95

MANAGING MENOPAUSAL SYMPTOMS

A Hot Topic . . . . . Level II

Nicole S. Culhane, PharmD, FCCP, BCPS

INSTRUCTOR'S GUIDE TO CHANGES IN THIS EDITION

CASEBOOK AND INSTRUCTOR'S GUIDE

- Entire case and instructor's guide revised to remove the "R" in HRT, as the preferred terminology is now "hormone therapy" (HT) rather than "hormone replacement therapy".
- The word progestin changed to progestogen throughout the case and instructor's guide, as this is now the appropriate terminology.

INSTRUCTOR'S GUIDE

Problem Identification

- National Osteoporosis Foundation (NOF) recommendation for calcium and vitamin D revised to 1,200 mg daily and 800–1,000 International Units (IU) daily, respectively.

Therapeutic Alternatives

- Added information from the 2007 reanalysis of the Women's Health Initiative (WHI) study regarding the change in coronary artery disease (CAD) risk in younger women and lower number of years since menopause.
- Added a statement about the use of desvenlafaxine and duloxetine for hot flashes.

Follow-Up Questions

- Question added regarding the use of bioidentical HT.

References

- Added two new references, including the 2007 reanalysis of the WHI study and a recent study on the use of desvenlafaxine for hot flashes.

CASE SUMMARY

A 50-year-old woman reports menopausal symptoms of hot flashes and night sweats associated with occasional insomnia during the past 3 months. She has a history of depression, gastroesophageal reflux disease, hypothyroidism, and HTN. She expresses concern about the safety of HT. The physician concludes that she is menopausal and would benefit from HT by decreasing her menopausal symptoms and providing osteoporosis prevention for the duration of the treatment. Paroxetine has been shown to have some benefit for the treatment of hot flashes but has not been effective for that purpose in this patient. Because she does not have significant risk factors for heart disease or a personal history of breast cancer, short-term, low-dose HT is an appropriate option. Estrogen replacement alone should not be used because she has an intact uterus. Cyclic or continuous HT with estrogen/progestin would provide optimal therapy to reduce the risk of endometrial cancer. Continuous HT is the most appropriate option for her considering her desire to not have a menstrual period.

QUESTIONS

Problem Identification

1.a. Create a list of the patient's drug therapy problems.

- Vasomotor menopausal symptoms (hot flashes), night sweats, and occasional insomnia (most likely precipitated by the night sweats) that are bothersome to the patient and have occurred for the past 3 months.
- Side effect concerns: The patient is concerned about the safety of HT due to recent media attention.
- Depression currently controlled on paroxetine 20 mg daily. Paroxetine not effective at decreasing her hot flashes and patient requests additional therapy.
- Hypertension currently controlled on HCTZ therapy. HCTZ may also provide her with osteoporosis prevention, as it has been shown to increase bone mineral density (BMD) slightly by reducing urinary calcium excretion.[1] HTN is a risk factor for CAD but given that this is her only risk factor for CAD, she is likely still a candidate for HT.
- Hypothyroidism currently controlled on Synthroid. Her TSH level is normal, and she is not complaining of any symptoms of hypothyroidism. It is important to assess this condition and correct this underlying disorder first before treating for hot flashes. A patient with a low TSH, indicative of hyperthyroidism, may present with similar symptoms as this menopausal patient.
- Gastroesophageal reflux disease currently controlled on omeprazole. Reassess patient symptoms and continued need for therapy.
- Elevated triglycerides; the patient has one risk factor for CAD (HTN). Her lipid panel is normal (TC <200 mg/dL, low-density lipoprotein goal <160 mg/dL but ideally <130 with one risk factor for CAD, high-density lipoprotein >40 mg/dL) except for her triglycerides, which are above goal of <150 mg/dL based on the National Cholesterol Education Program Adult Treatment Panel III guidelines. Further evaluation of the patient's diet and exercise is necessary.
- Osteoporosis prevention; the patient is not currently taking calcium and vitamin D. According to the NOF 2008 guidelines, women 50 years of age need 1,200 mg of calcium and 800–1,000 IU vitamin D daily. After adequate assessment of dietary sources, the patient will most likely need supplementation. Calcium citrate is the appropriate form of calcium since the patient is taking omeprazole, and calcium carbonate needs an acidic medium to be absorbed. HCTZ will reduce urinary calcium excretion and thus slightly increase BMD. HT will also prevent declines in BMD and possibly decrease fractures but only for the duration the patient is taking the treatment. After discontinuation of therapy, the BMD will continue to decline at the rate prior to HT therapy.

