eAudiology: Medication-Related Balance Conditions and Falls Risk

Presenter: Grady Campbell, PhD

Hi, I'm Grady Campbell. I work at NSU Nova Southeastern University in Fort Lauderdale, Florida. So that's where I'm coming to you from. And of course, as you know, the topic for today is drugs and falls. I've never actually done any research having to do with a particular drug, and I don't get any money from a drug company.

So I actually have no conflicts of interest for having to do with today's talk. All right, so the objectives are pretty simple. Basically, it's about drugs in the vestibular system. But also I thought it would be really useful to go into drugs that might cause problems that would be possibly attributed by a patient to their vestibular system and cause them to seek out an audiologist. So there are many, many drugs that are associated with fall risk and other disequilibrium problems.

And so I wanted to cover them and also not to just give lists of drugs, but to actually explain a little bit about more about what they are and, you know, what they do. And for a few of them, the link to balance problems will be something I can explain, but for most of them, I will not. Okay, so drugs, there are some that actually directly damage the vestibular system. So that's what I'll start with. There aren't so many.

And this falls under what we'd call iatrogenic, which is something during medical care that happens, that is unintended and bad. And of course, here we're talking about drugs that are life saving. So, you know, the risk to benefit ratio is there, even with the potential for damaging hearing or balance. And of course, these drugs can also be used as a therapeutic as well. As an example, we have Meniere disease, where sometimes they will want to knock out or knock down the action of the vestibular system.

And so they'll use typically gentamicin in order to accomplish that. Okay, so I'm sure you all know very well the aminoglycoside antibiotics, and hopefully I'll go into a little bit of useful detail about them. But basically they are permanently damaging to the vestibular system or the cochleotoxic, or they're

cochleotoxic. And also they're damaging to the kidney as well. But of course, we're interested today we'll try to focus just on the vestibular symptoms and of course, the rate of damaging the vestibular system.

The estimate is about 15% of those who take aminoglycosides. The estimates range very widely. I've heard as much as 60% which is hard to believe. And I've even heard 0%, which, you know, that's certainly not. Not true.

So 15% is a pretty good estimate. All right, so the mechanism of action of these antibiotics. Let me start with a little bit of cellular biology. So proteins are made up of amino acids. They're strung together, and there's a cellular machinery that takes the amino acids and puts the.

Puts them together in a certain sequence to make a protein. They make a protein with just the right structure, with all the right amino acids in the right place. And, you know, those. Those proteins then. Then go on to, you know, form structure or carry out chemistry.

So anyway, the machine that does this is called the ribosome inside cells, and the aminoglycosides will bind to the ribosomes. And the reason that it's a good drug target is that the bacterial ribosomes are basically carry out the same function, of course, as the animals ribosomes, but they're different enough that the aminoglycoside drug molecule will bind a lot more potently to the bacterial than to the animal form of the ribosome. And, you know, I used to actually have to explain MRNA a little more thoroughly, but now with the MRNA vaccines, I think more people appreciate the role of the mRNA, which is. It's a nucleic acid sequence that's copied from our genes and encodes the sequence of the protein. And anyway, the MRNA will go to the ribosome and kind of step along the ribosome being read off a base at a time to make an amino acid at a time in sequence for the protein.

Anyway, the MRNA kind of steps along through the ribosome, and the aminoglycosides will, in binding the ribosome in such a way, they keep the MRNA from moving along through the ribosome. So, of course, proteins can't be made, and then obviously that's going to be the end of it for the. For the bacteria. So the time course is very important to understand. And, you know, this is probably something, you know well, very well anyway.

But as far as the onset, it's sometimes only about a week, sometimes only months. And actually it can be several months, and that can even be after the aminoglycoside therapy has ended. So, of course, that has ramifications for the testing. And, and the ramifications of the testing are that the more sensitive the testing is, perhaps if testing were sensitive enough, it could detect damage even earlier than this. But, you know, with today's equipment, this is about the best that can be done.

So the aminoglycosides we'll use name them now because you of course, need to know the names. I'm sure that you already do. Amikacin, gentamicin, kanamycin, neomycin, nidomycin, paromamycin, plazomycin, and streptomycin and tobramycin. And so these of course are generic names. And you know, again, I'm telling you something that probably everybody already knows.

But there's the idea that when a drug company invents or discovers a drug, they will have a what's known as a generic name, but they also have their own trademark name, the brand name. And so these are all generic names. So once the patent protection ends, anybody can make the drug, but they can't use the trademark name. So they will instead use these generic names. And all the aminoglycosides are so old that they really are only known by their, by their generic names.

So anyway, these are the names that you'll recognize and their use is actually falling. Tobramycin is the most prevalent of the aminoglycosides that's used alone. And there are lists made of the amount of prescribing of each drugs. And so the list of 2020 is the latest one that we have. And tobramycin was actually 376th on that list.

