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TRANSCRIPT - GR 01 12 24 "***Menopause for the Internist***" Joann Pinkerton, MD, from the University of Virginia

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Internal Medicine Grand Rounds

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Hello, everyone! Welcome to medicine. Grin rounds. I have the pleasure of introducing our speaker today, Dr. Joanne Pinkerton who did ask me to be brief, but it is hard to be brief about her career. Dr. Pinkerton obtained her medical degree at Medical College of Virginia, and that was followed by her Obigion Residency at Uva. She's had numerous positions at Uva and throughout medical societies, nationally and internationally. Currently, she is the Mammy, A. Jessup Professor of obstetrics and Gynecology and Division Director of the Midlife Health Center at Uva and Emeritus, Executive director for the North American Menopause Society. She is a past president of both the South Atlantic Association of Obstetrics and Gynecology, and the North American Menopause in Menopause Society. Dr. Pinkerton is truly a sought after expert in menopause. She is one of the top publications in the world of our Pop top publishers in the world for menopause. She's won numerous awards for leadership, abilities, clinical care, and scholarly contributions. I will skip through them, based on her preference. But she has many peer review publications, papers, chapters, and served as pi on over 30 clinical trials.

- I think what might be most near and dear to her heart, and most impressive is she's the founder and division director for the Midlife Health Center, which is gonna be discussed today. This is one of the few centers in the country that specializes in care for women, 40 and older, and the Center offers outstanding highly rated, evidence-driven expert care to patients, and it serves as a site for medical and graduate medical education and is involved in national clinical research and is active within our community here in Charlottesville. We're so excited to learn from you today. Thanks for having us. Please welcome me. Dr. Pinkerton.

Okay, thank you. Okay. I'm trying to figure out where to stand, so I can see some of you. I'm really excited to be here, because, you know, menopause is getting a lot of press. It's getting a lot of talking about both in the workplace. And there are now treatment options, and I'm hoping that many of you will feel much more comfortable after our talk.

- So hang on. I'm trying to go forwards alright. Tell me where I aim just didn't try one more time.
- Okay, so I'm only gonna talk about cisgender. So that's what I do. But we're gonna talk about menopause management. Can you guys hear me? Okay, perfect. Some of them to want to talk about are, what are some of the common issues? What are some of the risk and benefits of hormone therapy? What are some of the special populations? What about these new non

hormones that are out there, particularly the newer ones, and who are the best candidates for hormone, therapy, or other options. And II did this for Andy Wolf's internal medicine course that he does, but it was. I'm looking at menopause across the ages. So the 18 hundreds, if you're suffering, take opium, call me in the morning. 1821 they coined the term and it was called La Menopause in 1966 Robert Wilson wrote outright murder, maybe a relatively rare consequence of menopause, but maybe not as rare as people may suppose, and some marriages may agree with that. 1973. In the New England Journal, Medicine estrogen alone increases the risk of uterine cancer. 2,002 first results from that large woman's health initiative that really took a deal tailspin for hormone therapy. 2,007 when we looked at it for women under 60 and within 10 years of menopause, and realized that it was a very successful treatment for them 2023. The New York Times article women have been misled about menopause. 2023. The first highly effective non hormone therapy for hot flushes, fisolinitent, and 2,024. I just did a Congress briefing in a white house, listening on menopause in the workplace, and something that United kingdom is already doing. But we're trying to look at in our country.

- So an overview amount of what's a typical person? It's a 52 year old woman who comes in lacking periods, having hot flushes and irritability. Lots of hot flushes. Mood swings, the irritability might affect your partner might affect her work or her family sleep might be disrupted 3 to 4 times a night, not 3 to 4 times a week, but 3 to 4 times a night. Last period, maybe 6 months ago and the common issues, the ones that everybody thinks about are the hot flushes and night sweats. But the sleep issues, the insomnia, the change in mood. What people describe is brain fog. Having difficulty with remembering things is really common weight gain. You know. Some people will be upset in your twenties if you gain 5 pounds. But around menopause, some of my patients are gonna gain 10 pounds a year.
- And it's really hard they get into this metabolic process. It's hard to stop and they put it mostly around their stomach and their hips bone loss, although if you don't do a bone density. You may not know that lipid profiles, risk of heart disease can change. And then this big mouthful called genital, urinary syndrome menopause. You might have learned it as vaginal atrophy, but it really involves more than the vagina. So the volva, the bladder the urethra, and so that we coined this term. Gsm. Or genital menopause. All right. So here is one little comedy night flash night sweats or hot flushes that occur when you're asleep, because catching on fire during the day just isn't enough all right. So what's a hot flash? It's this recurrent episode of flushing, often starting from the mid abdomen and going up some people. It's from their toes to their knees. Some people. It's their elbows. Sometimes just the back of the neck can be associated with sweating chills or flushing heart rate goes up. Feeling of lower blood pressure. Some people feel, tell me they feel like they have an intense sense of doom or dread and it's difficult if it's really interfering with sleep. And it's hot flushes by day, sweating by night, if sweating, and we still don't know exactly what causes it. We think it's a fluctuation in the temperature zone. So it's narrowed. Neurokin receptors are involved, which is where the 2 new products are coming from. And so you trigger your hot. If you get above that thermostat and cold if you get below. And I think I put this slide in. Yeah, it may be a little hard to see, but in asymptomatic women they have a normal threshold, just like most everybody in the audience. If you get the flu, you're gonna sweat or have chills. But for menopausal women that's really narrowed. And so they are way more likely to get hot or cold or go from one to the boat to the

other. So when I was going through menopause, I would, you know, sit with a heater by my computer and then I would want to turn the temperature down in the bed so I could sleep at night. And my husband goes. You can't have it both ways. You can't have heat and air conditioning on a puzzle, woman, I can do this. So just remember this.