1.b. What information (signs, symptoms, laboratory values) indicates the presence or severity of this patient's problems as she begins menopause?

- *Signs:* Pelvic exam normal except (+) mucosal atrophy.
- *Symptoms:* Vasomotor instability (complaints of hot flashes, night sweats).

- *Laboratory values:* Follicle-stimulating hormone (FSH) >30 mIU/mL. An elevated FSH level may indicate a woman is experiencing menopause. Female FSH value interpretation (*Note:* Values may vary among laboratories and institutions):
  - ✓ Premenopausal: 5–30 mIU/mL
  - ✓ Mid-cycle peak: 10–60 mIU/mL
  - ✓ Pregnancy: low to undetectable
  - ✓ Postmenopausal: >30 mIU/mL
- *Other:* She is 50 years old, her last menstrual period was 12 months ago (indicating clinical menopause), and she had a negative pregnancy test. Verifying the date of her last menstrual cycles allows for the full interpretation of the elevated FSH level. If she had been experiencing continual menstrual cycles, her elevated FSH may indicate that she is mid-cycle. A pregnancy test may be done to confirm an alternative reason why she is not currently menstruating.

Desired Outcome

2. What are the goals of therapy for this patient's menopausal symptoms?

- Reduce the number of hot flashes and episodes of night sweats and insomnia that the patient is experiencing as well as improve her vaginal dryness.
- Educate the patient on the efficacy (benefits) and safety (risks) issues surrounding the use of HT so that she may be involved in the treatment decision.
- Provide the patient and the primary care physician (PCP) with alternative recommendations to HT, including the prevention of osteoporosis.

Therapeutic Alternatives

3.a. What nondrug therapies might be useful for this patient?

- The patient would benefit from healthy meal planning, attaining her ideal body weight, and an appropriate exercise regimen to help control her HTN, elevated triglycerides, and prevent osteoporosis. She may also benefit from trying nonpharmacologic measures to decrease her vasomotor symptoms:
  - ✓ Limit alcohol and caffeine.
  - ✓ Limit hot beverages (coffee/tea, soups).
  - ✓ Limit spicy foods.
  - ✓ Keep cool and dress in layers.
  - ✓ Stress reduction (meditation, relaxation exercises).
  - ✓ Increase exercise.
  - ✓ Paced respiration.
- A diet rich in calcium and vitamin D will also help to prevent osteoporosis. Supplementation with calcium citrate plus vitamin D is necessary for adequate absorption of calcium from the GI tract.

3.b. What are the benefits and risks of HT for this patient?

Benefits:

- Relief of menopausal symptoms.[2]
- Prevention of osteoporosis (only for the duration of therapy); fractures are reduced by approximately 30%.

Risks:

- Increased risk of venous thrombosis.
- Established heart disease risk: According to the Heart and Estrogen–Progestin Replacement Study (HERS) trial, women with established CAD have an increased risk of nonfatal myocardial infarction (MI) and cardiac death in the first year on HT. Four years after initiating HT, no effect on the rate of nonfatal MI or sudden cardiac death was seen. The study concluded that patients with established CAD should not be initiated on HT therapy.[3] This study called into question the proposed cardiovascular protective effects of estrogen.
- Gallbladder disease risk: The HERS trial also demonstrated a "probable increase in risk" for gallbladder disease in patients taking HT.[3]
- WHI study results: The National Institutes of Health–funded WHI trial measured outcomes in healthy women (primary prevention) taking combined conjugated estrogens and medroxyprogesterone (PremPro).[3,4] HT increased the risk of MI, stroke, and thrombosis within the first 2 years. The absolute risks of MI and stroke were 7 and 8 more events per 10,000 women per year, respectively. In a 2007 reanalysis of the WHI study, the authors further clarified the cardiovascular risk, reporting that the risk for CAD was not increased in women taking combined HT less than 10 years since menopause and between the ages of 50 and 59 years. There was a greater risk for CAD in women 10 years since menopause and older than the age of 70 years.[5] Although HT lowered the risk of colon cancer and total fractures, long-term use (>4 years) increased the risk of breast cancer. The risk of developing breast cancer with long-term use of HT has also been reported in other studies. Additionally, it was found that combined estrogen and progestogen led to a higher incidence of dementia in older women, twice the risk in women >65 years of age.
- Women taking estrogen alone[6]: As a continuum of the WHI, a separate arm of the study looked at the effects of women without a uterus taking estrogen alone. Estrogen alone does *not* increase the risk of heart disease or breast cancer, but it does increase the risk of stroke at a rate similar to that seen with combined estrogen and progestin. With regard to dementia, estrogen alone does not provide any protection, and it may increase the risk. The estrogen-alone arm did not lower the risk of colon cancer but did decrease total fractures similarly to the combined HT arm. As a result of this study, estrogen alone is not recommended for osteoporosis prevention as the potential benefits do not outweigh the risks. In addition, estrogen offers protection only during the time the patient is actively taking the drug. Thus, if estrogen is used alone, it is suggested to be taken at the lowest possible dose for the shortest duration possible to alleviate symptoms.
- Long-term HT should not be used in women with a personal history of breast cancer and is the patient's personal choice if there is a family history of breast cancer. The clinician should weigh and discuss the risks and benefits with each patient. Advise women that short-term use of HT for relieving menopausal symptoms is appropriate in most women without a personal history of breast cancer, but recommend stopping therapy within 4 years.[3,4]
- Based on the HERS clinical trial results described above (see the section "Therapeutic Alternatives"), patients with existing heart disease who are taking HT (secondary prevention) may be at increased risk for cardiac events when HT is first initiated. The data from the WHI trial further showed that women without existing heart disease who are taking HT (primary prevention) may also be at risk for cardiac events early in treatment. However, a 2007 reanalysis of the WHI study demonstrated

that women taking combined HT for primary prevention less than 10 years since menopause or between the ages of 50 and 59 years were not at greater risk for CAD. The risk for CAD increased in women initiating HT after 10 years since menopause or at 70 years of age.[5]

Contraindications to HT:

Absolute contraindications to HT include:

- A personal history of breast cancer
- Estrogen-dependent neoplastic disease
- History of or active thromboembolic disease or thrombophlebitis
- Abnormal genital bleeding of unknown origin
- Pregnancy
- Liver disease

Uncertainties surrounding HT:

- Since the publication of the WHI study, many uncertainties surrounding the use of HT have been answered. There are outlying studies that have examined whether there is a lower risk of colorectal cancer in women receiving HT. To date, there is no definitive literature in this area, but according to the WHI, HT may potentially decrease the risk of colorectal cancer, although it is unlikely that this would be a sole indication for therapy considering the risks listed above (see Therapeutic Alternatives: Risks).

3.c. What pharmacotherapeutic *hormonal* therapies are available for the treatment of menopause?

- Based on the results of the WHI study, the FDA has advised that women who are considering the use of estrogen alone or in combination with progestogen discuss benefits and risks of such therapy with their health care providers. The products can be used short-term and in a low dose for the management of vasomotor symptoms and vulvovaginal atrophy in women without risk factors for heart disease, breast cancer, stroke, thrombosis, or dementia. Considering the multiple risks, the FDA has recommended that the use of these hormonal products be limited to short-term, lowest possible dose in women without risk factors. Lower doses have demonstrated comparable efficacy to conjugated equine estrogens (CEE) 0.625 mg for the relief of vasomotor symptoms and vulvovaginal atrophy and osteoporosis prevention.[7] However, it is not known whether lower doses are safer.

Pharmacologic options:

- *Oral estrogen with no progestogen.* Unopposed estrogen is not desirable in this patient with an intact uterus because it increases the risk of endometrial cancer.
- *Oral estrogen with cyclic progestogen.* Regimens vary and can be complex, so adherence may be an issue (refer to the textbook chapter on HT for more detailed information on specific cyclic regimens). This patient is concerned about getting her period back that will occur, albeit shorter and lighter, with cyclic regimens. However, light breakthrough bleeding/spotting can occur up to 6–8 months with continuous combined replacement therapy.
- *Oral continuous combined estrogen and progestogen.* This regimen is easier to take compared with a cyclic regimen, and adherence may be enhanced. A number of proprietary products are available:
  - ✓ Estradiol/norethindrone acetate (Activella)
  - ✓ Estradiol/norethindrone acetate (Femhrt 1/5)
  - ✓ Estradiol/norgestimate (Ortho-Prefest)
  - ✓ Estradiol/drospirenone (Angeliq)
  - ✓ Conjugated estrogens/medroxyprogesterone acetate (PremPro)
- *Vaginal estrogen cream (e.g., Premarin or Estrace Vaginal Cream).* Vaginal creams help relieve genitourinary symptoms but will not decrease the vasomotor symptoms she is experiencing. Women with an intact uterus may be at risk of endometrial cancer due to systemic absorption of the topical estrogen product over time. Although few data are available on the appropriate progestogen dose, some data indicate that 10 days every 12 weeks may be sufficient to prevent endometrial hyperplasia.
- *Transdermal estradiol system.* Seven different products are currently available: five of the patches are replaced twice weekly (*Alora**, *Esclim**, *Estraderm*, *Vivelle**, *Vivelle-Dot**) and two are replaced once weekly (*Climara**, *FemPatch*). Based on the FDA's recommendations, the new low starting dose of estrogen is 25 mcg of estradiol. The agents above listed with an asterisk (*) have initial starting doses available of 25 mcg of estradiol. When using one of these patches in women with an intact uterus, an oral progestogen tablet must be taken in combination with the patch to protect against endometrial cancer. In comparison to oral estrogen, the transdermal system has less effect on raising triglycerides. *Menostar* is a newer low-dose transdermal estrogen patch that provides 14 mcg per day of estradiol with the patch being replaced once weekly. This low-dose patch is only approved for osteoporosis prevention and not for the management of menopausal symptoms.
- *Transdermal estradiol plus progestogen system:*
  - ✓ *Estradiol/norethindrone acetate (CombiPatch)* is applied twice weekly.
  - ✓ *Estradiol/levonorgestrel (Climara Pro)* is applied once weekly.
- In addition to a convenient dosage regimen, these products eliminate the need for oral progestin. Both products raise triglycerides to a lesser extent than oral estrogen products. Their main limitation is that they are not currently available in the initial 25-mcg estradiol dose recommended by the FDA; however, it is important to note that increased safety has not been established with this lower transdermal dose.
- *Estradiol topical emulsion (Estrasorb).* This product is available as foil packets. The patient applies the contents of one packet to the top of the thigh or the back of the calf once daily. This product may be less likely to cause thrombosis in comparison to oral HT products, because it avoids first-pass metabolism by the liver. It should not be applied with sunscreen at the same time, and extended skin-to-skin contact between the patient and another individual may transfer a small amount of medication. Women with an intact uterus still need to take a progestogen with this product to decrease the risk of endometrial cancer.
- *Estradiol gel (EstroGel 0.06%).* This product is available in a metered dose pump that delivers 0.75 mg of estradiol in every 1.25 g unit dose of gel. It should be applied in a thin layer to the arm from the wrist to the shoulder. Educate patients not to wash this area for at least 1 hour as washing the area was shown to decrease mean concentrations of estradiol by approximately 22%. Women with an intact uterus still need to take a progestin with this product to decrease the risk of endometrial cancer. This product has similar risks and benefits as other estrogen-containing products.

- *Topical progestogen creams* are available without a prescription and are classified as cosmetics. They are purported to be useful for the management of hot flashes, irritability, and insomnia, among other symptoms. Women are directed to rub the cream on their neck, chest, abdomen, inner arms, or thighs providing for 30–120 mg of progestogen a day. No data are available on the efficacy of these products or the appropriate dose. It seems most reasonable to recommend that women take oral progestin when appropriately indicated.
- *Phytoestrogens* are weak plant estrogens that bind to estrogen receptors. They do seem to have mild estrogenic effects, allowing them to potentially benefit women with menopausal symptoms. Considering that they do have weak estrogenic activity, the same precautions should be taken when considering the use of phytoestrogens as in women considering HT.