So of course there are 376 drugs of all types, the head of tobramycin. But there's, you know, many dozens of antibiotics ahead of it on the list, too many antibiotics that are more prevalently prescribed. Neomycin is a little bit more seen, but that's only in topical combinations. And so neomycin with polymyxin B and hydrocortisone is 315th and of course that's not very much higher. And of course as a topical, it's not going to be tend to be as harmful.

All right, so now let's talk about what the aminoglycosides actually are doing best. You know, best we can tell, you know, we just can't figure out why, how they get into the vestibular parallel. But clearly whether they're systemically administered or transchemically delivered than they do get to the perilymph and they can enter the base of the cryptoepithelial and dark cells in the vestibular apparatus. And as far as the hair cells go, it's not really known whether it's from the perilymph or the endolymph. All right, so the way that they actually get into the hair cells is by this mechano electrical transduction channel that's attached to the tip links.

And the met channel is a channel that potassium and other positive ions can enter. And so actually the aminoglycoside drug molecule enters that way as well. Now, type 1 hair cells have a lot more stereocilia and therefore a lot more MET channels on the type 1. And so it's type 1 hair cells that really take the damage due to the aminoglycosides. Right.

So the other side of that is that compared to other cells in the body, the hair cells really retain the aminoglycoside drug. And also actually the kidney tubular cells do, you know, hence the Reno toxicity of it as well. And the kind of makes sense if we look back at the embryological origin of these different types of cells, the vestibular and cochlear hair cells, and then the renal tubular cells. And if we go back, you know, we have the fertilized egg and that forms the embryo and that forms a fetus. And then finally an infant is born with all different kinds of cells in all the right places.

And the hair cells and renal tubular cells all come from the same place in the embryo. So they end up having a lot of the same properties. All right? And so what ends up happening is oxidative damage. And I'll kind of summarize oxidative damage very roughly because that's a huge topic.

But basically it's about chemicals. And therefore there are some chemicals that are more reactive than others. So there are reactive oxygen species and reactive nitrogen species. And because they're so reactive, they can go in and react with molecules. And in this case, we're interested in the way that they react with biomolecules, so they can chemically modify DNA, which of course hurts the DNA's function.

They can modify lipids. And of course, lipids form all cell membranes. So they're going to kind of mess with the function of the cellular membranes, and then they can go in and cause modified proteins. And of course, we talked about how the proteins have that ability to form nice structures to carry out functions and have nice, you know, like pockets that carry out chemistry. And of course, when that is destroyed, then the function of the protein is destroyed and the cell is going to fare very poorly.

Yeah, I must have hit a hit the button. Anyway, because of the oxidative damage, hair cell death is going to ensue. And iron is something that's known to participate in this nerve adminic animal experiments done where they've supplemented iron or chelated iron, sequestering it harmlessly away in animals and subjected those animals to gentamicin or other aminoglycosides and actually looked at the damage to the hair cells. And so when iron is supplemented, more damage is done. And then when iron is kind of like downplayed, then there's less damage.

All right, so predisposing factors for the vestibular toxicity, there are a number of things known. So aminoglycosides are actually cleared by the kidney. The kidney and the liver are really big players in clearing drugs out of the body. And so in this case, we're talking about kidney clearance of the immunoglycoside drug molecule. And so if the kidney is not functioning up to par, then the aminoglycosides aren't gotten rid of at a high enough rate.

And then they build up and, you know, cause even more damage than they ordinarily would. And of course, the immunoglycosides also have that kidney toxicity as well. And so if there is kidney damage due to the drug, then that also is going to increase the risk of aminoglycoside damage to the ear. So anyway, other things can happen. Dehydration, that's going to increase the circulating concentration of the drug because there's, you know, the same drug in a smaller volume.

So that can be a problem as well.

All right, so another thing that happens is that there's a class of drug, antihypertensives, a blood pressure treatment known as the loop diuretics. When loop diuretics are being taken, then that seems to be something that causes aminoglycoside damage to be even, you know, higher, higher prevalence of the damage. So anemia is another thing that seems to be predisposing factor. And the way that that's thought to be understood is that again, we have the oxidative damage as the real end problem. And so in anemia, the blood can't carry a sufficient amount of oxygen, and then this low oxygen is going to cause formation of even more reactive oxygen species.

And I know that sounds a little bit backwards, but the idea is that there again, some chemistry going on that is utilizes oxygen. And so when there's not enough oxygen, it actually causes those chemical processes to go wrong and form more reactive oxygen species. So anemia is something else that's seen to be something that will increase the damage due to the aminoglycoside. So other things are. Well, actually, I want to mention something that's not.

There's so much talk been done, so many studies being done using different dosing schedules, using different concentrations of the drug, and looking at the serum drug concentrations, and it just seems like the damage, there's no way to dose the drug in a way that really is going to lessen the probability of damage due to the drug. So I know this is a little bit contentious, and I do hear different answers on this.

