#390 Resistant Hypertension

Hypertension FAQ Round #2 Dr. Jordy Cohen Strikes Back

Matt: Paul, you know, everyone knows that I'm a little bit of a bad boy. I remember, I'm a bit of an Arthur Fonzarelli, if you will, Paul. Well, I am embarrassed to say that I got cuffed yesterday, Paul. But they let me off with a warning. So, hopefully this new DASH diet prescribed by my doctor is going to help lower my blood pressure.

[laughter]

Paul: [crosstalk] stroke. I don't even understand it. [Matt laughs]

Deb Gorth: I don't get any here.

Matt: All right, we could throw this one out. I said I got cuffed yesterday, Paul, cuffed.

Deb Gorth: Cuff? Oh, like blood pressure cuff.

[laughter]

Deb Gorth: Is that it?

Paul: All right.

Matt: I think it means it's a good joke when you have to explain it for two minutes.

Paul: [laughs] Leave all of this in. This is perfect.

[Disclaimer]

[The Curbsiders theme]

Matt: Welcome back to the Curbsiders. I'm Dr. Matthew Watto, here with my great friend, Dr. Paul Nelson Williams. On tonight's show, we're talking about hypertension, specifically resistant hypertension, with a fantastic returning guest, Dr. Jordy Cohen. Paul, how are you doing? Have you recovered yet from that fantastic joke I just told you?

Paul: Yes, I'm not sure, I've fully recovered. I'm great otherwise, but thank you for asking. Other than apparently mismanaging hypertension, one of the most fundamental topics to internal medicine. [Matt laughs] So, feeling good.

Matt: [laughs] Would you like me to tell another joke, Paul?

Paul: I would not.

Matt: Okay. All right. Well, with us tonight we have a great producer, Dr. Deb Gorth. And, Deb, first I'll ask, how are you doing? You're in residency, so I know that can be challenging. How are things?

Deb Gorth: The things are great. There's nothing I'd rather do than talk about hypertension after a long day of heart failure service.

Matt: All right, perfect. So, Deb, would you like to tell the audience about our fantastic guest?

Deb Gorth: We had a great conversation with our guest, Dr. Jordana Cohen, Jordy. She's a nephrologist, hypertension specialist, and epidemiologist at the University of Pennsylvania, where she spends most of her time geeking out about blood pressure. She's a member of the Freely Filtered podcast team. She's the principal investigator of several NIH studies investigating the treatment and measurement of hypertension in high-risk patients. She has leadership roles related to this within the American Heart Association and American Medical Association. Dr. Cohen teaches us how to recognize pseudo-resistant hypertension and how to manage resistant hypertension. So, without further ado, let's get to it.

Paul: If there's going to be further ado let me just say, we are *the* Internal Medicine podcast. We use expert interviews to bring you clinical pearls and practice-changing knowledge. I mean, I don't do that much, so just give me this like otherwise I don't even-- [crosstalk]

Matt: I thought you said it. I got distracted by our banter. [Paul laughs] A reminder that this and most episodes are available for CME through VCU Health at *curbsiders.vcuhealth.org*. Now, let's get to the episode.

Jordy, welcome back to the show. A much-requested guest, last year, 2022, we had you on. It was a fantastic episode. So, we're going to try to recreate what was a fantastic episode with more cases in hypertension. Thank you so much for coming back.

Jordy: Thanks for having me. I'm so excited that people are willing to geek out about something that I think is often seen as one of these throwaways in medicine management. So, it means there's still hope in my world. I'm so excited.

Matt: Yeah. Paul, you still have questions about high blood pressure after all these years?

Paul: You've heard me say this before like this and aspirin dosing, the fact that we're still talking about like, human blood [Matt laughs] pressure goals is bananas to me. So, I always have questions.

Matt: Okay so, Dr. Deb Gorth. Deb, would you please read us our first case from Kashlak so we can jump right into this?

Deb Gorth: Okay, I'm going to take you guys to the Kashlak outpatient clinic. So, we are seeing Joanne. She's a 56-year-old woman coming back for a follow-up appointment for her high blood pressure. A month ago, her blood pressure in the clinic was 170/98. And because you had listened to Dr. Cohen's last episode, you started her on a calcium channel blocker and an angiotensin receptor blocker-combo pill containing olmesartan and amlodipine. Today in the clinic, her blood pressure is reading 160/96. And then when you recheck it, it's 150/94. Well, I feel like there's no more bread-and-butter topic than hypertension, but just so we all kind of start on the same page, how do you define hypertension?

Jordy: I personally ascribe to the ACC/AHA guidelines from 2017 and it sounds like everyone that I've spoken to recently really is sticking with this. There are some conflicting guidelines, like the ACP/AAFP guidelines, but for the most part, folks are agreeing 130/80 is really great to use for somebody as your goal blood pressure threshold for sure. And if someone has any risk factor, definitely for your threshold for diagnosing hypertension as well. So, this person's already on treatment, her goals should be less than 130/80.

In older patients, people over the age of 60, which doesn't apply to her, there are some of these less stringent thresholds, like 150/90 for the JNC8 for example. No one's ascribing to that anymore. In that case, somebody's running even in the 140s would be considered to be elevated. And I think that many people still have it fixed in their head that 140s is okay. 140s really not okay. I think some guidelines using that threshold of 140/90, it's reasonable depending on the patient. I'm still really a fan of 130/80, though, because of growing, growing evidence of how lower blood pressure really is associated with a lower risk of adverse outcomes.

Matt: And Paul, we've been talking about this now with blood sugar, with lipids, with blood pressure, lower is better. It matters a little bit how you get there, but especially for patients, like, if you can get them under 130/80, I wouldn't pull away medications and Jordy I think it's like if you have someone in the 130s/80 and they're already on four or five meds, do you really add another medication? That's kind of where I struggle with the 130/80.

Jordy: Yeah, and we can talk more about that as we go into the subsequent cases, too. I think that a lot of that comes down to, who is the patient. Having goals of care conversations. And this is someone who's going to tell you, if you prescribe one more medication for me, it's going to be one med [Matt laughs] that I don't take, then that's your decision right there. But I think it's worth a shot if the person can do it without ending up crawling out of the office.

Matt: Thank you. Okay, so mechanisms of hypertension. Reading about resistant and refractory hypertension, I came across this concept of sympathetic driven versus this sort of RAS driven. Can you speak to those a little bit?

Jordy: Yeah. Hypertension is multifactorial and this is we're talking about just essential hypertension. Or what a lot of us hypertension nerds think of as primary hypertension, just run-of-the-mill hypertension without a clear secondary cause. And there are two contributory mechanisms, and I think for most people, it's likely a mix of the two, but some people, there's one that's more dominant than the other. And it's either the RAS-driven mechanism, which is really your volume sensitivity, this is your renin–angiotensin system being on overdrive, meaning that you're most likely more salt sensitive. You most likely have some extra fluid or plasma volume on board, even if you're not seeing edema in somebody, even if you're not seeing signs of ascites. This isn't like the frank, "Oh, I need a nephrologist to help me do a volume exam type of situation." This is just extra volume in their body but in all the hidden places.

And then the alternative is this more sympathetically driven hypertension, people who have a little bit more active fight or flight process and that's the people who maybe are a little bit more anxious and say they think that their hypertension may be causing or linked to their anxiety, but not always people who maybe have a little more symptomatic hypertension. That's often the more sympathetically driven people and just people who you can see their hypertension tends to be a little bit more triggered by things besides salt.

People who have more hypertension may be triggered by drinking too much caffeine. We don't see that unless people really go overboard. But our generation introduced the idea of venti coffee.

[laughter]

Jordy: I love reading labels and realizing that Starbucks coffee has 150 mg of caffeine in their smaller coffees compared to a cup of old school Folgers that our parents drank that had less than 50 mg with the same size cup. I've learned when you ask a patient, how many cups of

coffee do you drink a day? If they tell you three, that could be 36 oz of coffee that are each 400 mg of caffeine. I never used to believe that caffeine could contribute to hypertension, but now I do, having seen some interventions that actually were quite effective at having people cut back. I think a little bit is absolutely fine. A couple of cups but sorry that's a sidenote, but those are the-

Matt: No, it's a good one.

