell you all about an article by Bramante et al, apologies if I mispronounced the name, from Lancet Infectious Diseases from just I think like this month. This is actually, I don't think even in the print yet. This is still ePublished right now. This is the outpatient treatment of COVID-19 and incidence of post COVID-19 condition

over 10 months. This is The COVID-OUT Trial, a multicenter, randomized quadruple blind, parallel group, Phase 3 trial. So, rolls right off the tongue. But basically, what they were looking at-- It's an interesting paper because this is a secondary outcome from another study looking at reducing the incidence of severe COVID with several medications I'll talk about. So, presumably, our listeners have heard of COVID-19 at this point now, and also long COVID [Matt chuckles] and prevention of long COVID.

It's starting to feel blessedly less relevant right now. I'm not treating and seeing as much COVID, though it's still out there and I still think we're thinking about. So, in any case, I think the paper does have some relevance, and also maybe even mechanistically understanding what's going on here. So, the research question, just to actually get to the meat of what the paper is, does outpatient treatment with metformin, ivermectin or fluvoxamine soon after COVID infection reduce the risk of long COVID? So, the investigators were looking at, do any of these study medications reduce the incidence of long COVID?

The long COVID question is important, because of all the patients that have had COVID, which feels like everybody at this point now, there's almost 20% according to the CDC reporting symptoms of long COVID, which unfortunately, to my mind, long COVID is not super well defined, other than having symptoms that persist longer than three months that can't be explained by something else, which still seems a little bit unsatisfying to me, but I just don't think we have anything better right now. It's also worth noting that long COVID disproportionately affects patients who are from racial and ethnic minority populations. So, it's important to figure out what's going on here and what things that we can do to address it.

So, I'll talk about the study design in a second, but the top line result, the thing that we should be thinking about as we're going through the study design is that, outpatient treatment of acute COVID with metformin, specifically of the medications that we're talking about, reduced long COVID incidence by 41%. This is important because that's a big number. We have something that has a fairly high incidence and prevalence and metformin safe and low cost and easy for people to get. So, how do they actually figure this stuff out? Any questions so far before I roll on, because that was a lot of words out of my mouth.

Matt: Yeah. One comment was that, because I looked this up, because 70% of the patients in this study had delta variant and maybe a third or something had the Omicron variant. Now Omicron has been the most recent variant as of this recording. Look, there was a paper that just came out recently talking about how about 10% of patients are progressing to get long COVID after the Omicron variant. So, that was my comment. The second thing I wanted to ask, Paul, the 41%, that was a relative reduction in COVID, right?

Paul: Correct.

Matt: The absolute reduction was like 4% or something?

Paul: It's 4%. Yeah, exactly.

Matt: Yeah. Rahul, can we call that a number needed to treat of 25 based on this? Is this the right type of study where you can calculate a number needed to treat, absolute risk reduction of 4%, roughly 25?

Rahul: Yes. The short answer is yes. Anytime you have an absolute risk reduction, you can equivalently think of it as a number needed to treat over the timeframe of the study. There is a slightly longer answer when you're using person time data like this that is not important for us to go into it on the air. But I did find this explained beautifully in a short letter that we can link in the additional reading section for this one.

Matt: Okay, great. Thank you. All right, Paul, sorry to interrupt.

Paul: No, I think this is good. But how the study was designed, I am fascinated by, just because it's complicated yet understandable, which is my perfect combination as far as I'm concerned. So, this was, as I mentioned, investigator initiated randomized quadruple blind, which means I think that you had to have your eyes closed when you wrote the paper. I think that's the last part of the blinding. It was placebo controlled. The primary outcome that they looked at was severe COVID-19 by day 14. And then the secondary outcome, as I mentioned in the focus of this paper, is the incidence of long COVID. And so, basically, what they did is they followed the patients over the course of 300 days with monthly follow up identifying who got long COVID by asking them, did your doctor tell you that you had long COVID? And then they went to the chart and confirmed that.

Matt: [chuckles]

Paul: The patients were recruited remotely. There was no direct patient contact. It was via patient portal, online advertising, and then their advertisements of the six clinical sites. You could make an argument that that might select for people who have a little bit more access to technology or a higher technological literacy. But not so much that I had a huge problem with that. It's a factorial design, so that the patients were randomized. All right, brace yourselves already. They received either metformin plus ivermectin, placebo plus ivermectin, metformin plus fluvoxamine, placebo plus fluvoxamine, metformin plus placebo, or placebo plus placebo. So, everybody got two pills. It's this factorial design that allowed them to compare and contrast the actual true effect of the medications that they were looking for, if I understand things correctly.