- So what happened in 2,002 was they started this large women's health initiative program. And you know, it was really to prove that hormone therapy prevented heart disease that that you should take it forever. And you either were enrolled with a uterus, in which case you received one product. It was conjugated estrogens with hydroxy progesterone, also known as prim pro standard dose. or if you had your uterus removed, they gave you estrinolone again, premarin point 6 2 5, and then they had a placebo group, and it was very large numbers, 10,000 in the prior hysterectomy, 16,000 in the women who had a uterus and what happened. And many of your parents might remember the ticker tape running across Cnn, you know, of coronary heart disease, 29% stroke, 41%, breast cancer, 26%, and not really talking about benefits, which was a 34 decrease in hip fractures and in colon cancer. So they stopped it early because it showed harm. They stopped at 3 point 3 years early, and they also looked at the women 65 and over, and found an increase in probable dementia, which is exactly what the box warning says. Probable dementia. So it's like, why would you take something that's gonna give you probable dimension? Because people don't understand as you do. That probable dementia is a medical term doesn't necessarily mean you can have dementia so you know, this is kind of where we were. There was just a lot of fear. Breast cancer, heart disease stroke in this probable dimension, and it's still driving the conversations. And I hope and I'm starting to see that everyone's getting the idea that it is safer. And we're gonna take the fear out of this conversation.
- So this was the estrogen, only arm, and so that also got stopped early, so that women have had a hysterectomy estrogen only, and what they found was an increase in stroke because it was older women. They were giving it to it orally. It didn't really affect heart disease, breast cancer, and hip fracture was decreased, and in fact, they found that there was fewer breast cancer cases and estrogen only arm at 7 years. So it was a little bit confusing, and it didn't get much play, but really tells you there's a difference between taking estrogen and a synthetic potent progestin. So then, in 2,007, we finally asked them to analyze it by age and time for menopause. And this is where it gets much more interesting. So if you look at the blue levels.
- Let's do the blue is the group that's under 60, and what you see is fewer heart events really no increase in stroke. A slight increase in vtees, because whenever you give it orally, particularly when you first start hormones, you might have that increase in Vte's, though they combined all the data together. So the breast cancer was lower. But that was really being driven by the estrogen. Only group and total mortality was lower in that group as well as the global index.
- But now look at the orange. The orange is the women who are in that 70 to 79 group, and if you start hormone in that group. You're gonna have an increase in heart disease, in stroke, blood clots and in total mortality. And again, this was an oral combination. And the group that's the hardest for me. And I think for a lot of you is the women who are 60 to 69, because for a while. It was like shortest time for your shortest dose shortest time and take everybody off at 60, and we now realize that it really matters when you initiate. So we're unlikely to initiate after age 60. But we don't necessarily take people off. We might lower the dose. We might change to transdermal, but we don't have a cut rule that says 60. You have to go off,

and I tell you that because I have a lot of people coming in from the community, from the primary cares who they just stop at cold turkey up 60. You have to stop. And you know, if you're even gonna do that. Think about it. Think about why you're doing it, and maybe how to do it safer or send them to us.