Jordy: -sympathetically driven patients. But we all see these patients. And so again, it's often a mix. It's rare that people don't have a little bit of both, which is why those fixed-dose combination drugs are really fantastic because it gives you a little bit of bang for your buck on all ends. You get a little bit of a vasodilatory effect from your calcium channel blocker, from your angiotensin receptor blocker or ACE inhibitor. You get a little bit of that RAS effect from the ARB/ACE inhibitor or from a thiazide diuretic or a thiazide-like diuretic with those first-line agents. And that's why they're so effective. They target all of this.

Matt: That is great.

Paul: In the background of the mix my dumb, dumb brain, back when I thought about essential hypertension, it was this nice, straightforward mechanistic, arteries are getting harder and that's why the pressure is going up. Is that happening quietly in the background? Have we thrown that out the door? Is that sort of more along the RAS-driven thing or sort of what do we do with that additional sort of-- is it historical at this point to even think that way now?

Jordy: No, it's completely correct. As people get older, your blood vessels stiffen. It's called vascular aging is the term for it. It's more common in developed countries than it is in places around the world who don't have as much sodium exposure. So, for instance, there's this really cool old research that was done in the Yanomami tribe in the Amazon that never had any exposure to Western food or Western diet and they are very isolated and researchers would go in and they had very regimented allowances of how many people were allowed to be there because they didn't want to introduce anything from the outside world.

Not to mention upset the way that the function of the tribe and sort of get in the way of their usual day-to-day activities. And they would measure their urine sodium content, they would measure their blood pressures, and they would capture it across entire villages. And what they observed is that in these villages, people at age eight had the same blood pressure as people at age 60 or 70. They did not see a rise in blood pressure with aging and so a lot of that is thought to be due to likely the fact that our sodium diets and just our western exposures, probably pollution, probably a lot of other stressors and things in our life that don't exist in that type of a world, contribute to vascular aging and contribute to why we develop hypertension as we get older, and there's also likely upregulation of RAS involved too.

So, it's a bit multifactorial. But we know for sure that vascular aging is real. We know that it's accelerated in certain disease states. For example, in chronic kidney disease people have worse vascular aging that's faster at a younger age, this vascular stiffening, especially in their large blood vessels, and that's related to a part of why we see a higher risk of heart disease and progression of chronic kidney disease in many of these patients.

Also, we know that as your blood vessels stiffen as you get older, it causes other damage to your small blood vessels. I led a study, actually, last year that was published where we found some causal suggestion that if you have high blood pressure and your blood vessels are getting

stiffer faster, and other factors that are causing your blood vessels to be stiffer, that actually can cause type 2 diabetes. That hadn't been previously really demonstrated using true causal mechanisms. I wouldn't say it's actually proven yet. We need more studies to show that. But this is a real problem, and I think that a lot of it comes from the things we put in our bodies and expose ourselves to.

Matt: Wow, I had not heard that before. I think I did come across something as I was reading about resistant hypertension, that those patients are more likely to have diabetes. I'm not sure if it's the same mechanism or not, but that's scary.

Jordy: There's more to learn in that space for sure, it's been like sort of there have been sneaky signals here and there over time, and so we're starting to understand why it's happening.

Matt: I think we've talked a lot in the past on the show about the various agents we might use for blood pressure. You just mentioned some of them. There're the RAS inhibitors, the ACEs, and the ARBs, there's the thiazide diuretics, the calcium channel blockers, and then some of the second line agents, the beta blockers, alpha-blockers, hydralazine, I know that's a favorite of yours, Jordy? [Paul laughs]

Paul: It's loved by nephrologists, rheumatologists-- [crosstalk]

Jordy: Shoot myself in the head. [laughs]

Matt: Yeah, yeah. We've have had a lot of episodes this year by the time this comes out on MRAs and nonsteroidal MRAs, so those agents. Because we see this a lot in clinic, the patient that just seems to be really anxious and their blood pressure is high, how do you handle that situation, maybe both with treatment and just making sure that it's not just they're anxious in clinic. Can you talk about that?

Jordy: Yeah. And so, I get a lot of these patients referred to me in my complex hypertension clinic because their primary care providers have been sort of at a point of I've tried several medications, and there's clearly anxiety component, and I don't know what to do. And so, I get asked a lot, do I treat hypertension when we know it's due to anxiety? My response is, I'd say that 9/10 of these patients, no one's ever said, "Hey, how is your anxiety doing? Do you feel that this is a factor?" And just asking them and getting their insight into it can really open a lot of doors. One of the things I prescribe most in my complex hypertension clinic is citalopram. It's incredibly effective at improving blood pressure, especially labile hypertension, in people in whom there's an anxiety component and many of them didn't realize there was an anxiety component until someone asked them.

And sometimes it takes two or three visits to get that out and for them to finally trust you and realize that you're listening to them and caring about what they're dealing with. It's so worth it, because I just see incredible benefits from it. Citalopram, specifically, there are some older pharmacokinetic data that I actually haven't found, I've learned about this from my mentor, Ray Townsend, that had demonstrated that it has more sympathetic effects than other SSRIs do and it tends to be more effective at lowering a lot of this blood pressure lability due to anxiety. So, citalopram specifically happens to be more effective in that space and I've seen it. I get a lot of people referred to me for-- people suspect that they have pheochromocytomas and they don't, and they've had metanephrines that are borderline elevated or maybe under-- We require metanephrines to be two and a half times the upper limit of normal or higher to really consider a

diagnosis of pheochromocytoma. And they might be at two or one and a half times the upper limit of normal.

And I talk with them. I figure out what's happening and a lot of them had this prior backstory of prior abuse or they've witnessed something traumatic. Some of them are people who are in law enforcement types of fields, for example, where they see people shot on a regular basis, unfortunately. This type of a person, it's almost become a phenotype that I see in my clinic where, talking to them about it, suggesting therapy, and if they'd like considering pharmacotherapy, really can help a great deal with some of these paroxysmal hypertension episodes including ones that have caused target organ damage, like strokes, and can actually really help to get that under control. Often you need antihypertensive medication as well, but I've had a couple of instances where all they needed was the SSRI.

Matt: This is fascinating. Paul, have you heard?

Paul: Yeah, I think I have heard, Dr. Cohen, correct me if I'm wrong, but I feel like I've heard some, you hear socioeconomic status or lower socioeconomic status cited as a risk factor for hypertension. Obviously, like, the money itself doesn't matter. But one of the theories I've read about this is it's the sympathetic responsiveness because you're just under so much stress that comes along with the lower socioeconomic status, whether it's finding money for food or affording visits and all that kind of stuff, just living around sort of heightened crime rates like all those things, contributes to this heightened sense of sympathetic state. But I don't know if that's been borne out-- [crosstalk]

Jordy: It has been yeah. There's a good deal of literature now also showing that structural racism specifically is associated with an elevated stress state and increased risk of hypertension and adverse cardiac effects. So, this is being shown. We're seeing this in a few other disease states as well. But the stress of dealing with certain factors can definitely in itself cause these types of health issues.

Matt: So, primary care doctors are sending people to you, maybe they're having these paroxysms of hypertension, maybe by some life event that happened or whatever their emotional state is. They think about pheo, they check like the plasma metanephrines, and they get these levels, that are slightly high. And then they're sending them to you saying, is this pheochromocytoma? And you're kind of digging into it further and be like-- [crosstalk]

Paul: You know, here's some citalopram.

Matt: This seems like this could be anxiety driven.

Jordy: Yeah.

Matt: Is that sort of how the presentation goes? I'm just trying to read between the lines of--.

Jordy: It's how it goes, but it usually requires a couple of visits to get to that and trying some other things and assessments first so that the person doesn't think you're just brushing them off as anxiety either. But there have been many where after ruling out other factors and making sure there's no severe target organ damage from what they've been experiencing, like getting an echo if appropriate and checking for proteinuria and microalbuminuria, and looking for other secondary causes that could be causing it.

