CLINICAL COMPENDIUM: REAL WORLD CLINICAL CASE STUDIES ON THE TREATMENT OF MENOPAUSAL SYMPTOMS: AN INTERACTIVE EDUCATIONAL ACTIVITY

Editor's Note: This is a transcript of a presentation on December 20, 2024. It has been edited and condensed for clarity.
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Case 1: Diagnosis

Helen Flores is a 49-year-old G_3P_{3003} patient (she/her/hers) who presents to the office with complaints of what she thinks are hot flashes. They happen 5-6 times a day and 3 or more times per night and wake her up from sleep. During the day, she must stop what she is doing to try to cool off until the symptoms pass. She had thought they would get better, but they seem to be getting worse. From what she has read online, she is not menopausal because it has only been 9 months since her last period, so she wonders if these are hot flashes. How should her clinician address her questions? What would you want her clinician to know?

1. **Which of the following is needed to diagnose menopause?**
   a. Determination of the date of her last menstruation
   b. Measurement of serum estradiol level
   c. Measurement of serum follicle-stimulating hormone level
   d. Measurement of serum luteinizing hormone level

Correct answer: a) Determination of date of last menstruation.

- Perimenopause and menopause are clinical diagnoses as there is no single biochemical test that is a reliable guide to an accurate diagnosis.
- Natural menopause is defined as 12 consecutive months of amenorrhea with no other etiology.
- Elevated FSH (>30 mIU/mL) with concomitant low serum estradiol indicates the absence of negative feedback as occurs when there is low ovarian reserve.
- Average age of onset of perimenopause is 46 years; range 39 to 51 years for 95% of women.

Faculty Commentary for Question 1

Genevieve Neal-Perry, MD, PhD: When you are thinking about and trying to understand how to make that diagnosis, in terms of whether it's perimenopause vs menopause, remember that a diagnosis of menopause is a retrospective process. Basically, the last time someone had a period was a year ago, then that would be considered menopause, providing they are not taking any medications that might interfere with their menstrual cycle.

In someone who hasn't had a period in a year, and they are symptomatic, certainly that's menopause. In someone who should still have periods, meaning they've had a period in the last 3 months, the last 6 months, it's going to be varying degrees of perimenopause, whether it's early or late. If they are still having periods, that's all perimenopause and if they are having symptoms that do warrant treatment or at least a discussion about how to manage those symptoms.

On occasion, when I have patients referred to me, I have them referred because their primary doctor or regular doctor did a test, and they would do a test that involved a follicle-stimulating hormone (FSH) level and then they would send the patient to me because the patient had an elevated FSH. Now, it's important to understand, when you are talking about an FSH as part of that evaluation, part of that diagnostic testing, you cannot interpret an FSH without an estradiol. If you order an FSH, you must always order an estradiol. If you have a low estradiol and a high FSH, that tells you that there is an absence of negative feedback and that is what you see when you have a low ovarian reserve, or no follicles left.

The reason that's important is because, remember, when you have a luteinizing hormone (LH) surge, you also have an FSH surge and the way that you distinguish that—an elevated FSH value that's related to positive feedback or negative feedback—is by the estradiol level. Don't forget that. It's so important and it's something that is commonly forgotten.

When we think about the average age of perimenopause, it's about 46 years. It ranges anywhere from 39 to 51 years. It tends to be younger in women of color, African American women. They may start in their early 40s, and with that in mind, sometimes women of color, Hispanic women, African American women, will present in their early 40s with these symptoms and they are often dismissed. Keep in mind that, while the average age is 46 years, there's a range anywhere from 39 to 51 years and people of color are more likely to present to you at that earlier age range with symptoms that are related to menopause.

Reference:

Sarri G, et al. Diagnosis and management of menopause: summary of NICE guidance. *BMJ*. 2015;351:h5746. doi:10.1136/bmj.h5746

2. What percentage of women who experience menopause have moderate-to-severe vasomotor symptoms?

a. 16%
b. 36%
c. 46%
d. 76%

Correct answer: c) 46%

- An observational study of 255 women in the Penn Ovarian Aging Cohort showed the peak prevalence of moderate-to-severe vasomotor symptoms reached a peak of 46% in the first 2 years following menopause.
- Vasomotor symptoms are described as mild, moderate, or severe
  - Mild (sensation of heat without sweating)
  - Moderate (with sweating but able to function)
  - Severe (cannot continue regular activities)
- The Study of Women's Health Across the Nation (SWAN) reported the median duration of vasomotor symptoms as 7.4 years.
  - Women who have frequent vasomotor symptoms early in the transition (during premenopause or early perimenopause) had a longer duration (11.8 years).
  - Race and ethnicity contribute to the average length of symptoms.
    - African American - 10.1 years
    - Hispanic – 8.9 years
    - Non-Hispanic White – 6.5 years
    - Chinese – 5.4 years
    - Japanese – 4.8 years
  - Other risk factors that impact the length of vasomotor symptoms
    - Longer duration
      - Current or past smoking status
      - Perceived stress
      - Higher symptom sensitivity
      - Lower education level
      - Symptoms of depression at first report of vasomotor symptoms
    - Shorter duration
      - High body mass index

Faculty Commentary for Question 2

Genevieve Neal-Perry, MD, PhD: Moderate-to-severe vasomotor symptoms are the ones that we consider to be disruptive. And they are one of the most common symptoms that women have who are in perimenopause or menopausal transition. In fact, depending on what you read, it's anywhere from one-third to nearly one-half of women who present with bothersome hot flashes. What is a bothersome hot flash? What does it mean to be mild or what does it mean to be moderate or severe? If someone is having a mild hot flash, they feel warm, but it's not disruptive. They are able to do whatever they typically do. Whereas with a moderate hot flash, you break out in a sweat, and you can still function, but for some women it can be very embarrassing. And then there is a severe hot flash, and these are people where it interferes with their ability to do their work, to do the things they typically do because they have to literally stop in order to figure out ways to improve their symptoms and reduce the sensation of feeling warm and often having anxiety with that.