- So on 2,017. I was the person who wrote the guidelines for the North American Menopause Society, and what we really said is, it's safe, and if you're healthy under H. 16, within 10 years of menopause, and then we just redid it in 2022 and had the same information. And we're still trying to get that information out. So I'm gonna go through some very specific things with you. Now about it's the most effective treatment for hot flushes that is out there. And it also people. When they take hormones they will have improved sleep versus around menopause. If you're having hot flushes, you have reduced sleep. If you take hormones, it actually turns out that you have fewer awakenings and better duration of sleep, and it increases the rem sleep, the dream sleep. And so people are more rested which makes them less irritable.
- Now, the fractured data was very interesting. This is not fractured data in a group where we identify them as osteoporosis, and then looked for benefit on fractures. What this group was, all comers, and what we found was that whether you took estrogen by itself or with the synthetic proges. You had a 33, 34% reduction in hip fractures.
- However, once you stop the hormone, you lose your benefit on bone density. But, unlike with prolia, you don't have an increase in rebound fractures. It's just you're losing your bone density. They also showed less joint pain and stiffness, although it's not an approved indication. But oftentimes, if you start somebody, even on low dose, they'll sleep better. They'll have less joint aching, and they'll tell you that their brain fog is better.
- Does hormone therapy help mood? Well, it's not a treatment for depression. It never will be it's not. The data is not there in small trials. If you're parinen estrogen, therapy does improve mood. If you're having hot flushes, proges often make mood worse. So we often use a micronized progesterone instead. But for women who have depression, and we add estrogen and get a benefit in mood you have to recognize that when you stop the hormones their mood may decrease. So need it. Right now, I have multiple patients that we share together run like you know, she's getting. She's 7 years old. I want to stop her hormones. You can't do it. Her mood is life threatening? That's worse than a risk of breast cancer. And so we, we have these conversations about what to do in these selected women does hormone therapy cause dementia? Well, we initially thought that it prevented it. And then in that study, if you were on the combination, there was a rare increase in the risk of dementia, so we don't recommend it to treat cognition or dementia unless you're surgical menopause. Early menopause. Those are the group that we really think that hormone therapy may really help the brain in the early post menopause we could show neutral effects really hard to say whether it actually prevents Alzheimer's because you gotta follow them for so long to get that data.
- There's some observational evidence for that. And then there was a study that was a database that came out of one of the Probably Denmark pay where they have a lot of database studies, and they showed an increase in dementia with all types of hormones, but they showed it within, if you took it only for a year, which doesn't really make any sense in terms of how the brain works. So that study has not gotten much traction. So if you said, What do I tell women? I say, you know I'm not gonna give it. Your mother had Alzheimer's. I can't tell you that I'm gonna present Alzheimer's but I can tell you that if you take it around menopause that you're

gonna be able to concentrate better sleep better, and those things are gonna help your overall health and maybe help cognition.

- It does reduce type 2 diabetes. This was shown in that trial and it may help attenuate some of that abdominal accumulation and weight gain that's associated with menopause. However, it is not a magic bullet. But it and more importantly, it means that if you have somebody who's prediabetic or metabolic syndrome, you don't need to be afraid to use it. It's just that I might use the patch instead of the oral for those people.
- Can I take hormones if I have a family history of breast cancer, you know, that's one of the biggest fears that people come in, and I think I think somewhere, I say that you should assess it. You should always assess it because we need to talk about the risk. And are we doing things to minimize that risk or make sure we're screening adequately? But in that large study in women who had a family history of breast cancer, they did not show an increase risk if they added estrogen.
- So your risk is really from your risk of breast cancer, not in the short term from adding the hormone therapy. And I'm seeing a puzzle block over there. But but it's it's
- I. I'm gonna keep going, and I'll come back to the puzzle book. We do think that adding synthetic or higher doses or longer duration may increase the risk of breast cancer.
- And I wanna talk, you know that. Everybody's getting notified about the density of their breast, and we have heterogeneially dense and extremely dense, and it turns out that those breast if you add estrogen, you may make them particularly with progestin, a little bit more dense, a little bit more hard to see through, hard to find the cancers. And so we have supplemental screening. At Uva. How many people are looking, getting, screening breast alternate for your patients who have extremely dense breast or dense breast.
- A few. Oh, what's up? Shit? You can't hear me. Okay, I keep trying to see the people hiding over in the corner. So maybe I'll just ignore them. Okay, I'm gonna ignore you guys over there. There's a big computer screen between me and you. So we have screening breast ultrasound, and we also have contrast enhanced mammogram, and the contrast enhanced name is really really good for people with dense breast.
- So they go in, we tell them to hydrate. They put an Iv in. They give them contrast. They do their mammogram and it is now in a big clinical trial here, Eva where they will compare a regular mammogram and a contrast mammogram, and a year later a mammogram and a contrast mammogram, and that's really good cause. It pays for the cost of the contrast which can be variable in terms of cost, very low dose radiation.
- Each mammogram is the amount of radiation you get flying to California. So if they decide to do the clinical trial, they flew to California and back again. So it's just for those extremely dense breasts a really nice option for those
- alright. So this top line, the effect of Harmon therapy on the risk of breast cancer is complex, was the first line and the breast cancer section on the guidelines because I had 24 people, and they all argued about, what does estrogen do on the breast? Because it is very complex, and it depends on how long you've been taking it. What dose you're on what you know. Whether or not you've got a synthetic progestin.
- Have you had a hysterectomy, your estrogen only no risk. It's 7 years. But in the nurses health study. At 15 or 20 we years we did start to see an increase in risk of breast cancer. So longer term use. So I put all the studies up and I guess if you ask me what I say when I talk to women

about it, I say, you know if you have breast cancer, we're gonna stimulate it. If we give you estrogen and we don't think it causes it breast cancer. But we think that higher doses, longer duration, that we're gonna find more cases of breast cancer. And so one of my conversations with the people who still are having hot flushes in their seventies and don't want to stop. It is to say if we find a breast cancer number one, we're stimulating it even with this little low dose of estrogen that you're on, and number 2, we're gonna not only take you off your estrogen, but it's likely to be estrogen sensitive, and we'll put you on an anti estrogen and just trying to kind of help them work through the risk benefit analysis. In a way that's a little more tangible.

