Managing the Symptomatic Menopausal Patient in Primary Care:

A Case-Based Approach

Welcome! As you read through this activity, please look for: "*What would you do?*" and answer the interactive "*Case Clinical Questions*". You will also see how your peers responded.

What would you do?

Case Clinical Question

Given Lena's case history, what would you prescribe for her menopausal symptoms?

A. Lifestyle changes only
B. Combination hormone therapy
C. Transdermal estrogen
D. Systemic estrogen therapy
E. Nonhormonal pharmacologic treatment

Release Date: January 31, 2008
Expiration Date: January 30, 2009

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In September 2007, a Menopause CME planning meeting was convened in Atlanta, consisting of primary care and women's health specialists. This group initially reviewed and discussed the results of a large recent primary care physician (PCP) and patient needs assessment analysis on menopause and the patient-PCP relationship. A number of barriers to good patient care were identified from this analysis. Chief among them is confusion generated by the initial published results of the Women's Health Initiative (WHI) – approximately 80% of PCPs in the needs assessment found the information generated by the WHI to be confusing and inconclusive. Another barrier identified was that very few women are proactively and systematically screened for menopause; unless patients raise the topic themselves, it is often not addressed. In addition, clinical knowledge gaps were identified, specifically related to the treatment of menopausal symptoms and the appropriate use of hormonal versus alternative therapies.

With these issues at the forefront, the faculty developed a series of cases that addressed the major concerns of primary care physicians and patients when faced with the various clinical aspects of menopause and perimenopause. This case-based approach puts these issues into a relevant perspective for primary care clinicians and provides practical, specific treatment recommendations based on the latest clinical evidence.

We believe you will find this monograph a valuable medical education resource that will help bridge the gap between the patient and the primary care physician. On behalf of the planning faculty, I thank you for your interest.

Jeffrey P. Levine, MD, MPH
Chair

Introduction

Helping women maintain their health during the perimenopausal and menopausal periods of their lives remains a significant challenge for primary care clinicians. Managing menopausal health requires an ongoing effort to keep up to date with the data on medical management of menopausal symptoms and treatments designed to prevent a number of disabling conditions associated with menopause and aging, such as osteoporosis, cardiovascular disease, and breast cancer.

According to a recent needs assessment based on focus groups, telephone interviews, and a national survey, however, several barriers to good patient care must be overcome for practitioners to develop skills that will help them identify and evaluate the menopausal woman's needs. Chief among them is the confusion generated by the Women's Health Initiative (WHI) study (Table 1).[1-5]

Table 1. Women's Health Initiative (WHI) Clinical Trials of HT[1-4]

- >27,000 postmenopausal women were randomized between 1993 and 1998
- Age at baseline ranged from 50–79 years
  - Mean age, ≈63 years
- Primary outcomes
  - Coronary heart disease (CHD) (nonfatal myocardial infarction, CHD death)
  - Invasive breast cancer
- Approximately 8 years' follow-up planned
  - 2002: Combination therapy arm halted, increased risk of breast cancer, cardiovascular events, strokes, and thrombosis
  - 2004: E-only arm halted. NIH update: risk of estrogen-only therapy for women without an intact uterus outweighs benefits; stroke risk increased; thrombosis inconclusive

The WHI study, which was sponsored by the National Institutes of Health, enrolled approximately 27,000 women aged 50 to 79 years between 1993 and 1998. It was a randomized, controlled clinical trial designed to evaluate the health benefits and risks of 4 interventions including 2 postmenopausal hormone therapy (HT) modalities, an estrogen monotherapy treatment arm, and a combination estrogen plus progestin treatment arm. The primary outcomes were coronary heart disease (ie, acute myocardial infarction, silent myocardial infarction, or death) and invasive breast cancer.