There are racial and ethnic differences in vasomotor presentation in terms of when they start, how long they last, and this is important because the duration and severity of hot flashes are a predictor of those who might have cardiovascular disease and other quality of life issues that can reduce the overall well-being of an individual.

From the Study of Women Across the Nation (SWAN), we know that the average duration of hot flashes is 7.4 to 7.5 years. And remember, that's an average which means that there are some people who are longer, some people who are shorter. And when we look at who's longer, who we find has the longest symptom duration are women of color. For African American women, the duration can be more than 10 years. Hispanic women can have symptoms for 9 years, for non-Hispanic Whites it's about 6.5 years, for Chinese and Japanese women it's somewhere around 5 years. So, there is a range in terms of the duration of the symptoms.

References:

Freeman EW, Sammel MD, Sanders RJ. Risk of long-term hot flashes after natural menopause: evidence from the Penn Ovarian Aging Study cohort. *Menopause*. 2014;21(9):924-932. doi:10.1097/GME.0000000000000196

Bevry ML, Stogdill ER, Lea CM, et al. Addressing menopause symptoms in the primary care setting: opportunity to bridge care delivery gaps. *Menopause*. 2024;31(12):1044-1048. doi:10.1097/GME.0000000000002439

Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med*. 2015;175(4):531-539. doi:10.1001/jamainternmed.2014.8063

3. Which one of the following processes most closely corresponds to the physiologic changes that occur during a hot flash?

a. Breaking of a fever
b. Anxiety
c. Allergic reaction
d. Prostaglandin release

Correct answer: a) Breaking of a fever.

- In women before menopause, the ventral hypothalamus sends pulses of gonadotropin-releasing hormone (GnRH) to the pituitary gland to stimulate release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) to direct the ovary to make hormones like estrogen from the follicles.
- The hypothalamus and the pituitary gland monitor the levels of estrogen in the bloodstream and adjust GnRH pulsing and LH and FSH release to match what is needed next in the cycle.
- Progressive lack of estrogen leads to the loss of negative feedback, leading to increased GnRH pulses and circulating FSH and LH levels.
- Loss of estrogen feedback leads to the activation of **kisspeptin, neurokinin** B, **and dynorphin** (KNDy) neurons, which then activate heat-sensing neurons.
    - If the temperature rises above the limits of the thermoregulatory zone, the body tries to cool down, using the same mechanisms it uses to break a fever:
        - Diverting blood from the warm core to the periphery
        - Dilating the peripheral blood vessels (flushing)
        - Perspiring to radiate off heat

Faculty Commentary for Question 3

Genevieve Neal-Perry, MD, PhD: Let's talk about what is a hot flash. If you talk to a patient about that experience, what they'll tell you is that it's a sudden onset of feeling warm, feeling hot and what is different about a hot flash as opposed to feeling hot when you are exercising is that sensation is typically from the chest up. It just involves the head as opposed to, if you are exercising, it involves the entire body. So, that is something that distinguishes a hot flash. It's very similar to what happens when you are breaking a fever. Suddenly, you feel hot and then when you break it, you sweat. It's a reflection of the thermoneutral zone shortening. Or another way to think about it is that the distance between shivering and sweating is reduced so that you become symptomatic when you otherwise would not. And this is what happens to women who have hot flashes.

We finally understand the biology of hot flashes which we did not understand for a very long time. We just knew that it happened, and that estrogen worked. We didn't really understand why. What we do know is that it involves unique neurons in the hypothalamus that respond to estrogen, and it is the loss of estrogen feedback or really wide changes in estrogen, going from a very high to a low level, that trigger hot flashes. We know that it's related to estrogen, and we know that it also impacts gonadotropin releasing hormone (GnRH) neurons and you know this even from your own practice. When you use leuprolide acetate, which is a GnRH agonist, to down-regulate for fibroid or to down-regulate for endometriosis, what it does is it reduces the activation of GnRH neurons, and this has an impact on estrogen and that estrogen will impact the neurons that trigger hot flashes. The same hot flashes that you may see when you are using leuprolide acetate are the same hot flashes that women who are perimenopausal and menopausal experience.

What are these neurons? These neurons are called KNDy neurons. They express 3 neuropeptides: kisspeptin, neurokinin B, and dynorphin. These neurons are located in the hypothalamus, and they project to areas of the brain that are important for thermoregulation. This area is also important for sleep, and it is the loss of estrogen feedback on these neurons that drives this whole process. And it's because of these neurons being activated and activating these other areas that triggers the hot flashes and causes the physiological changes that we see in a hot flash.

References:

Freedman RR. Pathophysiology and treatment of menopausal hot flashes. *Semin Reprod Med*. 2005;23(2):117-125. doi:10.1055/s-2005-869479

Khan SJ, Kapoor E, Faubion SS, Kling JM. Vasomotor Symptoms During Menopause: A Practical Guide on Current Treatments and Future Perspectives. *Int J Womens Health*. 2023;15:273-287. doi:10.2147/IJWH.S365808

Rapkin AJ. Vasomotor symptoms in menopause: physiologic condition and central nervous system approaches to treatment. *Am J Obstet Gynecol*. 2007;196(2):97-106. doi:10.1016/j.ajog.2006.05.056

Case 2: Treatment Options

Helen tells her clinician that she has done some online research and talked to friends and older family members. They all cautioned her to avoid menopausal hormone therapy (MHT) because hormones cause cancer and can make a woman bleed. She wants to learn about nonhormonal options available to her. She is working on her weight, trying to stop smoking and increasing her exercising, but the hot flashes just seem to be worsening. Having ruled out other causes of VMS, what nonhormonal options could she use and how effective would they be?

