Ruhoy and Kaufman AMA - Ask Me Anything. May 2024.

Edited Transcript - with headings, improved spelling, speaker names, and more.

A Clinician's Roundtable by Renegade Research - a 501(c)(3) non-profit, decentralized organization pioneering patient and caregiver-led research with a focus on MECFS, Long COVID (LC) and other Infection-Associated Chronic Illnesses (IACI). Donate, Newsletter Sign-up.

YouTube video that goes with this transcript.
Subtitles on video have been edited to closely match this transcript.

Table of Contents

[Isabel Ramirez-Burnett, CEO of Renegade Research]

0:00 Welcome everyone to today's session.

This roundtable is a special session. It's an AMA - ask me anything - with Dr. Ruhoy and Dr. Kaufman. They were at our roundtable, our first one, on March 15, and there were a lot of questions that were left unanswered so they have very graciously come back and given us their time to answer additional questions. So, thank you so much for being here. Thank you to our team at Renegade Research as well, for all of the efforts and putting all of this together. And thank you for you guys for attending.

A few housekeeping things: just wanted to let you know that we also have a roundtable this Friday at 1 PM Eastern with Todd Davenport. We also have another one on May 17th at the same time and that's going to be with Dr. John Haughton. And then in June, we have an amazing three-part session with Dr Afrin and that's going to be all about MCAS. So, tune in. All the registrations are up on our website. Everyone is welcome to join. And without further ado, we're going to have Dr. Ruhoy and Dr. Kaufman answer our questions. Thank you for being here.

[Dr. Ruhoy] Thank you for having us back.

[Isabel] Absolutely. Like we said before. Anytime. The floor is yours. All right, so we're going to start with our first question and that is,

01:35 Q&A

01:37 MCAS-when is it evaluated?

"Where do you rule out if MCAS is not a major factor and how many treatments do you go through and how long before ruling it out?"

[Dr. Ruhoy] That's a really good question, because I think, I mean, David, obviously you can interrupt me anytime you want, but you know I think that MCAS is always on our mind because you know those cells are very can be very reactive based on infection for sure and other kinds of exposures and so we always we always try to rule it in or rule it out. And I think you know, David and I talk a lot about how sometimes it's hard to rule in based on labs, but clinically sometimes it's very obvious that there's a mast cell component to the symptoms that a patient is having.
[Dr. Kaufman] Yeah. I would reverse it and basically say that when I meet a new patient or have current patient, I assume they have mast cell activation disorder or syndrome until proven otherwise. And proven otherwise means not finding negative labs, being unable to get confirmatory labs. It means not having even the slightest hint of an improvement with various efforts at treatment .
That's something not everybody agrees with. When Dr. Afrin speaks in a couple of weeks he will disagree with that he strongly feels you have to have positive labs. I don't find
that to be necessarily true, partly because it's hard to get positive labs and it's such an important diagnosis that I think we need to use some clinical judgment when we're making those decisions.

Yeah, I mean the labs themselves are technically difficult so it's hard to really know if they've been handled appropriately and if the if the normal result is actually valid and so I will occasionally repeat them I have found that when a patient is having what they refer to as a flare, um I have more yield with regard to those labs I have found positive labs where previously they were negative when a patient is having an acute symptom that clearly seems related to mast cell activity. So I do think there's a level of timing involved in the workup, but regardless you know I think both David and I, we both just treat empirically actually exactly that there's mast cell activity going on. And if patient symptoms improve I think we have our answer.

So. I'm sorry. No go ahead. Yeah so I and, I would add to that, or clarify, that I'll often it's often one of the first things I'll do in the first appointment first time I meet a patient let's let's have a trial of H1, H2 blockers antihistamines and Pepcid and they will say, the patient will say, well what should I look for what symptoms should I focus on, and my answer in general is I'm not going to tell you that because mast cells can do anything. They can do everything. They can cause anything you can think of, I mean, not them, but their mediator release. And it's important because otherwise I think the response gets missed or can be missed by the patient. So as an example, recent new patient take Zyrtec twice a day and Pepcid twice a day, message me in two weeks. Message in two weeks my brain fog is better and I don't have urinary frequency anymore. Now I would not have necessarily labeled those as the two symptoms to look for, and yet that's for me confirmatory evidence that this patient has Mast Cell Activation.

Yeah it should also be pointed out that you know there's 1,200 mediators of the mast cell, so it's not just about antihistamines - used to be a thousand just keeps growing, - just keeps growing, exactly, and some are already packaged and ready to go at the drop of a hat. Some are synthesized, you know, at the time of the assault or infection or exposure um, but regardless there are many, many mediators that are not histamine. So I think that's an important point because some of those mediators create some of the problems. And so um we have to sort of recognize that it's not just about the histamine.
[Isabel] This is not part of that question, but I think it's complimentary.

05:38 MCAS treatment order?

“Do you have a treatment order or do you choose your medications based on, you know, whatever symptoms are presenting at the time?”

A little of both I think. I'm really, I'm really a fan of stabilizing the mast cells overall so that you just get less release of most of the mediators. I know a lot of doctors really focusing on the antihistamines and I'm not saying one is right or wrong or better or worse, but I really just believe because there are so many mediators that if we can stabilize the mast cells we can probably get a lot of other clearly non-histaminergic related symptoms under control.

Yeah, it's a good question because Ilene and I were just talking about yesterday, at the end of the day. So traditionally or conventionally, we would start with the H1, H2 blockers and escalate up progressively from there. That's kind of the way doctors are taught and trained. You start with the

easy least expensive, least risky things and you gradually increase. I still do that most of the time, but I have to say every time I do it, I scratch my head and I say why am I doing it this way. I should start with the stabilizers or even the next level which is, are drugs like imatinib because I know that's where we're going to end up. But I still often especially since I'll do it on the first visit do the H1, H2 they're cheap easy to take inexpensive, minimal to zero side effects. You can buy them you know in any drugstore and a lot of times you get very good results.
[Isabel] Okay. All right. So the next question is,

07:18 Tests for MCAS?