- Okay in the long term follow up. And so they stopped the study. But they continued following many, many of the women out to 18 years. And this has multiple publications. But what they found is that when we look at those women, you know, 18 years after they stopped the study that the women who had their uteruses removed and took estrogen. Only overall had a lower risk of breast cancer and mortality.
- Okay, when we look at the group that was randomized to estrogen and progestin and had the uterus. There was a higher risk of breast cancer, incidence. But over that long period no significant difference in breast cancer mortality. So it's it's a discussion that you have to have based on whether you have a uterus or not, or whether you're taking something with a progestion or a progesterone and then I don't know if you can see this slide, but to ask you published it recently, and I think it's really helpful. And so if you look at the top line, that's the risk of breast cancer over that 22 years, and you can see that it's increased. And then, if you look at the 2 lines that are together, that's conjugated estrogen alone and placebo pretty much mirroring each other out at 22 years. With the and then the very last one, which is in the darker blue, is the conjugated estrogen alone, which had a lower risk all the way through. Does that make sense? Okay?
- So then we come to the heart, which is your area of specialty, not mine. And but what I can tell you is that if we start hormones early initiating that we, we may reduce morbidity. But if we start it later, it's like that slide I showed you. We have to talk about increasing the risk for heart disease and stroke. And this was seen in the monkey data and then seen in the Wi. And so when you calculating risk of heart disease, that's one of the components about whether to start estrogen or not, and we don't recommend it for primary prevention of heart disease, even though it does have some benefits in those younger women.
- And then just the risk that goes so that there's risk from being on your hormones. And then there's just the risk from aging, which is stroke and blood clots and pulmonary embolism. So when we have these older women. It's really more difficult to talk about what their actual risk is because they have their own health risks.
- Alright, how many people use a a patch. I've prescribed a patch a few yeah, great. So transdermal therapy, I'll come back over here transdermal therapy. Which could be a patch, a gel, a pump, a spray, a systemic ring bypasses the liver. So we don't have the same clotting risks, and it's considered much safer, and the lower doses have not been associated with blood clots and stroke, but there's no head to head trial.
- And it gives a much better steady state dose, so I will be using it. And people have migraines. People who have mood issues, people who do shift work because you need to be really steady with your levels or decrease libido, because the oral also increases. SHBG.

- So their testosterone goes down and libido goes down. So it's less likely to affect libido if you do it transdermal and then for people who medically, you need to do it, it would be metabolic, syndrome diabetes, fatty liver and higher gastric bypass because they're not gonna absorb their hormones very well. They also don't absorb their calcium. So we have a risk of osteoporosis in that group.
- Compounded bio identical hormones. You know. I talked about this, even though you may not see this when you're in residency or practice but many there compounded hormone therapy is a million dollar practice for people, particularly if they're putting pellets in. Pellets are super physiological. They put them in. They give them estrogen testosterone. Whatever they want they check their levels right before they put the next pellet in, so they never know how high they are. And it's like $600 a pellet, and there's a surgical fee. So there is a lot of money coming in this way.
- Why don't I like it? Because I don't think that it's really good to run estrogen levels of 300, when I could give you a level of 25 with a low dose patch and that if you have something going on that's estrogen sensitive, we're gonna be more likely to drive it.
- The theory from the pellet users is that because we give testosterone. We take away the risk of breast cancer. And I can only tell you there's no data to support that and sometimes they will give it to breast cancer patients because they believe that it decreases the risk. And again it got it. And then the newest thing that's out is called the Dutch test. So you're gonna have patients coming in and bringing you their Dutch test because this is being ordered by some of the natural paths. And it stands for comprehensive hormones to determine which ones need to be fixed. It I will. And the
- Bug line is, Are you? Are your hormones healthy. Take the Dutch test to find out. There's no clinically validated indication right now. Usually it's done by people who have access to selling hormone balance or adrenal health or so, and selling their supplements or special diet. So I always tell people watch the money, and if it sounds too good to be true. It probably isn't true, you know. Nice things to keep people, but they're bringing those in, so who shouldn't take it? Who are the ones we worry about. Well, if you, if they have bleeding, you don't know why. If they have liver disease, if they've had an estrogen, sensitive cancer breast uterine some of the sarcomas. If they've had a heart attack, a stroke if they have a high risk of any type of thromboembolic disease.
- The potential risk that we always talk about is the risk of breast cancer. And if you don't oppose the estrogen, you have a risk of uterine cancer. So what happens when you get super high levels with these pellets?
- You get unopposed estrogen at the level of the uterus. And so we're starting to see hyperplasia and cancer in patients who've been on these pallets. And they did a comparison study, but not head to head. And that's exactly what they found more mammograms, more bleeding, more hysterectomies than those when and then there's a ton of adverse events which are less likely if you start low and go slow, which is what we've done ever since the wi but headaches, breast tenderness, bleeding.
- All of those good things.
- So we'll talk about 2 populations. To to pay attention to early menopause and women who are over 60 or 65. So here's your patient. She's 42. I made it easy. She had her ovaries out for drermoid cyst, not for a cancer. She's 6 weeks out from her surgery. She's having 8 to 10

moderate to severe hot flushes, soaking sweats at night. So the question is, would you give her hormones? So I'm gonna ask for some nodding people saying, mostly yes, and are there health risk of having an early menopause? Yes, and hopefully, your endocrinologists are on top of this. But what they in its observational data. But what they showed was that if you have an early euphorectomy or an early menopause for any reason, not only do you have hot flushes and vaginal issues. But you have a higher risk of osteoporosis and fractures, heart disease and mortality. And there's also some cognitive issues and eye issues.