1. **Which of the following commonly used therapies is currently approved by the FDA for the treatment of vasomotor symptoms?**
   a. Black cohosh supplement
   b. Paroxetine 7.5 mg
   c. Estroven® menopause supplement
   d. Gabapentin 300-2400 mg

Correct answer: b) Paroxetine 7.5mg

- The only FDA approved nonhormone therapies approved to treat vasomotor symptoms in menopausal women are paroxetine mesylate 7.5 mg daily and fezolinetant 45 mg daily.
- Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, and oxybutynin have shown efficacy in reducing vasomotor symptoms.
  - Onset of action is typically 2 weeks.
- The North American Menopause Society's 2023 position statement on nonhormone therapy for vasomotor symptoms recommendations for medications are summarized as follows:
  - Recommended:
    - Fezolinetant
    - Oxybutynin
    - Serotonin-norepinephrine reuptake inhibitors (not pregabalin)
    - Selective serotonin reuptake inhibitors (not fluoxetine, sertraline)
  - Not recommended:
    - Cannabinoids
    - Clonidine
    - Soy foods/extracts
    - Supplements/Herbal remedies
    - Suvorexant

Faculty Commentary for Question 1

Anita L. Nelson, MD: Case 2, question 1, raises an important issue. As a clinician, I've been seeing patients for years, and I think we have been confused. Why do some things work, and other things do not work so well? As you looked at the choices there, I can remember the time that we did offer black cohosh because it seemed to work. A lot of therapies initially offered in the nonhormonal area were based on personal experience, and personal testimonials that people said, well, I used bromide, or I did this, and it worked well. But I think we understand today that hot flashes and many of the other things that women talk to us about, their symptomatology with menopause, are symptoms and they are very susceptible to placebo effects. And it isn't until we do the studies against the placebo that we can see evidence of efficacy. As we're looking at where the evidence is coming from, we know that you have to go against a placebo. We're asking women how many hot flashes or if they are comfortable, if they are getting enough response from their therapies. We're not actually putting a hot flash monitor onto their fingers to measure objectively what's going on. Based on clinical trials, the FDA approved paroxetine 7.5 mg and labeled it carefully for treatment of vasomotor symptoms which helped women feel more comfortable using it if they were embarrassed that maybe somebody thought that they had depression. Hopefully, that's something that's going away, but I have to tell you that, as I was using paroxetine in patients, that often times my patients would come back and call it their "happy pill." And it's just one of the serotonin selective reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) that we have evidence, strong evidence, that it is effective, and it is on the list of things, nonhormonal therapies, that the Menopause Society has endorsed in its 2023 recommendations. And those same recommendations also said we have evidence that there are some things that

don't work, and we really should not be promoting them and maybe even discouraging their use -the soy products, the over-the-counter supplements and herbal therapies- because the evidence is so very inconsistent. This wonderful resource that we have that gives us a measure of how effective different doses are and how to use each of the recommended nonhormonal therapies can provide a lot of value to clinicians.

Genevieve Neal-Perry, MD, PhD: Nonhormonal therapy is an important intervention for the management of hot flashes and one of the things that I do want to call out, particularly around the use of SSRIs, is that they don't work for everybody. And so it's important to listen to what your patient is telling you because SSRIs are sometimes metabolized differently, particularly groups where the metabolism is accelerated are African American

women, and so it may not work as well. Keep in mind that it doesn't work for everybody, so it's important to really get that feedback from your patients.

The other treatment that you would want to consider is gabapentin. It works fairly well. I will use gabapentin in patients who have pain, who may have chronic pain, who have hot flashes and in individuals who also feel like sleep is a big part of their concern. Gabapentin can also improve sleep for those individuals.

Reference:

"The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2023 nonhormone therapy position statement of The North American Menopause Society. *Menopause*. 2023;30(6):573-590. doi:10.1097/GME.0000000000002200

2. Which one of the following nonhormonal therapies for vasomotor symptoms should NOT be prescribed to a woman being treated with tamoxifen to reduce breast cancer risk?

a. Gabapentin
b. Oxybutynin
c. Paroxetine
d. Venlafaxine

Correct answer: c) Paroxetine

- SSRIs, such as paroxetine, inhibit the liver enzyme CYP2D6, which converts tamoxifen to its active metabolite, making it less effective.
- The following table lists side effects, cautions, and contraindications of recommended nonhormone medications:

Medication	Side effects	Cautions/Contraindications
Fezolinetant	Abdominal pain, diarrhea, insomnia, back pain, and hepatic aminotransferase elevation	• Do not begin if serum aminotransferase levels ≥ 2 times the upper limit of normal • Test serum aminotransferase levels monthly for the first 3 months, then at 6 and 9 months after initiation • Do not use in patients with known cirrhosis, severe renal impairment or concomitant use of CYP1A2 inhibitors
Gabapentin	Dizziness, drowsiness and impaired balance or coordination	• Black box warning for uncommon suicidal thoughts or behaviors
Oxybutynin	Dry mouth, urinary retention, possible cognitive decline	• Caution in using with other anticholinergic agents • Potentially inappropriate in adults older than 65 years due to cognitive impairment, risk of dementia or delirium
Selective serotonin reuptake inhibitors (SSRIs)	Nausea, dizziness, headache, sexual dysfunction	• Black box warning for uncommon suicidal thoughts in adolescents and children • Caution in patients with bipolar disorder, poorly controlled hypertension • Concurrent use of monoamine oxidase (MAO) inhibitors • Inhibits CYP2D6 (tamoxifen) • Neuroleptic syndrome • Serotonin syndrome • Withdrawal side effects with abrupt discontinuation
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Nausea, dizziness, headache, sexual dysfunction	• Black box warning for uncommon suicidal thoughts in adolescents and children • Caution in patients with bipolar disorder, poorly controlled hypertension • Concurrent use of MAO inhibitors • Neuroleptic syndrome • Serotonin syndrome • Withdrawal side effects with abrupt discontinuation

