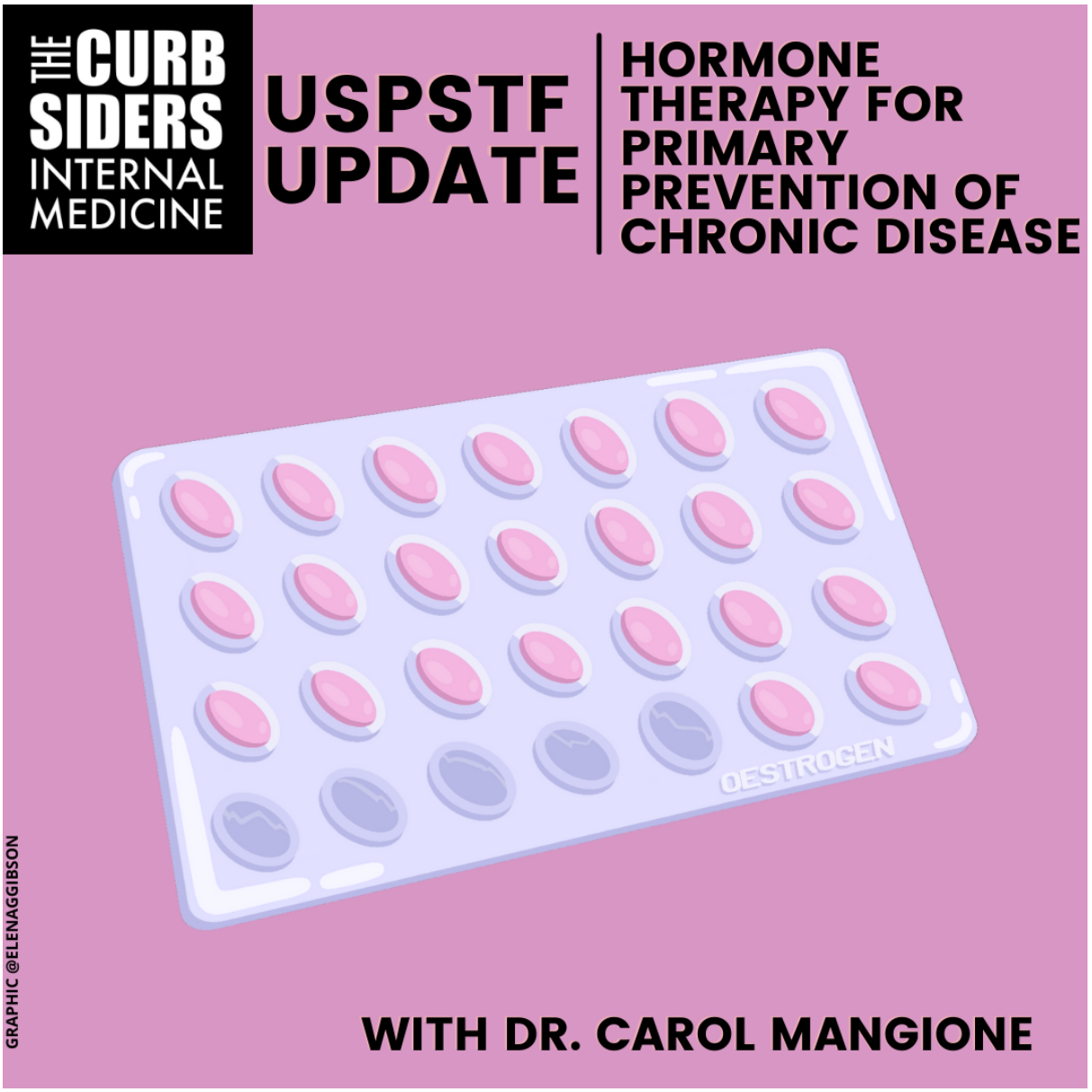
#376 Hormone Therapy for Primary Prevention of Chronic Conditions in Postmenopausal Persons - a USPSTF update with Dr. Carol Mangione



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[Curbsiders theme playing]

Paul: Welcome back to the Curbsiders. I am Paul Williams. Watto is not here. This is another one of our special USPSTF recommendation episodes and I am joined, as always, by my amazing cohost, Dr. Elena Gibson. Dr. Gibson. How are you?

Elena: Lovely. How are you? [Paul laughs] I had that energy.

Paul: On tonight's episode, we discuss the updated USPSTF guideline with Dr. Carol Mangione. This guideline specifically is about the use of hormone therapy for the primary prevention of chronic conditions in postmenopausal persons. We're going to tell you a little bit more about the guest and maybe tease some of the points that we learned. But before I do that, let me remind you what we do. We are The Internal Medicine podcast who use expert interviews to bring you clinical pearls and practice-changing knowledge. And now I will throw the mic, you know that's not the right way to say it.