The medications were given for 14 days. They delivered. They were prepackaged. The statistics that they studied, which I found fascinating, is the time between consent and the ingestion of the first dose of study medication was, on average, less than a day. So, by the time that the patients were qualified for it and consented for it, they had the medication the same day, and it was in their stomach. So, fascinating how efficient things were. And then after 60 days, surveys were sent every 30 days, up to date 300 via email, text, phone call, letter depending on what the patient actually preferred. So, so far it makes sense.

Matt: Yeah. I think a lot of the country was still locked down when this was happening too. So, that's even more impressive that they were doing this.

Paul: Yeah. Rahul, maybe you can jump in here and correct me if I'm wrong. But the decision to study this I think occurred after they had already designed the study to look at the primary outcome. I don't even think long COVID had been defined as a thing and then they decided to attack this on as a thing to study in additional, which is, again, not a criticism necessarily, but I just think an interesting that this was pretty early on in things when they were actually putting this together.

Rahul: That's right.

Paul: So, the patients that were included in this, they were aged 30 to 85. They had to be either overweight or obese and had COVID symptoms fewer than seven days with a documented positive antibody PCR or antigen test within three days of enrollment. Patients were excluded if they had prior COVID, if they were previously exposed to the study drugs, which I think is really important here, which means for most patients who have, say, type 2 diabetes who or on metformin were not included in the study population. And then patients who were treated with any of the EUA FDA medications were also excluded. Vaccination status did not impact enrollment. And then also importantly, pregnant and lactating patients

could be enrolled, but we were only randomized to metformin just for safety's sake. So, that is the study.

So, at the end of the day, we talked about the decrease that showed for the patients solely with metformin. The other study medications did not show a decreased incidence of long COVID. In fact, that was consistent with the primary outcome as well. So, the metformin reduced the development of severe COVID-19, the other medications did not. And then similarly with the secondary outcome that's being looked at here, only metformin showed a reduction in the development of long COVID, the fluvoxamine and the ivermectin did not show those things. So, this was the one medication that seemed to actually have real promise.

Matt: This was surprising to me, because I remember the initial results of this study coming out because that was part of the ivermectin fight that I think is somewhat-- Maybe it's still going on-

Paul: Thank God, that's [crosstalk]

Matt: -that's why I try to keep my head out of it. But the ivermectin that was part of that fluvoxamine-- Because I had patients calling me asking, should I take fluvoxamine, should I take ivermectin? We were trying to find off-the-shelf medications that already were around, cheap, and we know are safe to give to patients that would work. As you said, they tacked this on. What is the mechanism with this metformin? Did they say they?

Paul: They have a theory. Now the theory is that there are some that-- This is the usual theory for most things. There're some anti-inflammatory properties that for listeners at home, there's some hand waving going on there. And then there is potentially antiviral effect. Though I looked at the papers that was referenced and that seems to be primarily an in vitro and ex vivo effect and that has not been demonstrated in other circumstances. So, it really is purely theoretical at this point.

Matt: Yeah. Well, so, Paul, is this going to change practice for you? Where we are right now fortunately? I think people are largely demasked and we're not having our hospitals fill up with patients with severe COVID. So, I'm not sure if you'll be prescribing this for your patients if they call you and say, I have COVID.

Paul: No, I think that's right. This is not practice changing for me. I do think it's compelling because I think it hopefully offers some mechanistic information for people smarter than me as to who might develop long COVID and how it works, and some of the immunology behind that. I think the relationship between COVID-19 and the development of new diabetes, for instance, is really interesting. Patients with diabetes had worse outcomes and yet these patients without diabetes who were put on metformin seemed to do better. So, what do we do with that information? So, I'll leave it to the pharmacologist and the immunologist and the virologist and on and on to figure out exactly what that means. But it seems like there has to be some mechanism there that hopefully can be taken advantage of, maybe help patients or prevent God forbidden future pandemic- [crosstalk]

Matt: Future pandemics. Yeah.

Paul: -post-viral complications. So, I think it's promising and compelling, but is not practice changing I agree. So, if I were to give a hotcakes rating, I think probably 3 for being interesting, but I have to dock it for not being immediately practice changing.

Rahul: Yeah. When I read this paper, I couldn't help but think, if I had read this in 2021, that would be a totally different feeling for me. It just is a reflection of the fact of-- This is a

problem that affects all of the literature on COVID therapeutics, which is that the study populations that those were carried out in just don't exist anymore. PINETREE, the studies of nirmatrelvir, ritonavir. All the studies were carried out in a largely unvaccinated population. And nowadays, it's thought that upwards of 95% of people have some degree of immunity through combination of vaccination and prior infection. In this study, in their subgroup analyses in figure three, they did break out the results by vaccination status and the effect was attenuated completely in patients who were vaccinated.

So, the utility of this knowledge in 2023, I agree, we're really in a different place than were when we first learned about long COVID. All the millions of people who are affected by persistent symptoms, this is still an unmet need and deserves real attention and careful thought and problem solving. But I'm just worried that this study population is going to be really hard to identify in the current day and age.