Faculty Commentary for Question 2

Anita L. Nelson, MD: Case 2, question 2 asks about drug-drug interactions. For women who are being treated with tamoxifen, either to reduce the risk of recurrence or for primary breast cancer, we definitely don't want to mix it with the SSRI paroxetine because of the interactions that will reduce the circulating levels of tamoxifen and render it less effective. There are a couple of other things that we ought to know about this group in general and I think this is a great time to chat about that. And that is that unlike what we see in the use of the SSRIs and the SNRIs for the treatment of depression, we see a very rapid onset of improvement with vasomotor symptoms. We will know within a week or 2 of starting her on a low dose whether that's adequate therapy or not. We don't need to wait the 6 weeks that we normally wait to see a response to depressive disorders. But if she doesn't respond to a low dose, we can increase the dose slightly and see what level we need to get to within a reasonable zone that will give her adequate therapy.

The other thing is that—very importantly for these drugs—please tell her not to stop cold turkey, don't suddenly stop taking it or discontinue it because that will bring on a whole syndrome, maybe introduce symptoms she never had before. We need to always make her plan ahead, make sure she fills her prescriptions on time and if she is thinking of discontinuing, to taper the dose over time. And you can give her guidance on how to do that. Those are very important.

Reference:

"The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2023 nonhormone therapy position statement of The North American Menopause Society. *Menopause*. 2023;30(6):573-590. doi:10.1097/GME.0000000000002200

3. Which one of the following nonpharmacologic therapies has a Level I recommendation from consensus guidelines to treat vasomotor symptoms?

a. Cognitive behavioral therapy
b. Exercise
c. Mindfulness-based interventions
d. Relaxation techniques

Correct answer: a) Cognitive behavioral therapy

- Cognitive behavioral therapy (CBT) has good evidence to support its use in alleviating vasomotor symptoms. (Level I recommendation)
  - The Menos 2 study was a randomized controlled trial of perimenopausal or postmenopausal women (N=140) who had at least 10 problematic vasomotor symptoms per week.
    - Randomly assigned to group CBT, self-help CBT, or no treatment
    - Primary outcome was the change in hot flash/night sweat rating (1-10) at 6 weeks
      - Adjusted mean difference for group CBT compared to no treatment was 2.12 (P<0.001)
      - Adjusted mean difference for self-help CBT compared to no-treatment was 2.08 (P<0.001)
- Clinical hypnosis has also been shown to reduce vasomotor symptoms frequency and severity (Level I recommendation)
- Weight loss may be considered to improve vasomotor symptoms (Level II-III), but there is insufficient evidence to recommend diet, exercise, cooling techniques, or trigger avoidance as a primary intervention.
- Mindfulness-based interventions (Level II), paced respirations (Level I), and relaxation techniques (Level II) on their own lack sufficient data to be recommended as treatment for vasomotor symptoms.

Faculty Commentary on Question 3

Anita L. Nelson, MD: Case 2, question 3 deals with the nonpharmacologic therapies that are in the Menopausal Society recommendations. Clearly, the correct answer here is cognitive behavioral therapy. It may not be available to every woman, but to realize its potential is quite helpful in that it can reduce the symptomatology that she suffers. There can be other interventions that are approved that may help reduce the suffering that goes along with this, including mindfulness-based interventions. Many of those other ones that we had suggested in the past now have been shown to be insufficient.

References:

"The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2023 nonhormone therapy position statement of The North American Menopause Society. *Menopause.* 2023;30(6):573-590. doi:10.1097/GME.0000000000002200

Ayers B, Smith M, Hellier J, Mann E, Hunter MS. Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial. *Menopause*. 2012;19(7):749-759. doi:10.1097/gme.0b013e31823fe835

Case 3: Hormonal Therapy

A woman diagnosed with menopause 3 months ago returns after low-dose SSRI did not provide her adequate relief from hot flashes. She also noticed a decrease in her libido. She wants more information about hormonal options. Is she even a candidate for hormones?

1. **Which one of the following patients would be a candidate for systemic postmenopausal hormone therapy?**
   a. A 52-year-old woman who smokes tobacco
   b. An otherwise healthy 62-year-old woman
   c. A 51-year-old with hypertension, dyslipidemia and a 10% chance of heart attack or stroke in the next decade
   d. A woman whose only complaint is painful intercourse due to vaginal dryness