For example, another presentation that masks itself similarly is a suppressed renin hypertensive. This is people who have low renin but normal aldosterone. It's almost like a Liddle-like syndrome, if anyone remembers that from medical school. We get questions on that in our nephrology board exams all the time. But this is a state where people tend to be more salt sensitive. It's a mild aldosterone excess state where you have just enough aldosterone to suppress your renin, but not to cause the aldosterone to hang out being high.

Basically, the person's thinking that they're constantly volume depleted. That's how their body is behaving because of that abnormality of that excess aldo state with the suppressed renin. And so, in those individuals, they tend to be incredibly responsive to diuretic therapy. Often, they're already on a thiazide. It's not enough, and we have to add an additional agent. So, last time I talked about how I love adding amiloride in folks like that or adding a mineralocorticoid receptor antagonist. So, they also can present just like that with those paroxysmal hypertensive types of states. But typically, I'll check for that and when it's not abnormal and we talk more and I learn more about the person and start asking more about their social history and the things they're dealing with in life, we get down to figuring out that there's something deeper going on.

Matt: So, for the audience, you're saying that two of the patients that may commonly be referred to your clinic would be patients that are having these paroxysms of hypertension. And one of them is the anxiety phenotype that we just talked about-

Jordy: The sympathetic phenotype.

Matt: -the sympathetic phenotype, sorry. And then the other one is this, maybe they have low renin, normal aldo. And that's the patient we talked about last time where low renin, normal aldo sorry, I've been corrected by previous guests, renin [Jordy laughs] that those patients tend to be very responsive to diuretics, probably a thiazide is not enough, so those are the ones where we think about adding amiloride, which I haven't started using amiloride much yet. Can you remind us what would be typical dosing for that in those patients?

Jordy: It starts at 5 mg depending on where the person's blood pressure is. If I'm worried about hyperkalemia risk, I might start even at a half tablet at 2.5 mg, but it's only available in 5 mg tablets actually. You can give 5 mg or 10 using two tablets, but you can also do a mineralocorticoid receptor antagonist in those folks too. Either way, amiloride tends to be a little better tolerated than spironolactone in men because of the lack of gynecomastia risk. But now that eplerenone is increasingly more affordable, then any of those are great options for this scenario. I just find amiloride tends to be a little more potent. So, in my really severe uncontrolled patients coming in, I go for that.

Matt: Yeah. Okay. This is great stuff. All right, so with our case here, we gave you this patient, Joanne, this 56-year-old woman, blood pressure is high. she's on a calcium channel blocker and an angiotensin receptor blocker, a long-acting one, olmesartan, but she's still high. So, what might be your next steps in someone like this? Now we're starting to think, like, do we need to add another agent? What else should we do here to troubleshoot this?

Jordy: Yeah, so she hasn't yet proven herself as resistant hypertensive because she isn't hypertensive on three anti-hypertensive medications. I can tell you by her current blood pressures. I think it's going to be unlikely. We're going to get her to where she needs to be with one more agent, but we have to go through those motions before we go crazy, because she might just be really volume sensitive and missing that diuretic. In somebody like her, I would

have a very low threshold to put her on a three-drug fixed-dose combination, keep her life simple.

So, we can do olmesartan, amlodipine, HCTZ, keep her on the same two other drugs. And I would start there and see how she does because some people really do surprise you with how diuretic sensitive they are. I think that thiazide diuretics used to get this bad rap of just not being great antihypertensive drugs and it's not true. They can be incredibly effective. It just depends on who you treat with it them because different folks are more responsive to some agents than others.

Matt: And you mentioned a triple fixed-dose combination.

Jordy: Yeah.

Matt: I don't have anyone on this right now, and I'm not sure if Paul does. It sounds like it could be expensive, but is it expensive?

Jordy: It's often covered by Medicare or Medicaid depending on what year it is. They usually will cover it and which version of it they have. That they'll usually cover a triple pill fixed-dose combination as well, a lot of insurances, and if not, it might require PA, a prior authorization. But it's usually very quick. It's not like going through SGLT2 inhibitor prior authorization territory. It's usually just a very quick note justifying why and it gets approved.

I have not had trouble in the last year or two getting one of these approved because they are so inexpensive and they're available for very, very low prices if you go through some of these cost-plus drugs for pharmacies. So, I think insurers are becoming wise to that and willing to cover them typically. There are a couple of triple pill fixed-dose combinations of first-line agents that I'm aware of.

There's the olmesartan, amlodipine, hydrochlorothiazide fixed-dose combination, and then there's a valsartan, amlodipine, hydrochlorothiazide fixed-dose combination. I tend to go towards the olmesartan one a bit more because it is a little more potent than valsartan. Some folks argue that there's some older literature suggesting it might not be, but the literature that I tend to ascribe to shows that olmesartan is just a bit more potent. So that's been my preference. But if it's not covered, then I'd say go for the valsartan. You'll get a similar benefit. You're sitting there splitting hairs at the differences.

Matt: So, Jordy, the patient we gave you here, she's 56. Her blood pressures are in the 150s-160s/the mid-90s, and she's on a calcium channel blocker and an angiotensin receptor blocker. If we add that third agent, the thiazide diuretic, how much blood pressure lowering would you expect we might get from that.

Jordy: Yeah. It's a great question, on average, from a third agent and somebody who's like this, from my experience and seeing how high her blood pressures are, you do see greater blood pressure lowering, the higher your blood pressures are to start with. So, that's the reassuring thing, is that we know we'll get more bang for our buck with adding this agent, but I don't think we're going to get more than 10 mmHg from a thiazide diuretic. I think that's great. I think it's important to add, but that's something that we tend to expect when we're adding a new agent is somewhere in the range of 5 to 15 mmHg improvement.

So, I tend to have my expectation smack in the middle of that. Sometimes you'll see less because you'll only get that 5-mmHg improvement for a drug to be approved by the FDA as a new antihypertensive agent. Typically, the requirement is a minimum of a 4-mmHg improvement by ambulatory blood pressure monitoring, which usually equates to somewhere close to around 8 to 10 mmHg improvement in clinic blood pressure, depending on how and who is measuring it, which we can talk about in a little bit. But it's really interesting because the only agent that we really see something quite different than that with is when you add spironolactone as your fourth agent. There are meta-analyses that show that when your fourth agent is now spironolactone that you're adding to those three first-line antihypertensive medications that you get on average of 20 mmHg/9 mmHg decline in blood pressure in several studies.

And so, it's just this enormous added bang for your buck and I think it just says a lot about what a common mechanism of resistant hypertension is what we talked about is this upregulation of RAS that's just not quite getting hit enough by those first-line antihypertensives in some patients, and this just knocks it out. So, that's part of why I think we see so much benefit also because I think a lot of these folks have underdiagnosed primary aldosteronism, which we can get to. So, I strongly urge folks to add that MRA when you're ready.

Paul: I think we've talked about those studies before and actually has been my practice. I'd like to go back to not to dwell too much on this, but the sort of sympathetically driven patient. So, let's say you have someone who is on their three meds and not counting the citalopram that we started as well, and you feel like you still adequately treat their anxiety, but you suspect there's some sympathetic would that change your approach to, so that next line medication would you go for like a beta blocker to kind of block some of that activity or maybe even like clonidine, God forbid?

Jordy: Yeah.

Paul: It just sort of going into this mechanism?

Jordy: It's a great question. I. Would still use MRA as my fourth agent just based off of this preponderance of evidence supporting that as the fourth drug. But let's say they're on four drugs now and you're still seeing that they've got sympathetic hypertension-

Paul: That they're seeing you.

