Introduction to BHRT and Cognitive Decline

Hello, everyone, and welcome to the reverse Alzheimer's Summit. Once again, I'm here with Dr. Ann Hathaway, one of my favorite physicians who's done such incredible work and is a real world expert on on BHRT.

And this comes up again and again and again as we keep coming back to if you're going to understand what's driving cognitive decline, and then you're actually going to be able to reverse cognitive decline, then you really want to look, I kind of think of it often as three up and three down.

So you want to know, is there enough of energetics and neurotransmitters and and essentially a neurotrophic effect, hormones, nutrients, NGFB, the and afterwards and then the three down the things that you want to reduce you want to reduce inflammation, want to reduce toxins, you want to reduce stress.

So these are key. And of course, hormones play a role in many of these processes. And it's interesting to me, if you look just at the molecular species, estradiol binds to its receptor, enters the nucleus, affects hundreds of genes.

And interestingly, one of the genes that's upregulated is the alpha secretase, which cuts APP to give you the two synaptic blastic fragments as APP Alpha and alpha CTF.

So basically encouraging neuroplasticity. So this comes up all the time. So let me ask you some of the things that we keep hearing about. Number one, do you think BHRT is helpful for cognition in anyone?

I think the BHRT in almost all women, postmenopausal women, has a tremendously positive effect on cognition. Yes, mood. I mean, it has a tremendous impact.

It has an effect on many things cardiovascular health, bone health, bone health is the one thing that is not controversial. Right. And it's an a very important thing. Right.

Because the when you have osteoporosis, the the drugs that they can give you to help are short lived. You can only take this drug for a year or that drug for two years.

And in my opinion, you can take estradiol indefinitely in a 2017 report by a group of scientists, researchers and clinicians who studied the literature for 6 to 8 months reading everything meeting, wrote five or six papers that came out in 2017 saying that they saying all the benefits of estrogen, including benefits in some Alzheimer's patients and we can look at three studies that show benefit, cognitive benefit in Alzheimer's patients.

These are studies by Astana and Wharton, where they took out women with Alzheimer's and small studies put them on estrogen. Half on estrogen, half not on estrogen.

And it's important the estrogen they use, they use transdermal estradiol. If you use oral estrogen, usually it's conjugated equine estrogen, but even oral estradiol, you're going to have some positives, but also many negatives.

And that's one of the reasons why the literature is so confusing. But anyway, in the in the Worton Astana studies, the the largest one, they had 43 patients three months.

They showed absolute, very significant cognitive improvement in the women on transdermal estradiol and not on the women who were put on the placebo. So this was a randomized controlled trial.

Estrogen, Brain Health, and Alzheimer's Evidence

I, I believe that trial needs follow up. Absolutely. The other important piece that people don't know that most

gynecologists don't know is the huge amount of medical literature by neurologists, many of them women neuroscientists who have been studying the brain and estrogen for 40 years.

There's a 40 year treasure trove of research on how estradiol affects the brain there. You mentioned that the the neurons have estrogen receptors. They have estrogen receptors on the membrane in the cell body, in the nucleus, in the mitochondria, in the neuronal support cells, the microglia, the astrocytes, etc., they all have estrogen receptors more highly concentrated, more highly concentrated in the areas of the brain that are affected by Alzheimer's disease, the hippocampus, the posterior cingulate gyrus, the hypothalamus, the whole temporal lobe in general.

All of these areas, there's this there's this belief among most gynecologists now that it's okay to give hormones at the time of menopause and for five or ten years after that.

But after that, you get some negative impacts. And tat data is based on oral estrogen and medroxyprogesterone So I don't think it's valid data. And the 2017 North American Menopause Society Group that met they said the data do not support discontinuation at ten years after menopause, but the data do support continuation if you're using transdermal estradiol.

And of course, we don't ever want to use medroxyprogesterone. That's the hormone that was used in the huge Women's Health Initiative study that was reported out in 2002.

The result of that being everyone believed that estrogen and progesterone increased the risk of breast cancer. A careful study of that original paper and what they say in that paper is that with conjugated equine estrogen and medroxyprogesterone, the increase in breast cancer almost reached statistical significance the way the confidence interval, the 95% confidence interval.

And here I'm getting technical. I'm not a statistician, but I do know when the 95% confidence interval crosses one, that's not statistically significant.

And if you look at the paper that is in fact, what happened and there's some stories about this that are hearsay. I can't really report on those myself.

But when challenged on that, what people have told me who were in the room is that they were told we had to kick the statistical police out of the room when we were writing this paper, which is because the reason why I say that so important is because this changed dramatically changed the hormone replacement.