But in the end, in looking at a lot of literature, I want to come down on the side of saying that there's no way to take these drugs and not have a pretty big risk of damage due to them. And of course, again, I want to stress that this drug is being given to save a life. Antibiotics.

You know, we're talking about an infection, and a serious infection could mean death in hours. And so the idea here then is going to be that despite the dangers of the drug, definitely they have their place in medicine. Another thing to remember is that these. These drugs will cross the placental barrier membrane, and so they will endanger the fetus as well as. As the mother.

So I mentioned the ribosome earlier. So there are ribosomes kind of like throughout animal cells, and some of them are in some place, and some of them, their other. Some of the ribosomes are in the mitochondria, which is an organelle. Organelle that is responsible for making energy for the cell. And so anyway, the idea is that we do know of people who have ribosome sequence.

Their machinery is a little bit different from everyone else, right? I mean, we all have different color hair, different heights, different weights. Well, we have different ribosomes as well. And so some have ribosomes to which the aminoglycoside drug molecule will bind to a little bit higher than others. And so there's kind of like a little bit less distance between, or a little less difference between the bacterial and the mitochondrial ribosome in the person.

And so the drug will bind a little bit more readily to individuals with that particular type of ribosomal sequence. And so they will be even more predisposed to having the damage due to. Due to the drug. Another thing is prior history with any ototoxic drug or high noise. All this damage is cumulative.

And, you know, I've heard it said so many times once there's a little bit of damage, avoid noise and high noise for the rest of your life. And so that's really the case here as well.

Okay, so there are those predisposing factors, and that kind of leads us to ask, well, you know, what. What can we do to actually be. Take an active role in preventing the damage due to aminoglycosides on the vestibular apparatus. And, you know, I was just talking about that inherited predisposition. Find those people.

And maybe that would be a cost to pick another antibiotic or maybe use a little bit lower dose, because, you know, their effective dose is going to be higher. But the thing is that those people with those particular mutations are pretty rare. Okay. So doing a lot of testing for not so many people is. It just would be hard.

And there aren't any rapid screening tests that are out there. And again, kind of reminding ourselves that we're treating, you know, the doctors are treating something that could end life in hours. And so the one needs to know this information very, very fast, and it's just impractical. Another is that hypokalemia or hypomagnesic is another factor. And so treating low potassium or low magnesium in the patient before starting the treatment, if possible.

You know, we mentioned dehydration as being a predisposing factor. So one would want to correct dehydration. And then, of course, again, because these particular drugs are cleared by the kidney, we would want to avoid other medications alongside that that might cause kidney damage or impaired kidney function. Okay. So there might be some things that are active that we can do.

It is oxidative damage. So that's known. So the idea, of course, would be to prevent the oxidative damage. And so I wanted to talk a little bit about some studies that have been done trying to go at the prevention of the toxicity in that way. So there were two studies that were done using aspirin during gentamicin treatment, 2006 and 2009.

And the data from those studies looked pretty convincing. Although I've got to say that there were some things about the studies and the way they were done that I kind of, to me, cast them in a little bit of doubt. But anyway, to me, the fact that this isn't common practice now means that it just must not work as well as claimed in the. In the two studies, because this would be such a nice, simple solution to such a hard and terrible problem. So, again, kind of like the proof is in the pudding.

If this was a way to go about it that was very successful, we would be doing it. I've heard the argument that, well, you know, aspirin is cheap and, you know, nobody's going to make a lot of money selling more aspirin for this purpose. And so there's no reason to do the further studies that one would do to kind of underpin its use. But to my mind, you know, anybody who really put this on a solid footing would be very famous. You know, if they were a faculty member, they would get tenure and go off and give talks in Hawaii and so on and so forth.

So to me, this no reason to study aspirin and aminoglycosides. That argument, to me, just does not hold up. It's just too valuable a thing. So, again, the fact that we're not actually doing it means that this, the promise that we based on these studies just hasn't been borne out. All right, so another antioxidant that was tried is n acetylcysteine.

So 2007, it was tried during gentamicin therapy. 2011, it was tried using amikacin therapy, I should say during amikacin therapy. And again, there was pretty good data from this. But again, I have to say that if it worked as well as that, then it would have. Would be the way we do things these days.

So to me, also, this just haven't held up. And there's all sorts of times when smaller studies that are on the order of tens of people like these were, when you start going and looking at, you know, the tens of thousands of people that would be taking these drugs when and doing those larger efforts, then you know, that would be, you know, too likely to give a different answer. And it seems like that must be what happened. Right? So another one, and I want to catch this with.

Okay, so using antioxidants with aminoglycoside sounds like a good way to avoid damage to the vestibular system and other of the toxicities of the aminoglycosides. And so instead, let's talk about cisplatin. Kind of like by analogy, there was a cisplatin study done with cancer in 2017, followed up in 2018. Kind of as an aside, the 2017 trial actually showed a decreased overall survival of the patients that were treated using the sodium thiosulfate along with the cisplatin. And of course, that's something we never want to see in a human clinical trial.