[laughter]

Jordy: -and they're seeing me. That's when I'll start using these more beta-blocking and AV nodal-blocking agents. The reason that I don't do it sooner is because these agents are not proven antihypertensive medications associated with, like, cardiac benefit. If anything, actually using beta blockers, especially as your first three agents in particular, is associated with an elevated risk of congestive heart failure, elevated risk of nuanced cardiovascular disease in several studies. We did an emulated trial, for instance, in HIV patients with incident hypertension and we found that when they were treated with the beta blocker as their first-line agent, they had about a 70% increased risk of developing major cardiac events, about 50% increased risk of developing CHF compared to people started on any of the other true first-line agents.

This has been shown in several studies. We should not be using beta blockers in particular as first-line antihypertensive agents. It's so incredibly important to have that on our radar. As a fourth-line agent for appropriate patients, I think if there's a real indication to use it of course, if

someone has atrial fibrillation if somebody has migraine headaches and we want to use it for prophylaxis, I think they're fantastic. For anxiety, it's not quite clear if somebody has performance anxiety, yeah propranolol is a great option or a beta blocker. For more generalized anxiety, it's not 100% clear. I do use them sometimes in these patients when it's very clearly a huge anxiety component and you're not getting enough benefit from an SSRI and they're taking, like, benzos that are getting prescribed to them and whatnot? In those patients? Yeah, I'll try to use the throw a beta blocker on. If they're more borderline or I think it's a potential contributing factor but there's more at play, I wait.

And I actually will use a clonidine patch or guanfacine before I'll go to a beta blocker or alpha-blocker, because beta blockers I worry about are they really helping with the blood pressure, particularly and alpha blockers tend to increase blood pressure lability and I worry about worsening what's already there. I usually save those for last after I do a central alpha agonist like clonidine or guanfacine. If I do clonidine, though, I only do it in patch form. Absolutely will never do it in pill form because it can cause blood pressure lability because it's so short-acting, its pharmacokinetics are so inconsistent from one person to the next. Even if you're taking your clonidine correctly, then you can still end up with that rebound hypertension between doses. So, I really, really am a huge fan of either using the patch or using guanfacine, which is another central alpha agonist that works exactly the same way as clonidine does.

It's actually FDA indicated also for ADHD treatment. So, my patients who come to me asking if they have to stop their Ritalin, I say, "Hold on, I have a drug free." [laughs] And I try to convince them to stop their ADHD medications and switch them over to guanfacine and I've had quite a few people who've like given me hugs after that. I'm a big fan of central alpha agonists as long as they're long-acting. If they are the shorter-acting ones, they can cause a lot more harm than good.

Paul: I have to make sure I'm hearing you correctly.

[laughter]

Paul: All else being even you got your patient on four medications; they don't have heart failure, you would reach for guanfacine before a beta blocker unless there was something like compelling indication. Is this the thing that I'm hearing?

Jordy: You're hearing me correctly?

Paul: Okay. I just want to make sure that I was not misunderstanding and that you've blown my mind thoroughly.

Matt: What you were citing there, the increased cardiovascular risk with patients on beta blocker as a first line. If patients don't have an indication for beta blocker and you get one of those-- we see these sometimes in primary care. Patient comes to you like, "Why are you on a beta blocker?" And they're like, "Oh because I have high blood pressure." And you're like, "Why are you on a beta blocker?"

[laughter]

Matt: Yeah so, I think I might be stopping some beta blockers in those patients if I can't find a good reason that they're on it, which often I can't.

Jordy: Yeah, we debate this a lot in the hypertension specialist space because some folks won't stop them if someone's doing well on them. One thing I will say is if they've been on it for a long time and they're on a high dose, you actually have to taper it off, much like clonidine because you can end up with a rebound tachycardia and folks can feel quite bad. And so, I have had a handful of these really anxious patients who are on it because their doc was like, "Oh, I want to use this for your hypertension." And we had trouble weaning it off because they were getting palpitations and anxiety trying to wean it off. So, I actually put them on a clonidine patch to wean them off of it.

Matt: Yeah, so you wean off over depending on the dose, I imagine. It's like weeks to months or is it just a couple of weeks?

Jordy: Weeks. Yeah, I do weeks, I think I usually cut it in half every two weeks, but it depends on how long and the dose.

Matt: Okay. That's a good starting point.

Jordy: I've heard people do it slower even because of concern. So, maybe it's part of why I had a couple of folks not deal well with weaning it off as maybe I didn't go slow enough.

Matt: So, let's give you another slight variation to this case. Our patient, Joanne, if she was on either a quarter dose or half dose of this combination pill that she's on. So, she's either on a quarter of the max dose of both agents or half max dose of both agents and her blood pressure is looking like this. Would you go up to the full dose before you tried to add the diuretic or order would you do those things in?

Jordy: So, in her, I would add the diuretic first. The reason being, as long as you're on a moderate dose of each of the medications, when you try to go to a higher dose, especially when you get to the maximum dose, you're going to get much less blood pressure benefit than you will get adding a risk of an adverse effect. And so, I'd rather maintain her trust, get her really used to come into our clinic and get her taking this medication and thinking I'm not trying to wrong her, and then start working in higher doses. So, I'll usually try to-- somebody like this, I will add the third agent and then I'll increase doses next before adding a fourth agent.

Deb Gorth: So, Joanne comes back to the clinic in a month and her blood pressure is still high. It's 146/92 despite your prescribing three antihypertensive agents from three different classes. So, now that we have this patient on three antihypertensive agents, at what point would you consider calling this resistant hypertension?

Jordy: So, first we say that we need somebody to meet the definition of resistant hypertension that they have to be on the optimally tolerated doses. So, whatever your highest tolerated doses of at least three first-line antihypertensive agents and still have an elevated blood pressure. If she is on the optimally tolerated dose of three antihypertensive agents, we've got her on max dose of all three and her blood pressure is still elevated, then I would say this is apparent treatment-resistant hypertension. I would not yet say it's treatment-resistant hypertension.

The key word being apparent because we think it most likely is resistant hypertension. She meets the technical definition, but the question is, is it actually resistant hypertension or is it pseudo-resistant hypertension? So, the way that we know that for sure is we have to check a few things. First of all, we have to know, do we trust the blood pressures we're getting? If this was somebody coming into my clinic and just getting an initial triaged blood pressure, I for sure

would not be trusting the blood pressure that they are getting. I love my medical assistants, but they are under a ton of pressure to ask 20 questions at the exact same time that they're checking that person's blood pressure.

If I was a patient, I would still be stressed out by that line of questioning, and I don't think that my blood pressure would be particularly accurate when they're checking it. I'm a huge fan of bringing the patient back to my office space and doing a true high-quality office reading. What I do is I have the luxury of being in my complex hypertension clinic with having Omron 907 Excel automated office blood pressure devices that were used in SPRINT and ACCORD trials. So, I can just hook it onto my patient and get that perfect research-quality blood pressure.

I realizes that's not available everywhere, but technically, really, that's what you need to actually be hitting those guideline level required blood pressures is a really well-done blood pressure. So, this has to be someone actually resting for five minutes before their blood pressure is checked. It has to be somebody with their feet flat on the floor, not sitting on an exam table like myself as a 5'4" woman whose feet dangle like crazy on an exam table. Having your back supported also really hard to do on most exam tables, so at least the broken ones in our clinic. And then on top of that, you need to make sure that their arm is supported about at the level of their heart.

I don't know if you've seen, I mean, check a blood pressure recently, but it's pretty hard to even do that in general and often definitely not happening on an exam table. And also, on a lot of the armless chairs that people get their blood pressures checked on in clinic also. So, there are just so many factors contributing. You need to also make sure it's being done on a bare arm. People often will have their winter clothes on and not getting a bare arm blood pressure or they'll do the wise thing of pushing the sleeve up on their arm thinking that they're going to get that great bare arm blood pressure. And instead, you're creating a tourniquet effect that's going to give you a falsely elevated blood pressure. So, so many things we do wrong in checking blood pressure in the clinic. So, either we try to actually do it right and get the average of three high-quality readings using an automated device, not using our horrible ears and our miscalibrated manual blood pressure devices that are hanging on the wall that has been smashed into 15 times by cleaning devices and medical students who are too afraid to be too close to the patient. But instead, we're using these automated validated devices where we can actually get an accurate reading. So, all these are incredibly important and if it's not feasible, then we should be getting really good home blood pressures on our patients.