Matt: Yeah.

Paul: Yeah, find someone who has not been exposed or who's not had a COVID infection now. It's almost not easy to do-- [crosstalk]

Matt: Yeah. Or been vaccinated 16 times.

Paul: Yeah. [laughs] Exactly.

Matt: So, let's move on. We have two quick hot takes. So, the USPSTF, Paul, who we've been doing some shows with recently, have put out a draft recommendation on breast cancer screening, which is certain to make a lot of headlines once it's finalized. I think we're certainly going to look at-- Right now, we're screening people at age 50 every other year, so every two years, starting at age 50 for women who are at average risk. And now they're going to start to recommend screening every other year for women at age 40 up through age 74. So, this is a big change, dropping the age by 10 years. They say that this is driven by, we're seeing breast cancers in younger women, and also there are some disparities, especially particularly black women tend to have worse outcomes with breast cancer. And so, they're hoping that by starting the screening age earlier, more people will get screened will catch more cancers, more people will benefit from this.

The other two things they comment on are, what to do with women over age 75. They continue to give that an I grade, which is, we don't know, inconclusive. The same thing for what to do with women who have dense breasts, which, again, they gave an inconclusive rating there. Do we get supplemental MRIs or ultrasound, which is a question I get all the time and I just don't have a good answer for. So, basically, we do whatever the patient wants. Usually, they're coming into me with an opinion about what to do. Paul, any comments on that?

Paul: No, I think that'll be the challenge. I'll be curious to parse through all of the data that went into the recommendations and calls for revision. By moving the age to a younger bracket, we're going to be seeing more women with dense breasts. Since there is uncertainty as to what to do with that, I'll be curious to see how that plays out.

Matt: Yeah.

Paul: So, I'll have to really do the deep dive in literature.

Matt: Yeah. So, the American College of Radiology and the Society for Breast Imaging, they put out a joint public comment, Paul. And this is not just like, we think this is good, we think this is bad. This is like 11-page document. There're 37 references. They are taking-- line by

line they go through about what they agree with, what they disagree with. So, they agree with the screening age of 40, but they think it should be annual screening of women starting at age 40. They think that we should continue to screen women, not just indiscriminately stop at age 74, but that we should continue as long as the woman is in reasonably good health and has a reasonable life expectancy. So, I'll link to that as well.

To me, looking at this someone who's not an epidemiologist, this seems like you have a bunch of smart epidemiologists at USPSTF and clinicians there and then you have a bunch of smart people, radiologists, and the people in the Society for Breast Imaging who have just a differing interpretation of the literature. The ACR and the Society for Breast Imaging, they were upset that no breast experts were included in the USPSTF group making the recommendation. That was one of what things they called out, but that's it. Rahul, as an epidemiologist, any comments on this? Is this normal for epidemiologists to fight over the same data set and have different conclusions?

Rahul: I think you have both hit on important points about the challenges in translating recommendations for a population to the care of the individual patient. We were talking before starting recording about, if you have a patient who's living a very healthy life and has an expected life expectancy of many more years, you might decide to continue screening after the age at which the recommendations say, you can start to peel that back. So, yeah, it takes a lot of individualized thought. This kind of tension exists a lot between clinical medicine and public health for sure. It's difficult.

Matt: Yeah. All right, Paul, so take us home with-- Tell us a little bit about kratom, which apparently-- It's not new, but maybe new to some people in the audience who aren't in the loop with this kind of thing.

Paul: Yeah. It's something I heard of relatively recently and I think I saw it even advertised when I was doing my tour of that. I believe it was the Southwest, where I saw billboards for it and advertised availability. So, it's around and has been around. So, kratom, for those of you who don't know it, is not a specific substance actually. So, kratom derives from the leaves of a tree that's indigenous to Southeast Asia, where it's actually been used there for centuries-- as I wrestle with my cat, apologies, where it's been used for centuries as a medication. It's been used to treat things like hypertension and chronic pain and cough and fever. It's been used a lot. The way it was traditionally used is you would either chew the leaves or brew it into a tea, which becomes relevant because of course, as it's made its way west into the United States, we're now selling it in this hyper concentrated form at doses that-

Matt: Of course.

Paul: -previously people have been exposed to, because if a little bit is good, then a ton is obviously much better.

Matt: Doesn't Red Bull have like a kratom flavor or something?