“Can we find a list of the tests that you order anywhere? Are they published somewhere?”

[Dr. Ruhoy] I mean. Not that I know... No they are... [Dr. Kaufman] Sure they are. I mean, Larry's papers and things. He has a whole that's list of what the workup is.
Yeah. Are they asking specifically about our workup. Or... Yes, the workup that you do. Okay so I haven't published my workup yet. Okay. I mean, we can say it. Yeah if you want to go ahead and say it that's great. Sure. So I will order and it's different I think for different docs so I'll start only with blood work. I don't do urine testing in the beginning because it's a pain in the neck for the patient. And it's histamine, chromogranin A, prostaglandin, and D2.

I don't do heparin because it's nearly impossible to get a measurement of that out of the regular labs. Am I missing one? And D2. No. Those are the three biggies. If they're negative, I usually repeat them. If they're still negative and I'm still suspicious and I still feel the need to get confirmation in the labs, which I often don't feel the need for, then I might go for urine testing which is for several different chemicals. If there's any history of endoscopy done within the last five years or so I will always try to get special stains called CD17 on the biopsy pathology material if it's available. That's a great way to confirm diagnosis. I think tissue samples are just ideal. I mean labs can be hard and they can be pointed in time and sometimes show up normal. I do what David said. I add MMP9, which is a protease that targets collagen, and it comes from mast cells, so I like to see the levels of that. I often find them elevated. I also do an early Sjögren's panel because the salivary glands are so concentrated in mast cells that if there's excessive activity, there's usually at least one antibody that's elevated. So I ... sometimes I think if I'm thinking about different treatments, and, if certainly the first line treatments fail, I want reasons to try more aggressive type therapies, so I'll do an early Sjögren's panel.

And sometimes I'll do an antiphospholipid antibody panel, though not always, but sometimes just based on symptoms. I will say that I do that core group of tests that David had said, and I add as I said the MMP9, but based on symptoms that a patient gives me, I might add other things on because of, again, the other mediators and the mast cells. We don't have assays for all of the mediators. We can't test for all of them, but we can test for quite a few so sometimes I'll tailor it based on the patient's history and symptoms. Yeah, I actually do the antiphospholipid and early Sjögren's routinely on every new patient, but I don't think of it as related to mast cells. So, that's very interesting.

[Isabel] All right. Thank you. All right. So next question is

10:16 Lorazepam-how does it work?

“What do you think is the mechanism for why lorazepam can give temporary Improvement to ME symptoms?”

[Dr. Ruhoy] I think benzodiazepines in general get a bad wrap. I think when used appropriately, they're a great class of medications. They bind to the neuronal GABAA receptor, which is actually a chloride channel, a ligand gated chloride channel. And, what lorazepam does it actually enhances the binding of GABA to the receptor. So, and what that does is it increases the frequency of the opening of the chloride channel, so not the duration, and so it just results in basically what's referred to as hyperpolarization of the membrane. And so there's a reduction of neuronal firing and that's how it's an inhibitory, how it has its inhibitory effect. It basically enhances the inhibitory neurotransmitter GABA.

That's what it does, and so there's inhibitory neurotransmission. And that's why there's, you know, there's a sedative state. It's relaxing.

It enhances parasympathetic. And so because it puts the body in more of a parasympathetic state, it actually reduces the the triggers of the mast cells so the mast cells are stabilized. They release less of everything basically. And so that is what, how it's thought to work to help stabilize the mast cells, just by its effect on enhancing the GABA function.
[Dr. Kaufman] I would just say that in the way you phrase the question, why does it help ME patients? I think the answer is it helps because it stabilizes mast cells. And again it comes back to what we think is that MCAS is such a major player in ME/CFS. And the more the more you read the ongoing research, the more evidence we have of that. So yeah, benzos are great drugs. They have a terrible reputation. One of the most frustrating things I experience is these... the absolute resistance and unwillingness of other physicians to prescribe it to our patients. It's infuriating, frankly.

[Dr. Ruhoy] And interestingly, it doesn't have to be at high doses; so, they get really great benefit at very small dosing. I think that there's no reason to give it, to NOT give it to them.
[Dr. Kaufman] Right. And unlike you know the reputation of drugs of abuse, they don't ask for increasing doses. They don't develop tolerance. They don't abuse it, and I've actually not even seen a withdrawal problem when we stop it.
[Isabel] Right. All right. Next question:

13:00 Metformin for Long Covid?

“What is your opinion on metformin for treating long covid? Any potential issues on its own or in combination with the other treatments you use?”

[Dr. Kaufman] Well, I think the literature for metformin in Covid and long Covid is is pretty compelling. There are very good trial results and it's a very easy drug to take with remarkably few side effects. I had covid finally and I took my metformin right away. And in terms of long covid, I think it clearly reduces the risk of of long covid after you've had covid. I don't think we fully

understand the reasons, but almost for sure it's related to, you know, decreasing insulin resistance that occurs with illness and its mitochondrial effects.

[Dr. Ruhoy] Yeah. No, I agree with everything you said. I don't think we completely understand its mechanism in terms of long covid, but it just it does pose the question with regards to glucose metabolism and and glucose dysregulation and insulin resistance as, you know, what role is that playing in in these chronic illnesses because metformin is definitely very therapeutic for many many of these patients.

[Dr. Kaufman] Yeah, I have many of my ME/CFS patients unrelated to covid taking metformin because I find it beneficial for them and they find it beneficial excellent.
[Isabel] Okay.
[Dr. Ruhoy] I wonder, you know, with regards to the mitochondria of course, there's that mitochondrial aspect. You know when you think of chronic fatigue, we find a lot of a mitochondrial component that's, you know, very significant that needs to be addressed. And so metformin has been known to sort of support mitochondrial bioenergetics and mitochondrial respiration and so and helps to reduce mitochondrial stressors. So I think that there's also a level of its effect on the mitochondria that seem to support improved symptoms in patients with long Covid and ME/CFS.
[Isabel] Have you seen any

negative responses?

