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Investigating the Link Between Hypertension Medications & Dementia

Dr. Wilner:
Hypertension affects nearly half of adults in the United States and is associated with cognitive decline and dementia. A wide variety of antihypertensive medications are prescribed to millions of people to control blood pressure and prevent vascular dementia. Could it be that certain medications are better than others in preventing brain injury from chronic hypertension?

Welcome to *NeuroFrontiers* on ReachMD. I'm your host, Dr. Andrew Wilner. Joining me today is Dr. Zachary Marcum, lead author of a provocative paper just published in *JAMA Network Open*. His study explores the association of different classes of blood pressure medications and reduced cognitive impairment in older adults. Dr. Marcum is an Associate Professor in the School of Pharmacy-University of Washington. He is also the Assistant Director for Research at the Plein Center for Geriatric Pharmacy Research, Education, and Outreach.

Dr. Marcum, welcome to the program.

Dr. Marcum:
Thank you. It's great to be with you.

Dr. Wilner:
So Dr. Marcum, let's zero in on your recent study. How is it designed? And what were you trying to learn?

Dr. Marcum:
Yeah, so this was a secondary analysis of a landmark clinical trial called SPRINT. And just as a brief background, the SPRINT trial tested two different blood pressure targets. And so what we did was we used the data that were already collected from SPRINT and analyzed in a secondary post-hoc fashion a comparison of different antihypertensive drug classes to look at their association with our outcome of amnestic mild cognitive impairment and/or probable dementia. And so our hypothesis in this analysis was based on decades of basic and clinical human data that has suggested that different antihypertensive subclasses could have differential effects on cognition.

And so what we did was we grouped the blood pressure medicines into 1 of 2 categories: those that stimulate or activate activity at the type 2 and 4 angiotensin II receptors and those that do not stimulate activity at these receptors. And to be very clear, the drugs that we thought could have potential benefits on cognition include the ARBs, the dihydropyridine calcium channel blockers like amlodipine, and thiazide diuretics like hydrochlorothiazide, so all of those drugs were grouped in one category. And then the other category were the ACE inhibitors, which are very commonly used, beta blockers, and nondihydropyridine calcium channel blockers, things like verapamil and diltiazem. And so we compared these two groups to one another in this cohort study where we looked at the medication use at the six-month visit of SPRINT, and that was chosen because that's about when the medication classes kind of stabilized, and then we followed people over time to look at the occurrence of our outcome—again, that was amnestic MCI or probable dementia. So that was kind of the setup of the study. And, of course, the main limitation of observational research is a lot of confounding that can come into play, and so we used a variety of different statistical approaches to try to mitigate some of that potential confounding.

Dr. Wilner:
So just to be clear, you were looking for an effect above and beyond the control of blood pressure. In other words, if all the patients in both groups had the same blood pressure control, one group would actually to better because of the nature and the method of controlling that blood pressure. Is that correct?

Dr. Marcum:
Yes, that's correct. And thank you for that question. It's a very important point. So we know that controlling blood pressure, especially in midlife, is a promising strategy to reduce late-life dementia. What is unknown and what we're trying to get at here in this study is whether or not there are direct effects of the drugs above and beyond their effect on blood pressure control, and so that's really the central question here is: What is the effect of the drug? And this is an active area of inquiry. There are ongoing clinical trials testing strategies that are aligned with this hypothesis that we tested in our paper, as well as future trials that are planned.

Dr. Wilner:
Well, Dr. Marcum, I did read your paper, so I know the answer, but I'm sure the listeners are on the edge of their seats, so tell us what you found.

Dr. Marcum:
Yeah. So what we found is over a median of 4.8 years of follow-up, so about 5 years total, we found a significantly reduced risk of, again, our outcome of amnestic MCI or probable dementia among those users of regimens that contained exclusively the stimulating medications. And again, those are the ARBs, the dihydropyridine calcium channel blockers or the thiazides, as compared to the inhibiting. And again, those are the ACE inhibitors, beta blockers, and nondihydropyridine calcium channel blockers. And for those who are more quantitative, we found a hazard ratio of 0.76 with a significant confidence interval.

Dr. Wilner:
Wow. So you really found that there was a difference even amongst antihypertensives that are different—for example, thiazides are different from ARBs, and yet they're in the same group—and it seemed that you had this group effect because they were stimulating the receptors. Is that right?