Correct answer: a) A 52-year-old who smokes tobacco

- The 2022 position statement on hormonal therapy from The North American Menopause Society discusses several key points:
  - Hormone therapy remains the gold standard for relief of vasomotor symptoms and can reduce frequency by 75% compared to placebo.
  - For women younger than 60 years or within 10 years of menopause, the benefit-risk ratio appears favorable for treatment of vasomotor symptoms.
  - For women 60 years or older or who initiate hormone therapy more than 10 years from menopause onset, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, thromboembolism, and dementia.
  - After excluding open-label trials, meta-analyses of menopausal hormone therapy show a null effect on the cardiovascular system; consequently, benefits of therapy should be weighed against potential increases in risks of breast cancer, venous thromboembolism, and stroke.
    - The American Heart Association stratifies the risk of hormone therapy into 3 categories (with selected risk factors):
      - Low risk – recent menopause, 10-year atherosclerotic cardiovascular disease (ASCVD) risk <5%, low risk for breast cancer
      - Intermediate risk – 10-year ASCVD risk between 5% and 10%, high risk for breast cancer
      - High risk – congenital heart disease, 10-year ASCVD risk ≥10%, history of ASCVD, venous thromboembolism, or breast cancer
  - The risk of breast cancer related to hormone therapy is low, ie, <1 additional case per 1,000 women per year of hormone therapy or 3 additional cases per 1,000 women for 6 years if using combined estrogen and progesterone therapy
    - The Endocrine Society has recommendations based on breast cancer risk
      - Low – 5-year breast cancer risk <1.67% - can use hormone therapy
      - Intermediate – 5-year breast cancer risk 1.67% to 5% - use caution with hormone therapy
      - High – 5-year breast cancer risk >5% - avoid hormone therapy
  - Systemic hormone therapy is generally not advisable for women with a history of breast cancer
  - Hormone therapy has a neutral effect on lung cancer and smoking cessation should be encouraged.

Faculty Commentary on Question 1

Anita L. Nelson, MD: Hormonal therapy has really been shown over the decades to be the most effective first-line therapy for vasomotor symptoms and, of course, it offers relief of so many other menopausal symptoms. If a woman doesn't find that she got adequate relief or she had a side effect from nonhormonal or maybe she's just so symptomatic that she wants to jump to the most effective method that we have traditionally offered, then we do have hormonal therapy, either estrogen alone for women who don't have uteruses or estrogen with some progestin or some other compound to reduce the risk of endometrial hyperplasia.

Question 1 asks about the candidacy for systemic postmenopause hormone therapy and I think what's important here is that we are introducing the concept of the timing hypothesis. What we learned from the WHI (Women's Health Initiative) clinical trial is that issue of the safety in appropriate candidates for estrogen-containing postmenopausal therapy for women who are within 10 years of menopause or in their 50s, whichever is younger. If we look at some of the answers that we have, there is no contraindication to smoking and people get confused about that because, well I'm over 35 years old and I couldn't use hormone birth control pills, but I can take these hormones? And I think just explaining to them the difference in the potency of these drugs is important, and that it would be safe for her to use. Of course, we want her to stop smoking, but otherwise it's not a contraindication if she's otherwise healthy. And we can see the 62-year-old, healthy women couldn't start it because of the timing hypothesis, but I think it's important here to ask, what if she started when she was 52 years old and she's still needing the hormone? There's a difference here between initiation timing and continuation and we know from the earlier work that many women maintain significant symptomatology into their 60s.

When you say that she's a candidate, I think the beautiful thing of the latest recommendations from the Menopause Society is that they've given us a comprehensive tool that we have linked in the atherosclerotic cardiovascular disease (ASCVD) recommendations, and we can see what a woman's health is. And if she is low risk for cardiovascular disease in the next 10 years, then she is low risk for hormone therapy. If she is intermediate risk, she does smoke, as our lady did, then you are going to calculate her risk and see, with that in there, whether she might be a

candidate or not. It's not as clear there. And particularly when you add many different risk factors, smoking, high BMI, and hypertension, then those obviously are going to play out and make us hesitate to offer it. But we'll individualize in that. And then there are definitely high-risk people who have a calculated score of greater than 10% risk in the next couple of years. I think it's important about breast cancer. Patients are more worried about that I find than they are about heart disease, but I think here we have some really reassuring data.

We must separate out what is the risk with progestin and estrogen and from estrogen alone. It surprises people that the estrogen alone arm, when it was followed out for 18, 20 years in the WHI trial, that those people had a reduction in the risk of breast cancer and certainly a major reduction in the risk of dying from breast cancer. Now, I'm not suggesting we offer people estrogen alone to reduce the risk of breast cancer, but I think it can be very reassuring. But that combination that was studied in the WHI of the higher-dose estrogen with the higher-dose progestin that we would use these days did result in a higher risk for developing breast cancer that has held out for the last 20 years. But what's interesting is breast cancer mortality was never increased compared to placebo, but we don't want women to get a cancer that we can treat. We'd rather she didn't get it if we can.

References:

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause.* 2022;29(7):767-794. doi:10.1097/GME.0000000000002028

Cho L, Kaunitz AM, Faubion SS, et al. Rethinking menopausal hormone therapy: For whom, what, when, and how long? *Circulation*. 2023;147(7):597-610. doi:10.1161/CIRCULATIONAHA.122.061559

Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100(11):3975-4011. doi:10.1210/jc.2015-2236

2. In the Women's Health Initiative, estrogen-alone therapy increased the risk above placebo of which one of the following disorders?

a. Bone fracture
b. Breast cancer
c. Colon cancer
d. Heart attack
e. Stroke

Correct answer: e) Stroke

- Progestins or tissue-selective estrogen complex is needed with estrogen in postmenopausal women with a uterus to protect against endometrial hyperplasia or cancer.
- The Women's Health Initiative (WHI) trials showed different risks for women taking estrogen alone compared to estrogen plus progesterone:
  - Combined estrogen plus progesterone therapy increased the risk of heart attack, stroke, breast cancer, venous thromboembolism, and pulmonary embolism.
  - Estrogen therapy alone increased the risk of stroke and pulmonary embolism.
  - A 10-year follow-up of the WHI trials showed that neither therapy increased mortality.

Faculty Commentary on Question 2

Anita L. Nelson, MD: Case 3, question 2 asks about the estrogen alone therapy and I think there's an awful lot of misunderstanding there. It's very interesting that the only category of risk that was increased was stroke. Women on estrogen alone therapy did not have an increase in heart attack or colon cancer or breast cancer or even bone fracture. It was a totally different answer altogether and it surprises people.