[Dr. Ruhoy] Negative meaning well I mean sometimes you know anybody with mast cell activation can have a negative response to any medication we try, certainly initially. But no, not in general with metformin.
[Dr. Kaufman] Yeah. I certainly have never seen any problems with hypoglycemia or anything like that. I mean the only negative is GI. Many, not many, but some people have GI, you know, discomfort diarrhea, epigastric pain, etc. Usually that can be completely avoided by slowly tapering up.

[Isabel] Okay. Next, go ahead. Did you have something else to say? Dr. Ruhoy, did you have something else to add?

[Dr. Ruhoy] I was just thinking about the gut effect, because it delays the absorption of glucose so sometimes I've sort of guided patients in terms of what foods they eat, so that there isn't a glucose load. Because the metformin will delay absorption of the glucose, and so sometimes, I think, that, you know, it can be, it can result in an osmotic effect if there's too much glucose that's not being absorbed. And I'm just you know sort of speculating that's I maybe you saw my face and that's why you thought I had something to say but I was just thinking about what David had said with regards to the gut effects. So I do often ,will just sort of counsel patients. I should say I, you know, I don't preach to them, but I counsel them on potential food choices while taking certain medications and Metformin being one of them because of its effect on the intestine.

[Isabel] Thank you. All right. The next question is

16:40 Triple therapy in ME?

“What is your opinion on triple therapy in ME? Do you use it and if so in what cases?”

[Dr. Kaufman] All right. Well, this is cool. What is triple therapy? Sorry, but I don't know what that means.
[Dr. Ruhoy] Referring to the triple anti-coagulant therapy.
[Isabel] Yeah.
[Dr. Kaufman]
Oh oh oh. Okay. Ilene, I'm going to let you answer that one. and then I'll ...

[Dr. Ruhoy] So okay I so ... I don't do triple anticoagulant therapy. I will do mono and I will occasionally do dual. I feel that I don't... I've read all the research and I've read the literature and I understand the reasons why some doctors have chosen triple anticoagulant therapy. It is not all that convincing to me. And, in fact, in sort of the vascular neurology world, the stroke world, you know, there was a large study that showed, you know, we were putting everyone on aspirin to prevent strokes, right? That's what we've done for decades. And there was a large study that showed that in fact what we were doing was increasing their risk of bleed more so than we were protecting them from strokes. So I don't think that these drugs are without concern. And so I, you know, ...well I believe in anticoagulant therapy because I do agree that there seems to be an increased risk of clot formation in Long Covid and ME/CFS patients, I don't believe in the triple anti-coagulant therapy. I just think that puts my patients at too great of a risk for my comfort level. And so I, but I do do anticoagulant therapy. I start with an aspirin and sometimes I'll add Plavix or Brilinta or another, a second anti-coagulant, pentoxifylline, I've been using a lot more. I've been getting a lot of great response with that. So that's where I stand on the triple anticoagulant.
[Dr. Kaufman] Yeah I totally agree with Ilene. I think the question actually is an opportunity to make a point here. *Virtually everything that we do in ME/CFS, Long covid world is, treatment-wise, is off label.* Meaning there is no FDA indication for the drugs we use. There are no FDA indicated drugs for these problems. Okay, so for me and I know for Dr Ruhoy the decision is a constant assessment of risk versus benefit. It's a calculation. I have zero hesitancy to say go by Zyrtec and Pepcid, as an example. Triple anti-coagulation- there is no solid clinical trial data to support that yet.
And while there's some compelling evidence the risks of triple anti-coagulation are pretty daunting. They're pretty huge. Take an orthostatic intolerant, ME/CFS patient whose heart rate pops when they stand up, put them on triple anti-coagulation. And then they have a fainting or syncope episode and hit their head on the ground. Game over. And I'm not going to take that chance. Yeah.
[Isabel] Thank you.

19:45 Clinical trial info?

“What is the best way for clinicians to be informed about available clinical trial opportunities for patients with long covid?”

[Dr. Ruhoy] That's a really good question. I don't there's a centralized place where they are listed.I mean, I know clinicaltrials.gov has, you know, it's list. Every clinical trial that's available but is there a specific location long Covid trials I think right Yeah. I think recover the the NIH program has a list of trials right. The question of course is how do you access those trials. Most of them not atypically

most of them are being done in major academic centers. They're not working with frontline clinicians like us. That's meant as a criticism by the way. okay um and so you know they're hard to access or can be hard to access.
[Isabel] okay. Next question.

20:42 Rx & supplements you use/watch?

“Please address what prescriptions you use in our watching for more clinical findings but also what supplements you use and are watching for additional information.”

[Dr. Kaufman] Could you say that again? I didn't quite follow that question.
[Isabel] Yes.

“Can you address or speak of what prescriptions you use and which ones you are watching or waiting for more information, and also the same for supplements?”

[Dr. Kaufman] Well, that could use up the rest of the hour. I think.

[Dr. Ruhoy} That's a lot. Yeah. You go, David you go first.
[Dr. Kaufman] Yeah. I'm trying to think. Okay so I'm going to pass on the part that says what are we using because that could take a long time. I mean, we use, I prescribe a lot of different things. And focus for a minute on the watching, all right? So, I am watching and also using and also reading endlessly and participating in some research projects on drugs like the triple anti-coagulation. I'm not doing that,

I'm watching it. Rapamycin, more general use of metformin, plasmapheresis, stellate ganglion block, although not FDA approved - exosomes, stem cells. I am uh looking at a drug I learned about from Ilene called ibudilast, which looks really interesting.Trying to think-

There's so many drugs like this. I should have prepared for a question like this. Ilene, where you go?