Matt: Fantastic. Yeah, I think the automated cuff has become something ever since SPRINT. I was just convinced that that was the way that we should be trying to check blood pressures, preferably, when the patient has had time. And then reading the 2017 ACC guideline where they have like five pages dedicated to how to check a proper blood pressure.

Jordy: Yeah.

Matt: It tells you that that's an important thing. So, we're talking about pseudo-resistant hypertension. One of them is, can you trust your readings? What are some other common causes of this apparent resistant hypertension?

Jordy: So, does the person have white-coat hypertension? And so automated office blood pressure can get through past some of that. A big part of why that is is because you're getting three readings. If somebody has white-code hypertension, you've now given them some time to rest, and the three subsequent readings actually each lower quite a bit, and you can get a much

closer glimpse to what their real blood pressure is, or you get out of office blood pressures, as I mentioned to rule out white-coat hypertension, because we know that once you're on treatment, white-coat hypertension is actually called white-coat effect because you already have hypertension and it's just the effect of white coats that's raising your blood pressure.

And we wrote the data on that. We wrote the meta-analysis showing that the white-coat effect is not associated with elevated cardiovascular risk. We should really not be treating people based off of office readings if they have a white-coat effect, because we could be causing undue side effects from medications and hypotension that the patient doesn't need causing mistrust and causing them to be more likely to have pseudo-resistant hypertension because we think they're taking their meds and they're not.

I mean that's the last case is, nonadherence. So, if people are not taking their medication as prescribed, then they don't really have resistant hypertension. They just are prescribed three antihypertensive medications and are walking around with a high blood pressure. I love the fixed-dose combination tablets because they help to limit this to some extent, but they're not perfect. And it's really hard to know if our patients are being adherent. There's been really great data by Dr. Wanpen V. I cannot pronounce her last name, unfortunately, but she's at the University of Texas Southwestern, and her-- [crosstalk]

Matt: Vongpatanasin.

Jordy: Thank you.

Matt: Vongpatanasin.

Jordy: You're amazing.

[laughter]

Jordy: Vongpatanasin, thank you. So, Dr. Wanpen Vongpatanasin has amazing literature, amazing papers that her group has done down in UT Southwestern showing essentially that pharmacy fill data has nothing to do with a lot of patients actually taking. We can try to see what the patients actually telling to give us some idea of what they're taking because I think that's the best tool we have right now.

A lot of our electronic health records just let us look and see. They're not 100% accurate, but it gives us something. But even that's not really that accurate, patient report has been shown, of course, to, unfortunately, be pretty wildly inaccurate. And the worst assessment of whether a patient is actually taking their medications is physician assessment. If we have our own personal biases and judgment as to whether someone's taking their meds, chances are it's wrong according to really well-done studies that have measured blood levels of medications in patients.

Unfortunately, it's a tough itch to scratch. Best we can do is try to build a really good rapport with our patients and try to get them to be honest with us, whether they're taking their meds or not. The way I usually pose it is, are there any side effects I can help you with? Anything that's bugging you about these drugs or anything making it hard for you to take it that I can do to try to help make it better. Sort of making an open-ended offer to change their meds if they are having a problem taking them. I find that that's helped to some extent. I find the fixed-dose

combinations has really been the biggest bullet, though, that I have in terms of fighting the nonadherence issue.

Matt: Yeah. If they're taking one pill once a day and it's giving them three meds, even if you tell them that they still feel like they're taking one med and it's easier than they're like, you're adding a third med. Why do I need three meds? I've had a lot of luck since I've moved over to a lot more of the combination pills, which earlier in my career, it just seemed like a lot of them weren't affordable. But now that has swung and now, I'm able to get lots of different fixed-dose combinations. I have to start prescribing these triple pills, Paul. Paul, are you prescribing them yet? I'm not-

Paul: No, actually not.

Matt: -but I think I need to start. You're not. We talked about-- this is apparent resistant hypertension. So that was okay. Can we trust the blood pressure? Is there a white-coat hypertension or white-coat effect? And then are they adherent with their medications? Even if they're filling their meds, we still can't be sure they're taking them. Just ask them, what barriers, how can I make it easier for you? Side effects, cost that sort of thing.

Jordy: I'll put it on you, not on them. [laughs]

Matt: Yeah. What should we think of what secondary causes do you think of and look for before you're going to call someone like resistant hypertension and not secondary hypertension from something else or how do you think about that?

Jordy: Yeah. I think it really depends now on the patient to patient. I think absolutely everybody who I am convinced has resistant hypertension should get a renin and aldosterone. We have good evidence to support that, that about 20% of these people have primary aldosteronism and only about 2% of them get tested for primary aldosteronism. That was another one that we actually wrote the literature or one of the papers on that. There are quite a few now just showing that somewhere between 1% and 3% of people get checked. 20% of resistant hypertensive patients have primary aldosteronism. This is treatable and everyone's excuse for why they don't check it is well, it's not going to change my management why should I check it? But then you run into the situation of, well, their kidney disease is getting worse because their primary aldosteronism is probably attacking their kidneys. And then you end up seeing that they can't stay on the MRA anymore.

Jordy: You have to decide, am I giving them an MRA or an ARB? It's getting harder to test them because of other complicated issues happening. Test as soon as you have the opportunity so that you don't have to make those hard decisions later. Not to mention, our study actually showed that even though people say that they're starting people on mineralocorticoid receptor antagonists in lieu of testing for primary aldosteronism, but people actually aren't. We looked at 280,000 veterans nationwide and we found that only 14% of people ever over about an 18-year span were started on a mineralocorticoid receptor antagonist even though literally 100% of them had an indication. We excluded anyone without an indication for a mineralocorticoid receptor antagonist.

So, 13% were started on one. People who were tested for primary aldosteronism were four to seven times more likely to be started on a mineralocorticoid receptor antagonist than people that were never tested during that 18-year span. So, what that tells us is if you're thinking about testing or thinking about starting it, and a lot of folks are saying, it's not going to change my

management, but clearly, you're just not managing it and you're not starting them on the mineralocorticoid receptor antagonist. So, it's all for not you should be testing. [laughs]

Matt: And these patients do worse Paul right. Lots of MAKE and MACE, right Paul?

Paul: Sure, tons of MACE you just MAKE all day long.

[laughter]

Jordy: That was a crazy outcome. [laughs]

Matt: Yeah. So, major adverse cardiac and kidney events for those who haven't heard our previous episodes talking about that. Okay, so that's one of them; renin and aldo, we're checking that. What else should we think about for patients with resistant hypertension?

Jordy: So, that's the only one that I really think of as ubiquitous, where I check in everybody except also CKD, because a lot of these folks may have had creatinine a couple of years ago, but haven't had recent BMP, and most of them have not had microalbumin checked and so I always will check urinalysis and microalbumin just to make sure we're not missing some occult proteinuria. Maybe their creatinine of 1, we weren't noticing that their creatinine was actually 0.5 a couple of years ago and just thinking that perhaps it could be more occult kidney disease contributing to their worsening hypertension that we weren't thinking about. So, those are the two I check in absolutely everybody.

Then I start getting to, who is this patient? What else am I worried about? So, for example, if somebody is more obese, has a thicker neck, or they respond positively to some of the sort of queries I ask about obstructive sleep apnea. Like, do you wake up with morning headaches? Do you feel like you're not well rested? Do you have witnessed apnea? Of course.

Then in those folks, I have a low threshold to check for obstructive sleep apnea. We find a lot of it in these patients. Is it going to cure their resistant hypertension to treat it? Not necessarily. But will it help them make them feel a lot better and probably lower their blood pressure a little bit? Yeah. It has been shown that when people actually adhere to the CPAP, we end up seeing a reduction in sympathetic drive during the day, and then you end up seeing an improvement in daytime blood pressures, of course, in addition to nighttime blood pressures. So, I think that there is a lot to be gained by checking for it. And then the other things that we think about are rarer and that I tend to check for less unless I have a specific reason to.