And the authors did a lot of work trying to kind of figure that out and be sure that they hadn't actually harmed anyone. And they came up with some pretty decent reasons in the end why this subtle effect happened. But, you know, it's kind of an interesting, like I say, kind of an aside, because the last thing one would want in a trial like this is to decrease overall survival, no matter how much it spared the hearing. Anyway. Again, these are potential things.

Using sodium thiosulfate. It didn't Work versus flattened so well. And so it probably is not going to work for the aminoglycosides as well, although I know I'm kind of reaching, but there was a study done using gentamicin in rats and using sodium thiosulfate in that context, and it didn't show any protection. So that study, and then the fact there's no human data for sodium thiosulfate along with the aminoglycosides kind of means to me that that also is not going to be a profitable avenue to follow. All right, so now let's turn to antimalarials.

They're another group of drugs that directly cause vestibular toxicity that we want to talk about. And the first of these is quinine. So it is an antimalarial. It's also used to treat babesiosis, which is the tick borne disease that causes flu like symptoms and sometimes very bad symptoms will persist for years from babesiosis. So it's a good thing to be able to take care of anyway.

We don't actually know exactly how quinine works to kill the parasite, but there's some speculation that it will affect the function of certain intracellular vesicles in the parasite. It does clearly affect muscle contractile activity and it has documented adverse effects of dizziness that are moderately prevalent, you know, greater than 10%. And also vertigo, again pretty prevalent at a rate of higher than 10%. Quinine is actually also in tonic water. So it's possible to gives oneself a quinine overdose by drinking loads of tonic water.

And dizziness and vertigo actually aren't the only things that are side effects or adverse effects of quinine. There's actually so many, and they're so pronounced that it's called synchronism, this constellation of symptoms. And then typically that'll stop with discontinuation of the, of the quinine. And quinine, because of the muscle thing I talked about a minute ago, that was a rationale for trying to use it for leg cramps. But it's pretty much been, you know, studies have really shown that it's not useful for preventing leg cramps.

Another one is quinidine combined with dextromethorphan. And this is for treatment of behavioral symptoms of dementia. And it is something that's clearly associated with fall risk. In other words, people were studied, they were on this drug and they suffered falls at a significantly greater rate than their control groups. Another one is hydroxychloroquine.

It's used both for treatment and prophylaxis. When one is Traveling to malaria, written areas also used for rheumatoid arthritis, systemic lupus erythematosis, discoid lupus erythematosis and lupus nephritis. Okay, and so again, we don't know how it acts against the parasite. Again we think that it binds to DNA and inhibits DNA replication. And again we say that it impairs the function of the intracellular vesicles of the of the parasite.

So in a person it also seems to act as a pretty good anti inflammatory and modulation of the immune system to, for the treatment of lupus. And there again we don't know, but there's speculation that it

reduces cytokines which are part of the response. Also immune effector cells might be slowed down and then intracellular lysosomes. In the same way that intracellular vesicles in the parasite are impaired, intracellular lysosomes in the human taking the drug may be impaired as well, bringing about this effect that's helpful with lupus. The autoimmune disorder, hydroxychloroquine.

I'm kind of continuing with that. It does have documented adverse effects. Dizziness, nystagmus and vertigo. And this drug actually has a very long half life, 40 days. So one expects the vestibular effects and other effects of this drug to last for quite a while after stopping taking the drug.

Okay, so the last animal I want to mention is Mefloquin. It also is used in prophylaxis for people who are traveling to malaria ridden countries and then in treatment of malaria and those who actually have it. So kind of the same story here binds to DNA, inhibits DNA replication and impairs the function of intracellular vesicles. Not surprising. You know, these are all very related drugs, both related molecularly and related in their mechanism of action.

So again, adverse effects that are known, Dizziness, vertigo and loss of balance. And here again we have a case where the effect can last for months after the drug is discontinued. And there's this evidence, animal evidence that it is actually damaging to the vestibular system. So even with pharmacological doses, which means that doses in rats that were comparable in amounts by weight to what a human would take normally did cause vestibular hair cell loss. So evidence that it is actually directly damaging to the vestibular system.

All right, so I wanted to include some industrial chemicals that also damage the vestibular system. And of course these are involve permanent damage. We have ethyl benzene that's used for making styrene a plastic and ethyl benzene is also one of the ingredients of gasoline styrene that's used for making plastics and rubbers. Toluene is used for making paints, lacquers and adhesives. Trichloroethylene is used as a degreaser.

And I kind of wanted to mention, and this is kind of in terms of how people should protect themselves from all of these industrial chemicals. So I once worked in the semiconductor industry, and we use trichloroethylene for decreasing our silicon and our germanium to make devices with. But I had a face mask, I had a rubber apron, I had rubber arms guards on my sleeve, I had double gloves. We did it all with the trichloroethylene in a fume hood. So its dangers are well known.