Elena: Pass it.

Paul: [chuckles] I will turn the mic over to Elena. Tell us about a little bit more about what we talked about and who we talked to.

Elena: Thanks, Paul. We have a fantastic conversation about hormone therapy for primary prevention of chronic conditions such as cardiovascular disease, fractures, cancer, and postmenopausal persons with our guest, Dr. Carol Mangione. Overall, the potential risk of hormone therapy to prevent chronic conditions and postmenopausal persons outweighs the benefit. We'll get into more of those details in the episode. So, a little bit about Dr. Mangione. She is the Chair of the U.S. Preventive Services Task Force and the Chief of the Division of General Internal Medicine and Health Services Research. She holds the Barbara Levy and Gerald Levy endowed chair in medicine and is a Distinguished Professor of Medicine and Public Health at the University of California, Los Angeles. And the Executive Vice Chair for Health, Equity and Health Services Research in the UCLA Department of Medicine. Wow. She is an impressive educator and clinician.

Paul: Yeah, it's always like start the episodes by feeling bad about myself, [Elena laughs] but unless you have a pun.

[crosstalk]

Elena: You're Paul from Twitter.

[laughter]

Paul: Yes, that’s right. Very niche fame. Any puns for us for this one?

Elena: Oh, no, I'm not punny.

Paul: I'm putting on the spot. No is no cancer.

Elena: Oh.

[laughter]

Paul: Well, with that, we will start the show.

Hi, Dr. Mangione. Thanks so much for agreeing to talk to us about the new USPSTF recommendation. We're really excited to have you here. But before we get started like we always like to do, we'd like to get to know you a little bit better first. So, I'm wondering if you could just share a one liner about yourself, just telling us who you are and maybe including something outside of medicine that you're interested in.

Carol: I'm Carol, and thank you, Paul, for inviting me to be on Curbsiders tonight. I am a general internist, a Bruin. I practice at UCLA, and I have for a number of decades. When I'm not seeing patients or doing research or working with the Task Force, I'm watching a lot of NBA basketball.

Elena: Nice. Who's your team?

Carol: Sadly, Lakers.

Elena: Oh, yeah. Not the year. I felt that was going to be my luck with the Jazz.

Carol: It may not be the decade.

[laughter]

Paul: Yeah, I don't follow closely enough to know if should be offering condolences or not. It's living in Philadelphia, it's such a banana sports town. I can tell how the teams did just based on traffic and the commute and how people are driving. I'm not sure if it's the same there or not.

Elena: It's like the emotional feeling of the city. [laughs]

Paul: Yes. Marginally more angry than normal. [laughs] [crosstalk] -how things went. We're here to talk about the newer recommendation or actually the updated the recommendation or at least regarding hormone therapy for the primary prevention of chronic conditions imposed menopausal persons. So, to do that, I think, as we always do, start with the case. And, Elena, why don't I let you talk us through our first patient, what we're going to do for her or to her.

Elena: The first case today, Judy, she's a 52-year-old woman. She's coming to the clinic for a follow up. She went through menopause last year and wonders if she should be started on hormonal supplements to prevent fractures, as she knows a friend who has osteoporosis and takes supplemental estrogen and progesterone. So, thinking about Judy's case, why is hormone therapy for primary prevention of chronic conditions like cardiovascular disease, cancer, and fractures being considered by the USPSTF.

Carol: Right. I think the important thing is when you think about taking hormones, you have to have a really holistic view of it. Hormones might help you to prevent one chronic condition, but if it's making a bunch of other chronic conditions more likely to happen, you really need to take that net set of conditions. In the Task Force's hands and going over this topic, we really felt that the potential harms for Judy, would cancel out the potential benefits. So, Judy's friend's doctor is right. People who take hormones are less likely to get fractures, but that needs to be balanced against all of the things that are more likely to happen.

When taken in the balance and we'll get into this, what you're going to see is that for women or people who take combined estrogen and progestin, the moderate harms include increased risk of invasive breast cancer, stroke, venous thromboembolism, dementia, gallbladder disease, and urinary incontinence.

We know there are a lot of other safer approaches to prevent fractures. So, when taken together, the potential harms really cancel out the benefits. We wouldn't be telling Judy to start hormones.

Paul: Yeah, I do want to talk about all the various conditions that were looked at and how that was parsed out. But before we even get there, can you speak to a little bit about the types of hormone therapy there that were considered when updating this recommendation?

