

Rounding@IOWA: New Treatment Options for Menopause

Transcript

[Upbeat music plays]

Dr. Clancy

Welcome to Rounding@IOWA, a Continuing Medical Education Podcast, developed by and for healthcare teams. I'm your host, Dr Gerry Clancy, Senior Associate Dean of External Affairs for the Carver College of Medicine here at the University of Iowa. Today we will discuss menopause, traditional treatments and new treatment options. Our objectives include first, we want participants to have reviewed the physiology and associated symptoms that women experience during the menopause transition. 2nd, we hope participants can cite the effectiveness and safety of hormone replacement therapies for problematic symptoms associated with menopause and help identify appropriate candidates for treatment. And 3rd, we hope our participants can discern the pros and cons of new treatments for menopause symptoms, including new non hormonal medications for vasomotor symptoms, as well as some behavioral intervention. We have the great advantage today to host 3 guest experts to help us sort through a complex set of symptoms and treatment options for those with significant symptoms for menopause, Dr. Evelyn Ross Shapiro, Dr. Sara Schaefer and Dr. Emily Walsh. Dr Ross Shapiro is a Clinical Assistant Professor of Internal Medicine here at the University of Iowa. She graduated from medical school here at the University of Iowa, where she also completed her internal medicine residency and Masters of Public Health. Her areas of expertise include Women's Health and LGBTQ health, important for today's discussion, she has partnered with our OBGYN department to provide services in our menopause clinic.

Dr Schaefer is a Clinical Associate Professor at Obstetrics and Gynecology here at the University of Iowa. She graduated from Steele Medical School in Kirksville, MO. She completed her OBGYN residency at Saint Vincent's Hospital in Indianapolis. She also earned a master's in medical education from the University of Iowa. Along with her broad clinical duties, she serves as the vice Chair for Education in the University of Iowa, Department of Aesthetics and Gynecology.

Dr Emily Walsh is a Clinical Pharmacy Specialist at the University of Iowa. She is a board-certified Ambulatory Care Pharmacist. She earned her pharm degree from the University of

Iowa. She then completed pharmacy residency through Saint Louis College of Pharmacy. Dr Ross Shapiro, Dr Walsh, and Dr Schaefer, thanks for being on Rounding@IOWA.

Dr. Ross-Shapiro

Thanks for having us.

Dr. Shaffer

We're happy to be here.

Dr. Walsh

We're happy to be here and talk about menopause today.

Dr. Clancy

Well, I'm happy to have you as well. So, I just provided our listeners A brief official description of your educational backgrounds and your current titles. Could you tell us what drew you to this work? And Emily, let's start with you.

Dr. Walsh

So during my pharmacy residency training, I was able to uniquely rotate through a high risk obstetrics clinic where I assisted in managing chronic disease states during pregnancy. I'm and this helps solidify a strong clinical interest that I have in Women's Health. I currently in my clinical practice spend some time in our IVF clinic. So while both of these experiences are somewhat. Anti menopause if you will. I'm very passionate about supporting women and their medication needs throughout the entire lifespan and think the area of menopause is a growing area that pharmacists can certainly contribute to.

Dr. Clancy

Great. Sarah, how about you?

Dr. Shaffer

Great question. I began at Iowa mentoring being mentored by Colleen Stockdale and the vulvar and Vaginal Disease Clinic and I was there a couple of years when I really started to acknowledge how much overlap there was in patients that I was treating and them, you know, eventually asking me about perimenopause and menopausal symptoms, I think. A lot of these patients were patients that were surgically menopausal at a young age.

And they were very much in need of hormone therapy. And so as I started kind of dabbling there and had a partner that was doing menopause clinic that approached me about

helping out and she retired it just kind of all came together. But it definitely is a source of joy. And I really, really enjoy taking care of women.

Dr. Clancy

Excellent. Agree. And boy, there's there is a lot of suffering and a lot of impairment that we'll talk about in a little bit, but glad you're doing this work. Evelyn, how about you? How did you get started into this?

Dr. Ross-Shapiro

Yeah. Thank you. You know, I'm a primary care doctor and I have always had a strong interest in Women's Health and it was actually in residency. We had to give these, you know, lectures to our peers and I wanted to do something about Women's Health. And I started researching menopause and I realized how much it overlapped with primary care. And general medicine and how little education received about it in in residency and in medical school I know in residency, the only education I received was the lecture that I gave to our class. So that gave me a lot of interest in making a difference with our patients in the long term. And actually, Doctor Schaffer has been a long time mentor for me. And so when I ended up joining at the university, I reached out to her. To see if they would have room for me to join their practice.

Dr. Clancy

Great. Great. Well, Evelyn, let's stick with you. What does a typical work week look like for you? I know all of us in academic medicine. It's not the same thing every day at all. But what's it look like for you?

Dr. Ross-Shapiro

Yeah. So I'm primarily just do primary care. And then on Fridays, I go over to North Dodge and I work in the OB, GYN department doing menopause care specifically. So that's four weeks out of the month. And then my 5th week of the month, I'm just staffing the resident clinic at IRL.

Dr. Clancy

How about you, Sarah? What does a work week look like? You have a lot of duties.