3.d. What *nonhormonal* alternatives may be used to manage menopausal symptoms?[1,8,9]

- *Black cohosh (Cimicifuga racemosa):* Evidence regarding the efficacy of this herb is conflicting, although it is generally well tolerated, with the most common symptoms being GI disorders and headache. Recently, there have been a number of case studies of patients taking black cohosh experiencing liver toxicity. A direct causal association between the product and the toxicity has not been made, but caution should be used when recommending these products in patients with underlying liver dysfunction. It has not been shown to be effective for vasomotor symptoms in women with breast cancer and should be avoided in this population due to lack of efficacy and safety data. If the product is taken, the dose used in most studies was 20 mg of black cohosh taken twice a day for a short period of time (<6 months).
- *Serotonin–norepinephrine reuptake inhibitors (SNRIs):* Doses of venlafaxine 37.5–150 mg daily have been shown to reduce the number of hot flashes in women with or without breast cancer. In addition, desvenlafaxine has been shown to be effective in women without a history of breast cancer in doses of 50–100 mg daily. However, duloxetine has only been studied in an open-label trial and was not effective in reducing hot flashes. Therefore, venlafaxine or desvenlafaxine may be reasonable agents to try in patients with contraindications to HT and/or underlying depression.
- *Selective serotonin reuptake inhibitors (SSRIs):* Paroxetine (Paxil) 10–20 mg daily or 12.5–25.0 mg of the controlled-release formulation has demonstrated the most reduction in hot flashes among the SSRIs. Fluoxetine (Prozac) has also demonstrated efficacy while sertraline and citalopram have been proven to be less beneficial. Most of the efficacy data with this class of drugs have been in breast cancer survivors. Paroxetine may be a reasonable agent to try in patients who have contraindications to HT and/or have underlying depression.
- *Clonidine (Catapres)* is a centrally acting β-adrenergic agonist used primarily for the treatment of hypertension. In one trial, transdermal clonidine decreased symptoms in women experiencing tamoxifen-induced hot flashes. Although these patients were experiencing the hot flashes due to tamoxifen, there have been case studies also supporting clonidine's potential use in menopausal hot flashes. An oral dose of 0.1 mg or a topical 0.1-mg transdermal system has been used. Use of this drug is limited by its anticholinergic side effects (e.g., constipation, dizziness, drowsiness, dry mouth).
- *Gabapentin (Neurontin)* 300 mg TID has been shown to reduce hot flashes in patients with or without breast cancer and may be an alternative for women who have contraindications to HT or risk factors that preclude the use of HT. If this patient had more risk factors for CAD, currently had CAD, or had a personal history of breast cancer, this may be a reasonable alternative as the patient is already being successfully treated for depression with paroxetine but is still experiencing bothersome hot flashes requiring treatment.

Optimal Plan

4. What drug, dosage form, dose, schedule, and duration are best for this patient?

- She is an appropriate candidate for HT. Once the risks and benefits have been discussed with the patient, it may be appropriate to initiate a regimen of estrogen with progestogen therapy. Low-dose, continuous oral therapy and combined hormonal transdermal therapy are feasible options in order to decrease the likelihood of breakthrough bleeding (spotting). Below are explanations of the two appropriate options (the patient should be involved in the decision and could choose based on preference):
  - ✓ Transdermal patch: The patient should ideally be started on a patch with the lower estrogen dose of 25 mcg of estradiol. Proprietary products: Alora, Esclim, Vivelle, Vivelle-Dot, and Climara are all available with 25 mcg of estradiol. Climara is the only one available as a once-weekly patch, and that may be a reason to choose it over the others. However, the patient does have an intact uterus and will need to take an oral progestin daily, which negates the convenience of applying a once- or twice-weekly patch. Therefore, a combined hormonal transdermal product is preferred. Proprietary products: CombiPatch or Climara Pro.
  - ✓ Oral continuous combined estrogen and progestogen: Start the patient on the lowest dose possible such as CEE 0.3 mg plus medroxyprogesterone 1.5 mg once daily. Reassess continued need for HT every 6 months and discontinue therapy after 2–4 years.
- If the patient declines HT after discussing the risks and benefits, a nonhormonal option may be considered. Black cohosh is not recommended due to lack of efficacy and safety concerns. Phytoestrogens should most likely be avoided due to potentially similar safety concerns as HT. Antidepressants previously mentioned may be effective and are relatively safe; however, the patient is already receiving treatment with paroxetine without relief of hot flashes. The dose may be increased for a trial of 1–3 months to see if the hot flashes diminish. Oral clonidine may also be an option at a dose of 0.1 mg daily. However, the side effects associated with its use may lead to nonadherence or discontinuation. Gabapentin is a viable option and is most likely the most appropriate alternative product for this patient.