Carol: Absolutely. There's one large longitudinal study that really provides most of the evidence that we know about the benefits and the harms of taking hormones after menopause, and that studies the Women's Health Initiative. It used two hormones, one called Provera, which is medroxyprogesterone, and the other called Premarin, which is conjugated estrogens. Most of the evidence base that we have is really about those two preparations.

Elena: So, no local hormone therapy was considered?

Carol: We did not look at the evidence in terms of topical hormone therapy. If you're thinking about vaginal estrogens or estrogen patches, the amount of data or information on the benefits and harms of those preparations is really relatively small at this point.

Paul: But I guess that raises the larger point about who this recommendation is for, because we're not talking about actually treating symptoms of menopause. Specifically, we're talking about prevention of chronic diseases. So, I just want to make sure that I'm clear in terms of the recommendation that this applies to are patients who are postmenopausal, but you're trying to prevent certain disease states and not addressing symptoms like perimenopausal symptoms, things like the vasomotor symptoms or other symptoms like that. Am I understanding that correctly?

Carol: Yeah, you're absolutely right. Our current final recommendation is really that the USPSTF recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal persons. We give that a grade D like dog because the harms really cancel out the benefits. The second part of the recommendation is that we recommend against the use of estrogen alone for primary prevention of chronic conditions in postmenopausal persons who've had a hysterectomy, and that's a D recommendation also.

Now you asked about the management of perimenopausal symptoms like hot flashes, insomnia, things that happen early in the menopausal phase, and hormones are highly effective for treating those. If you look at the recommendations of other groups such as the American College of Gynecology, what you see is that they recommend that you use the lowest dose for the shortest amount of time to manage those symptoms. That's a whole different story than what the Task Force is looking at.

We're really looking at the long-term consequences of being on hormones in terms of your risk for specific chronic conditions.

Elena: And I think one thing, the term chronic conditions is really encompasses quite a lot of different diagnoses or potential outcomes. I wonder how did the USPSTF decide what to focus on or was it just a consequence of what there was evidence for?

Carol: A lot of it is what there is evidence for. In the Women's Health Initiative in particular and their longitudinal follow up, they had specific chronic conditions that they were interested in tracking and understanding. One of the big motivators for the Women's Health Initiative in

the initial design stage and implementation was that from observational data. It looked like taking hormones actually prevented cardiovascular disease. But then once we did a randomized trial, what we found was that there was no beneficial effect on the risk of coronary heart disease. This really emphasizes how important it is when trying to understand the long-term benefits and harms of a therapeutic to have well designed clinical trials and adequate numbers of people for adequate numbers of years to be able to get an unbiased answer.

Paul: We talked about this before we got started and I think our listeners, and even if they're not, I am in particular interested in the inside baseball discussions that kind of go into recommendations like this. I guess the first question I have is you talked about the outset. This is a D graded recommendation because the harms outweigh the benefits. But when you're looking at a multitude of conditions, so it looks like the benefits might be nebulous in terms of cardiovascular disease prevention, but then also fairly good for-- maybe fairly good is overstating, but maybe some benefit with osteoporosis. But then the downsides are gallbladder disease, which wasn't even on my radar.

I guess my question is how do you make the ultimate determination whether there is net benefit or net harm, when you're comparing all these different disease states and potential disease prevention benefits, I guess, what does that discussion look like and how do you ultimately decide the harms outweigh the good or vice versa?

Carol: Task Force always commissions an evidence review and we go to some of the very leading experts in putting evidence together for us. Not having a benefit on cardiovascular disease is not nebulous, Paul. It is clear that there's no benefit. That's why we would not recommend taking these for that purpose.

Now, we know both from observational data and from other studies that there were certain conditions that one could hypothesize might be hormone sensitive, like things like osteoporosis. I mean, if you just look at the natural history of osteoporosis, it is a condition of postmenopausal persons for the most part. Not that men can't get it, but they get it at a much older age and lower rate. There were conditions that the Women's Health Initiative was right sized for, to have adequate power for and length of time for, to study.

Among, if you say how did you pick what to include, a lot of it is what is in the evidence space, beyond the Women's Health Initiative too. But I think that study dominates for a lot of looking at chronic conditions. What is there that we know about benefit? We know that there is moderate benefit for reducing fractures. We also know that for the combination of estrogen and progestin that there is small benefit for reducing the risk of diabetes and colon cancer. There are a lot of safer choices if you want to reduce those risks. You really don't have to turn to hormones for the small benefits there.