Dr. Shaffer

Yeah, it's pretty variable. Break it down. I typically have one day a week where I do just while bar and vaginal disease. I will do a whole day in clinic. With that, I do have one full day of clinic where I do general obstetrics and gynecology, but from there it's kind of a

hodgepodge of I will staff, resident clinics, all staff, labor and delivery. I will have all our time, the majority of my cases being vulvar, vaginal sorts of things, although I still do. Topic pregnancies and ovarian cysts and things like that with laparoscopy and there's some other smattering of things rolled in there, but those are the big ones.

Dr. Clancy

Got it. Emily, how about you? What does a work week look like?

Dr. Walsh

So I'm I spend time in a couple of different clinical areas in the outpatient setting across UI Health Care, but kind of the two things I break it down into is on patient education and then cost or access assistance. So educating patients when they're starting new therapies and then completing follow up as indicated. Otherwise, I think a large part of my job is just trying to get patients on the medicines that they need. And so I'll help assess or write appeal letters to insurance to help patients get access to those therapies. Our team up with our social work colleagues to try to obtain medication for free for those patients who have insurance issues as well.

Dr. Clancy

Great, not an easy job, and something that takes some patience so. You're doing that. So before we talk about treatment options for menopause, let's talk about the basics of menopause. Let's start with reviewing a definition of menopause. I'm not sure who's the expert here on that one. It's not me.

Dr. Shaffer

I'll run with this one. So what is typically taught, and this is what I teach in my medical student lecture about menopause, is the clinical definition of. And that is 12 months or one year without a spontaneous menstrual cycle. However, this definition, it's really difficult to apply to a considerable number of patients, especially as medicine advances, because we do more and more procedures and have more and more treatments that modify menstrual bleeding. So one just. Simple and relatively I think recognizable example is a woman who has her uterus removed so she undergoes A hysterectomy, but her ovaries are left inside and. Reminder, those ovaries are actually the hormone generating female reproductive organs. So when those ovaries are still left in, they are not menopausal, despite their uterus, the organ that bleeds being gone. So these women don't have menstrual cycles and they may not experience cessation of production of ovarian estrogen for years after their hysterectomy. And so it's only when their ovaries decrease or stop making estrogen that they really are perimenopausal or menopausal. That's another common example is just

women that have a hormonal IUD in place, and these are quite common nowadays. And while they don't cause amenorrhea in everyone they can. And that can again sort of muddle the waters. Thinking of this clinical definition of absence of a menstrual cycle.

Dr. Clancy

Let's move on to really the set of symptoms that can come along with menopause. What do we see as far as kind of the list? Because it's a long.

Dr. Ross-Shapiro

Yeah, you're right. There are a lot of symptoms. So we talk about classic and non classic symptoms that are associated with menopause, the kind of most common thing that we talk about are hot flashes, the technical term for that is vasomotor symptoms as well as night sweats. Sleep disturbances are very common.

Often related to hot flashes, but not always, only from hot flashes. Psychological symptoms are very common as well. We hear about irritability and moodiness and then new onset depression and anxiety in women going through this menopause transition. The genital urinary syndrome of menopause refers to changes in the vulvovaginal tissues in response to estrogen decline. This can lead to symptoms such as vaginal dryness, painful intercourse. And then there are many other non classical symptoms that are associated with menopause. These include cognitive concerns, so many patients will talk about memory difficulties, concentration, difficulties. And generalized joint pain stiffness, dry eyes. And then we also hear a lot about changes in body weight. We'll talk about this, I think more later. But what we see in menopause transition is that there is a change in body mass distribution, so more abdominal fat. Loss of lean muscle mass and then we see weight gain as well. But we attribute that more to just natural chronologic aging rather than the estrogen decline. So it's really important for healthcare practitioners and our patients to know that there's not a universal set of menopause symptoms. There's not one menopause syndrome. Every woman will experience the transition differently.

Dr. Shaffer

Dr. Ross-Shapiro

We try to be really open to hear about each person's experience so we can help them.

Dr. Shaffer

And just to throw in there, they do not have to stop having a period when they have these symptoms to be considered for treatment.

Dr. Clancy

Sure. Good. Let's talk about how bad it can be. What is the level of impairment that some individuals experience?

Dr. Shaffer

We have insufficient research to provide a sufficient and generalizable answer to this question. There are some well done, and in rare cases some large volume research studies that say that vasomotor symptoms and genito urinary symptoms can cause significant impairment both at work and at home. Women that are getting quality sleep won't be as effective in their role at work or at home. Those that have cognitive changes and mood disturbances clearly can't be as effective as parent to partner an employee. Vasomotor symptoms can cause significant embarrassment and distraction, especially in the workplace or people that have more of a client or a customer facing. Goal women who are fatigued or have joint pain are limited in their ability to be physically active at a time. That, as Evelyn just mentioned, we know that weight gain is likely to occur, that there are, that distribution is changing and usually is just kind of distressing to them. And finally, low libido and genital urinary concerns. And cause significant disruption to relationships. Sure, sure.

Dr. Clancy

When you do see patients who are struggling with this, what are some of the things you worry about when it's not effectively managed?