It's not something that's acutely an effect, although it'd certainly knock you over if you take a good whiff of it. But accumulation is definitely a problem. And then lastly, xylene, which is a solvent.

Okay, so platinum, we all know that from effect on hearing, but it just doesn't seem to harm the vestibular apparatus. There are occasional reports, they're really inconsistent, of vestibular damage, but it just is like it's. It's terrible for hearing and really not so not so much for the vestibular system. So there's kind of an explanation for why that might be. Would be really hard to actually go out and prove this.

But the real differences between the cochlear potential and the endolymph, it can be plus 80 plus 100 millivolts. Okay. That's what drives the potassium into hair cells as part of the potassium recirculation. Well, in the vestibular endolymph, that is only about plus 10 millivolts. So it's really thought that.

And I guess I should also mention this is part of how platins are trafficked into the hair cells through the endolymph. And so their thinking is, the best thinking is that the differences between the endocochlear potential and endovestibular potential is why there's this big difference in how much damage there is. Kind of like the traffic trafficking of the platinum drugs in the cochlea is very, very much more efficient than in the vestibular system. And therefore it is the cochlear system that sustains damage there.

All right, so again, we didn't talk about very many drugs, but there aren't really very many that actually damage the vestibular system directly. But there are so many drugs that affect our sense of balance and could be thought of to be a problem that an audiologist could take care of. You know, it's kind of like one extreme, I hear, you know, when one is 90 or 100, one tends to have what one might interpret as vestibular problems, causing them not to be able to stand or walk very well, when the truth is that by the time one's 90 or 100, the muscles don't have enough power to keep us upright. Our reflexes are so slow, again, can't do very well in keeping us upright. And so really, there's not much that can be done about the normal pace of aging.

So kind of like the same thing. There are many drugs that might be brought to an audiologist's attention or cause a problem that would be brought to an audiologist's attention. And we want to keep in mind that there can be more than one thing wrong. And any of these drugs that I'm about to mention might not actually cause a problem with our equilibrium. It's just at a rate that they tend to cause problems in some people.

And so, of course, one would want to go through all of the normal assessments that one does. And then, of course, the drug history would be one of the findings at the end of the assessment.

All right, so there are a lot of drugs that produce what we call orthostatic hypertension. Oh, shoot, I did this again. Orthostatic hypotension, not hypertension. And they are going to produce dizziness or lightheadedness. And of course, that might lead to falls.

And of course, this would be a symptom that is not part of the vestibular system, but due to other reasons. Okay. And these drugs include diuretics and other antihypertensives and many cardiac drugs that I'll go through in more detail. But the idea is that we have a very good regulatory system to govern our blood pressure. And I wanted to go through that because the drugs that I'm going to introduce you to as being those that are associated with these kinds of effects work in these ways.

And I kind of did think that it'd be good to know in a little bit more detail. Exactly. More exactly how these drugs worked. Okay. So I don't really want to teach blood pressure control.

I just want to kind of touch on each part and give you a little bit of perspective. And just by running through it, I think at a light level, you'll get a lot of appreciation for the drugs. All right, so it's kind of like one level to kick things off. The blood pressure is sensed by the body. And one thing that happens is that the liver is going to secrete something called angiotensinogen into the blood.

And then at the same time, and again, this is in response to where the blood pressure is. The kidney is going to release an enzyme known as renin into the blood. And the renin converts the angiotensinogen into angiotensin I. Okay. And then as the blood circulates through the lung, there is an enzyme known as angiotensin converting enzyme, or ACE, that converts the angiotensin 1 into angiotensin 2.

And it's angiotensin II that actually does the signaling. So one of the main things that angiotensin 2 does is to cause aldosterone secretion in the kidney. And that's going to act on the kidney tubules, and it's going to cause the movement of sodium and water in and out of the nephrons, the tubules, in order to control the blood pressure. Okay, so there's another element to that. And when talking about the way that sodium and water are moved around, I have this drawing here.

It's something called osmosis. And then, so when concentrations are high, then water follows, in that case, in this particular case, water, where sodium goes, then water follows. Okay? So if the body is causing sodium to be secreted into the urine and urine has lost the body, then water follows that out of the body. And then of course, there's less circulating volume of the blood.

And of course, well, if there's less of it, then that forms less pressure in the blood vessels. So you see here in this case, they're adding sugar, but you can think of adding salt as well. And where salt is added

to one side, water is going to diffuse through this semi permeable membrane that you see at the bottom and increase the water on the other side. So kind of think about it. In the case of lowering blood pressure, one wants the sodium, that's what's the sodium.

And water is what leaves the body. And then the water where the sodium is left, that's what remains in the body. And you see that there's less of it on, on the right.