- And so currently hormone therapy is recommended until the average age of menopause, which is 51 in those women, and then we reevaluate. But remember, it's not a contraceptive. So what happens? If you have a poi, somebody's got an endocrine reason. An autoimmune something that's causing them to have early menopause, they are more likely to have a spontaneous ovulation and maybe get pregnant.
- My favorite case was an endocrinologist, who I delivered her second child, and she was working very, very, very hard, and she came in because she wasn't having any periods, and she was having weight gain. She had been. We had diagnosed menopause early menopause. About 2 years before she had gone on hormones. She decided to go off the hormones, and she comes in, and I take one look at her, and I'm like, Hmm!
- Let me get the fetal dap tones because she was 7 months pregnant. And this is one of us, you know, just because she was had premature. No pause. So she thought, she's gonna get pregnant. Sometimes when you stop the hormones, you can trigger an ovulation, or it can just happen spontaneously so premature. No pause. You always have to think about contraception and hormone therapy is not a contraceptive, so the pill is 5 times as strong as your ovary, and the hormones are a fifth as strong as your ovary, and that's why it doesn't work.
- So how about this 1? 63 years old. She started hormones. About age 55. She's out in the community at 62. Her primary care said you need to stop and wouldn't write the prescription. She tried 6 weeks. She's miserable. She comes in to see you. We get a bone density scan. She's got significant osteopenia, but not osteoporosis?
- So the question is, what do you think? Would you let her go back on our homes? Let's see some nodding around here who's scared?
- Who's brave you know. It's an unanswered question. It's a gray area, right? She started early, and we don't have data on those starting early and stay longer. I probably would put her back on, get everything calm down, and assess. You know what her other risk for? What about a risk for heart disease? How low can we go? Can we weigh her off slower? And then think about, are there other ways to manage her loss of bone density? But I might not have this number exactly right. But up into the 80 s. About 5% of women are still having hot flashes.
- So and there's now trajectories where you start them before menopause, or you start them at menopause, and in African American women they start them early and they go long. So Caucasian women average is 7 years japanese women Asian women average of 5 years African, American and Hispanic 10 years longer. Hot flushes time. So that is now word that's gotten out into our community. So you may have people coming in and and talking about that.
- So there's no general rule that says you have to stop it. If you're over 65 it's just that the insurances don't want to pay for it. But there's a lack of data. And so if we do have somebody that we're keeping on it long term, we really individualize it, talk about it every year, go transdermal, go low. Try to get them off. Try to think about what what other options are out

for them, and talk about their risks now, for not everybody needs hormone therapy or wants to take it. And some people have contraindications. So when we look at treatment, estrogen is the most effective, and that can be by itself. If you don't have a uterus. The product that is estrogen combined with a ceram basadox went off the market because of a blister plaque problem and is back on the market. So that is a combination therapy for women with a uterus that is estrogen, but is not a progestin or a progesterone. It's a serm that is an antiestrogen on the breast. And then such a strong anti estrogen on the uterus that it protects against uterine cancer. And so for women with bleeding breast tenderness, breast cancer. It's a great model, because at 2 years there was no breast tenderness, no increase in breast density, and we didn't find any difference in breast cancer compared to placebo. But we only have 2 year data. So it's out there. It's an option to treat softwatches.

- And then we have micronized progesterone. It's in peanut oil, but it is a safer treatment in terms of risk of breast cancer, but it's less potent. So you have to make sure you dose it adequately to protect the uterus. So just a couple of pearls on that. So what else is out there. So we've got and I'm gonna use the trade names because I think people recognize them. I'll say each one. So vindloxin, which is a factor progesterone by itself. Paroxetine approved on at a low dose at 7.5 milligrams as brazel, but available as paxil gabapentin neuront. And you think about it for diabetic neuropathy. I think about it for night sweats. And then the new one Phasolinitin, which we'll talk about a little bit more, which is a neurochine. 3.
- Clonidine does work, but it's not a great option for people cause it lowers blood pressure. Black cohash didn't work better than placebo. But there's a lot of over the counter products that people with mild symptoms may take, and it's not an estrogen and not effective in trials done actually increase hot flushes like tamoxifen and Avista soy products, red clover, Saint John's wart, and the newest one is bee pollen.
- I'm gonna say something about Soy. There is a product called Eql on the market that did show in a trial some improvement in hot flushes. But remember, if you're getting enough soy to improve hot flushes. You may be getting some estrogenic effect. So that's just a caveat and then at the very bottom, I put the proxy in salt is the also sold as Brisdell, and then the neurokine one is called Vizay. And I'm gonna show you that data.
- So neurokine and receptor antagonist are in the hypothalamic candy neurons. And what happens is when your estrogen level drops.
- they become hyper activated and they stimulate the thermal regulatory pathway, causing hot flashes, started out with data in the rats, and then moved into people. The very first one caused liver issues. So it went off the market. So liver remains a big issue for every product. The N receptor antagonists do effectively treat hot flushes.
- and the one that we've been testing. Here is a n in, and the NK one is also effective with sleep and mood. So these are therapies that you're gonna be hearing a lot more about. I did show. The FDA approval was in May. It's 500 $600 a month, $500 a month if you don't have some way to get coverage. But there is a mail order that can get it for you for $50 a month. So it is, they've made a way to make it accessible for people. Very rapid onset, similar to hormones does not affect the uterus. Don't need a progesterone, but they are recommending baseline liver tests, and every 3 months for 9 months because there were a few liver issues, but none of them that were critical.