Outcome Evaluation

5. What clinical and laboratory parameters are necessary to evaluate the therapy for achievement of the desired therapeutic outcome and to detect or prevent adverse effects?

Efficacy parameters:

- At each encounter, ask the patient about the adequacy of relief from hot flashes, night sweats, insomnia, and vaginal dryness.

Adverse effect parameters:

- At each encounter, ask the patient whether she has experienced cramping, bloating, headache, irritability, or vaginal bleeding.

- Each year, recommend that the patient have a mammogram to screen for breast cancer and a pelvic exam and Pap smear to detect endometrial cancer.
- Advise the patient to perform monthly breast self-examinations to check for breast cancer.
- Check cholesterol and triglycerides (transdermal patches have little to no effect on serum triglycerides) at least annually to prevent cardiovascular disease since the patient's triglycerides are slightly above goal of <150 (180 mg/dL).

Patient Education

6. What information should be provided to the patient to enhance adherence to the medication, ensure successful therapy, and minimize adverse effects?

- CombiPatch or Climara Pro (one potential option):
  - ✓ You have been prescribed a patch with two hormonal medications to decrease the hot flashes you are experiencing.
  - ✓ This combination of medications is used for HT in postmenopausal women. It will help decrease your symptoms of hot flashes, night sweats, insomnia, and vaginal dryness.
  - ✓ While using this product, you may also prevent the development of osteoporosis. Because this benefit lasts only for the time you are using the patch, you will need to consider other means of osteoporosis prevention after stopping the estrogen. Continue to eat foods rich in calcium and vitamin D and take adequate supplementation of calcium citrate and vitamin D to help to build stronger bones.
  - ✓ These medications have been associated with breast cancer and heart attacks in women who are already at higher risk for these diseases. However, because you do not have a history of breast cancer, have only one risk factor for the development of heart disease, and you have not had a heart attack, these medications can be used for a short period of time (less than 2–4 years) to decrease hot flashes.
  - ✓ To apply the patch, open the pouch and remove the patch. Peel off the liner. Apply the patch to an area of clean, dry skin on the lower stomach or the top of the buttocks. It should not be applied to the breast area or at the waistline due to tight-fitting clothing. Once the patch is placed, press it firmly in place for 10 seconds. Reapply a new patch twice weekly (CombiPatch) or once weekly (Climara Pro). Discard it by folding the sticky side together and disposing it out of the reach of children or pets.
  - ✓ While wearing the patch, if the area around the patch becomes red, itchy, or irritated, try a new site. If this irritation continues or becomes worse, call your physician, nurse, or pharmacist.
  - ✓ If you forget to change the patch, do so as soon as you remember. Do not double the dose.
  - ✓ You may experience adverse effects such as nausea, bloating, breast tenderness, or dizziness. However, the gastrointestinal side effects tend to be milder as compared to an oral product. If these side effects occur and are bothersome, please contact your physician, nurse, or pharmacist.
  - ✓ Do not discontinue therapy without first consulting your physician. HT should be tapered and not stopped abruptly in order to minimize the risk of recurrent hot flashes.
- Continuous combined HT tablets (other potential option—any of the proprietary products may be used):
  - ✓ Take one tablet each day at the same time every day.
  - ✓ If you forget to take a dose, take the missed dose as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses at one time to make up for the missed dose.
  - ✓ You may experience nausea, vomiting, stomach upset, breast tenderness, dizziness, lightheadedness, or bloating. If these side effects occur and are bothersome, please contact your physician, nurse, or pharmacist.
  - ✓ Store this medicine in a cool, dry place.
  - ✓ For general health maintenance, it is important that you perform monthly breast examinations and schedule regular gynecologic follow-up exams and doctor appointments.

FOLLOW-UP QUESTIONS

1. What is the optimal dose and length of time for a patient to continue on HT?

- Considering that this patient does not have a family history of osteoporosis and does not have a BMI <22 (her BMI is 27), she is not currently at high risk for osteoporosis. Additionally, her vasomotor symptoms have subsided. With this in mind, as well as the added potential for breast cancer in women taking HT for >5 years, she should use the lowest dose of therapy for the shortest time possible. In most women, and according to the FDA, this time period would optimally be no longer than 2–3 years. However, she should continue to ingest 1,200 mg of elemental calcium daily, exercise regularly, and maintain a healthy diet to aid in osteoporosis prevention and maintenance of appropriate lipid levels.