I would say most of the immunotherapies, right. I think, we both, we talk a lot about, David and I, that is about how we are diving into more immunotherapies that really do seem to hold some benefit for a lot of our patients. None have proven to be a complete cure yet but I've had a lot of patients respond well to different immunotherapies. And what makes it nice these days, and I think I might have said this at the initial webinar we gave, but is that - now we have these nice targeted therapy. So as opposed to the old guards - which just sort of shut down the immune system, now we have ones that just sort of target a piece of the immune pathways. And how you pick and choose really, there's, I mean, that's an art over science at this point,
to be completely honest. And I suppose that's one of the things that I'm watching and reading and waiting for, to learn more about, but I still will sometimes try trial them on certain patients. And so I think that a lot of you know, there's a lot of immune dysregulation in these patients. And while we rarely find a particular autoantibody, there's clear immune dysregulation because you can do lots of

labs with regards to the immune system function and the health of the immune system. And they usually are off, so that's where immune therapies, I think,
have played an important role for patients. So along those lines, it's that those classes of drugs of which there's quite a few classes in the immunotherapies, so I've been watching and waiting and reading on those. With regards to supplements, I mean and I have to say, I know this is an unpopular opinion, but I, you know,

I think our patients are just, they're, I mean they're very sick obviously. And they've been chronically sick importantly. And so I don't think that supplements are going to be the answer.

I think they are good for a supportive role, an ancillary role. I think and I definitely advocate for targeted use of supplements when we've identified a particular pathophysiologic problem. But I have patients who come in and they are on like 30 different bottles of supplements, and I just don't see where that's frankly good medicine. And I, you know, they're not FDA regulated. They're not, interactions between them and the drugs that the patients are on are not are not monitored or not studied. So I don't think, so there aren't any supplements that I'm waiting and watching and waiting to hear about. I have like a a handful of favorites that I think are effective and are good. Like I said, supportive use, but beyond that

I don't feel strongly that supplements are going to be the answer for our patients. [Dr. Kaufman] Yeah, I'm going to chime in. I completely agree on the supplement issue. Patients come in with two pages of supplements often, and I'm sitting there discussing Mast Cell Activation Syndrome, and I can't. In the back of my head, there's this voice that's saying two dozen supplements. Think of those excipients. Maybe that's why the person keeps, is not getting better. And it's
a difficult situation. I understand why people take supplements. They're desperate and it's available. You don't need a doctor. And there's constant chatter and buzz online. But I worry about all the excipients, the lack of regulation, and that we don't really know, you know. I mean, yes, I do use some supplements, but fairly stingy I would say.
[Isabel] All right next question is...

25:53 CCI - what %, how affects symptoms, tx?

“What percentage of your patients have CCI? How much of that is affecting the symptoms? And what is your line of thinking for treatment for the different categories of patients with CCI?”

[Dr. Ruhoy] I think that the majority of chronically ill patients have some level of instability somewhere in their cervical spine. And I think that because I very regularly get their MRI of the cervical spine and I see instability. To the extent that it is moderate, severe, and contributing to the symptoms, I think that is not always the case. But when they have moderate to severe cranial cervical instability to the point where now there's cervical medular syndrome - which is compression of the lower end of the brainstem, then I do believe that that is a big contributor to their disease. In fact, I mean, I'm fairly certain of that, fairly confident of that, and it's just, because if you look at the anatomy of the lower end of the brainstem and its nuclei and the lower, you know, cranial nerves 9, 10, 11, and 12, you can localize a lot of the symptoms. And so I think that it's an important thing to

at least look for, to try to rule out or rule in. And then if it does, if it does present with as CCI, both radiographically and clinically, then I think that that should be addressed because…
It's an anatomical problem that, you know, no medication or supplement frankly is going to completely correct.
So I think it's important.
[Dr. Kaufman] Yeah.
[Dr. Ruhoy] I feel like you're you look look you're itching to to pipe in.
[Dr. Kaufman] No, no. As usual I completely agree with you. I was just going to maybe put a little other spin on this. So we know or we think, and we know based on literature and research, that chronic inflammation basically injures connective tissue.
And chronic inflammation, over a long term, injures connective tissue more. If a person happens to have a connective tissue disorder, i.e. hypermobility EDS, or whatever other term you want to use for that condition, they're just that much closer to significant injury of their connective tissue. But I want to emphasize, you don't have to have EDS to be in this conversation that we're having about that. So I regard every patient as at risk, which is exactly what Ilene said. I would characterize it a little further by saying the following, which is is perhaps heretical:

If I meet a bed-bound patient that [CCI] is the first thing on my list of considerations.

I may not go there first, but I'll tell you that if you're a new patient to me and you're 100% bed-bound, the first thing on my list is, this patient probably has CCI. And so far you know I'm batting about, I don't do batting averages, I'm running about 80 or 90% correct. Okay.

Similarly those patients who make zero progress, or make progress and hit a wall, I reassess for CCI because the wall may be that they now have an anatomical mechanical problem and no drug in the world is going to fix that.

[Dr. Ruhoy] Yeah. I completely agree especially when patients get, when they get worse instead of getting better despite all of the work that we do, you know, because CCI does worsen. So it might exist on a mild level when I first meet a patient, but over time, especially when they're not responding to other interventions, then it likely has worsened. And then now we need to really consider addressing that diagnosis. And so I guess your next question is,

29:50 CCI- how to address it?

“How do we address it?”

With regards to, I think, I often get asked about the surgery and so I think people, you know, surgery. Nobody wants surgery right. You know, David and I don't want our patients to get a fusion of any part of their spine much less the cranial cervical joint. So it's not that we want our patients to have surgery and to have fusion. But it really has been shown under the right circumstances, that it is a very effective treatment option. And those right circumstances, you know, there's a lot of hoops to jump through before you're deemed a surgical candidate. And the neurosurgeon will do the surgery. In fact, I'm very regularly recommending the invasive cervical traction to patients, because, and if I talked about this at our webinar I'm going to repeat myself, but the invasive cervical traction