Dr. Ross-Shapiro

Yeah. So I. Think about many different levels on the individual level. My biggest concern is always just low. Quality of life. You know that there are significant symptoms that we can intervene with. So Sarah highlighted this already, but we know that the visual motor symptoms can disrupt people's sleep, ability to focus, ability to perform their. Job at work. Mood symptoms, even as mild as just irritability. And then ranging to clinical anxiety and depression can have a huge impact on a patient's day-to-day functioning, her family life and relationships, and then this sexual symptoms like low libido, vaginal dryness, painful. Of course, can have really detrimental effects on romantic partnerships. Specifically for women who experience premature menopause, so people who go through menopause before the age of 40. Lack of treatment can actually lead to very poor long term health outcomes. So that's development of osteoporosis and having high cardiovascular risk. So I kind of put that group in a separate category as. What do I worry? About it's been imposed, not effectively managed. Those patients can really have poor outcomes if that's overlooked. There's also concern that early, untreated menopause can impact cognitive health and the sexual dysfunction and mood. Like we talked. About Sarah mentioned. This as well, but on a society level. Lack of menopause treatment really matters in the

workplace, so we see reduced efficiency and loss of skilled workers who are often at the prime of their career. There's some great research out there that's estimated that \$1.8 billion is lost annually in the United States due to menopause related work absences. And we really think that a lot of this is preventable with patient education, patient support and medications really.

Dr. Shaffer

Good spot to just jump in and kind of say things the way that I will say it to my patients when they've given me this list of symptoms and all the ways it's disrupting their life, you know, I want to validate what they're experiencing. And so a lot of them, I think it really helps to acknowledge that they're going through this menopausal transition when they're trying to balance more things than they ever have before in their life. They might have seniority or leadership in their career and they have growing children and they have aging parents and they have partners that are doing all their own stuff. And you add to that these unprecedented changes to physiologic and cognitive function and it just highlights what it means to go through.

Dr. Clancy

So let's turn the corner a little bit and start talking about what we can do for this. And so let's start with some of the lifestyle changes we can do to limit the symptoms.

Dr. Shaffer

I'll tackle this one and I really like this question because I think there are a lot of things that are overlooked and under counseled me included that these things can really be helpful for some women. They may be the only support that a woman needs through the amount of puzzle transition. So there's good advice to be given if people avoid or limit exposure to common triggers of vasomotor symptoms like spicy foods, caffeine, alcohol, hot temperature drinks and things like that. We will often advise that people dress in layers that can be easily removed to manage minor hot flashes during the workday or in stressful situations. Some people will choose to keep a fan nearby and then there are actually tons of products that are marketed to women with menopausal symptoms like fans. That kind of sit around their neck and blow directly on their face and their neck. There are devices that can cool the wrists and the back of the neck to ease hot flashes as well. For night sweats, you can keep the bedroom really cold. Usually, partners are not super keen on this. We hear about that a lot. But there are a variety of things like cold sheets or moisture wicking sheets that can be helpful, and often we will talk with people that struggle to sleep about sleep hygiene. Having a schedule and a routine for bedtime, making sure the room is dark, quiet and as free as possible from sleep disturbance. It is important to avoid stressful

people in situations as much as possible, because these really do trigger hot flashes. They are very tied to high emotions and then for the mood disturbances. And I think Evelyn will address some things a little bit later on related to this, but there are tons of online courses and. Maps that can really help guide people through mindfulness meditation, deep breathing exercises, and things that are helpful is as a lifestyle changer and approach that is nonmedicinal.

Dr. Clancy

Very well. We live in a day of very targeted and accurate advertising and marketing. So are there vitamins and supplements that you might recommend as well?

Dr. Walsh

You took the words right out of my mouth, Gerry. So as a pharmacist I really approach with questions about supplements. No matter my clinical role on almost a daily basis. Just due to this direct-to-consumer advertising, where a celebrity or an influencer is getting paid in some capacity to tout these natural remedies that will fix almost any symptom. So menopause is unfortunately no different. Especially as now this has become the ability to discuss these menopausal symptoms in the public has become less taboo and more abundant. So in preparing for this conversation, I came across this term called Meno Washing, which I guess is a term coined to kind of poke fun at the aggressive marketing that some of these companies are using really to focus on these menopausal women who are really at a. Tough. State in their life as I counsel all my patients, regardless of what type of supplement that they're trying to use for their chronic conditions, I really just try to tell them that we have to take these recommendations with a grain of salt. So we'll rediscuss some of these pearls in a bit when we talk about compounded bioidentical hormonal products. But supplements are not regulated by the FDA like other prescription medications are like hormone therapy which we'll get into in a second. And these also lack government regulation to ensure that they're pure and they're safe and truly that even whatever it says on the bottle is what they actually contain. And because of all of these arrays of formulations and combinations of various products, we really can't identify supplements that provide benefit because there's few design clinical trials that can really assess them. The way that these things are working. The Menopause Society recognizes that these previously discussed challenges in their 2023 non hormone therapy position. Treatment and they recommend that these supplements or herbal therapies are not used to manage vasomotor symptoms, especially given the safety and the efficacy of our other therapy options, especially those hormone therapy options that we have. They do note mixed evidence for the use of soy foods or soy extract, but otherwise they do recommend against other supplements that you'll often see kind of pond. On these kind of social media

applications. Some that you might have heard of are Primrose Black Co, hash, thistle and vitamin E as well.

Dr. Clancy

I am really glad we sent you the questions ahead of time. You know your stuff, which. Is great any. Other non pharmacologic treatment options that we might want to consider or recommend to patients before we get into. More, more replacement therapy and some of. The new drugs.