Okay. So in addition to blood pressure regulation, osmosis has something to do with laxatives as well. So we have osmotic laxatives and they draw water out of the body and into the gut. And of course that causes dehydration. Okay.

And then of course, when I've already said this, when diuretics draw water out of the blood vessels into the urine, that's going to be leading to a lower volume of blood. And of course if there's less volume of blood, then there's less pressure in the blood vessels. Another thing that angiotensin too does, in addition to causing aldosterone to be secreted in the ions and water to flow in and out of the body, there are something called beta receptors. And the nerves will activate the beta receptors and have a number of things to go on throughout the body. Body arteries will contract.

Okay, when the arteries are smaller, that's less volume for the blood and that is going to prop up the blood pressure. And so if we kind of think about it, if we block that activity, then that's going to cause a lower blood pressure. Okay. Beta receptors also are going to induce the heart. The contractions will be more frequent and with more strength.

Again, that's going to cause more output of blood and of course that's going to cause higher blood pressure. We also have calcium being released in muscles, both cardiac muscles and then muscles that surround the blood vessels. And of course that's going to regulate how kind of like the diameter of the blood vessels. Anyway, when there's more calcium, there's a squeezing of the heart and vessels

and then a high blood pressure. So kind of again, thinking ahead, if we are going to block this calcium in some way, then that's going to keep the, you know, keep it be the opposite of squeezing and therefore the blood pressure would, would fall.

So we'll talk about drugs that do that. Kind of incidental to today's topic because these are not drug targets, but just to give you an overall appreciation of blood pressure control, we have antidiuretic hormone coming from the pituitary that has some effects. We have atrial natriuretic peptide from the pressure sensors in the atrium of the heart that's going to have some effects. And then same thing the ventricles have, the heart have pressure sensitive cells and so they will release the brain natriuretic peptides. So again that's kind of like as an aside, these aren't part of any drugs we're going to talk about today.

I guess kind of one incidental thing I'd like to say is if you think about it, this blood pressure control and this control of the heart rate, if we start running like within seconds, heart rate can go up 50% or 75%. And it's just a normal natural thing for that big a change to take place if we're going from lying down to standing up again, the body just kind of like, instantly responds to that as well. And so that's something that we want to talk about, too. Again, thinking, let's lay down and think about the blood as the bowling ball. Boy, we can roll a bowling ball very easily, roll it down the bowling alley lane.

But if we think about throwing the bowling ball up in the air, same thing with the blood going from feet to head. If we're standing, boy, that's just a whole different matter. Right? It's just a very different thing. And then the same thing with blood.

When we're l or even when we're sitting. The heart doesn't have so much of a trouble keeping blood in our brain. If we stand up, then it does become a problem. But like I say, normal regulatory controls will take over. Okay, so here I'm kind of saying the same things that we talked about a little bit earlier.

When we stand, the blood has a harder time to get to the brain. It's known as orthostatic hypotension, which is said. I spelled it right this time. We get dizzy when we fall. And then, of course, ordinarily, we cope with that very well, naturally.

But when we are taking antihypertensive medications that are going to keep the blood pressure control from acting as well or as robustly, then of course, that's going to be a problem. Okay, so with that said, let's talk about some drugs that have associations with fall for that reason. Inability to get blood throughout the body into the brain. So we have our ACE inhibitors. And of course, I'll ask you to remember that we have this ACE converting enzyme that's converting a signaling molecule on the way to blood pressure control.

And these are lisinopril, Benazepril, Ramipril, quinapril, and enalapril. And so I should mention here that we do have these drug lists that are made that show how often a drug is prescribed. So statins and antidepressants are way at the top of those lists. They're very highly prescribed. The value of that list is that I've listed these in order of their number of prescriptions.

So in the US Lisinopril is prescribed more often than benazeprilla, and enalapril is prescribed less than the others. And of course, these drugs are all pretty old. So again, it'd be a case where I'm only giving generic names. Okay, so angiotensin acts on receptors in order to potentiate that signal. And so there are angiotensin receptor blockers, losartan, Valsartan, omisartan, irbesartan, and telmisartan.

And again, in order of their, how many times they're prescribed. And of course, here's another good example of where the suffix tells us a lot about what class of drug it is. And I've always wished that they'd named them rbans instead. So angiotensin receptor blockers. And so that'd be a little bit easier for me to remember than remembering that the rtans are the arbs.

Okay, loop diuretics. You know, we talked about how those kidney tubules, and you'll see that they're. They form kind of loops. You know, there's a tubule that goes down and a tubule that goes up and another tubule that goes down those loops. And, you know, we talked about diuretic, you know, loss of water volume from the body.

So we have the loop diuretics that cause. That are also associated with falls. So we have furosemide, which is lasix, torsemide, which is. Well, let's leave it at that. Bumetanide, ethacrinic acid, which is edocrine.