is a really important not only screening tool but diagnostic tool, because we find that traction. And so if we put space in that joint where there's lots of compression and it's crowded. If we put some space and relieve a lot of that compression, do the symptoms improve, and if so, to what extent do they improve? And if, so you know, we take X-rays at every incremental level based on how much weight we've added, and we do the measurements again, and then we look for the change of measurements in a clinical correlate, But also during the ICT, we do transcranial dopplers. We get cerebral blood flow velocity. We also do ICP bolt monitoring so we get changes of inte cranial pressure in different positions over a period of time as well as under traction. So we gather so much critical information that we can't do in a clinic. right So we get so much information on these patients and how their central nervous system is working, that, to me, ICT is its own, like, I just I see it now as a sort of a separate like testing other than in addition. It's also the preop requirement to be deemed a surgical candidate, and if you're not a surgical candidate then surgery is not an option for you. But regardless, we've gained a lot of information about the patient and then there are other things that we can do. I mean, there are other interventions, you know, with regards to cerebral blood flow. There's other interventions with regards to cranial pressure, dynamic alterations. There's other, you know. And there's even other things that we can consider for CCI though I haven't found anything to truly obviate the need for surgery when CCI exists in a severe fashion. But you know, again, reducing inflammation by all comers can be really helpful because it helps you know the ligaments definitely, you know. They have an inflammatory burden that can sometimes flare a symptom of CCI. So, yes, I, we work with patients to try to reduce the inflammation so that they minimize the symptoms from the cranial cervical instability, but it doesn't remove that anatomical diagnosis it doesn't cure it. So.

[Isabel] All right. Thank you. The next question is from a GP.

32:46 Can GP's start a clinic?

"Can GP's start a clinic? Do you think we, as GP's are well equipped to start a clinic given the overlap of symptoms?"

[Dr. Kaufman] I'm going to go into that. I absolutely think that can be done. I think the requirement, so to speak, is basically a physician. And I think a gp's ... Let me back up. Okay. So a GP generally means the person's trained as an internist or Family Medicine, Family Practice. That means they are not trained as a subspecialist with tunnel vision and silo thinking related to medicine. We need that general approach. This illness, these illnesses, that's the approach that's required. So that's the first thing. The second thing is if this physician or a physician has curiosity, interest, and knows how to use the internet, they can do this work. And I'll tell you now it is the most challenging and interesting work around. It is, you know. Yes. It's exhausting. And it's hard and can be frustrating and at times tear-making, you know, tearful making, but it is incredibly rewarding. And you're right on the edge of all this new medicine and new science. And I think a GP is perfectly positioned to do that if they have the interest and the curiosity to learn. I, you know, as I've said in other venues, when I started seeing ME/CFS patients 10 or 12 years ago, I knew nothing. I knew a lot of medicine and I knew a lot of HIV disease and infectious disease, I knew nothing about ME/CFS. And I have learned not only all about ME/CFS, but because of the lack of specialists and help that's just they don't want to see our patients, I've learned endocrinology. I've learned neurology. I've learned more

infectious disease. I've learned physical therapy. I mean all these things. And you know how you do it? You just put your fingers on the keyboard and find it it is all there. It's so easy to find. So whoever that GP is, go for it. Call me up. I'd love to do anything to help you.

[Isabel] Thank you. Anything to add? [Dr. Kaufman] What? [Dr. Ruhoy] I said I second that. I too knew nothing when I first started. I mean, if anyone had known me 10 years ago, I was as conventional neurologist as they come. But I just started to see these chronically ill patients, and I thought what the heck is going on? It just - you know and- it bothered me, because they were suffering and their quality of life was different and I just sort of decided to take this on to help figure it out. And then I met other doctors like Dr Kaufman who were doing the same and I learned from them. And I googled and I read and, you know, before I knew it, I knew a lot more than I ever thought I would. And so I realized that, you know, I'm a specialist, but I don't think it makes a difference where you start I guess is my point.
[Dr. Kaufman] Right.
[Dr. Ruhoy] So you just start. You just start.
[Isabel] Excellent. All right. Next question is

35:50 Rapamycin Trial?

“Regarding the rapamycin trial wondering if you're seeing any preliminary or noteworthy or exciting observations, and what you're seeing outside of the trial if you're using it in your patients.”

[Dr. Kaufman] So I'll start with that. I need to be a little cautious on what we're seeing because it's a trial. So it's, you know, you're not supposed to talk too much about this stuff until you publish. I will say that we are seeing the changes in the protein that's being measured ,that are those changes are consistent with the hypothesis that was generated after the protein was discovered. Okay. And although it's too soon to say, we are seeing trending in the questionnaires and the patients in the trial. They do serial questionnaires that are demonstrating improvements in various parameters even if the patient doesn't tell you that. All right. It's showing up in these measurement tools, you know, I think I probably can't say more than that other than it's really exciting and we're seeing the changes we would expect in that protein while they're on rapamycin. In terms of non-trial patients, because I have many patients on rapamycin that I started before the trial and most of the new ones go into the trial, but it's the same exact protocol, I would say that I see a a significant portion who improve with respect to pain, brain fog, and fatigue. And I see a portion who tell me they don't have any changes, they don't feel anything that doesn't mean it's not working. It's not a drug that's for a specific symptom. It is a drug that's altering autophagy and that's not something you necessarily feel. And then I've had a few patients who just didn't tolerate it for some reason, but that's literally like a handful of patients, it's very very small. So I remain very excited about it. I think it's a really important drug.

[Dr. Ruhoy] I feel the same.
[Isabel] Wonderful, wonderful.

38:02 Pregnancy & LC, ME/CFS.

“Any concerns in the pregnant patients that you're seeing in regards to Long Covid and ME/CFS and anything that you change when you see patients who are pregnant?”

[Dr. Ruhoy] The only thing, I don't have many pregnant patients right now so I don't have a whole lot of subjects to refer to. But I definitely hold off on immunotherapies, of course. I won't do that in a pregnant patient. I will do some mast cell work, for sure. And there are a couple of actually anti-seizure medications that are known to be safe for pregnancy that if they are having, you know, neuroinflammatory kinds of symptoms which can be very bothersome, I'll try some anti-seizure medications for them. But I definitely avoid the immunotherapies.