Dr. Ross-Shapiro

Yeah. So I will talk about kind of like evidence based treatments and also the ones that. Are not evidence based. But we know that some mind body therapies, so cognitive behavioral therapy and clinical hypnosis can help with management of vasomotor symptoms. So targeted kind of behavioral therapy. CBT involves education around the Physiology of menopause. Vasomotor symptoms and then kind of incorporates how thoughts and emotions affect the perception of the physical sensation that a person experiences and provides training and strategies to manage. Your physical and emotional response. So this type of CBT is usually available in individual or group therapy settings led by a clinical psychologist. To be honest, I don't know of providers in the Iowa City area that are specifically trained for this, but there are also many self-directed CBT apps available online. I don't. Though you know of their efficacy with regards to evidence based if CBT app is as good as CBT that you might receive from a clinical psychologist, but those resources do exist and there have been a couple randomized control trials that have shown that CBT helps. And then also that clinical hypnosis. Can improve vasomotor symptoms. Again, I'm not sure how. To get clinical. Hypnosis in the Biocity area or vasomotor symptoms. There is also some limited evidence that weight loss is associated with improvement of vasomotor symptoms. We see that effect more strongly in the perimenopausal transition and early postmenopausal phase. However, diet and exercise we know are so important to general physical and mental health. And obviously important for weight loss, but the evidence that those specific interventions reduce vasomotor symptoms is really limited. And then Sarah already described many behavioral interventions that can help patients cope with vasomotor symptoms, like lowering the temperature in your bedroom, wearing layered clothing, avoiding triggers, and those things help patients cope. They don't necessarily take the vasomotor symptoms away or reduce the incidence, but they help people get through it better. Other non pharmacologic treatment options that you might hear about would include acupuncture. Evidence shows that that's about the same efficacy as placebo, although we know that in some cases placebo helps. So there's that still at ganglion nerve block is always mentioned. In these paragraphs about what else can you try? I've never

seen it done. I do think that it obviously would have some risk as a procedure, and apparently it only provides benefit for less than 6. And then there's other things that come up in the literature, like calibrating neural oscillations, chiropractic interventions. And other things that really haven't shown. Any clinical? These are all everything I'm talking about, though, is based on, you know, what research do we have? And we always tell patients if it's helping you and it's not. Hurting. It's OK to try.

Dr. Clancy

I'm with you, but I do like straight shooters as well. So great job. Great job on that. So let's move on to the complicated subject of hormone replacement therapies, a treatment option where the recommendations have changed overtime. As long term study results have become clearer. What are the pros and cons of hormone replacement therapy as we know it today?

Dr. Shaffer

Well, I I'm excited to answer this one because one of my favorite things to do when I'm talking to patients about hormone therapy is let them know that there are pros. I think it was so demonized for so long, they're, you know, still kind of shaking in their boots. And it's just nice to see. There's a lot of health benefits that we can really confidently states the first and foremost. It's just that. All these symptoms that we've been talking about get better to some degree, typically. Vasomotor symptoms are often the low hanging fruit because really we can fix those in a lot of different ways, but just feeling better and feeling like you can do a better job as a partner or parent and an employee is truly what a lot of women are looking to get really for. I will let patients know that there is good evidence to say that their colon cancer risk is reduced. The use of estrogen containing hormone therapy. The risk of. Osteoporosis and related fractures is one of the things that we've acknowledged for the longest time and this is reduced because of the prevention of bone density loss when women have ongoing estrogen in their systems. One of the newer things that we feel more and more comfortable as more and more studies come out is quoting that there are cardiovascular benefits that we could state. We know that most studies show a decreased risk of coronary heart disease and often there is this all cause mortality kind of lumped together cardiovascular conditions. And when we look at things all sort of piled together. Where we see a reduction there, it's just it is kind of a grab bag that we're looking at all together. So that's pretty consistent in studies and the greatest benefit for these cardiovascular benefits has been shown consistently to be when hormone therapy has started closer to the onset of either vasomotor symptoms or clinical or surgical menopause. So as close as you can to when that menopause starts, you want to get that hormone therapy on boy. Hormone therapy has also been associated with a lower risk. Of

developing type 2 diabetes. So those are some. Pros that I try to review with every patient. When it comes to cons estrogen, we always have to acknowledge increases the risk of venous thromboembolic clots including deep venous thrombosis, pulmonary embolisms and related clot strokes. The greatest risk for these is measured during the first year of use, and in women that are older than 60 or older when they start menopause greater than 10 years from the onset of menopause. And these women also, as you could probably guess from what I said previously, don't demonstrate the same cardiovascular benefit. So you know well, it's not a con. There's not a bazillion risks that come with their cardiovascular health. They certainly can't be quoted the same benefits over time, and only combination estrogen and progestin therapy, not estrogen only therapy. Has been shown to increase breast cancer risk, but this is typically not statistically significant. So we usually note that and then finally, hormone therapy is consistently associated with increased risk of gallstones and gallbladder disease. But that's true of birth control pills and pregnancy and lots of other high estrogen states as well.

Dr. Clancy

You did touch on this, but just let's just circle back as far as how does age and time of onset menopause play into your recommendations for hormone replacement therapy. And you mentioned that, you know, if you can get it close to onset, things go better, but other times and maybe you would wait. A little bit.