How much hormone replace was done? My generation, women who were turning 50, 52 around that time completely missed right. The chance to get hormones and now they're too old to get hormones.

Now you can't start hormones supposedly in women who are over ten years out from menopause. Right. Even though there's some research that suggests otherwise.

And I have to say, I do start women on hormones with a careful evaluation about all their risk factors. It has to be done on an individual basis. You have to be careful.

I do start women who are more than ten years out from menopause on bioidentical topical estrogen in real progesterone. And I see benefits in cognition.

Now I'm doing the reversal of cognitive decline programs. So women are getting the full spectrum of benefit from that program, which is, as we all know, many, many interventions are being done.

But sometimes you can really see once you get that estradiol up over 60 or 70 that that serum level. Yeah. There's a change in cognition. They notice they notice a difference in in many cases not all certainly.

But in many cases they, they notice a significant benefit. You know, I'm fortunate in that when the 2002 paper came

out, I already knew that it was based on the wrong hormones because I'd been studying hormone replacement since around the early nineties right?

So I already knew what women needed to be on and what I needed. And so I'm I'm here, you know, in part I would say because I started hormone therapy immediately at the time of menopause.

And that is the optimal time to start, no doubt about it. That is when you want to initiate hormone therapy. That is the optimal time in the most beneficial time.

Right know we continue to see cardiovascular benefits, bone benefits and brain benefits, muscle benefits. Women on estrogen say they feel younger, they look younger.

Those are also important things. So that's that's the the bulk of what I want to tell people about why I think estrogen and progesterone should be considered for most women no matter what their age.

Okay. That's very, very helpful to know. Okay. So you've already said the optimal time is at menopause. Okay. And what's the optimal dose that you start with?

And I assume, as you said, you want to get kind of up there above 80, somewhere in there in terms of the serum level, what's the a typical way use get it started?

So you you usually start a little lower with prescription then what you want to absolutely attain except if the woman is right at perimenopause or menopause, then I think you can go ahead and get her on a full dose, whatever dose she needs.

And the thing to understand is that the same dose is going to give a difference here result in different women. So in some women, if you give a, you know, 2.3 milligrams of topical estradiol a day, they'll get a good serum level immediately, up to 50 or so other women.

You'll need to go up to a milligram, but somewhere in that range is going to give you a good a good level. Estradiol is an extremely potent molecule.

Starting and Titrating Hormone Therapy

Tiny, tiny amounts of estrogen are have a powerful effect in the body, unlike progesterone, which is a very you have to give a thousandfold amounts of progesterone to get a significant effect with progesterone.

Progesterone turns into many other things, right. It has a has a big metabolic pathway turn turns into it has a pathway to turning into testosterone. And in some women and it goes down the chain to aldosterone and cortisol, etc., etc..

Yeah, okay. That would be a starting dose. So somewhere between point three. Now if you're using the patch, the patch has five different doses starting with point 0 to 5, up 2.1.

And in an older woman, I would start with the lower dose because if she's been on no estrogen for many years, you don't find a shocker system because that might lead to feelings of breast tenderness, etc.

So I start low and let them build up gradually to the goal level of hopefully 80. And if you have osteoporosis, you can reverse osteoporosis. I see 12% increase in bone mineral density over four or five years.

In many women, there is no medication that can do that for bone density. And bone density is very important. If you're over 70 and you have a fall, your risk of death is profoundly elevated because that fracture results in immobilization.

When you're elderly, immobilization is tragically dangerous. Yeah, very good point. Now, what about any sort of

postmenopausal bleeding? Do you see bleeding with people who are going back on?

So I know that's that scares people. Yeah, I checked women's history. If they've had a history of fibroids or heavy bleeding, anything like that, you want to check their have them have a pelvic exam and a pelvic sonogram to see.

Because if you're looking at if you're looking at uterine fibroids, that project in the inside of the uterus, the chance that when you give estrogen, you're going to get bleeding is is much, much higher.

So you do run into that problem. Some women are prone to develop polyps on the inside of their uterus when you give them estrogen. And those will also bleed.

And so you need to be very careful to keep the in some of those women, if you give a high enough dose of progesterone, that will balance it out and they will not have bleeding.

But yes, bleeding is a problem. And you do need to worry about bleeding because over time, if there's too much estrogen for the level of progesterone, you have this imbalance in the lining of the uterus called the endometrium will grow.

And if it grows excessively, that hyperplasia, hyperplasia can turn into dysplasia. Dysplasia can turn into a form of uterine cancer and endometrial cancer.