[Dr. Kaufman] Yeah, I don't actually have any pregnant patients amazingly, at least that I know of. So but if I did if, my focus would initially be on their autonomic nervous system and their blood pressure, heart rate issues, and most importantly vascular volume since all of that is potentially altered and aggravated - whatever you want to say - with respect when they're pregnant for obvious reasons. Okay.

[Isabel] Next question is, let's see.

39:28 Venous Compression Suspicions?

“At what point do you start to suspect there could be a venous compression disorder such as May-Thurner? What steps do you take to confirm this and what options do you consider for treatment?”

[Dr.Kaufman] So love this question, partly because it brings me back to what I said to the GP question a few minutes ago. I would say that a year ago I knew nothing about venous compression syndromes. I mean I remember vaguely in medical school May-Thurner and Nutcracker, and I thought oh these are these arcane syndromes that you'd never see. So over the last year, I have dived or dove into this partly because it's become a big issue on our our masterminds group, and I started from zero and have learned a huge amount by talking to other doctors and going online and reading and asking questions. I do now think it is a huge issue in patients particularly those who have treatment resistant POTS and orthostatic intolerance. Meaning no matter how many drugs and how we juggle the drugs, they still have their problem. I think that suggests a the major possibility of venous compression and stasis of blood in the lower extremities and the lower abdomen and decreased return to the heart. So I think it's a huge issue.

[Dr. Ruhoy] Yeah, I do, too. I mean, I now think of it a lot sooner than I ever did before. I now understand it a lot more than I ever did before because the abdomen and pelvis, obviously, is was not my anatomical area. But you know, when nothing else, I mean, so I learned to test them for SIBO and for, you know, dysmotility, and I you know I do. And I work with them to help improve their just their gastrointestinal sort of environment, whether it's mast cell activity, but when nothing else is working, then I make sure that there isn't compression going on. And I will say that, you know, the more you look, the more you find. And I'm sort of actually a little shocked at how often I'm finding.

[Dr. Kaufman] Right, right. And so I think that's a good example of like the mast cell issue I mentioned before. We should probably be, that should be part of the initial evaluation.
[Dr. Ruhoy] Right.

[Kaufman] The problem that I encounter is the same problem I encounter with CCI and tether cord and imaging. I can't trust the radiology reports. And I can't trust the vascular interpretive reports on the tests we do - the MRV's and MRA's and dopplers. Trust meaning I think they underead them. And so part of the challenge has been finding people who are willing to look at the Imaging knowing about these syndromes and then find the problem. You got to, you got to, you got to know about it and think of it, or you're going to miss it in the imaging.
That's next question,

42:26 Role for Hormone Replacement?

"Is there a role of hormone replacement therapy in management of ME or long covid? For example, there are some case studies suggesting remission with testosterone replacement."

[Dr. Ruhoy] I don't consider myself a hormone expert so I'll defer to Dr. Kaufman to that.
[Dr. Kaufman] Yeah, I mean, I obviously I check for hormones and, most specifically, thyroid, testosterone And I feel less competent looking at progesterone, estradiol, but do consider those. I have definitely found testosterone deficiency in a very significant number of male and female patients. And I have no problem putting them on replacement testosterone. And many patients will feel better with respect to fatigue. Sometimes it helps brain fog and it definitely can help muscle, you know, muscle strength. But I have not seen it put anyone into remission so to speak. So.
[Isabel] Okay.

43:31 IVIG for POTS?

"What point do you consider IVIG in POTS. Do benefits last or do patients tend to require ongoing IVIG?"

[Dr. Ruhoy] I really like IVIG. I think it's helpful for POTS as well as for MCAS as well as for the clear autoimmunity going on with patients. It's hard to get approved because none of these are classic indications, so insurance does not like to cover it. And it's super expensive as everyone knows, but it's very effective for a majority of patients with severe POTS. So when all of the POTS drugs are not working I find IVIG to be very helpful, very helpful actually. You know, it's a very viscous fluid and sometimes I wonder if it's just sort of this volume replacement kind of thing. But I really like IVIG. And you know I do a lot of labs looking for reason for the insurance to cover it, so you know the patient doesn't have to pay out of pocket. Sometimes we find evidence of imunodeficiencies - which is technically a diagnosis that can get covered- for low dose of IVIG and that can be just, that could be fine actually. In fact, most patients will respond specifically for POTS, will respond to the low dose. For autoimmunity, it's really the higher dose, the two gram per kilo and the low dose is one gram per kilo. But uml really do think that it's very, very effective for both POTS and MCAS. [Dr. Kaufman] Yeah. I would say it even more strongly. If it wasn't so expensive and the insurance companies weren't so criminal in their approach I would treat every POTS patient and small fiber neuropathy patient with IVIG. But that's a fantasy.

[Isabel]. All right. So those are the questions we had sent ahead of time. Richelle, we can go into the questions that are now posted from the audience. Okay. So, let's go to the top.
[Richelle] I'm just trying to see if I can get participants up to be able to answer their questions so it's like all my different lists of things and screens and everything I got in front of me so
[Isabel] All right. I go ahead oh go ahead I was just gonna start with the first one if you haven't figured out. Okay. yeah. I'll go ahead and I can ask her if she wants to talk so. Is Kat on? there we go.
[Kat] Yes, I am here. All right. So my question was for labs.

46:05 Timing of tests for MCAS

“If you're running labs for MCAS in particular, how long should patients withdraw from antihistamines or mast cell stabilizers prior to testing?”

[Dr. Ruhoy] It's a good question. David, what do you tell patients because…
[Dr. Kaufman] So, so theoretically, you don't have to stop H1 blockers and H2 blockers. They are treating the horse after it's out of the barn. So the mast cell's already activated, so that's not going to change your numbers, your lab numbers. Stabilizers obviously are a different story. If you, if they're successful then there should be less histamine and you're going to not see the histamine, but I'm not sure if anyone knows the exact number of days. I usually will say, you know, 3 or 4 days hold the medications, that includes stabilizers but it also includes things like NSAIDs, ibuprofen, and naproxen, things like that. Yeah, but for mast cell, that's one of the reasons, by the way, that I have no reluctance to start H1, H2's at the first visit, even though I don't have the labs back, because it won't affect the labs.