Dr. Ross-Shapiro

Yeah. So I'm going to take this one and I do think age of onset of menopause and then age and timing of initiation of hormone replacement therapies is extremely important. When we talk about safety. So talking about the age of menopause, I'm going to go back and separate our patients into two groups, patients who experience premature menopause and then patients who experience natural menopause. I already talked about this a little bit earlier, but patients who have premature menopause would be someone who has loss of ovarian function before the age of 40. And that can be due to premature ovarian insufficiency or patients who have experienced iatrogenic menopause from bilateral oophorectomy. Medical treatment of some kind like chemotherapy, radiation that caused ovarian failure. So those women need hormone therapy right off the bat in the everyone else group. So those who experience natural menopause, it's not the age that they go through menopause, but it's the timing of initiation of hormone therapy that matters to us when it, when we talk about safety. So standard guidelines recommend that you initiate menopause hormone therapy within 10 years of the patients' menstrual period. But really sooner is better. And this recommendation dates back to findings from the Women's Health Initiative in 2002, which showed that older women who received hormones at an older age remote from their last

period, you know, 10. Years or more? Had higher risks of heart disease, stroke and venous thrombo embolism. This has led to the timing. Hypothesis or what we call the window of opportunity, which suggests that menopause hormone therapy can have a protective effect on vasculature in women if it's introduced in the perimenopausal or early postmenopausal years before permanent vasculature, neuroimaging or development of atherosclerotic plaque has occurred. But in older women. Who are you? Know remote from their last period they've been post menopausal for 10 years or longer. This duration of low estrogen state in combination with you know normal aging factors. Can give rise? To the development of vascular stiffness atherosclerotic plaque, other cardiometabolic risk factors like hypertension, insulin resistance, hyperlipidemia that make the reintroduction of hormone therapy much more risky. So as a rule, we generally recommend start within 10 years of a person's last period. Earlier is better. And before the age of 60.

Dr. Clancy

Got it can. You make general recommendations for homeowner replacement therapies. Or are the guidelines really tailored toward case-by-case review?

Dr. Shaffer

Yeah, it's absolutely a case-by-case basis, but I think more women are candidates for hormone therapy than might realize it. So one thing we kind of felt would be helpful here is just to list what are the absolute contraindications to systemic estrogen containing hormone therapy.

So we'll run through. Use a history of breast cancer or current suspicion for breast cancer is an absolute no no may these patients. There's a lot of really good data to say. If you have a woman with a history of breast cancer who is having genito urinary syndrome of menopause symptoms that most the vast majority of those. Women that have a history of breast cancer can use localized vaginal estrogen for their genital urinary symptoms. But for systemic estrogen, history of breast cancer, suspicion is an. No. Anyone with abnormal uterine bleeding that you don't really know why they're bleeding is irregular or heavier than it should be in this kind of perimenopausal phase, especially if that patient has risk factors for hyperplasia of endometrium or endometrial cancer. So if they are obese or they've had irregular. Periods their whole life.

Those patients really warrant a work up to make sure there's not something else going on with their uterus before you stimulate their uterine lining with estrogen. So they need to work up for that abnormal uterine bleeding before you start any estrogen containing hormone therapy. Some of the ones that the students can always get right if you ask them who maybe shouldn't have hormone therapy, are anybody that has a personal history of a

DBT PE or a thromboembolic. Stroke anyone who has a personal history of cardiovascular disease or cardiovascular events, including a myocardial infarction and arterial clotting event that resulted in a stroke or unstable coronary artery disease. And then one of the other ones, it's a little easier to forget, but it really is important as anybody that is has liver failure, cirrhosis, active liver disease or anybody who has a known liver Hemanta. Comma. But I think you know, just to give a couple of examples of people that I hear a lot, I'll get questions like can this person have hormone therapy, current smokers? There's no reason not to give them hormone therapy. We don't take their ovaries out because they smoke. So when their ovaries start to fail, there's not a reason we can't treat their symptoms. One thing that sometimes will come up is patients. That have focal. Nodular hyperplasia of the liver, just as we have more and more imaging. Studies to find these things. As long as it is not a Hemangioma, they can have hormone therapy. I get a lot of patients that think their family history of cardiovascular disease or venous thrombotic thromboembolic events can't have. Hormone therapy. But as long as it's not a personal history, we can have a good discussion. Another one that's come up just recently was a patient who had an inherited thrombophilia. She was prothrombin gene mutation, but she never had a personal history of a clot. This was found in a workup for something else. That's not even a workup. We do anymore. And so we talked about what does this mean? What are the risks? So, you know, if there are these kind of iffy. Things I think it's really important for people to reach out to someone with a lot more knowledge about menopause medicine just to you know way is this somebody that should be offered hormone therapy or maybe not.

Dr. Clancy

Great answer and definitely supported case by case. So recently, the FDA removed the black box warnings on most menopause hormone therapy products. What does that mean for our patients? Obviously there's some education that needs to get out there.

Dr. Ross-Shapiro

Yeah. So this is new. And so I'll say with our, you know, one month of. Experience my thoughts. But first I want to just mention what the black box warning was. So for decades the FDA included this black box warning on menopause hormone therapy products, which highlighted increased risk of serious adverse events. So including cardiovascular disease, which included heart attack, stroke or blood clots, breast cancer and probable dementia. This was based on data. From the Women's Health Initiative and that study began in the 1990s and was prematurely discontinued in the early 2000s due to excess identified risk. Based on the findings, the FDA approved a class wide labeling change in 2003 to menopause hormone therapy products. To note these risks. So now 20 years later, we know that the Women's Health Initiative was an imperfect study. It gave us a ton of evidence to

work with and a lot of information about menopause hormone therapy, but also gave us conclusions that may not have been perfect. The average age of participants in that study was 63.