References:

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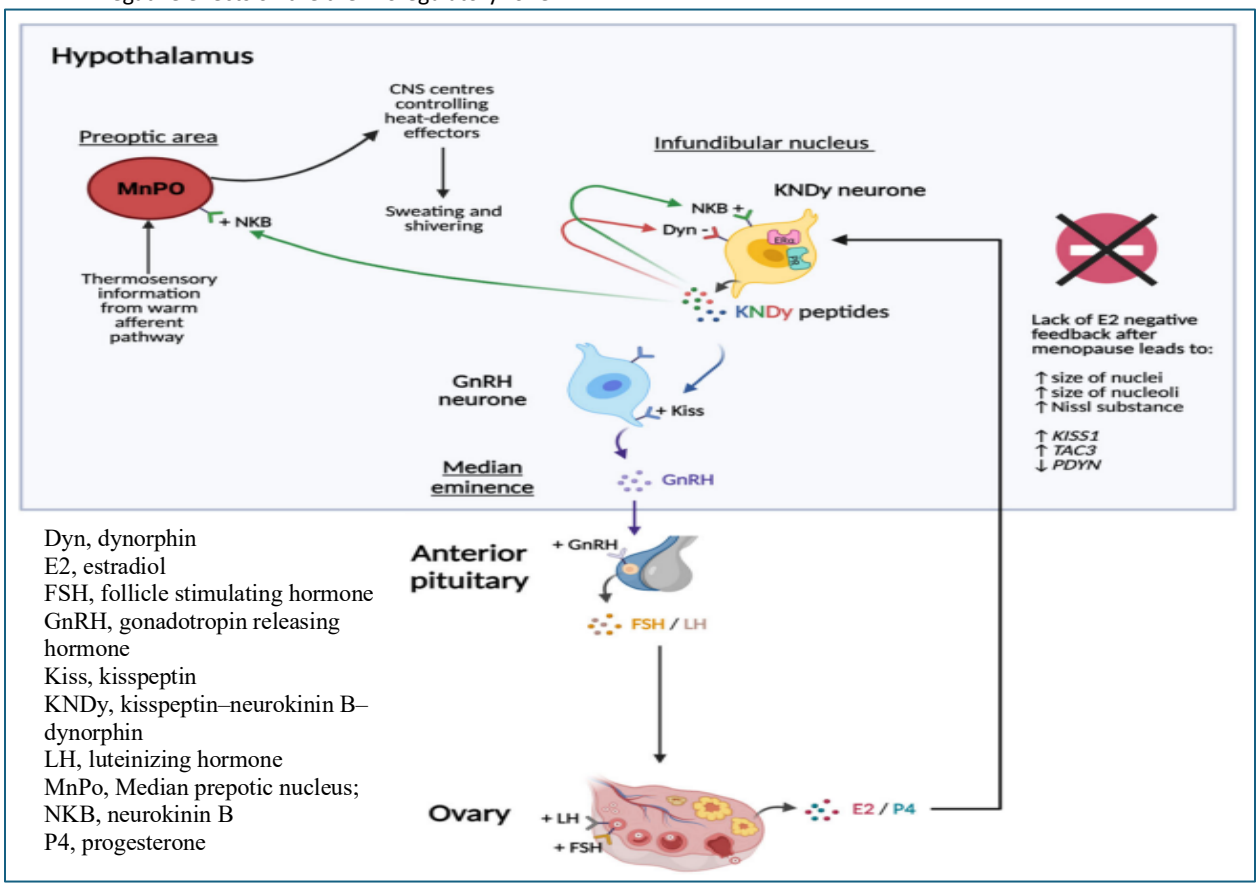
Case 4: Emerging Treatment

Helen experienced a deep vein thrombosis (DVT) 3 months ago and was advised to stop postmenopausal hormone therapy. She continues to have 6 to 8 hot flashes per day, and she complains of poor sleep despite following the recommended lifestyle modifications. She feels embarrassed when she experiences a hot flash at work and has contemplated reduced hours, but she needs the income. She does not want to go back on antidepressants because of the side effects. She has not smoked since being diagnosed with a DVT. She would like more information on the new menopause drug she saw on TV and her peers are talking about.

1. **Which one of the following is the mechanism by which estrogen affects the kisspeptin-neurokinin B-dynorphin (KNDy) pathway in thermoregulation?**
   a. Estrogen stimulates neurokinin 3 receptors expression
   b. Estrogen increases neuropeptide neurokinin B
   c. Estrogen promotes the growth and differentiation of KNDy neurons
   d. Estrogen inhibits activation of KNDy neurons

Correct answer: d) Estrogen inhibits activation of KNDy neurons

- Pulsatile GnRH secretion is driven by KNDy hypothalamic neurons that produce kisspeptin, neurokinin B, and dynorphin.
  - When activated, the KNDy neurons have a direct effect on the hypothalamic thermoregulatory and sleep centers.
  - As part of a negative feedback loop, estrogen blocks KNDy neurons activity and decreases GnRH and LH pulses.
  - Lack of estrogen during menopause causes hyperactivity of the KNDy neurons and an increased release of neurokinin B that auto stimulates KNDy neurons and acts on the thermoregulatory center in the hypothalamus causing a narrowing of the thermoregulatory zone and an increased risk of vasomotor symptoms.
  - Neurokinin-3 receptor antagonists, such as fezolinetant, an oral medication used to treat patients with moderate-to-severe vasomotor symptoms, reduce the activation of KNDy neurons and neurons in the thermoregulatory center of the hypothalamus, thereby attenuating negative effects on the thermoregulatory zone.