The estrogen plus progestin HT arm of the clinical trial was halted early, in July 2002. Statistical endpoints reached indicated an increased risk of breast cancer, cardiovascular complications, stroke, and thrombosis. At that time, the investigators concluded that the therapeutic risks exceeded the benefits of this treatment. However, there was no increase in cardiovascular or overall mortality, and the increased absolute risk of cardiac events (7/10,000/yr), breast cancer (8/10,000/yr), and strokes (8/10,000/yr) noted in this treatment arm were small.

The estrogen-only component of the clinical trial also ended early, in March 2004. The NIH issued an update that stated that the risk of estrogen-only therapy (for women without an intact uterus) outweighed the benefits, due to an increased risk of stroke. The results were inconclusive as to the risk for thrombosis. However, there was no significant increase in cardiovascular events, breast cancer, or mortality in this treatment arm. The increased absolute risk of stroke was also small.

The study, however, far from resolving the debate about hormone therapy, has raised serious and important questions about generalization of the study findings. Practitioners have found that in most cases it is difficult to apply WHI results to healthy younger or early perimenopausal and postmenopausal women, or to different ethnic groups for a number of reasons. First, the study population included older women, with the average participant being 12 years postmenopausal. In actual clinical practice, most patients seek treatment for menopausal symptoms within the first 2 years of menopause. Secondly, the selection criteria excluded women more characteristic of those seen in daily community practices. These women are typically younger, less obese, and healthier than the women recruited for the study. Also, the study did not evaluate the efficacy of hormonal treatment in managing menopausal symptoms and vaginal atrophy, symptoms which, according to the WHI, constitute the major reason women choose and remain on treatment.[1-5] In fact, women with severe vasomotor symptoms were excluded from the study population. As a result, the majority of physicians (according to the needs assessment, approximately 80%) find the information generated by the WHI study to be confusing and inconclusive. Finally, knowledge gaps can be found in the profession itself, specifically about the following:

- Individualizing treatment of menopausal symptoms: how to best treat each patient's symptoms, and for how long?
- Appropriate use of therapeutic options – hormonal, non-hormonal, and non-pharmacologic
- Comparing the efficacy and safety of Food and Drug Administration (FDA)-approved estrogen/hormonal therapies versus compounded estrogen/hormonal therapies
- Distinguishing hormonal-related menopausal symptoms from depression, other mood disorders, and other causes of sexual dysfunction – overlap among these symptoms can cause confusion, and finally,
- Lack of access to clear, current, unbiased, evidence-based data – this was cited as a major barrier with significant consequences. The result of being deprived of solid information is that primary care clinicians lack the confidence needed to be able to discuss menopause and its issues with their patients

Table 2 includes a list of obstacles to medical management that study participants cited.

This monograph is part of a larger program designed to educate primary care clinicians about the perimenopause and menopause so that they can better care for and communicate with their patients. A case-based approach to learning about the perimenopause and menopause and how best to manage these stages may help physicians to better guide their patients through the treatment decision process to improve and help maintain patient overall health and quality of life.

Table 2. Menopause From a Woman's Perspective: Results of Needs Assessment[6-9]

- Although 85% of women were experiencing hot flashes lasting 3 to 5 years, less than 10% sought medical assistance for symptoms
- More than half of women surveyed said they left health appointments with unanswered questions about menopause and hormone therapy
- The majority of women interviewed favored communication about the risks and benefits of HT to facilitate an informed personal choice
- Women are seeking information on their own
- Women surveyed about their attitudes and perceptions about HT greatly overestimated the risk associated with the therapy. Despite that, most (about 65%) would recommend HT to their friends
- Herbal therapies have become increasing popular. According to the data, 96% of women have tried herbal therapies of some sort to treat their symptoms

For consistency throughout this monograph, the following terminology will be utilized:

•ET	Estrogen therapy
•EPT	Combined estrogen-progestogen therapy
•HT	Hormone therapy (encompassing both ET and EPT
•CC-EPT	Continuous-combined estrogen-progestogen therapy (daily administration of both estrogen and progestogen
•CS-EPT	Continuous-sequential estrogen-progestogen therapy (estrogen daily, with progestogen added on set sequence)
•Progestogen	Encompassing both progesterone and progestin