- And I, here's the data. And I don't know. Can you guys see this in the back? So what you can look at is the gray is the placebo lines, and on the left is the frequency, and on the right is severity. So lots of things work better for how frequent they are. But we really want the severity cause. That's what's bothersome and they looked at 2 doses, and both of them pretty much had to. We got our 50% decline with placebo. And then we got our 75% decline with Azaleena 10. And then it did work better for severity. It's not quite as impressive, but it still was statistically significant. And so before I can I go back? I guess not. Quite.
- Yeah. Let me go back. So you may have seen in the paper the top line data from Ella Zenita, which is the oasis trials, and that's the one that we have here at Uva we were oasis 2, and that showed it's a neurochine in one and 3, and it showed improvement in hot flushes, frequency and severity at 4 weeks and 12 weeks improvement in sleep and in minute pause quality of life. So you know that one is gonna be going to the FDA, and you'll hear more about it down the road.
- So I'm gonna change subjects because you're also gonna see this. This is a 60 year old woman. She comes in. She's got vaginal dryness, pain with sex had hot flushes. They went away. She didn't need treatment. She's tried lubricants. We change her from Kygl to some of the better ones that are out there like Uberloop. That's the best of the best and in the past she really enjoyed sex. But now they haven't had sex for 12 months or could be 6 years. I see both and both she and her husband are distressed, and they're gonna and the problem is, if you don't ask, they don't tell. And that's why the 6 year people are coming in, even from gynecologist, because people don't ask but if you ask, they'll say, Well, it hurts. It feels uncomfortable. It feels like he's hitting a wall part way in it feels stingy and Bernie. I get a bladder infection afterwards.
- And so this is that janitor urinary syndrome of menopause, and if you can see the little schematics. Lots of things happen, but your urethra changes, you lose the connected tissue, and so, instead of being tucked down, it kinda looks right at you. So it's easier to get bladder infections and more likely to get irritated. And then the vagina and choice goes from being like this to this, to this, to where I can't even get a pediatric speculum in. If you don't do anything and it worsens over time, it's progressive. There's decreased elasticity. So you know you learned in when you're a student to do a by digital exam to put 2 fingers in? Well, it turns out that if, in order to have sex with kind of a normal size partner. You need to be able to get 2 fingers in the vagina. And what happens with these women is. You can't get 2 fingers in. They hit elevator spasm. It hurts, and they they and then you go to one finger. But that's not enough for normal partners, let alone if we have large partners. So dilators don't really help by themselves, because they they stretch. But they're not making an elastic enough to be able to get from a small dilator to a medium dilator, even to a large dilator. So that's where estrogen or intervaginal D Hta comes in. We get that started. Get the estrogen more elastic, estrogenized? And then we'll add the dilators to stretch and successful in getting most couples back to having sex. My severely narrowed and extra large are my difficult ones, because it's hard to get it stretchy enough.
- So then we talk about. There's, you know regular sex. And then there's, you know, around the clock sex, and there's brownies and ice cream. We talk about sex in different ways.
- Alright, so lubricants do help, and there are better ones on the market, and so the ones they can get you sell, refund is refresh, are all local. And then there's some that like good love and

silk, E that you can find. And then there's one that comes out of Germany called uberloop, which is a silicone based, which is really probably the most effective for people who really need it.