2. How should HT be discontinued after successful treatment?

- The patient should be educated not to discontinue therapy without first consulting her PCP. The therapy should be tapered (dose or duration taper) in order to decrease the risk of recurrent hot flashes. Hot flashes are due to fluctuations in estrogen concentrations and the severity is increased with abrupt declines in estrogen concentration such as in surgical menopause. Therefore, doses of HT should be tapered. The exact duration of the taper is not known but should ideally be done slowly over about 3–6 months.[10]

3. Would your recommendation for HT change if the patient had been complaining of genital symptoms only? Why or why not?

- The patient could have been prescribed any of the topical estrogen products. Because she has an intact uterus and absorption of the topical products could vary, a supplemental progestin for about 10 days every 12 weeks may be warranted in order to decrease the risk of endometrial cancer. Systemic HT would not be indicated in this patient for genital symptoms only. It should only be considered in women complaining of vasomotor symptoms.

4. Would your recommendation for HT change if this patient were to have had significant risk factors for CAD or a personal history of breast cancer? Why or why not?

- Although this patient is suffering from hot flashes, she would not be a good candidate for HT due to her CAD risks and/or breast cancer history (see risks and benefits in earlier section of the case). If this were to have been the patient situation, a nonhormonal therapy such as gabapentin may be appropriately recommended instead of HT. Gabapentin would be an appropriate choice since she is already taking paroxetine without success for hot flashes but successfully for depression.

Recommending an additional antidepressant such as venlafaxine would be a less-preferred option due to the potential drug–drug interaction with paroxetine and risk of serotonin syndrome.

5. How would you respond to the patient if she asked you about taking bioidentical HT?

- Bioidentical hormones are exogenous hormones that are identical to those produced in a woman's body (e.g., estradiol, estrone, estriol, and progestogen). They are either commercially manufactured or chemically compounded in pharmacies into formulations such as topical creams, gels, and suppositories. The commercially manufactured prescription products are subject to regulation by the FDA and have been tested for potency, purity, efficacy, and safety. Conversely, pharmacist-compounded formulations are not subject to the same regulations and, therefore, the efficacy and safety is questionable. Some patients view bioidentical hormones, particularly the pharmacist-compounded formulations, as "natural" and assume these formulations are safer than currently marketed prescription hormone products. However, due to a lack of regulation, these products could potentially cause more harm than benefit. There is little evidence comparing the safety and efficacy of conventional HT to prescription bioidentical HT and, thus, the same risks and benefits should be assumed.

CLINICAL COURSE: ALTERNATIVE THERAPY

Because Mrs Peterson is considering stopping her HT because of her family history of breast cancer but still desires some relief from hot flushes, she asks for additional information on other alternatives. She has heard that black cohosh should not be used in women with breast cancer, but she has a friend who also has a family history of breast cancer who has been on black cohosh for about 9 months on the recommendation of her physician, although the friend must have a checkup with lab tests every 6 months. Mrs Peterson asks if black cohosh or soy would be an appropriate option to help keep her hot flushes under control. See Section 19 in this instructor's guide for questions and answers about the use of black cohosh for managing menopausal symptoms.

REFERENCES

1. Bolland MJ, Ames RW, Horne AM, Orr-Walker BJ, Gamble GD, Reid IR. The effect of treatment with a thiazide diuretic for 4 years on bone density in normal postmenopausal women. Osteoporos Int 2007;18:479–486.
2. Grady D. Management of menopausal symptoms. N Engl J Med 2006;355:2338–2347.
3. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605–613.
4. Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–333.
5. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007;297:1465–1477.
6. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701–1712.
7. Utian WH, Shoupe D, Backmann G, Pinkerton JV, Pickar JH. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. Fertil Steril 2001;75:1065–1079.
8. Fugate SE, Church CO. Nonestrogen treatment modalities for vasomotor symptoms associated with menopause. Ann Pharmacother 2004;38:1482–1499.
9. Speroff L, Gass M, Constantine G, Olivier S. Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms. Obstet Gynecol 2008;111:77–87.
10. Grady D. A 60-year-old woman trying to discontinue hormone replacement therapy. JAMA 2002;287(16):2130–2137.