Dr. Ruhoy] Yeah. I mean, I completely agree. I also don't know how many days. I think, you know, I think about the half life of some the medications, but it's the mediators that all have different half-lives. And so I generally just say 48 hours.
[Kat] Thank you.
[Isabell] One quick question before we go to the next person that actually realized I forgot to copy over.

47:40 Neuropathy in ME/CFS?

“Could you talk to us about peripheral neuropathy in the context of ME/CFS? What do you think are the potential root causes and what do you usually do to address it.”

[Dr. Kaufman] You're on, Ilene.
[Dr. Ruhoy] Well, I, you know. Peripheral neuropathy can be small fiber or large fiber, right? So I think it's important to one, you know, depending upon the severity of the symptoms of the neuropathy - I do think it's important to get EMGs because it can show things like demyelinating polyneuropathy, axonal polyneuropathy, sensory motor, and so on. Small fibers won't show up on an EMG so you need a skin biopsy for that. And I do think it's an important part of the workup to sort of try to distinguish because you could have a mixed picture. I have patients with both small fiber and large fiber neuropathies, and then you know you do for, especially for large fiber, you do a

whole host of... There's a whole neuropathy workup that I do that is a bunch of labs. And it's sort of more of a conventional kind of neuropathic workup because they're all treatable causes of of peripheral neuropathy. So I make sure that I'm not missing anything in that regard. And so I do that kind of workup, but I also do a full autoimmune workup for looking for autoantibodies that contributing to the neuropathy. And if I do find an antibody, then obviously that gives me reason to consider things like IVIG ,or plasmaphoresis, or some of the other immunotherapies for small fiber neuropathy. As David said, I mean, I love IVIG. It definitely helps, but it's important to objectively make these diagnoses, because that can, that is often what's needed when, for example, you're trying to get approval for IVIG. Well how do you know it's a ___ just because you said so? Yeah, you know, I want, sometimes I want to say yeah because I say so. But no you need the skin biopsy because that's the gold standard to confirm the diagnosis. And you also need an EMG to confirm that a very common diagnosis is CIDP in these patients and so but you need an EMG to confirm it even though literature suggests that you don't technically need it. And if there's response to IVIG and there's clinical symptoms and they have no reflexes then it's CIDP until proven otherwise, but insurance companies insist on EMG's so that's my workup approach for it. And I I do treat it. I mean I treat it with, if I could, IVIG. I treat it with plasmapheresis. I treat it with all these immunotherapies. I've been treating it with more regenerative kinds of therapies that we have mentioned. And often, and it's notoriously difficult to treat, especially when it's idiopathic, when there's sound on the labs um then it's it's considered idiopathic, but I also think that there's a mast cell component, right. So the mast cells, so take demyelination,

the mast cells.. there are mediators that will break down the myelin and what's interesting about that is the myelin degradation products trigger mast cell activity. And so it's this vicious cycle that happens. And so when all else fails, so all the labs are normal, and even the immunotherapies that I'll still empirically try, especially the ones that are just oral and usually very easily approved by your insurance you know ,from an order through the pharmacy. I will like double down on my mast cell work trying to just sort of and you know it's hard to reverse the neuropathy that's you know the damage that's already exists to the nerve, but
you definitely could slow down progression, if not halt it, and so I really double down on trying to get those mast cells under control because the the mediators will break down that myelin. Did I answer your question?
[Isabel] I think so.
[Dr. Ruhoy] Okay.
[Isabel] All right so the next question is from Athina.
[Athina] Thank you.

51:25 Collaborative Research with Patients with CCI

“Do you see any future possibilities for patient collaborative research for improvements with severe CCI patients ,whether trauma or ME? For example there are some patients that have improved ,had complete loss of mobility, have improved with MCAS stabilizers, a rigid regime phospholipid therapy, peptides GHK-CU, BPC, and I recognized the limitations when I say peptides, and photobiomodulation, for example. So I bring up four therapies that were very effective. Do you see any opportunity for these mid-spectrum patients that may never get to see you?”

[Dr. Ruhoy] Oh, I definitely do. I think, David will agree, I mean patients are very regularly telling us about their response to one or all of those things that you mentioned, Athina, and so I absolutely I support them, you know. I believe they play a role. I think the problem really is that there's no blueprint, right, so it's a lot of different modalities that are coming to the surface about how they can help, and it helps with regards to ___ information and regeneration - that's what all those therapies that you mentioned will do - which again we support.

And we think that, we know that there's a place for it, but again it's becomes very complicated, also very expensive for patients, right, these are a lot of different therapies. We have to figure out all the different therapies that, and how they're going to use them, and when they're going to use them. It's so, and I'm not saying that that work is not worthy enough to avoid a a fusion for the patient, I think it is, it's just, it's just, we don't, there's no blueprint to it, right. There's no, there's nothing that tells me exactly how to prescribe all of those therapies for any individual patient. So patients are sort of left of their own to figure it out how they do.

[Dr. Kaufman] Yeah, I think part of the question or what I like about the question was, were those two words collaborative research. Okay, so I agree with Ilene and patients are doing this. The data is getting lost because we're not collecting it and measuring it and categorizing it etc etc. And and I absolutely think that that can be done and should be done. The work I did with oxaloacetate and now that we're doing with rapamycin is entirely online. All of the data collection, all of the fatigue tools and cognitive tools are all online. And we could move the needle here if, if we could get organizations and funding to do more studies like that. Take 50 patients doing photobiomodulation. Give them a bunch of measurement tools to fill out every month, all online, and bingo, you know, we have data results. So yeah, I think it's an incredible opportunity, I think, you know, organizations like Renegade Research, can really pull that off. So, and I will tell you, it was easy. I mean the oxalo study and the rapamycin study. They're easy studies, you know. It doesn't require what big pharma does, and you know, CROs and millions of dollars. So it definitely can be done. I love that term collaborative research.
[Dr. Ruhoy] Yeah.
[Athina] Thank you both for your incredible work in the community.
[Isabel] All right. Thank you, Athina. And Suzanne is next.
[Suzanne] Yes my question is about, you know, trying to identify the mast cell activation and understanding that you don't necessarily need all of the labs.