So you need to watch for that and you need to be conscientious and careful about that. And when women have bleeding and there's not a good explanation for it, they need to have a full evaluation.

Okay. Very helpful. And then you already indicated you would continue this basically for the life of the person who has at least for the person who has cognitive decline and for someone presumably that you're treating, you know, bone density issues, cardiovascular issues, things like that.

All right. What do you do about so you've talked a little bit about where you want the estradiol to be. Where do you want the progesterone levels to be?

Yeah. Again, I want to say that, you know, the same amount of estrogen with the same amount of progesterone can give different results in different women.

Right. So you have to measure most gynecologists who treat with post-menopausal hormones. They never measure hormones. I always measure periods. It's instructive and it's helpful to know.

And by the way, I want to mention the benefits of progesterone, calmness and sleep. In most women, sleep onset is improved, deep sleep can be improved in, duration of sleep can be improved.

So many women love their progesterone for that reason. So you have to match the progesterone level to the estrogen level. And the medical literature is very unhelpful in this regard because again, because gynecologists don't measure it.

So, you know, they typically will give X dose of estrogen and progesterone, but not, you know, but not know what the blood levels are, what the serum levels are.

Progesterone Delivery, Cycling, and Side Effects

So over the years, I've come up with my own safe evaluation because you want that if your estrogen is around 30, it's a good rule is if your estradiol is 30, you want your progesterone to be at least two.

If you're if your estrogen is 40, you want your progesterone to be at least three. And you can just go up like that because each level and that's a crude measurement, it could be an 80 anastrozole, 86 or seven is probably going to be fine.

The nerve protection and then 100, which is where I keep my estradiol and what Phyllis Gersh and O'Keefe recommend in their paper on cardiovascular benefit, they say keep the level at 100 or at least at 50 to get cardiovascular benefit.

It's a very good it's a very good paper that reviews a lot of what I'm reviewing here in terms of the right hormones versus the wrong hormones. But that's that's where they recommend keeping the stridor level in women who tolerate that.

If you run into bleeding or breast tenderness or other issues, you might have to drop drop back a bit. By the way, for breast tenderness we usually treat with iodine, there's usually an iodine deficiency.

Iodine works extremely well. I'll drop the estrogen back for a little bit, build up the iodine level, then gradually go back up on the estrogen. So there are three different ways that I prescribe progesterone.

It can be given orally. That's the most common because it's easiest and there is orally available commercially available progesterone trade name permit trim but they're generics now the problem with it, it's only in the dose of 102 hundred.

Those work for many women, one of those two doses. But for some women, they need a different dose, a little bit lower or quite a bit higher sometimes.

And then you can use an oral compounded progesterone. There's a small group of women who have a bad reaction to oral progesterone. It's complicated to explain why, but it has to do with the fact that progesterone in the brain transforms into a pregnant loan, and that binds to the gabbar receptor.

And that's why in most women they get calmness and improved sleep because GABA is a calming neurotransmitter. But in some women they have some kind of difference in their gather receptor, some genetic alteration or some certain kind of alteration, and they get a lower mood or irritability of patients.

Call me, they say, I want to strangle my husband. I have no reason. He's a really nice guy. I'm just really, really crabby. And that is often the progesterone problem.

I switch them either to transdermal or vaginal suppository. Vaginal suppositories work the best for that kind of reaction to progesterone because apparently you get much less aloe pregnant women in the brain.

I don't know absolutely for sure. But there's a vast literature on this in the Scandinavian medical literature. So most of the time, if you switch to bad, you know, in those women it's about 8% in my practice book, call me and say I hate this progesterone, right?

Usually you can get a benefit from from using one of those other two deliveries. Okay. So there are some claims that say, well, it's the estradiol that really seems to help the Alzheimer's and the progesterone doesn't seem to enhance the effect, in fact, may mitigate the effect to some extent.

So the question is, do you cycle these or do you keep them together at all times? How do you approach this? Some women are three weeks on, one week off.

Some people believe that, you know, because before menopause. Yeah, the way that our cycle works, the way that a female cycle works is that you only make progesterone for the second half of the cycle.

So some people theorize and it may be true that you get better progesterone receptor sensitivity, you get a better response to progesterone if you cycle it on half the month in off half the month.

And that works for some women. The problem you run into is that some women will have spotting or bleeding every time they go off. That's a classic progesterone withdrawal in post-menopausal women.

I'll tell you, they do not want to have bleeding. They feel they're done with that and they want to be done with that. So that's the problem. It's a little better.

You have a lot less likelihood of that if you do three weeks of progesterone and one week off. So we do that sometimes. But many women want to be on the progesterone every night because of the sleep benefits.