Faculty Commentary for Question 1

Genevieve Neal-Perry, MD, PhD: We talked a little about KNDy neurons, so let's talk about them a little more in detail because they are an important neuron in terms of us having specific treatment for hot flashes and it is because of our understanding of these neurons and how they work that we now have specific nonhormonal therapy for hot flashes.

KNDy neurons, as I alluded, are located in the hypothalamus and, in humans, they are located in the preoptic area. You'll see in the diagram it describes this area in rodents, but humans have a very similar area within the brain. And these neurons have estrogen receptors, and these neurons make kisspeptin which many of you may know is important for puberty and for just the generation of the LH surge. They make neurokinin B and dynorphin and dynorphin tends to be a little bit more inhibitory whereas neurokinin B is stimulatory. These neurons have estrogen receptors and in response to estrogen, they are quiet. They are quiescent.

In the absence of estrogen, these neurons up-regulate which means they make more of these peptides, particularly neurokinin B, and in addition to making more of these peptides, they will release the peptides to stimulate not only themselves, so that they continue to hyper-stimulate themselves, but they are stimulating these neurons in areas that are important for sleep and generation of hot flashes. Since we understand this, we were able to develop treatments for hot flashes and the 2 treatments that you may be familiar with or heard about are fezolinetant, and there is another drug that is under study called elinzanetant. The difference between these treatments is fezolinetant is the neurokinin-3 receptor antagonist, that means it blocks the receptor. It will block the receptor on KNDy neurons as well as the receptors in the hypothalamus that may regulate hot flashes and that may regulate sleep. Elinzanetant is a neurokinin-1,3 receptor antagonist, so it interacts with 2 different types of neurokinin receptors to mediate pretty much the same effects.

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2. Which one of the following should be measured before prescribing fezolinetant therapy in a patient with moderate-to-severe menopausal-associated vasomotor symptoms?

a. Blood glucose
b. Liver function
c. Serum lipids
d. Thyroid function

Correct answer: b) Liver function

- Fezolinetant is a neurokinin-3-receptor antagonist that was approved by the FDA in 2023 for the treatment of moderate-to-severe vasomotor symptoms.
- The prescribing information for fezolinetant was revised in December 2024 to include a black box warning about the occurrence of hepatotoxicity based on postmarketing surveillance data from 1 patient.
  - Liver function testing should be performed before initiation, then monthly for the first 3 months, then at 6 months and 9 months.
- Skylight 2 was a phase 3, randomized, double-blind, placebo-controlled trial comparing fezolinetant 30 or 45 mg to placebo in women 40-65 years old who had a minimum of 7 moderate-to-severe vasomotor episodes per day.
  - 12-week trial with a 40-week active treatment extension
- Efficacy persisted through the 40-week extension study
- Improvements in quality of life as measured by MENQOL were statistically significant for fezolinetant 45 mg compared to placebo at week 12
- Headache was the most common adverse effect across the 3 groups
- 5 patients in the 45 mg fezolinetant group had serum alanine aminotransferase (ALT) values 3 times the upper limit of normal and 1 patient in the 30 mg group had an ALT 5 times the upper limit of normal.
  - ALT levels returned to normal in 2 patients with continued treatment, with treatment interruption in 2 patients, and with treatment discontinuation in 1 patient
- Results of Skylight 2 confirmed results seen from Skylight 1.
- Clinical information for fezolinetant
  - Dose is 45 mg once daily
  - Onset of action is less than 1 week
  - Contraindications

- Known cirrhosis
- Severe renal impairment or end-stage renal disease
- Use of CYP1A2 inhibitors (eg, amiodarone, ciprofloxacin, verapamil)

- Laboratory monitoring
  - Do not start fezolinetant if serum aminotransferases or total bilirubin levels are ≥2 times the upper limit of normal
  - Retest liver function monthly for the first 3 months, at 6 and 9 months after initiation
- Common side effects (>2%)
  - Abdominal pain, diarrhea, insomnia, back pain, and hot flashes

Skylight 2 Results				
Endpoint	Fezolinetant 30 mg (n=166)	Fezolinetant 45 mg (n=167)	Placebo (n=167)	*P* value (compared to placebo)
4-week LS mean change from baseline for VMS frequency per day	-5.53	-6.26	-3.72	-
4-week LS mean difference vs placebo per day	-1.82	-2.55	-	<0.001
12-week LS mean change from baseline for VMS frequency per day	-6.83	-7.50	-4.97	-
12-week LS mean difference vs placebo per day	-1.86	-2.53	-	<0.001
Drug related TEAE	14.5%	15%	6.6%	-
Drug-related TEAE leading to discontinuation	0.6%	3%	0	-

LS, least squares; TEAE, treatment-emergent adverse event

Faculty Commentary on Question 2

Genevieve Neal-Perry, MD, PhD: The studies that have focused on fezolinetant are the Skylight studies and those studies have led to FDA approval of fezolinetant for the treatment of moderate-to-severe hot flashes. Let's talk a little bit about how effective this is. If you look at your documents, I want to pull out 2 things when you are looking at—fezolinetant and elinzanetant—that are really important because they are not quite comparable from the numbers, but they are comparable from the overall effect. Fezolinetant, what they did was they enrolled women 40 to 65 years old who had on average about 10 hot flashes a day. Whereas elinzanetant, what they looked at is they looked at individuals, same age range, who had greater than 50 hot flashes in a week. One is looking at hot flashes over a week; the other one is looking at hot flashes per day. And then they looked at, over a 12-week period and then an additional 40 weeks for the fezolinetant group, an additional 24 weeks for the elinzanetant, they looked at the frequency and intensity of hot flashes over this window of time. And what both studies demonstrated was that individuals who have hot flashes that were treated with these drugs had a significant improvement. For fezolinetant, it was a reduction of about 7 over 12 weeks. And for elinzanetant, it was also about 7 by 12 weeks of hot flashes. And with this reduction in hot flashes, you had an improvement in quality of life with both studies and you also saw an improvement in sleep with both studies.