And all three of the. I'm sorry, three of these are very cochleotoxic as well. Torsemide is not so much. But for reasons I won't go into, we expect ethacrinic acid, furosemide, and bumetanide to be very cochleotoxic and also to be vestibulotoxic as well. It has to do with the potential forming and the endolymph.

Anyway, there's another type of diuretic with a different action that I want to mention, which is hydrochlorothiazide. All right, so beta blockers. Remember we talked about one of the steps. Is angiotensin 2 causing that neural activity that's mediated by a signal molecule referred to as beta. And then the receptors are beta receptors, more properly called beta adrenergic receptors.

Anyway, if those are blocked, that is going to end up blocking that blood pressure response system. And so these are metoprolol, also called metoprolol. Seems like half of the very renowned people I know will call it either one. We also have carvedilol, atenolol, propranolol, labetalol, nebivolol, and bisoprolol.

All right, so we mentioned calcium and its role in causing muscle contraction. Both the heart and the muscles that surround the Blood vessels and keep them either a little bit constricted or a little bit open. Right. Our body has this beautiful way to get blood flowing to all the right areas. So open up the blood

vessels.

And other times it may want to conserve blood flow. So tighten down and close, close down those blood vessels. Anyway, Amlodipine, diltiazem, nifedipine, verapamil and pholodipine are the names of these drugs. And I'm, you know, I hesitate to just give you list and list of category of category of drugs, but this is what you're going to take out of the patient history, assuming, of course, that they know what drugs they're on. But if they don't, then you kind of know what category they lie in.

And just by them telling you what's being treated, you can make some good guesses as to what they're on. But, you know, it's not precise, but it still can be valuable. So, anyway, again, that's why I'm giving you the names of a lot of drugs. Way too many to remember. Okay, so other drugs, cardiac drugs, the class known as nitrates, these allow vessels to dilate, kind of like the same thing I mentioned earlier.

There are muscles around blood vessels. They can constrict or they can dilate. And so these are isosorbide. We have nitroglycerin, which everybody knows you pop the nitroglycerin under your tongue and it allows blood vessels to relax. And those blood vessels are your coronary blood vessels.

And so you get better blood flow. And the chest pain, the angina can go away. Isosorbide, dinitrate is another. Digoxin and digitalis are others.

We talked about osmotic laxatives a little bit earlier and how these will be depleting volume from the body. And so these are docusate polyethylene glycol 3350, which goes under the brand name of Miralax. We also have lactulose, obesitil and psyllium.

Right, so switching gears a little bit now, let's talk about drugs that involve more the brain and nervous system. And I think most of the rest of these are going to fall into that category. We have hypnotics. Some of them are what are known as benzodiazepines, which has to do with their molecular structure.

And so these are hypnotics that are not that particular structure.

These are non benzodiazepine hypnotics. And so these are vectorly known as the Z drugs. And these are given for sleep or Sedation and also to treat anxiety. So these are some that you'll hear by the brand name a lot, too. So I've provided them as well.

But we have Zolpidem, which is Ambien. We have S. Zepiclone, which is Lunesta, and then we have Zeloplon.

All right, so we really don't know the tie between Z drugs and falls, but there is clear association. And of course, association doesn't mean causation. But there is enough evidence here that the feel like the Z drugs will be, you know, patients taking Z drugs will experience disequilibrium. Okay. So there is another member of this group called Zopiclone that I'll talk about a little bit more in a minute.

But let me first say that it's not approved by the US fda. It's not available in the US but it actually seems to be more tied to experiencing falls than the other three that I just mentioned. Okay. And so here I wanted to talk a little bit about that. So we have what are called meta analyses.

I imagine everybody's familiar with those, where somebody looks at a number of studies that all have the right attributes and study kind of like the same thing. Well enough. Okay. And so with fall risk, almost always, these meta analyses will group drugs into their class to judge the fall risk. And the reason for that is simple, is that there just simply aren't enough studies of any single drug of the class to make a good big enough grouping to get solid judgments from.

Okay. And you want to also consider how many drugs there are, how many adverse effects there are. And, you know, when, you know, we got to study more than just falls. I know we're talking about falls today, but there are just so many adverse effects. And one really would like information in detail about

every single one.

But it's just not practical to do that for every drug and for every adverse effect each drug does. And of course, it's drug manufacturers that do the most study of their drugs, and they're not really going to want to study adverse effects as much as they want to study the benefits of the drug. Okay. They're going to sell pretty much the same amount of drug anyway. And of course, there is the surveillance that's done even once the drug is on the market.

That's very important in removing drugs that are found. Again, kind of like we're talking about earlier, when tens of thousands of people are taking a drug, we want them. You know, there would things be things that are crop up that are not seen, where instead we're studying tens or hundreds of people taking a drug. All right, and fall risk is generally low in these studies. We'll see odds ratios of 1.25 to 1.5, which kind of roughly, statistically, a statistician would kill me for saying this, but roughly, we can think of this as well 25% more often to fall than a control group or 50% more likely to fall than a control group.