Right. Right. And so that's a reason why in many of my patients, maybe 75%, even 70, 75%, they're on it continuously and they do well. Medroxyprogesterone the progesterone that was used in the Women's Health Initiative study, and that was the progesterone that was used from the late sixties until the Women's Health Initiative study changed everything.

Medroxyprogesterone was what was used to counteract the uterine effects of estradiol right that caused many women to have irritability and depression, by the way.

So the women who did continue on their hormone therapy in those days were generally women who would tolerate in the doxy progesterone well, or they'd had a hysterectomy, so they didn't need to take medroxyprogesterone and they just took estradiol.

And by the way, back in those days, women who were on estradiol alone, there were many, many studies showing benefit, showing a decreased risk of dementia on oral estrogen.

But the difference those women were almost all started on the oral estrogen at the time of menopause. Right. And so there's there's a meta study analysis, 29 studies showing benefit, cognitive benefit in women that was published in the late 1990s.

I mean, just after the published especially there's some studies on all the women were, you know, average age and women were 70 in the sub studies conjugated equine estrogen and the doxy progesterone.

The problem the reason why later use of conjugated equine estrogen is so bad is that when you have no estrogen for ten years, 15 years, you develop black estrogen protects you from the development of coronary and cerebral artery disease because of its many benefits.

Right. But if you're off estrogen for many years, then you've developed an ordinary and cerebrovascular disease and then you give oral estrogen, which increases clotting and increase it increases fibrinogen and increases INFLAMM by increasing C-reactive protein.

Transdermal Absorption and Estradiol Adjustments

Those two negatives are very bad for older women, and that's why there's this belief that no older women should get any hormone replacement. And I think that is a very unfortunate general overall generalized statement.

If you give transdermal estradiol, you have no increase in inflammation, CRP is on unchanged and you get no increase in fibrinogen. There's multiple studies that show that.

So that's why, you know, the evidence and the people like groups like the U. S. Preventive Health Services Task Force says, you know, don't give these don't give hormones.

You know, do everything you can to avoid them. Yeah, absolutely. So you're one of the very first patients I saw, you know, way back in 2012. 2013 was a woman who started doing pieces of the protocol and she was clearly getting better a little bit with each thing.

And then when she she got her HRT optimized, which she, you know, she really had a big leap. She she noticed the difference, like, wow, that was the thing that affected me the most.

But then after about a year, she came back and said, you know, something's going backwards again. I don't know

what's going on. So we started talking about like what's happened to her.

Well, it turned out that she had been switched from transvaginal delivery of estrogen estradiol to transdermal, and her level on transdermal was zero.

So the question is, do you see people where transdermal is just not getting absorbed very well? Yeah. Yeah. I mean, some patches don't work very well.

You know, a lot of a lot of physicians like to use the patch and certain patches on certain people. Some women skin absorption varies. That's why I say you can't rely on X Dose is going to give you X level.

Right. And yes, I certainly do have that experience where I switch some women, we just cannot get a good level and we switch them to a vaginal application of estradiol and right back up.

Absolutely. Absolutely. I don't usually need to do that, but sometimes you do. Sometimes you can just increase the sometimes you know, you have to talk about how to put it on and how long to rub it in.

And, you know, there's there's these various things that can be amiss for someone. You know, they they put it on just very casually and then they put a shirt on over it.

And, you know, they have very little exertion. So, you know, there's all these little problems that need to be solved absolutely, constantly and continually.

But, yes, doing doing a trans badge application, there is incredibly good absorption in that tissue. So you do get a very good level that way. Right. All right, then last question here then, would be what about testosterone in men?

Have you seen and and do you deal with that? And have you seen improvements in cognition when you use that as part of an overall protocol? Well, let me first just say, I use testosterone in women, too, even though in the United States there is no commercially available testosterone product for women.

By the way, in Europe and in Canada, there is a commercially available product dose for women. In the U. S. It's held up for reasons that really don't make any sense. But and women benefit from testosterone in terms of libido, muscle, muscle growth, you know, especially if you're doing a strength workout, you can benefit from that.

Yeah. So, yes, I have male patients who benefit tremendously from testosterone. There is commercially available testosterone for men. It's tremendously expensive.

So I often use compounded for men because it's much more reasonably priced and there's a certain kind of form formulation of testosterone in a compound called attributes that gives very good absorption in men, particularly good absorption.

Testosterone in Men and Women

It's only available from some compounding pharmacies. So yeah, I certainly see men who have benefits in terms of mood libido. A lot of times men come for testosterone because of of sexual dysfunction or wanting to improve their libido.