Another example is renal artery stenosis, which can be either due to atherosclerotic disease or due to fibromuscular dysplasia. Fibromuscular dysplasia, we tend to diagnose at a younger age, whereas atherosclerotic disease, of course, older people, someone who's got more risk for it. So, somebody who has other atherosclerotic diseases, someone who's a smoker, who's got known hyperlipidemia, those are the folks I'm thinking about atherosclerotic renal artery stenosis in, and even then, I don't push incredibly hard to search for it unless I'm seeing worsening kidney function because the interventions are sometimes worse than the disease. And most of what we can do to help these patients is just medically manage them and make sure they're on a statin, make sure that their blood pressure is under control.

Matt: See our NephMadness 2023 episode, we talk with Matt Luther about that.

Jordy: He is the expert on it and he sees the most fascinating cases of this and unfortunate and difficult cases of this, and he's incredible at managing it. So, I've learned a ton from him actually, on that topic.

Matt: Okay, so OSA, renal artery stenosis, and what else?

Jordy: I leave things like pheo for later, because pheochromocytoma, paragangliomas, these are as rare as we think. We do see them, obviously, like our center sees so many of these a year because they get referred to us and we have a whole neuroendocrine center. But it shouldn't be the first thing you're checking for. You should be checking for these other things and then asking yourself, do I have a suspicion for pheo? You don't want to miss it, of course, if somebody has one. But I'm really only checking for it in people with really severe hypertension that's really refractory to treatment and symptomatic hypertension, people with headaches, palpitations, diaphoresis, those types of symptoms, then, of course, I'm searching for it.

But it's important, as I'd mentioned earlier, that you're interpreting it correctly. If it's mildly elevated, we don't consider that positive. We really look for two and a half to three times the upper limit of normal just for plasma metanephrines as our diagnostic tool for pheochromocytoma. There is not great evidence to support checking 24-hour urine metanephrines. There's really no evidence I'm aware of that really supports screening with urine catecholamines or plasma catecholamines in these patients. Those are tools that we use in research and tools that are used later on to try to nail down specific nuances of the diagnoses. But for some reason, a lot of folks check catecholamines in these patients and just please don't do that. [laughs] Just check plasma metanephrines. That's what the board question is too. [laughs]

Matt: So, it's just plasma? Yeah, because sometimes when you order it gives you multiple-- it'll be like epinephrine, normetanephrines. metanephrines. And then you're just looking at the plasma metanephrines and is it greater than two and a half to three times upper limit normal?

Jordy: Yeah, and the normetanephrine is part of that too, that comes with it. But you're not looking at like dopamine and there's like a whole other panel of catecholamines that you can get epinephrine and you don't need those.

Matt: What about medications? I know there're a lot of medications and other substances. How often are you seeing that as a problem? I mean, is it fairly obvious most of the time or is it like someone's, I don't know, chewing ibuprofen and that's putting their blood pressure through the roof?

Jordy: Yeah, this is definitely the ubiquitous we should check for this in everyone before we do anything else. This should be like before you even send the renin A and aldo, after you check whether you're convinced the person's adherent or not. Ask them about substances, that can even be honestly earlier on before they get to resistant hypertension just so that you can educate them to know what we're thinking about could be contributing to high blood pressure. And this is huge. This is a large portion of what I even see in my clinic. We know the more common ones, for instance, NSAIDs can increase blood pressure, the degree to which is a little bit controversial. But I do tend to counsel folks that if you can tolerate other agents to try to use non-NSAIDs to manage their pain. But if it's really the only option, I just let them know they're probably going to need additional antihypertensive therapy to treat their blood pressure sort of polypharmacy on top of the NSAIDs.

But then there are other drugs, that are a little bit tougher, oral contraceptives with estrogen in them. That's something that's really tough, always a lot of folks really don't always remember that that contributes to hypertension in women. Folks often don't even know if their female patients are on it because it's prescribed by a gynecologist and they're seeing somebody at another center who's their primary care doc and they didn't mention this on their medication list for whatever reason.

It's always really important to ask about oral contraceptives and to offer alternative options if someone does have hypertension to rule out that as a contributing factor to their hypertension. So, that's incredibly important to be thinking about. And then there is other more unusual things. For antidepressants, certain antidepressants can cause increase in blood pressure. Not all antidepressant medications, but like SNRIs, for instance, we think about amphetamines, of course, we mentioned that earlier and several of the treatments we use for ADD and ADHD are problematic unfortunately.

We think about other prescribed medications, such as, for instance, we deal with this a lot in the kidney transplant space. People who are on tacrolimus or cyclosporin, they have very difficult to control hypertension and a lot of drug interactions. They're the one group that we actually do treat with beta blockers as one of their first-line antihypertensive medications because we can't often treat them with other agents because they can harm their kidneys or kidney excuse me, single, or they can end up having an adverse interaction with the tacrolimus and creative challenges in managing it. We tend to only use it in that situation that I'm aware of.

And then we deal with a lot of cancer therapies that people don't often think about really can cause very severe acute hypertension. American Heart Association put out a scientific statement on management of hypertension in cancer patients. And a huge part of that is all about VEGF inhibitors and tyrosine kinase inhibitors. And how it's incredibly important to be thinking about checking your patient's blood pressures daily initially upon starting these medications because you can end up with a stroke within a few days by how severe your blood pressure can be elevated by one of these agents.

And then alternatively, if they're being held, you have to quickly reduce the antihypertensive agents because these are older folks often with more stiffer blood vessels. As soon as you stop one of these agents, it's similar to having preeclampsia go on and then shut off, in terms of the mechanism. You can end up just seeing a very sudden drop in blood pressure as well. My father-in-law actually has renal cell carcinoma and is treated with a VEGF inhibitor, and he ended up developing a stroke because nobody told him to hold your antihypertensive agent-

Matt: Oh my God.

Jordy: -when we're holding your VEGF inhibitor. So, he was off of it for a week because of another adverse effect and developed much worse secondary effect to his antihypertensive medications. So, he's doing okay. He's actually still working full time. He's like a crazy guy. But something that didn't need to happen, it was iatrogenic. This is really common in these patients. I've seen this quite frequently in patients referred to me.

Matt: So, these patients are getting started on blood pressure meds to accommodate for the VEGF inhibitor if they develop that high blood pressure and then you just have to be careful.

Jordy: And then someone forgets to stop it.

Matt: That you just have to stop it when they're going to take a drug holiday. Okay.

Jordy: Yeah.

Paul: I don’t like any of this sort of uncontrolled hypertension as a great excuse to go back and revisit a lot of your med student history, I think social history, specifically like alcohol use. I feel like we just ask them one time and then never ask again. And that is certainly fluid, it may change for certain people. It's a great chance to check and ask about cocaine use or alcohol use, or even tobacco to some extent, or new medications that you may not talk about like this is-- anytime you see blood pressure that seems to be kind of creeping up to my mind, is a good chance to go back and revisit things that maybe you haven't touched on a little bit.

Matt: And of course, lifestyle, physical activity, those things as well.

Jordy: Of course. I was going to say herbal supplements. It's hard to ask patients about that because it becomes almost a political discussion now in some cases. But it's really important because several herbal supplements can worsen hypertension or interact with anti-hypertensive agents. So, Ginkgo, ginseng, St. John's wort is concerning because it has a lot of interactions, particularly to black licorice from other countries, from outside the US-- [crosstalk]

Matt: Same of whatever that's called.

Jordy: Glycyrrhizic acid, I can never pronounce it that well.

Matt: Yeah.

Jordy: But yeah, those are incredibly important to ask about and hard to get patients to often really talk about because they're worried, they're going to be judged for it in some cases. The other thing is other iatrogenic causes of labile hypertension from medications besides the ones that we think about typically. One that I'm seeing a lot of, I've had like a half a dozen consults for this in the not-so-distant past is tizanidine-induced hypertension.