Dr. Marcum:
That's right. So we put them all into the same category. And so if you think about how this might be tested in a clinical trial, you could examine two groups, one that had a stimulating regimen approach, so the prescriber could pick from among those three categories and then compare that to an inhibiting classification, then the prescriber could pick from among those antihypertensive categories. And so that's really where this is leading. Often times this is what we do in research. We find suggestions and observational data and then test it in randomized clinical trials, and so that's clearly where this line of research is pointing.

Dr. Wilner:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and I'm speaking with Dr. Zachary Marcum about his recent study investigating the association between certain hypertension medications and reduced cognitive impairment.

Dr. Marcum, why would one group be different than the other?

Dr. Marcum:
Yes. That's a great question. And so we don't know exactly why, but the current thinking, based again on decades of research including animal studies as well as some human studies, is that it's thought that activity at these angiotensin II type 2 and 4 receptors leads to reduced ischemia, enhanced cerebral blood flow, and particularly at the type 4 receptor, there's some evidence to suggest that it can improve spatial memory processing. So the renin angiotensin system overall is quite complex, and there's still a lot to learn, but

that's the current thinking about why this mechanism could be in existence.

Dr. Wilner:
And did you mention that there are clinical trials ongoing prospective that are going to look at group A and group B for five years and see if it makes a difference?

Dr. Marcum:
Yeah. So we are some of the first people to test this specific categorization of the different subclasses, but there are trials that are essentially testing one stimulating subclass versus one inhibiting subclass. So, for example, a classic test to be an ACE inhibitor versus an ARB because the ARB is stimulating and the ace inhibitor is inhibiting, and that would really elucidate a subgroup of this overall hypothesis. In fact, there already is a published pilot clinical trial comparing an ARB versus an ACE inhibitor among people with MCI, and it found a brain benefit in terms of executive function, so there's already published trial data, and there are more that are currently registered in clinicaltrials.gov.

Dr. Wilner:
Well, that's exciting. And I'm just going to make a comment as a clinical neurologist myself that vascular dementia is pretty frustrating because we have no treatment at all, and the idea that in addition to controlling blood pressure that our selection of drugs might help even more to prevent it, well that's pretty exciting.

Dr. Marcum:
Yeah, it is really exciting. And even if there's a small effect on a population level, we think that this could be a pretty sizable difference because of the prevalence of hypertension. Right? It's so common that even if we find a small effect from the drugs, it still could make a difference. And this is all in the context of having no truly disease-modifying therapies right now for Alzheimer's disease and related dementias, and so there's a lot of attention that's been given on prevention through lifestyle as well as using hopefully some pharmacologic strategies such as prescribing certain antihypertensives.

Dr. Wilner:
Now were there any limitations to the study that we should be aware of?

Dr. Marcum:
Yeah, of course. But as an observational study, there's still the potential for unmeasured confounding, and so our estimates may not be as precise, as we would hope. In addition, some listeners may be familiar with who the SPRINT trial enrolled, but it's important to keep in mind who it did not enroll. And so it did not enroll people with type 2 diabetes, previous stroke, advanced kidney disease, or symptomatic heart failure, and so we can't really extrapolate our findings to those folks.

Dr. Wilner:
Well, that's very helpful. And before we close, Dr. Marcum, is there anything you'd like to add?

Dr. Marcum:
I would just like to add the importance of prevention efforts, especially in midlife. I think there's a lot that we can do today in terms of keeping our blood pressure under control that can ultimately reduce our risk of late-life dementia, and I think there's a lot of public awareness that needs to be raised about this. As far as our specific paper though, I think the message is "Stay tuned." Hopefully in the next few years or so, we'll have more clarity on specifically what prescribers can do at the time of prescribing to try to reduce the risk of dementia for the patient sitting in front of them, but we're not quite there yet, but we're hopeful.

Dr. Wilner:
Well, really exciting research. This has been an insightful look at how certain antihypertensives may address two common health threats among our older patients: hypertension and vascular dementia.

I want to thank my guest, Dr. Zachary Marcum, for a great discussion. Dr. Marcum, it was a pleasure speaking with you today.

Dr. Marcum:
Thank you so much.

Dr. Wilner:
For ReachMD, I'm Dr. Andrew Wilner. To access this and other episodes in our series, visit ReachMD.com/NeuroFrontiers, where you can Be Part of the Knowledge. Thanks for listening.