And it doesn't prove that, definitely. But the biggest change that men report to me is improvement in mood. I had a patient who told me, you know, he just really hated his job.

He was, you know, everything irritated him at work. He was irritated with all his coworkers, etc., and jobs just boring him. Death. He got on testosterone.

We got his free testosterone level up to 12 or 13. And he completely changed his attitude towards his work. He was engaged. He liked it again. He was finding interesting new avenues, etc., etc..

And of course, his wife was thrilled because she didn't have a crabby guy around the house all the time. So, you know, we see certainly a lot of benefits for men.

Certainly there's bonus strengthening benefits, muscle strengthening benefits that it is worse. Androgens have a history. The synthetics are being abused for certain muscle building.

But you know, in the doses that we use, you know, somewhere around 50 milligrams, etc., the best delivery system, by the way, for just throwing in men is actually to give a subcu injection.

There's a commercially available testosterone subunit that is very you can use a tiny needle, a tiny syringe, and give a subcu injection twice a week.

Small, very small injection. And I find that that is actually the best we get the best results with that. So men don't want to give those injections and we do use the topical testosterone as well, especially for older men, you know, really older guys who don't want to deal with, you know, putting a needle into a little vial and drawing it out, etc..

But both both work, both are effective. And I would be remiss if I didn't ask about people who come and say, well, look, I'd like to go on estradiol, you know, be HRT, or I'd like to go on testosterone.

But I have a history of a hormone sensitive cancer in the past, and I seem to be fine now, but I'm concerned breast cancer, uterine cancer or prostate cancer or what have you, what do you recommend to them?

So most women who've had breast cancer have careful follow up. And you know, before I put any women on hormones, I do insist that they have a mammogram or a new technology that's available.

Really, I think only here in the Bay Area now, which is a 3D sonogram by QT health. And I'm hearing that there's another company that's doing 3D brands now that I'm looking into, but QT breast health will eventually be known around the rest of the country, hopefully, and people will have that as an option anyway.

You have to be conscientious about your follow up and taking care about breast health. I do not believe that estrogen the top of the estradiol or real progesterone increases the risk of breast cancer.

But I cannot say that for absolute certainty in every woman. So we have to be conscientious and careful. So I would yes, certainly I would put a woman who has post breast cancer on hormone therapy after the appropriate treatment has been completed.

And she's had a good study and is cleared by her breast.

Hormones After Cancer and BRCA Considerations

And I have oncologists who I work with who are okay in certain cases within a year of treatment to restart women on hormone therapy carefully and with careful follow up.

I see cancer depends on what how complete their treatment was for prostate cancer. I would want to talk to their oncologist, their urologist, etc., to clear them for testosterone therapy after prostate cancer.

As you may know, higher testosterone levels in general correlate with a decreased risk of prostate cancer. Certainly, if your PSA goes up quickly, that's a dangerous signal and you need to be evaluated for prostate cancer.

But in General, a lower prostate, a lower testosterone level correlates with an increased risk of of prostate cancer and a higher level, a decrease risk.

All right. So hopefully that that answers your question to some degree. It's a long that would be a long topic. Yeah, I do have one brca, one positive patient.

I do want to mention this. Who both her mother and her sister have had breast cancer. She's been with me for 19 years on hormone therapy. Wow. She Found out 12 years ago that she had the BRCA gene when her sister developed breast cancer premenopausal.

Then her mother got tested. They're both cancer survivors. Their mother and her sister, she wanted to stay on her hormones. And now she's she's followed appropriately by a team that follows BRCA, a women.

She has a MRI alternating with a mammogram every six months, but she stayed on hormone therapy. She's cancer free. And she's she's very aware and very happy with the benefits and the therapy.

So, you know, and I tell her at all times, it's totally her whether she wants to continue or not. But, yeah, it's an interesting case. Absolutely. I mean, one of the most fascinating epidemiologic article studies I read was the claim that BRCA was is a, of course, an important risk factor for breast and uterine cancer.

But if you go back to the late 1940s, the old the old literature and, you know, before BRCA was discovered, if they actually recover samples, they can show that these people who actually had BRCA mutations were not at increased risk earlier.

And so, you know, something changed. It's not of course, it's the interaction of the genetics with the environment. And if you change the environment, the genetics don't have the same impact on you that they did before, which I thought was fascinating.

So, all right. This is fantastic. Thanks so much, Dr. Ann Hathaway. Thanks so much for being part of the reverse Alzheimer's Summit. Great to talk with you as always, and great to hear your expertize as always.

Yeah, I really enjoyed talking with you about this. Thank you. Thank you.