So, tizanidine is a muscle relaxant increasingly being used for chronic pain in the era of we're trying to avoid opioids, of course, and I think it was great that folks were starting to think outside the box to find alternative pain medications. I find a lot of the pain specialists are prescribing tizanidine, particularly for back pain. I've also been seeing it used for some migraine prophylaxis as like a late-line agents in people with refractory migraines. And tizanidine is actually a central alpha agonist just like guanfacine and just like clonidine, and tizanidine is really short-acting. And so, it's often prescribed for multiple times a day, but people might only take it at night to help them sleep, for example.

So, what happens is, just like clonidine, your blood pressure is going to lower acutely when you take it. And then if you're primed, if you're somebody with hypertension with stiff blood vessels, somebody a little bit more sympathetically active, you're going to have this huge rebound effect. And I've actually had a couple of patients who've had strokes as a result of that rebound effect.

Paul: Oh my God.

Jordy: And we identified that it was because of tizanidine. Matt Luther, who you just had on your show, he actually wrote an amazing case report on this and hypertension that was published a couple of years ago about a patient with a very similar case. That's how I learned

about it and started looking for it. It was a very similar idea, where it was somebody who was taking tizanidine sort of PRN intermittently for their pain and developing paroxysmal hypertension. Then he captured it on 24-hour ambulatory blood pressure monitoring and it's incredible in terms of the breadth of blood pressures, you see, like my patient that I had, one of my examples, their blood pressures went from the 70s/40s after taking it up to the 190s-210s/120s after it rebounded.

This, of course, was, again, somebody who was a little more sympathetically active, a little bit more primed to have a really high rebound effect but it was quite terrifying and quite real. Does everybody get this who's receiving tizanidine for their hypertension? Not necessarily, but I think that it's something to just be thinking about. I wouldn't stop every patient who's on it who's got reasonably well-controlled hypertension, who's not running into any issues, but if you're running into problems with blood pressure control, I would think about it.

Paul: The case report is incredible because I think if I remember correctly, the patient was hospitalized because they were working her up for pheo at the same time before they kind of figured out what was going on. It was a whole to do. But luckily there's no evidence for use of muscle relaxants in chronic low back pains. That makes this all the--[crosstalk]

[laughter]

Matt: That's not totally true, Paul. It's in the ACP guideline, so there must be some evidence. But it you--[crosstalk]

Paul: Is that for chronic or for acute? Am I mistaken?

Matt: I think it's for chronic. Oh, we'll have to double check.

Paul: All right.

Matt: Anyway.

Paul: Just edit out these last 15 minutes, just don't waste the time now.

Matt: [laughs] All right. One of the first things that past guests have told us is, like, okay, I like to swap out the hydrochlorothiazide for chlorthalidone and then add an MRA essentially to fix the blood pressure. But we have patients on this fixed-dose combination which has hydrochlorothiazide, so why don't we have fixed-dose combinations with chlorthalidone? And how do you handle it if you're at that point where you're like, "Oh, I got to get rid of this hydrochlorothiazide, I'm going to put them on chlorthalidone." What do you do there?

Jordy: I was one of those past guests who said that too, so I definitely still do this. Just a sidenote, the VA Cooperative trial just came out in New England Journal of Medicine recently showing that switching patients who are reasonably well controlled on hydrochlorothiazide to chlorthalidone had no benefit. But that's different than your-- we don't really know from that trial about these really uncontrolled severe resistant hypertensive-type patients. I do think a lot of these patients, particularly who are very volume overloaded, but if we can't see it. There's that hidden volume can benefit more from chlorthalidone.

I do also think that the long-term effect of chlorthalidone pharmacokinetically could still potentially have benefits. But to be clear, randomized control trial evidence has now shown that

switching from hydrochlorothiazide to chlorthalidone doesn't necessarily provide benefit in people with blood pressures in, like the 130s/90s or 80s and otherwise no other major risk factors. But yeah, in my higher-risk patients, I have a low threshold to switch them. It stinks because you do have to take them off of that fixed-dose combination because there are no fixed-dose combinations or there are a couple we'll talk about in the US. But very little options in terms of fixed-dose combinations with chlorthalidone.

And so, it does cause a little bit of shake-up in terms of the regimen. But I do find that in some patients it's really incredibly effective, particularly I think, because of that long-acting effect. The reason being hydrochlorothiazide only has a half-life of about 9 hours to up to 12 hours. If you're on it for a long term and actually taking it consistently, chlorthalidone has a half-life of up to 40 hours,

The typical American has their biggest meal at dinnertime. This is different depending on what country you're in, obviously. But in the US our big meal is our big American dinner with steak and French fries and whatever else you'd like that's got a sodium content that's more than what our daily total content should be.

What ends up happening is you take hydrochlorothiazide in the morning and by the time you get to dinnertime, if you're one of these people who's a faster metabolizer of it, then it's now worn off and you're more sodium avid later in the day, you're more likely to absorb every last bit of that sodium from your high-salt meal and more likely to have nocturnal hypertension. It might not show up during the next day because you've now taken hydrochlorothiazide again in the morning and its peak activity happens just within around 2 to 6 hours. So, it's pretty quick to start working. But during the nighttime, you're having high blood pressures.

The VA Cooperative trial didn't show any difference in terms of cardiovascular risk from hydrochlorothiazide versus chlorthalidone or in terms of benefit. But I think in longer-term follow-up in a different population or a higher-risk population, we may end up potentially seeing that there really is much, much more benefit from chlorthalidone. I'm not sold yet that we have all the answers. It was an amazing trial, but it's missing that. I'm still doing this, but it sucks. Why aren't there any fixed-dose combinations with chlorthalidone in them? It's a long story.

But I'll give you the short version-ish. Chlorthalidone is really hard to compound apparently and so it's very hard to mix it with other agents. It's available in the US, combined with azilsartan, which is like the last remaining non-generic ARB because it came out pretty late and it's also incredibly long-acting. And so, the chlorthalidone, azilsartan fixed-dose combination is probably phenomenal for people who either might forget their drug every once in a while because it's like got a half-life of the combined of 40 hours or just-- [crosstalk]

Matt: I think they gave it out in SPRINT. I think that was one of the ones.

Jordy: Yeah.

Paul: Yeah.

Jordy: Exactly. So, maybe it is like part of the magic bullet of why SPRINT is so great. But I think for now, I'm not prescribing that because it's really expensive. I haven't had success with prior authorizations for it in general, so I just don't think it's worth it. And really, there's very little else that chlorthalidone has been able to be compounded with. It's hard to prescribe on its own because it's really only available in 25 mg tablets in the US. It's very hard to divide. If you give a

patient a pill splitter to cut it, they're going to end up with chlorthalidone dust and trying to pick up little pieces of it from the table and you can still do that because even if you take like one-third one day and two-thirds another day, it's so long-acting and it builds up a steady state quite effectively, so you're not going to run into blood pressure liability from doing that and you're still going to get great coverage from doing that. But you're probably going to lose some drug by doing that. [laughs] So, what I sometimes will do and I know that other folks have mentioned this too, is prescribing chlorthalidone every other day instead of daily because of that long half-life and it makes it a little bit easier just not to have to deal with cutting it. But it takes a special patient to remember to take a drug every other day.

Matt: Yeah. And what about indapamide? Because that one is also a longer-acting thiazide, like diuretic, and I feel like it gets no love. Like it's never mentioned anything I read, but it's around. Is that something people should think about using?

Jordy: Yeah, it's another really good option. It's easier because it comes in two doses instead of one like chlorthalidone, you get 1.25 mg or 2.5 mg, so I'll often start it at 1.25 mg and that's a little bit of a step up from hydrochlorothiazide as a typical dosing that most of our patients are taking. And then the 2.5 mg is really a little bit more of a potent dose. So, I'll tend to get a little more bang for my buck with 2.5 mg. So, if I'm not starting it fresh, if I'm switching them from hydrochlorothiazide, I'll actually put them on 2.5 mg of indapamide. It is long-acting, not quite as long-acting as chlorthalidone. Why isn't it used more? I think it's another one because it's not available in any fixed-dose combinations in the US to my knowledge. So, again, it has to be prescribed separately, but a lot of folks prefer prescribing separately.