And then in terms of harms, we know that there are moderate harms. When you think about the Task Force and how do we get to a grade, what we do is we look at the magnitude of harm or benefit, and then we look at the certainty of that estimation. It's a combination of both the magnitude and the certainty that gets us to a grade.

So, we know that the harms are moderate for increasing invasive breast cancer, for people who take both progestins and estrogen, and for stroke, for venous thromboembolism, for dementia, for gallbladder disease, and for urinary incontinence. We're not kind of using an I recommendation here. What is an I? An I means that the Task Force has insufficient evidence to recommend for or against using a therapy. In this situation, we don't have insufficient evidence. We have clear evidence about certain harms or increased probability of chronic conditions. We have clear evidence about some benefits too. But when you net that out, basically we decided that the potential harms really canceled out the small benefits.

And again, when you think about those domains where the benefits are, we have better approaches. There are a lot of things that people can do to preserve their bones as they're getting older. For people who have osteoporosis, we have good medicines to prevent fractures and they don't carry the burden of causing all these other problems.

Paul: That's really helpful, and I feel kind of dumb because that's the piece I was missing. I'm like, "Well, if there's kind of benefit, then how are they making the determination?" But you're right. We have other tools that don't carry the same risks and why not just use those. Which should be obvious to me, but it was not. But it makes sense. That was part of the calculus.

Elena: Yeah, I agree that's helpful. And certainly, part of it is to your point, what other prevention tools or treatments are available and not necessarily that the outcome itself. I'm sure that comes into consideration, like how severe is the potential harm, but also is there anything else you can do to prevent it. I think to that point, there was some discussion in the review of evidence and then also in the recommendation about any difference in the benefit or harms based on the age at which hormone therapy was started for postmenopausal persons. It seemed like at this time there wasn't enough evidence. Could you speak to why that was included or what the thought is behind that?

Carol: There have been some small studies and there certainly have been a lot of opinions written that maybe hormones are very safe and good for you if you start them right when menopause happens and you only take them for five years or you only take them for seven years. But we really don't have those comparative effectiveness studies with the kind of long-term follow up that one would need to tell if you're increasing or decreasing major chronic conditions. Whenever we see a big evidence gap like that in the recommendation, we make a call for future research. And certainly, this question about starting time, stopping times, duration, there just isn't much evidence to support a strategy at this point.

Paul: That's helpful. And I guess another question we like to ask whenever an update of a recommendation comes out is what prompted it. It sounds like sometimes just enough time lapses that it's time to do it, and other times new evidence declares itself that prompts the review. What was the rationale behind addressing this particular topic at this particular time?

Carol: I think important topics like hormone replacement need to be revisited. In general, the Task Force likes to revisit things on about a five-year schedule, though oftentimes if there is a new big clinical trial or if there's an older clinical trial that identified more harms longer term or more benefits longer term, that would make us want to revisit it sooner.

When we think about this recommendation, we had longer term follow up from the Women's Health Initiative, but I would say that our recommendation is very consistent with what we said in 2017's final recommendation. And, again, after reviewing the marginal increased evidence, we found that the potential harms of using hormones for primary prevention of chronic conditions and people who've gone through menopause canceled out the benefits. It's a similar story or to what we said in 2017, but there was longer term follow up and there were a few more studies to look at.

Paul: That's great. Yeah, I think one of my favorite things about doing the series with you nice folks from USPSTF., I think this came up in the vitamin episode with Dr. Barry, if I'm not mistaken, where rather than taking these "negative recommendations" or these D recommendations, and as a mandate to not do stuff, actually use them as an opportunity to discuss the things that we can do to actually improve and promote health. Rather than leaning into the negativity, actually using it as a way to as a springboard to have a conversation about other more effective or more efficient health approaches. I just I think

that's such a helpful way to frame the discussions, as opposed to just saying, “Nope, we don't do that,” and just kind of closing the door. So that's terrific.

We've covered a ton of ground in a short amount of time, technical difficulties notwithstanding, but once we got going, just firing all the cylinders. So, this is extraordinarily helpful. I think it's a nice framework for a conversation that comes up with my patients, and it'll help me be a little bit better armed to have that conversation. I just want to thank you for your time and expertise and give you a chance to give any takeaway points or anything else that you'd like to emphasize before we let you go for the night.

Carol: Well, first of all, just thanks for this really wonderful opportunity. I guess my only take home point would really be whenever we think about the evidence and we think about the gaps, there are important things to always keep in mind.