- Can be used with other therapies. And if they have irritation you can get them preservative, free, and then moisturizers are mostly hyaluronic acid and you use them 2 to 3 times a week to just maintain the moisture. They don't fix the problem. They don't give you back your superficial cells. They don't give you back your elasticity. Any of that, but they do make it more moist. And mimics the normal vaginal secretions. And sometimes can help. The Ph changes. It says it doesn't reverse the cellular changes, but some of them are Ph based and can improve the vaginal ph and then I put this up. Just because you don't live in the world of GSM. The way I do. But we have estrogen as a cream, a tablet a ring, and a suppository. And so some people one will be approved by the insurance. Sometimes it'll be that one works better than the other, and then you can always get the creams compounded preservative free. If you need those for people who get irritated, there is a systemic ring. So I always wanna make people remember that there's a standard dose estrogen ring for the vagina and then there's a vaginal atrophy ring called S. String that you and you change that every 3 months and sometimes it's on the formulary, and sometimes it's $500 per ring, and then interventional. Dha works. It's a daily suppository and then there's an oral serm called usemophone for people with like rheumatoid arthritis that works well. Because they don't have to use. Put it in the vagina.
- So 2024. Who's a good candidate?
- If you're under 60 within 10 years, healthy you're going to potentially get benefits or elevated risk of osteoporosis, and you're not ready to take bone specific medicine.
- You have to individualize it. Look at what works, what you get comfortable with. I use a lot of low dose, transdermal patches and micronized progesterone micronized progesterone. Take it at night because it makes people sleepy. So that's great. Cause. Sleep is an issue. Extended use send them to me. But if they only have gsm, you can just use vaginal estrogen. I think people are getting more comfortable starting the creams and the tablets and clinics. So please do that, and I'm looking at Joe, back there, and you know for you the aspen might be good, because if they have really bad arthritis on, it's an oral product that is approved for vaginal. Join us and then the non hormones, the Ssris Smrs. Gabapentin, and these new antagonists are your options that work.
- So here's your pearls. The symptoms can start early. So I see a lot of people in their early forties who've been told you can't be menopausal. You're still having periods. I don't know why you're having hot flashes, but in reality one of the trajectories of hot flushes starts during perimenopause, and it's very variable. And, as I said, it's longer and more intense. If you're African, American and Hispanic the non pharmacological options that are not medicines, that you can try weight, loss, hypnosis, cognitive behavioral therapy acupuncture doesn't work better than sham. But if it works. It works for about 6 months. So that's another great option to try. Cognitive behavioral therapy is great. We don't have anybody in Charlottesville who's really joined hypnosis for vasomotor symptoms. But it has been shown to work in randomized trials.
- We talked about the non hormones. I'm gonna throw in oxybutin because that's a medicine that we use for urinary incontinence, but it also has been shown to decrease hot flushes and gabapentin. I usually use differently for pain. You might use 3,600. I will start it at 300

milligrams at night, go to 600 milligrams at night, and then maybe add one daytime dose if I need it for the supersensitives, I'll start with a hundred, but 600 300 to 600 at night will often make the difference in being able to get enough sleep to be rested the next day.

- Hormone therapy's most effective hormone therapy is not a cure. All for weight, gain, aging skin, low energy, thinning hair or brain fog. It might help those things. But I do not promise magic for these women.
- So now here's your quiz. We have 2 patients. One's 51. Her last period was 9 months ago. She's got phasal motor symptoms. She's having difficulty concentrating her. Bmi is only 28. She's exercising and her mother had a fractured hip at 72. I do wanna see a raise of hands. How many people feel comfortable giving her hormones pretty much, not everybody, but mostly okay.
- Next 1, 65 years old. She's been menopausal since age 53. She is having disturbed sleep and sweating at night. Her BMI is 32. Her waist circumference is 95. She has a history of hypertension, and her mother had a stroke at 63.
- Who wants to initiate hormone therapy in her?
- Who wants to get a hemoglobin a one C, and see if she's developed diabetes now. Because that's the most common thing, or thyroid disorder that I see. Alright. So I wanna leave just a few minutes for time. I'm not gonna go through these cases, but these are the ones that I deal with in my clinic. Somebody who's Brca. Positive, had her tubes out at 35, but is now having her ovaries out at 40. Because we can actually give her estrogen. We've got observational data to menopause without increasing a risk for breast or ovarian cancer.
- We'll just use low dose hormones a breast cancer patient whose estrogen is sensitive and is on an aromatase inhibitor with dysperonia.
- That's a hard one, right? Because we're knocking her estrogen levels all the way down to undetectable, and even though very little gets absorbed from vaginal estrogen, it might interfere. So that's the group that I say, lubricants, moisturizers come back when you go off your AI and and sometimes with the oncologist. When we get further out we may add some vaginal estrogen, but we try to delay or avoid that and we use the hyloronic, vaginal moisturizers on a routine basis well differentiated, early endometrial cancer hysterectomy. Now 5 years out with painful sex.
- We can give it to her 5 years out from individual cancer. Your your biggest risk was a local recurrence. In the first 5 years it was well differentiated. Get your cancer, doctor to say yes, and we can do that. But a very bad uterine add no sarcoma. Kind of a cancer. No way. Stromal cancer is no moisturizers, and then go from there. Severe Vasil motor symptoms on aromatase inhibitor. This is probably something you're seeing a lot of. So this is the group that you might start with a vexor 37.5 to 75 milligrams.
- But I also really like Escitalopram or lexipro, because when they tested that at 10 or 20 it worked as well as half dose estrogen, and it doesn't have as many side effects. And it's a little bit easier to go on and go off. So that's one of my common to go ones. If it's just night sweats. I may give them the Gabapent at night, and if they're really, you know, 7 to 10 soaking sweats, they've tried other things. Then we'll get the neurochine receptor antagonist for those people. So that's kind of my algorithm that I go down for women. What if she had a prior blood clot and severe sweats, and she's not in an anticoagulant.