I don't know why it's not used more otherwise. It's really common in Canada. It was used in all the Canadian trials, like HYVET and these other huge trials that the Canadians did, and that was their version of chlorthalidone, but for some reason the US just never bought into it. I really think a lot of all of this has to do with pharmaceutical reps in the 90s when these drugs were first coming widely into use and the fact that they did a really great job of marketing hydrochlorothiazide when it was first being compounded with mixed agents.

My dad was a primary care doctor and I was a kid in the 90s and very, very much still have a drawer full of his old pens that say Diovan HCT, excuse me for brand name and all these other brand names, the HCT combinations that I couldn't even tell you what the generic is, so I don't even prescribe it. But yeah, it's quite fascinating how much folks were really pushed to buy into sort of that pharmacy rep world. And I think we obviously live in a different age now where that's far from the case, but we're taught by those folks in terms of how to practice and which drugs to choose, and some of that heuristic sort of stuck with us.

Matt: All right, Jordy, we've talked about extensively the first-line agents. At this point, let's say we've switched our patient over to chlorthalidone, plus she's on a max dose of an angiotensin receptor blocker and a calcium channel blocker. Fourth line agent, I'm thinking is an MRA, but can you talk us through what would be the fourth line, fifth line agent for someone with resistant hypertension?

Jordy: Yeah, so with her, I would definitely do an MRA. Let's say we checked for primary aldo. She does not have it. I would still do the MRA. With a woman, I tend to start with spironolactone because it's more potent than eplerenone. I'm sure you learned a lot more about this from Matt Luther. So, I'll defer to the expert. But that's always my fourth agent in just about everybody unless there's a contraindication. For instance, if their potassium is more than about 4.5 in a chronic kidney disease patient, I'll shy away from using it, but otherwise, I typically will use it.

In terms of after that, it depends. We talked a little bit about how I really tend not to favor beta blockers, but if somebody has a cardiac indication another reason, I may now introduce that beta-blocker, if they didn't have a hard indication, just a soft indication, then I'm okay with it. But I'll often do clonidine or guanfacine before that because I really tend to see that it hits a lot of the sympathetic causes of hypertension a little bit better. They're quite effective antihypertensive medications. But like I mentioned earlier, if I'm doing it, I'm only using the long-acting versions. I will never, ever do it using a short-acting clonidine pill because it can worsen blood pressure lability.

After that, then I'll consider using a beta blocker. But be cautious, because that plus and if you're using multiple AV nodal blocking agents or antisympathetic agents, you're causing a risk of a potential for bradycardia. So, just make sure you're watching their heart rate. Home blood pressure monitors are great for that. Apple Watches are decent for that. So, just make sure that you're making the patient aware that they need to be checking their heart rate and that they need to be making sure they can pick themselves up out of bed in the morning because a lot of these are agents that are not only antianxiety in some ways, but they can really depress things a bit as well.

I think I find a lot of low energy in people when I put them on a multiple of these. Usually just one is reasonable, but two or three, I start worrying about adverse effects. I tend to reserve alpha antagonists of to like your zosin's like prazosin, doxazosin. I tend to reserve those until last because they do cause a bit of blood pressure lability unless there's another indication. If someone has BPH, of course, I will very gladly have them treated with one of those agents sooner. But if they don't have an indication to be on it, then I tend to shy away unless there is a specific reason. I use doxazosin in pheochromocytoma patients because those patients are the ones that you need to alpha block.

Then I really very rarely have anyone on hydralazine, I haven't tended to need it. Usually by now, I'm thinking is this person more volume expanded than I'm realizing? Do I need to be adding on a loop diuretic? Often these are patients now with chronic kidney disease where you're needing like six agents or seven agents, and I'll do that, and I'll max them out on diuretic therapy, watching their electrolytes and their kidney function very closely while doing that. Before I'll consider adding hydralazine, before I would ever consider minoxidil, I've actually never initiated minoxidil on anybody. I've only ever stopped minoxidil. I'm a huge fan of avoiding it because it's such a potent vasodilator that you end up sending people to the hospital with pericardial effusions with heart failure as a result of it, more so than you see any huge benefit. It's a potent antihypertensive medication, but this is another one where the treatment is much worse than the disease.

Matt: Wow. Paul, I am stunned, but I think we have to ask take-home points. At this point, I need to go to sleep and consolidate all this knowledge.

[laughter]

Paul: Just think about the minoxidil prescriptions you've been firing off.

Matt: [laughs] It's my first line, Paul. [Paul laughs] I've been doing things very wrong. Okay, Jordy, can you please give the audience some take-home points? There's been so much, but if you just had a couple of favorites from what we talked about tonight.

Jordy: Yeah. So triple fixed-dose combinations are underutilized. We should use them more. We're not testing for primary aldosteronism enough in our resistant hypertensive patients. So, anyone that you're convinced has resistant hypertension have a very low threshold to check for it, but make sure you're pretty sure they actually have resistant hypertension before you peg them with that diagnosis. Make sure you're checking blood pressure accurately. Make sure that you're checking that they're actually taking their medications. Put it on you, say, "Hey, if you're having trouble with your meds, it's because I'm probably prescribing something giving you a side effect, let me help you or prescribing something that's too expensive for you, so let me help you and figure out what we can do better." And sometimes that can be quite effective.

Also, make sure that they're not taking in any other agents that could be contributing to their high blood pressure, particularly iatrogenic hypertension, because we often don't think about that, but we can often be causing it. But, of course, Also thinking about herbal supplements as being a critical contributor as well. Besides that, I think just in terms of our agents, beta blockers should not be first-line antihypertensive therapy. I hope I scared enough people about that.

Matt: Scared me.

[laughter]

Paul: And Jordy, we're trying to save a little bit of space for people who have a pick of the week or recommendation here towards the end. Now we sort of restructured things, so anything that you think our audience would benefit from or anything that you got excited about recently?

Jordy: Yeah, really excited about Perry Wilson's book that came out about a month ago. I guess now it'll probably be almost two months ago. He wrote an amazing book, it's called *How Medicine Works and When It Doesn't*. I think that it's a great read for anybody who's currently in clinical medicine dealing with a lot of our patient interactions and understanding why patients are frustrated with medicine and why we're frustrated with medicine. It's a really fantastic take on the combination sort of the philosophy, the psychology, and the statistical interpretation of medicine right now. It's a great marriage sort of a lot of what we're struggling with.

I found it both incredibly helpful and insightful, so I strongly recommend it to folks. So, that's *How Medicine Works and When It Doesn't* by Perry Wilson, full disclosure, he was a fellow three years ahead of me in fellowship who gave me a ton of amazing advice that helped me get to where I am in my career. So, I might have been a little bit primed to like his book in advance, but I think I'm not too biased.

[music]

Matt: All right. All our listeners will buy that book, of course.

[laughter]

Paul: The famous Curbsiders bumps.

Matt: [laughs] All right. Thank you so much, Jordy. This has been fantastic. Definitely invited back anytime you want. We probably should make this a recurring thing. So, this is great.

Jordy: I'd love it. Thank you for having me.

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

Deb Gorth: Yummy.

[laughter]

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

Matt: We're committed to high-value practice-changing knowledge, and to do that, we need your feedback, so please subscribe, rate, and review the show. We're on Apple Podcasts, Spotify, we're on YouTube now. You can also send an email to *askcurbsiders@gmail.com*. A reminder that this and most episodes are available for CME through VCU Health *@curbsiders.vcuhealth.org*. Wanted to give a special thanks to the great Dr. Deborah Gorth for helping to write and produce this episode. Our technical production is done by the team at Pod Paste, Elizabeth Proto runs our social media, and Stuart Brigham composed our theme music. With all that, until next time, I've been Dr. Matthew Frank Watto.

Deb Gorth: And I've been Dr. Deb Gorth.

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

[music]

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