And so, you know, we know in the United States, the average age of menopause is about 51, 52. So many of the women in that study were more than 10 years out for menopause when the hormone therapy was reinitiated. And as we talked. About. Earlier timing of initiation makes a huge difference. Also, the Women's Health Initiative used many different types of hormones that we don't use today. So over the past two decades, reanalysis of that data, as well as many other research studies have shown that menopause hormone therapy really is safe to use in appropriate populations like we talked about younger women who are within 10 years of menopause and do not have other medical contraindications. So from my perspective, the removal of this black box warning. Is like a blessing and a curse. I want patients and providers to feel safe accessing these medications when it's indicated. But we also know that the medications are not 100% risk free. And it's very important that healthcare practitioners are able to counsel patients about potential risks and know what the contraindications are. And are able to identify appropriate candidates before prescribing.

Dr. Clancy

Let's talk about some of the other options. What about compounded or bioidentical hormone therapies? What's the role of these products in treating menopausal symptoms?

Dr. Walsh

So the Menopause Societies 2022 position statement on the use of hormone therapy has an excellent section on compounded bioidentical hormone products. So as we've discussed, the FDA has some bioidentical hormone products so specifically estradiol or progesterone and those are approved to treat symptoms associated with menopause these medications. Or like other prescriptions that you may prescribe in your clinical practice and send to a pharmacy and so these products have a package labeling that contains a lot of product information and information on safety and efficacy that was seen to approve these trials through the F. Compounded products may be bioidentical hormones, but they can also be other hormonal products. So kind of variations of estrogen like estrone or estriol formulation of testosterone called DHEA. But these are prepared in a compounding pharmacy which uses a prescriber specific prescription that is unique and allows a prescriber. They really write for whatever dose of their selected estrogen, progestin or testosterone product, or any of those derivatives that we've talked about in the formulation and the frequency that they think will work best for the patient. So we talked about

supplements earlier and compounding products do have some similarities to supplements in some regard. So again, they maybe don't have that specific FDA regulation like a prescription product might have. So there are limited clinical trials available showing efficacy and safety of those various formulations, doses and frequencies. There is not testing for purity and often a little bit less regulation, so still regulation the compounding pharmacy needs to be licensed and held to a certain standard. But kind of just a little bit less regulation when it comes to things that are FDA approved. So overall, the menopause society only recommends these products and patients who meet one of two classifications. So those who have allergies who currently available hormone therapy products or those who require a dose or formulation that's not currently approved or available through the. So when it comes to the example of allergies. A lot of. Our progestin products are formulated with peanuts and so anyone who's needing to use a progestin for that endometrial protection maybe can't take oral progesterone. So maybe they need a formulation in ethyl oleate or some other capacity. Another example of maybe something that's not regularly available through the FDA is patients who are desiring to use a testosterone or estrogen combination product to boost libido. And there's just no currently available FDA products. And so then a compounding pharmacy would be able. To supply that.

Dr. Clancy

Great answer. So let's turn another corner here and let's talk about some of the new medications available for some of the symptoms of menopause, particularly the vasomotor symptoms. And that is the hot flashes. Talk about those meds and do you need to fail hormone replacement therapy before you can qualify for these new non hormonal treatments?

Dr. Walsh

And that's a great question. And I think some of the newness of some of these therapies that I'll get into in a little bit makes this question a little bit difficult to answer. But historically some of our non hormonal therapy options for the management of these motor symptoms included antidepressants like SSRI's, SNRI's and then other therapies like gabapentin, pregabalin and. CC. Then, in 2023, a medication called Physalis Natant, or brand name Diosa at Synera Kainin 3 receptor antagonist, and it was a non hormonal treatment approved by the FDA for moderate to severe hot flashes. We'll get a little bit more into an additional agent that was very recently approved in this medication class in a in a second. But insurance coverage can vary. Quite widely, so it's really hard to say whether insurance would just right off the bat and approve these newer therapies for the treatment of hot flashes prior to the use of either our hormone therapy options or our other kind of

non FDA approved but kind of off label uses of SSRI's or SNRI's or things like that. So. Given these agents are new and are branded only options and they were just recently approved by the FDA, they do carry a pretty hefty price tag and so it wouldn't be surprising if insurance did require step therapy before paying for a more expensive product.

Dr. Clancy

Great. Great. So. I know they're new, but what are you seeing as far as pros and cons of these new medications?