Paul: Well, I think it is included in sodas as well, because the taste is apparently fairly gnarly is my understanding. So, anything to mask the flavor is probably an important thing to do. It has over 40 alkaloids, I want to say, and probably the most important ingredients-- I'm going to probably butcher the pronunciation is mitragynine along with 7- hydroxymitragynine which is actually a metabolite of mitragynine. It's fascinating. It seems to work on every psychoactive receptor there is. So, it is a mu agonist, but it works in such a way that it does not cause respiratory depression, sedation that is sometimes seen with opioids. It also seems to have some adrenergic agonism. It has some alpha-2 agonism. So, at different doses it seems to have different effects and includes-- People have been using it for

increased alertness, they've been using it for analgesia. I've heard about it being used as almost like a pre-workout, because if you're treating pain and also trying increasing your energy level, it makes sense, right?

Matt: Yeah. I heard that the stimulant effects are at the low dose, right? Forgive me if you already said this. The stimulant effects are at the low dose and the opioid effects, the pain effects are more high as you go up on the doses?

Paul: I believe that's my understanding. And then also, whether or not there are higher proportions of the 7-hydroxymitragynine is also important, because that's the one that is really active. I think it's like more I forget how many times, like, 10 times more active than morphine, I want to say. We'll go back and correct the show notes if I'm wrong about that. But certainly, more potent than morphine too. So, there's a lot of variability. The question is like, should we be panicked about this? The legalities behind it are fascinating, by the way, Matt. It is not recognized by the FDA as nutritional supplement. It was going to be made Schedule I by the DEA, but there is this large Kratom Advocacy Group, because people are using it to treat their pain that actually halted that and the DEA backed off, which I've never heard of anything like that. So, it is now listed as a substance of concern, but is not federally legal. It is not legal in certain states, but at the federal level, it sounds like as a result of advocacy by people who are really helped by it, it's just being watched for right now.

It's important to note, I think, it's substantive concern because of this mechanism, it seems to be safer than full opioids. The adverse effects are largely from case reports. It's not super well studied. Overdoses associated with it are almost always in the setting of polysubstance use. So, the question is, how worried should we be about that? And right now, we just don't know yet. There is this Dr. Kirsten Smith who's a recognized national expert on this, she's a PhD who has made kratom her whole expertise. She's quietly one of the most interesting people alive, has made really thoughtful and articulate pleas for just good research and good case reports on patients who are using it. So, the whole big takeaway for our listeners is, know that it exists. It's out there. It's becoming more prevalent. Maybe ask your patients who have existing opioid use or substance use about their use, so that you're aware of it. But it's not something to panic about yet, but just keep your eyes open and pay attention to it. I should mention case reports of people with kratom use disorder, and people who've developed the dependency and withdrawal syndromes to the extent that they are actually even treated with buprenorphine.

Matt: Wow.

Paul: So, there are people who are treating kratom use disorder. So, I'm not suggesting it's entirely benign. I'm just saying it is not super well studied, and there's not a whole lot that's known well enough about to make broad sweeping generalizations, but just keep your eyes peeled because it's becoming more prevalent here in the West.

Matt: My recent trip south in gas stations in, I want to say Virginia, South Carolina, they just had it right there at the counter. So, it's [crosstalk] around.

Rahul: Gas stations?

Matt: Gas stations.

Paul: Yeah. It's at gas stations, pet shops. Yeah.

Rahul: Wow.

Paul: I should mention real quick, and I'm sorry for running so long about this. The other really fascinating use for this is for harm reduction. So, patients with opioid use disorder who are experiencing withdrawal have been using it to mitigate those withdrawal symptoms, and successfully I might add too. So, there may even be a therapeutic role for it. But again, it's still very new kid on the block and not a whole lot is known about it, but it's just something to watch, I think.

Matt: Paul, did you want to promote a podcast by Dr. Kirsten Smith?

Paul: Oh, yeah. She was on The Addiction Psychology podcast. There was an episode with Dr. Smith about kratom use specifically that I thought was really eminently listenable and really, really helpful. She's written about 20,000 million papers on it. So, we will link to a couple of good reviews in the show notes.

Matt: Excellent. All right. Well, guys, I think we've done a great show. Any last comments before we get to an outro?

Rahul: I'll just say, I was poking back through the methods section of the hot flash treatment paper. I stand by what I said. It's really confusing.

[laughter]

Rahul: I don't think I fully understand. I also asked ChatGPT to explain it to me like I was a 12-year-old. It didn't really make it that much clearer. So, I feel better about that.

Matt: Oh, that's a good idea. I should start doing that for statistical stuff to see if it helps. Maybe it will.

Paul: Which makes me feel world better, by the way, Rahul.

Rahul: [laughs]

Paul: If this is where you're at, I feel like heroes. That's great. Thank you for sharing that.

This has been another episode of The Curbsiders, bringing you a little knowledge food for your brain hole.

Rahul: Yummy.

Paul: There, it's your time to shine, Rahul. 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 each month, you'll get our Curbsiders Digest, which recaps the latest practice-changing articles, guidelines, and news in Internal Medicine.

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Rahul: I've been Dr. Rahul Balvant Ganatra.

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

[music]

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