And if the fall risk was greater than that, it probably wouldn't be a very good drug. For one thing, it would be a lot of falls if it caused twice as many falls as someone who's not taken the drug. And probably a drug that caused that kind of action would have other problems as well. I mean, it really is affecting the body, so probably not a good drug. All right, so Zopiclone I talked about is not in the US it is used in Canada.

So there is a reason to study it and reason it has been studied. And so the fact that it seems to have a fall risk that's higher than the other three Z drugs probably raises the overall fall risk of the class. All right, so we also want to talk about the benzodiazepine drugs as well. Again, they're for anxiety and sleeping and sedation. And so again, the brand names are seen pretty often.

So I'll say those as well. We have Alprazolam, which is Xanax, Clonazepam, which is Klonopin, Lorazepam, which is Ativan, Diazepam, which is Valium, and Termazepam, which is Restoril. I do want to mention another benzodiazepine. Hopefully you'll never run across this one. It's Rohypnol with the street name of Rufi.

And so it is the date rate drug. You probably have heard of it. Not approved by the US fda. It's not legally available in the US and it's only used for very bad purposes. And all of the benzodiazepines have the property of causing one not to remember when one is on them, particularly at a high dose, a dose that would knock one out.

There will be no memory of what went on. And the Rohypnol is particularly has this effect to a high degree, this not being able to remember what's going on or what went on. Okay, so antidepressants, these work by increasing the activity of various neurotransmitters such as serotonin. Norepinephrine is a little bit less important, but also useful to tamper with the activity of that. And they just simply change the way the brain works.

And it just so happens that that change is often that the depression is that one is experiencing is lessened. So they fall into a couple of categories. The SSRIs that were work on serotonin alone and the SNRIs that work with both serotonin and norepinephrine. All right, so the SSRI antidepressants are Sertraline, which is Zoloft, Escitalopram, which is Lexapro, Fluoxetine, which is Prozac, Ciltelopram, which is Celexa, Paroxetine, which is Pipaxil. Okay.

And then Snris are Duloxetine, which is Cymbalta, Venlafaxine, which is Effexor, and Destiny Vaccine, which is Pristiq. And there's another that I want to bring your attention to again, associated with falls. It's an antagonist to serotonin receptors, which means that it would lessen serotonin activity rather than increase it. Well, it just so happens that, and this is not really very well known, well understood, but it seems like the overall serotonin in orepinepreparab norepinephrine activity is enhanced when using

this particular drug. And we do see that it works for depression as well.

And the drug is Mirtazapine, which is Remeron.

Okay, so antipsychotics to know with fall risk are quetiapine, aripiprazole, risperidone, loratidone, zipresidone, haloperidol, and prochlorperazine. Anti epileptic stenone with all risk are carbamazepine, phenytoin and phenobarbital. Parkinson's disease drugs are also notably associated with falls. Well, so is Parkinson s as well. But it really does seem like these drugs will are responsible for increasing the frequency of falls.

We have ropinirole, diphenhydramine, Pramipexol, Benztropine, and then the combination drug of carbidopa, Levodopa. All right, so we're just about done. I didn't want to talk about polypharmacy, which is simply when more than one drug is used. This is pretty prevalent. For one thing, a patient may have two problems or more problems.

And so that would be two or more drugs. Sometimes it takes multiple drugs to treat a problem. There are a number of people that are on multiple anti hypertensives. It takes that much to bring their blood pressure under control. And actually sometimes doctors will prescribe multiple drugs when there are too many.

Anyway, lots, like I said, drugs that cause falls generally have a pretty low fall risk. But if you combine several drugs, all of which fall with a fall risk, then the overall fall risk is just goes through the roof. Okay. And then of course, if one has been on a drug that's caused past vertibular damage or in the past has caused fall risk to the patient, then that seems to be a problem as well. So definitely this multiple drugs with that same adverse effect is a real problem.

Okay, I just wanted to end by quickly giving you a couple of really great references to use. Beers list is just a really cool list. It has to do with geriatric patients and so it is tied to things that go on with age that make one drug more or less likely to to be helpful. But of course fall risk is one of the things that is considered in this list. And of course fall risk in the elderly is a real problem.

Another is this list from Britain. England has a single payer health care system, which means that everybody is on their kind of like grouped into one. And so for that reason everybody has the same formulary of drugs, the same list of drugs that are used to treat. And so this is kind of a nice list that they did. And it's based on the drugs that are in the formulary in that country, in those countries in the aisles.

Okay. But it's kind of nice because it names names of the drugs and it has a color coding of green, yellow and red to show the level of risk of each drug. And then lastly, I mentioned polypharmacy earlier. This was actually written by and for pharmacists, but it has a lot of very good information and even talks a little bit about assessing risk associated with drugs too. All right, and so with that I'll go ahead and end and thank you very much for listening.