These are 2 new drugs, fezolinetant is US Food and Drug Administration (FDA) approved and elinzanetant is on the horizon to be approved, I believe, by the FDA, that are effective therapies for hot flashes. When you compare these NK-3 receptor antagonists to an SSRI or estrogen, what's notable about each one is that they work quickly. In less than a week, you start to see an improvement in symptoms for people who have hot flashes, both in terms of frequency as well as in terms of the severity of hot flashes. You see improvement with both.

The other important thing with both studies is that we looked at bleeding. One of the biggest concerns with hormonal therapy is with bleeding. Neither study demonstrated a relationship between their treatment and uterine bleeding. The studies do not suggest, like estrogen, that there is an increased risk for uterine cancer.

Other things that are notable about both elinzanetant and fezolinetant are some of the side effects. Both had side effects. Both were done primarily, particularly fezolinetant, during COVID and so one of the most common side effects was headache. But you also saw some individuals who had elevation in liver enzymes with fezolinetant and, for that reason, the FDA has recommended that you do liver tests, that you do not start this medication in people who have liver disease. What I will say about the liver function tests is that there was no evidence of drug toxicity or liver toxicity in those individuals who had elevations and after treatment, their liver enzyme levels recovered, and we didn't see sustained damage. They didn't have evidence of what's called Hy's law, which is basically evidence that there's no toxic effects to the liver. So that is an important thing to keep in mind that, one, you don't want individuals who have liver disease using it and because of the way it's cleared, you also don't want individuals who have kidney disease using fezolinetant.

With fezolinetant, I want you all to be aware that the package labeling recommends liver enzyme testing every month for the first 3 months, again at 6 and then at 9 months. In context, so you can help your patients understand that it was one person that triggered this recommendation. So there are going to be some patients who may have an elevated liver enzyme and so we want to do that, we want to know so we can manage them properly and certainly if there is someone who develops icteric eyes, their eyes are looking yellow, they are looking jaundiced, that is something that you want to counsel the patient to stop the agent. But they should know that their risk is quite low and again this really is an abundance of caution that this recommendation is made.

When we talk about drug-related adverse events for fezolinetant, it ranged from 14% to 15% for those who were taking the drug and about 6.6% for those who were taking placebo and, again, the most common symptom was headache. There were some people who had nausea, but most importantly the symptoms were not typically enough that you want to stop their treatment. In those who used the drug who stopped treatment, it was 0.6% to 3% for fezolinetant. And this 0.6% was for the 30 mg dose of fezolinetant and the 3% was for the 45 mg dose of fezolinetant which is what is on the market.

When using fezolinetant, it is also important to make sure that you are not using it in people who are using CYP1A2 inhibitors, such as ciprofloxacin, which is probably one of the more common drugs that you would use.

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Key Concepts

- Vasomotor symptoms such as hot flashes are burdensome with 46% of women complaining of moderate-to-severe vasomotor symptoms in the first 2 years following menopause.
- Race and ethnicity are factors that contribute to the length of vasomotor symptoms with African American women reporting the longest symptom time and Japanese women reporting the shortest.
- Citalopram, escitalopram, paroxetine, duloxetine, venlafaxine, gabapentin, oxybutynin and fezolinetant have a Level 1 recommendation from NAMS as nonhormonal medications to treat vasomotor symptoms.
- The therapeutic efficacy and safety, as well as patient-specific factors such as age, time since menopause, concurrent disease states, and cardiovascular risk, should be assessed when considering systemic estrogen-based therapy for the treatment of vasomotor symptoms.
- Fezolinetant is a neurokinin-3-receptor antagonist that was recently approved by the FDA for the treatment of patients with moderate-to-severe vasomotor symptoms.

Anita L. Nelson, MD: I think vasomotor symptoms, the hot flashes that women suffer, really do cause a burden to the quality of life of women. I hear people saying, well women don't die of hot flashes, but it certainly affects their productivity and their enjoyment of life and we're trying to improve that one-third of the years that women spend after the menopause. This is a new frontier for women overall and particularly the moderate-to-severe hot flashes that really persist for years and years beyond what people think. For most women they last 2 years, but for many others, it goes on for longer than we thought. And we know that race and ethnicity can contribute to the intensity and the length of suffering, so we really want to deal with women one on one. I think this is the way they come into our office, and this is the way we love to talk with them and to deal with them. Guidelines help us a lot, but we love to be able to individualize. We have Level one recommendations for several drugs from the Menopause Society for treatment and, certainly, the SSRIs, SNRIs, gabapentin, oxybutynin and, of course, the newest addition, which is the most effective that we've had, the only thing that has really compared effectively to estrogen and that's fezolinetant. And I'm very excited by the introduction of fezolinetant which is that neurokinin-3-receptor antagonist that was recently approved by the FDA for the treatment of moderate-to-severe vasomotor symptoms.

Genevieve Neal-Perry, MD, PhD: When thinking about treatment, you also want to remember about therapeutic efficacy and safety and again, you want to remember about age factors, time since menopause, whether they have other disease states, such as cardiovascular disease, poorly treated diabetes. These are going to be important in terms of whether you use an estrogen-based therapy or not. You are also going to consider other comorbidities, such as bone disease. If someone has bone disease and hot flashes, estrogen is going to be probably on the top of your list, provided they don't have any other contraindications. In terms of FDA-approved treatments currently, there are 2. That is fezolinetant and paroxetine.