54.47 Endoscopy slide for MCAS

“When you take the slide from the endoscopy wouldn't that always show that the mast cells are elevated simply because you're undergoing an endoscopy?”

[Dr. Kaufman] I don't think that it happens that fast and what they're looking for, or what's being looked at in the slides, is literally a count of the number of mast cells present in a high power field. So we're not counting, we're not looking at the mediators that are released. I mean, it's a good question. Yes. there's probably mediator released just stick a scope down somebody, it probably does cause mast cell degranulation. But we're looking at the actual mast cells, and they're not going to, you're not going to get, go from 3 to 30 in a high power field during an endoscopy. It just doesn't happen that fast so I think it's still an accurate result.

[Suzanne] Okay, Thank you. Can I also ask my other question about

55.53 Sensory Sensitivities Cause?

“[What] causes the sensory sensitivities, sound, light, etc., and are there specific treatments for them?”

[Dr. Kaufman] Suzanne, that's a really easy question. Thanks.
[Dr. Ruhoy] Are you referring to like photosensitive, like sensitive to light, and so…
[Suzanne] Yes.
[Dr. Ruhoy] Okay,

so we know that there's hyperactivity of the of the cortical neurons with these kinds of sensory overload disorders. And so that is the presumption that there's a level of just hyperactivity of the cortex and so that's why there's a lot of photosensitivity. And photosensitivity, and to the extent that that is related to, for example, crania cervical instability, you know, the brainstem controls a lot of autonomic functions, but it also has a lot of communication with the rest of the brain. And so while we haven't yet proven the specific fascicle of communication, that is sort of the underlying theory. And in fact, epileptics, as I had earlier for my pregnant patients, I use a lot of anti-epileptics for these exact symptoms with great success. I will say it doesn't necessarily completely resolve the photo and phonos sensitivity, but it does minimize it, for sure, and the patients aren't nearly as bothered by it.

So I think it's something to think about, I mean, you know, the brain, you know, don't forget, so the brain has mast cells as well and the brain has H1, H2, H3, H4 receptors and so, and they're histaminergic neurons and so there's lots, and of course, you know ,we see ME/CFS and long Covid, they're in a predominant sympathetic state. And so if you just sort of think about like that state of being, and I always do this whenever I think of it, because like I feel like that my patients are just in this like state of of fight or flight so there's just hyperreactivity and hyperactivity and hyperexcitability of, not only you know, the peripheral nerves of course, but the central neural tissue as well. So you know I use a lot of those kinds of medications. Obviously there aren't you know - it's off label right. They're not seizures though we use anti-seizure medications off label all the time for lots of different things. And then if there's a concern that there's elevated cranial pressure, I've actually used acetazolamide with some success of those symptoms as well. Just wanted to throw that out there - that sometimes elevated cranial pressure can result in things like not being able to tolerate sound or light or anything for that matter.you know, so acetazolamide can actually also reduce those symptoms, too.

[Dr. Kaufman] Yeah. I think it's important to emphasize there's not going to be one single answer to the what is causing these hypersensitivity syndromes which are devastating for the patients. They're just, they're so awful. I think it's, as Ilene is saying, it may be from CCI and and compression in the brainstem. It can absolutely be from mast cell activation. It can be from infection. It can be from neuroinflammation caused by whatever underlies some of the ME/CFS pathology. And as a result, most of what we do for treating that is, going through this list that I just said and trial and error of drug after drug after drug. It's a very frustrating problem.

[Dr. Ruhoy] Yeah.
[Isabel] All right. We are coming close on time. Do you guys have time for one more question or do we need to wrap it up? Okay, so the last question is,

59:18 Do you work with Pain Clinics?

"Do both or either of you work closely with integrated pain clinics, including pain anesthesiology, wondering in particular for your patients with hypermobile EDS and MCAS, who have structural spine issues, how do you feel about stellate ganglion nerve blocks, occipital nerve blocks, trigger point injection, spinal cord stimulator, especially for patients who are not good candidates for surgery?"

[Dr. Ruhoy] Oh yeah, I mean, I love working with my pain colleagues. I really do. I think they do a lot of really great work in stellate ganglion blocks, I mean, David and I were just talking about them, have really shown to have, be a promising treatment option for patients to get some relief, at least temporarily. And so I'm, I would regularly refer to pain docs to do the stellate ganglion blocks. You know I do occipital nerve blocks and trigger point injections and those things, but I also love when my pain colleagues will do them as well. Yeah we work very collaboratively with them. Even like ketamine IVs.
[Dr. Kaufman] Yeah.
[Dr. Ruhoy] Some of them do that. Ketamine has also been proven to be a very, again, effective treatment option.
[Isabel] All right. Anything to add, Dr. Kaufman?
[Dr. Kaufman] No. I agree I'm particularly interested these days in still at ganglion block. I have had patients use ketamine for pain relief which has been great, as well as psych, you know, psychiatric reasons, but the pain relief with ketamine can be truly great. I think the not negative, but the caveat or qualification I say is that there aren't enough pain clinics out there. And they're overwhelmed because of what's happened with respect to pain management. You know used to be that I as an internist would think nothing of prescribing you know opioid pain meds. Now I won't do it partly because of what's happened in the sort of health care environment. So the pain docs are over overwhelmed. I also think that they tend not to have as much familiarity with our with our patient population, which can be an issue for them. So the answer to that would be more collaboration if they have the time and we have the time. So it's a great question.

[Isabel] All right. Wonderful. We are out of time. Thank you so much, Dr Ruhoy and Dr Kaufman, for coming back in answering these questions. And I will say it one more time, you are welcome to come back anytime that you want to. And thank you everybody for attending today. We'll have the recording ready as soon as possible so everyone can watch the recording as well. Thank you everyone. Thank you very much. Thank you. Bye bye bye.

1:02:12 End