One big evidence gap with the Women's Health Initiative is that it was a rather homogeneous group of people, and a lot of the people who have the highest risk for the conditions that we would love to prevent were not really included in very big numbers in that trial. You always want to take any evidence base with a grain of salt, and you want to pay attention to where we need new evidence. I would say we still need to learn a lot about the most effective ways to do primary prevention for all people at greatest risk.

[Curbsiders theme music playing]

Paul: So, Elena, that was extraordinarily helpful. I feel like we’re talking prerecording. This is just not something that I've considered very much. I guess I'm wondering I'm glad that this recommendation came out, because it kind of call of attention to a topic I've not really thought as much about as I probably should have. I'm wondering what has been your experience with this? Have you had conversations with patients about this?

Elena: Yeah, certainly. I think to your point, it's probably not something historically, I was curious how this, like, it came from somewhere, the thought to prevent chronic-

[laughter]

Elena: -and maybe I should know that, but it was a really good chance to see. Okay, so early on, there was thought that it would help prevent cardiovascular disease and some evidence there, and I do think I've definitely had patients ask about hormone therapy as a replacement to prevent health decline as they age and not specific-- I think fractures are something that's probably in the public knowledge because of osteoporosis. But then I think even beyond that, it's something I had before, and now why wouldn't it be helpful to replace that.

I think really pivoting the discussion to your point into how we can use this, "Okay, we haven't found it helpful for these reasons." Even though there was a small benefit for fractures and for diabetes in some patients. We have better ways to prevent that and to improve that risk. I think that was a really helpful way to frame the conversation to me.

Paul: Yeah, no, for sure. I think also the distinction between treating symptoms of perimenopause for which there is evidence, and using these medications to prevent chronic health issues, I think the discussion, at least in my head, got a little bit muddied and it was just like no hormone therapy for anyone. It just gets mooshed together and there are times when it's appropriate, but this is one of the instances where it is less than. We have other tools for prevention of disease, but it certainly can be used for the management of symptoms and other conditions. It's important to kind of tease those things out and think about what

you're actually using it for, which I think it was also helpful to kind of clarify and have that conversation with Dr. Mangione as well.

Before I let you go, I know we're trying to streamline these things but I feel like of all the people that we work with, I think your picks of the week are the ones I almost get the most excited about. Do you have anything for me this week?

Elena: Oh, yeah. So, I read it a book recently called *Red Plenty*. Have you heard of it?

Paul: No, I have not.

Elena: I'm trying to say Francis Spufford, and I might have said that incorrectly, but it's a very interesting Soviet Union fairytale is what they call it. But not fairytale in the sense that we would consider. It just kind of goes through multiple short stories of individuals living in the Soviet Union around the 1940s to 60s, kind of this idea of being plentiful. It's an interesting concept and a very well written novel.

Paul: Is it like historical fiction?

Elena: Yes.

Paul: Because that is very much my jam. All right. [crosstalk]

Elena: Historical fiction meets Soviet Union fairytale.

[laughter]

Paul: I thought [crosstalk] niche.

Elena: But not in the way that-- Yeah.

[laughter]

Paul: One more of those, but all right, I still give them a try.

Elena: Very good on audio, too. So, I recommend.

Paul: I will spare the audience pick of the week for me. Real quick, *Smile* is great, by the way. If you like horror movies [crosstalk] I got all the love this year, but *Smile*, I like very, very much. Very gross and scary. If that's [unintelligible [00:25:38] maybe enjoy that. Having said all that, let's go to the outros. I will now say this has been another episode of The Curbsiders. Bring you a little knowledge, food for your brain hole.

Elena: Yummy.

[laughter]

Paul: That’s not the right level of enthusiasm for that. Get your show notes at *thecurbsiders.com*. And while you’re there, sign up for our mailing list to get our weekly show notes in your inbox plus twice each month you’ll get our Curbsiders Digest which recapping the latest practice-changing articles, guidelines and news in internal medicine.

Elena: We're committed to high-value practice-changing knowledge and to do that, we need your feedback, so please subscribe, rate, and review the show on Apple Podcast or Spotify or email us at *thecurbsiders@gmail.com*.

Paul: I think that's been updated to *askthecurbsiders@gmail.com*, if I'm not mistaken.

Elena: You're correct.

Paul: Okay, great. Which is is Watto's personal email address. Any specific questions you have or fashion advice, you can just email him there. A special thanks to our writer and producer for this episode, Dr. Elena Gibson, and to our whole team. The Curbsiders is produced and edited by the team at Pod Paste, who did especially our work this time around. Elizabeth Proto runs our social media, and Stuart Brigham composed our theme music. Until next time, I've been Dr. Paul Nelson Williams.

Elena: Elena Gibson here. Thank you and good night.

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