Dr. Walsh

Just to briefly touch on some clinical trials that led to the approval of these medications. So the felinety it was approved through or was studied in a couple of phase three trials called Skylight 1 and Skylight 2. And we assessed the efficacy of this medication compared to placebo. So what they found was there were significant reductions in the frequency of those motor symptoms. By about 60% from about 11 times per day on average to 5 compared to placebo. And then there was also significant reductions in patient reported severity of these symptoms compared to placebo. This improvement was evident pretty early on, so from Week 1, after starting therapy and then in a long term extension study, they did notice that this was maintained over about a year. Pull data from these trials also found that maybe facilitate could. Improve sleep disturbance and impairment as well as reduced impairment of activity, productivity, loss and absenteeism, which we already talked about. How important that that can be when this a menopause symptoms can be really disruptive to a woman's life. That Elinzanetant some of those longer term studies are not available because of its recent approval, but it was in a similar study compared to placebo and those studies were called Oasis One and two and patients were again followed for 12 weeks. There were similar reductions in the vasomotor symptom frequency of about 65% and patients also noted reductions in the vasomotor symptoms severity as well. So the obvious pros for this therapy are that it's an another medication that's a non hormonal therapy option to add to our toolkit for the management of these motor symptoms. It's also nice to see on these neurokinin receptor antagonist provide benefit maybe for other symptoms of menopause like sleep disturbances and quality of life and productivity. So far couple of the cons now. Data are lacking because these agents are so new on this class's affect on other menopausal symptoms, so things like mood, those genital urinary or sexual symptoms, cardiovascular risk, and metabolic risk, and bone health as well. These agents were overall well tolerated in clinical trials, the physicality and their main side effects were abdominal pain, diarrhea and insomnia. And then the one thing that came out in post marketing surveillance was that the Fezolinetant did find some cases of serious drug induced hepatotoxicity within the 1st 40 days of the start of therapy.

Some patients LFT's rose higher than 50 times the upper limit of normal. So definitely something to maybe be concerned about. So because of this, the physical limitation requires pretty frequent hepatic laboratory testing. After it started and we shouldn't start that in anyone with hepatic impairment, Elinzanetant, their side effect profile is pretty similar to. To that of the Fezolinetant in the requirements of hepatic function monitoring before and after the start of therapy. But those LFT elevations in those 12 week studies weren't quite. Profound as in the physical annuitant study. So we'll see what comes out in some of that post marketing surveillance too. The side effect profile, potentially because it's working on two of those neurokinin receptors is a little bit different where the Elinzanetant causes more CNS depression and related side effects like headache and dizziness and somnolence. Both of these drugs are substrates of the. Glycoprotein P-450 enzyme Fezolinetant specifically for SIP 1A2, and Elinzanetant for sip 3I four. So just a careful review of the patients. Current medication list should occur before prescribing to make sure there's no drug interactions and again in my job everyday cost is a main issue so there might just be some barriers to access to therapy through insurance. Or just from a cost perspective. As well.

Dr. Clancy

So for patients who are really struggling, can you pair these new medications with hormone replacement therapies?

Dr. Shaffer

I think this is another yes, no. Or it depends question. I can definitely say. With how new these medications are that I haven't used any neurokinin receptor agonists with hormone therapy. That said, many patients who present with symptoms of the menopausal transition. Will already be. Taking medications like an SSRI or an SNRI for other indications. And so if we're talking about starting hormone therapy or, I would defer to Emily on this. But you know, if we they're taking an SSRI or SNRI and then they want to look at. You know one of these neural risk neurokinin receptor agonists. I think that we would continue those medications if there weren't significant interaction. It's probably a question for the future, because I'm sure there's some Unicorn out there that could potentially need both.

Dr. Walsh

And in my brief review of the literature, there's if you type Fezolinetant into pub Med, there's only 120 citations, so there's really not a lot out there about combination therapy at this time, which isn't super surprising.

Dr. Clancy

These research and treatment options continue to expand for menopause. Let's talk about the tissue selective hormone therapies and how they work and what they can be helpful for.

Dr. Walsh

Yeah. So I think in the interest of time, we just think that it would be best to discuss some of these other currently available products and especially the ones the audience may be and are hopefully now more comfortable, umm prescribing. But a brief comment on these therapies are just that some of these therapies like the basic doxycycline with the conjugated equine estrogen and the ospemifene, they are available. That use is limited really to kind of certain patient situations as they're expensive and there really aren't a lot of reasons to prefer the use of these therapies over the highly efficacious hormone therapies that are more widely and readily available that we've discussed. OK.

Dr. Clancy

For Emily and Evelyn and Sarah, you know you're in this world of prior authorizations and approvals with these new medications and treatments. They are expensive, as you mentioned. What's the success rate with getting commercial Medicaid and Medicare coverage for these meds for our patients?

Dr. Walsh

Since we're practicing in Iowa, I'll kind of focus on what I was able to find for our specific insurers that might affect our patients a little bit more. Yeah, but generally, just since the Elinzanetant was approved just about a month or two ago, access to this therapy is going to be pretty limited. So currently it's not listed in our Iowa Medicaid formulary nor in our various well mark or Blue Cross Blue Shield formularies. Just looking at the manufacturers website a little bit more to see what kinds of savings that we're offering to patients. They do offer a copay card for patients who have commercial insurance or insurance through the workplace and that might bring the cost down to as low as \$25.00 a month. And there's also a patient assistance program for patients who are uninsured or underinsured. And this would be a whip pathway for them to access therapy for free. The big caveat with patient assistance programs, I like to remind my patients of is this doesn't mean for sure access to the therapy, there's often pretty stringent income eligibility guidelines. The Thessaloniki and since it's been on the block, a little bit longer, appears to be a little bit more widely covered. I'm happy to share it's preferred on the Medicaid formulary and there's just so many Medicare plans we could sit and talk about Part D plans all day, but some Medicare plans will likely also provide coverage as well, so. Some insurance plans, however, so other Medicare plans, or on Walmart specifically, didn't list fizzle unity and as a preferred

product, or did not list it on their formulary. So that doesn't mean that that's kind of a hard no. I like to always see if we can challenge insurance to get coverage for the medications that my patients need and might just mean that there might be extra hoops to jump through to ensure coverage. Or there still just might in general not be any coverage for the drug at all. So. The Fezolinetant also has a copay card like the other therapy. It's for commercially insured patients. It will actually give the medication to patients for free for the first month, then drop that copay down to \$30.00 a month and then also has some of those patient assistance programs as well for uninsured or underinsured patients.