- No, no, If it was unprovoked, and the oncologist said, we really didn't find anything, and you've tried everything else. Maybe I'll give a low dose transdermal with the help of the hemonkers. But if if we're worried about BTE. We try to avoid the hormones and the last one is migraine headache with aura and severe hot flushes. So you know, we worry about stroke with birth control pills. If you have aura, and we worry about it with hormones. It's not as well defined, but, interestingly, some women whose migraines get worse at menopause get better when you put them on a patch. So it's something that I always will talk with the neurologist about trying and I separate out for a month the estrogen from the progesterone.
- So I see if they get migraines with estrogen, or when I add the progesterone in. But I've actually had a lot of improvements in in migraine headaches, and as long as they're not worsening, that's something that we can talk about.
- So that's all. And I left you guys 10 min for questions. Thank you for your attention.
- Do we? Have we have somebody brave? Thank you.
- Thank you so much for that. One population I have trouble with is patients who stay on ocps into their fiftys. So they don't really know necessarily, especially if they're on like Seasonik or something. If they're menstruating and are very fearful of coming off. Do you ever transition them to the hormone therapy dosages to come off? Or how do you decide when to make that?
- So the question is about that person who went on Birth control pills. Maybe long term maybe started in their late forties for cycle control and contraception, because, remember, the second highest unintended pregnancy rate is in the forties. So we always have to think about pregnancy. So that's a group that's a little harder to decide what to do. There's some data suggesting that the 30 mic and higher Birth Control pills increase the risk of breast cancer.
- So that's the group that the first thing I do is try to get them to the 20 mics. There is a 10 mic birth control pill, but it hasn't worked very well in my patient population, but it's out there. I used to get hormone testing during the placebo week at 50, and then 51, and then 52. And now what I do is say, you know, we talk about risk and benefits, and if they're starting to have symptoms during the placebo week we'll either get to work at the very like on Friday of their placebo week, so that we can see if we're starting to see Menopausal testing, or if they're ready to go off, I might take them off for 4 to 6 weeks. See if we can document, because the range of menopause is 45 to 55. So we have people who are still going to have the risk of pregnancy. And you know the caveat in the books is that you can use birth control pills but 55 if they're not, then a puzzle. But you know, like everybody else, I get chest pain from from doing that. So my goal is always to try and and get them over to hormones. I will often step them down to an oral product just because they're if they're using an oral birth control pill, we have the same hormones in something like the generic equivalents of active Ellis, nor syndrome and estrogen. So I might do that and it's just a tough group. And so that's we don't recommend hormone testing just to prove menopause or for dosing. But that's a group that I am probably gonna do it to kinda see where they are, and then if they're willing to just go off and see and use condoms. Then we'll go off for 4 to 6 weeks to make sure that the ovary is no longer suppressed, and we see whether or not they're truly Menopausal.
- Thank you. Aye so much. I think the women's Health initiative is just a really fascinating story. And as a researcher, I'm I'm curious of your perspective of this time where kind of the the research came out and the media got it. And you know, there's a lot of fear, and I think I still

find a lot of patience remembering that story, and they haven't gotten a new news. What do you wish that? This group of future researchers could take away from that. And what do you? What lessons you wish we had learned, or what did we learn, and how we changed since that experience. So obviously, that's a complicated related questions. Because, a big part of what happened in 2,002 was a rush to publication because they found these adverse events that they weren't expecting, and they were rushing to get it publicized. Some of the authors and co-authors and investigators didn't even know what was happening. Until their patients started calling. So it was not handled. Very well. I think the biggest thing that we learned from it was that we picked the wrong population. So you know, the drive was to show that it prevented heart disease and dementia, and in reality it doesn't do those that was the wrong population. The right population is the young, healthy women. So the question I really wanna know, is, if you started at 52 or 53, or 55. And now you're 62, or 63 is your risk for heart disease up or down is your risk for dementia, up or down. And again, that's a big, you need a big study. And so when I was asked at the White House, listening, what study I really wanted them to do. It was that

- I also asked for maternal stuff with ob and Joan ontology funding. But you know that's just the study that we really need, and also that study was done with a standard dose, oral estrogen and progestin one product. And then everything that the FDA has put goes on that if if estrogen is in the product they get the box warning.
- So what's really scary is, you have vaginal estrogen, and you've somebody you'd given it topical. You're just trying to decrease her risk for UT. I's. It is not being increased absorption. And yet she has the same boxed warning of breast cancer, heart disease, stroke, blood clots and probable dementia. So I thought, I'll fix this. I'll take all my experts. I'll take the red hot mamma consumer group. We'll go to the Fta. We'll spend a day. They will understand the difference and they'll change it.
- They understood the difference, they said. It's Pandora's box. We're not changing it. So it's just an interesting thing how the FDA has to think about stuff plus the Nih. So at the end of the day. What I would tell you is, if you're doing research, try to get specialisttry and look at the broadly, and then make sure that that what you say is true, because what they needed to say was that if you start hormones at average age 63, your risk are increased, and that data was there right from day one. They didn't look at it.
- That's great. Thank you. Okay alright. Let me give you 6 min back to your day. I'm up here . Thank you very much for having me that. Okay.