Dr. Clancy

Great, so some help in this area then. Nice, nicely, great. So as we look to the future, what new treatments are in the pipeline, what do you see on the? OK.

Dr. Walsh

Yeah. So there's obviously a lot of buzz surrounding this new kind of novel neurokinin receptor antagonist the last few years as our new non hormonal option for vasomotor symptoms. A couple of things I could find were more related to novel therapies or delivery systems of currently available drugs that are in the pipeline. So interestingly, in some of my research, there seems to be maybe some data or interest in delaying ovarian aging as opposed to the management of these. So what I was able to find was there's maybe anti malarian hormone analogs that could preserve ovarian reserve and maybe extend the onset of menopause by 5 to 10 years. On clinicaltrials.gov, there's currently a study that's ongoing that's investigating the use of rapamycin, or more commonly known as sirolimus, and its effect on ovarian aging as well. I did find another non hormonal agent, more specifically targeting symptoms of menopause. This was called send offend scene. I mean, it's a novel monoamine modulator that targets serotonin, norepinephrine and dopamine. It just had a positive phase two trial that reduced severity and frequency of hot flashes. And then interestingly, kind of touched on a couple of those other symptoms of menopause. So mood, food cravings and fatigue as well. So we'll see if that kind of makes it to phase three and what those results. Back to when it comes to alternative delivery systems, I found something about liposomal estradiol and so the way that that would be delivered would maybe improve bioavailability and absorption, but would reduce some of that systemic exposure to minimize some of those more significant side effects that we've discussed on previously that can rarely occur with hormone therapy as well.

Dr. Clancy

That's one of the reasons I love medicine. Changing all the time, it's great. So you 3 have been great. Just thank you for doing your homework and getting ready for this. You did a

great job as far as where we are right now and what's in the pipeline. So as we close, what are some of the take home points for our listeners and any one of you can start.

Dr. Shaffer

So I kind of mentioned this earlier, but. I think one of the things that women are really recognizing is they don't have to wait for menopause. As in, they don't have to wait until they don't have that you know, year of no periods or whatever. A lot of women are coming in in their early 40s with the first whispers of symptoms and asking questions and I. Think. That that is really great, right? So symptoms of perimenopause menopause are really common. They can be really disruptive and I think we should be talking about them earlier and sooner to really prepare people for what's to come.

Dr. Ross-Shapiro

I would just make a plug to my colleagues and internal medicine and family medicine and even an OB. Just to know how much information is out there and how many treatments exist to help our patients and really encourage all of our providers across the university to to delve into this, it's a rapidly expanding field our. Menopause clinic is. Small and there's a long wait list and. Many more providers can. Give this therapy to patients with some training. And so I really want to give everyone some encouragement to, you know, do the research, get some training and also like, know that a lot of this is new. And so it does feel hard and it is a new skill set. But I want to encourage you all to, to work on it.

Dr. Clancy

Great, you've inspired me. Even so. Emily, you ready to bring us home?

Dr. Walsh

Yeah. And I think I'm kind of speaking to Evelyn's point. You know, I I, as a pharmacist, have been wondering how I might counsel a patient differently with the removal of those black box warnings. And I'm sure a lot of my colleagues are thinking the same. I'm so we're glad that, you know, some of maybe the misconceptions or some of the craziness that happened with the Women's Health Initiative study in the way those results were kind of related to the public before being scientifically available. Well, glad that that's maybe reducing some of the stigma associated with menopause and then the use of hormone therapy. I'm just as more people are talking about it. So really hoping that this can, like everyone said, empower prescribers to help women feel better and help make my colleagues just feel more confident when they see those orders and verifying them given the patients past medical history than as a pharmacist. Just an exciting time as newer,

more novel agents come to the forefront and really excited to see what other things become available and the ways that we can help patients access these medications too.

Dr. Clancy

Right. Well, just a short little story before we close on your point around the Women's Health study. I was the Dean of the Medical School at the University of Oklahoma in 2002, and we were asked by Blue Cross Blue Shield of Oklahoma to man a phone that's on where anybody from across the state of Oklahoma could call in and. Talk to our doctors. And we were banning that phonathon at 11:00 when the movements Health Initiative study results came out. And every single phone call was about this. And we didn't know about it. The patients knew about it before we knew about it in it. So I remember that very well just because we were. Stunned by it? Things have come so far and it just really it's really hopeful to all three of you. Dr Wallace, Dr Schaefer and Dr Ross Shapiro. Thank you so much for joining us today and for your great work in Women's Health. To our listeners, thank you for joining us for this session of Rounding@IOWA. You can access show notes and instructions for CU's and see any credits in those show notes. And we look forward to you joining us again on. Routing it up.

[Upbeat music plays]