NAMS position statement. *Menopause. 2007.*

Case 1: Postmenopausal Patient With Vasomotor Symptoms and Vaginal Atrophy

Case Presentation

Roberta Johnson is a 53-year-old Caucasian female who presents for her annual physical exam. Her last period occurred approximately 1 year ago. She says that she experiences hot flushes about twice during the day and twice at night that are bothersome enough to awaken her. Although she has so far been able to tolerate them without treatment, they are causing her increasing distress. She has also developed painful symptoms of vaginal dryness, dysuria, and dyspareunia, all of which have adversely affected her libido. She has recently entered into a serious relationship and wishes to address her sexual problems. However, her urogenital symptoms are now severe enough to prevent intercourse and are affecting her relationship with her fiancé.

Past Medical History

Roberta's last menstrual period occurred when she was 51 years old. Her medical and surgical histories are notable only for seasonal allergic rhinitis. Her last Pap test and mammogram were performed; she has never had an abnormal Pap smear or mammogram. She had a normal colonoscopy at age 50 years. She does not take any prescription or over-the counter medications. She takes a multivitamin and calcium supplement, but no other supplements.

Family History

- Mother with osteoporosis; positive hip fracture
- No CAD, HTN, VTE, or DM
- No cancer of breast, uterus, ovary

Social History

Roberta has been divorced for 9 years and has been sexually active recently. She is employed in a clerical position. She does not smoke but consumes alcohol socially. For exercise, she walks regularly.

Physical/Laboratory Findings

- Height: 5'6"
- Weight: 149 lbs
- BMI: 26
- Blood pressure: 115/70 mm Hg
- Total cholesterol: 184
  - o HDL: 81
  - o LDL: 69
  - o TG: 147
- Pap smear: normal
- DXA: Normal (T score: +0.11 of the hips; + 0.06 of the lumbar spine)

Speculum examination reveals significant atrophy of the vaginal mucosa – pale vagina without rugae, petichae on cervix. The bimanual examination demonstrates no uterine or adnexal masses or tenderness. Clinical breast examination reveals no masses, discharge, or axillary adenopathy.

Case Clinical Question

Given Roberta's case, what would you offer her? (select only one answer)

A. Lifetyle changes only
B. Local vaginal estrogen therapy
C. Systemic estrogen therapy (ET)
D. Systemic combination estrogen/ progestin therapy (HT)
E. B & D above

What would you do?

Case Discussion: Therapeutic Interventions

Roberta Johnson is a 53-year-old woman in good health who is now experiencing menopausal symptoms that require treatment.

Vasomotor symptoms such as hot flushes, night sweats, sleep disturbances, and irritability usually begin late in the menopausal transition stage and early postmenopause (Table 3).[10]

Table 3. Stages of Reproductive Aging Workshop[10]

						Final Menstrual Period (FMP)		
Stages:	-5	-4	-3	-2	-1	0	+1	+2
Terminology:	Reproductive			Menopausal Transition			Postmenopause	
	Early	Peak	Late	Early	Late*		Early*	Late
				Perimenopause				
Duration of Stage:	variable			variable		(a) 1 yr	(b) 4 yrs	until demise
Menstrual Cycles:	variable to regular	regular		variable cycle length (>7 days different from normal)	≥2 skipped cycles and an interval of amenorrhea (≥60 days)	Amen x 12 mos	none	
Endocrine:	normal FSH		↑ FSH	↑ FSH			↑ FSH	

* Stages most likely to be characterized by vasomotor symptoms ↑ Elevated

Soules MR, et al. Executive Summary: stages of reproductive aging workshop (STRAW). Park City, Utah; July 2001.

However, hot flushes, one of the most uncomfortable of these symptoms, may continue well into the postmenopausal stage of life (Figure 1).[11]

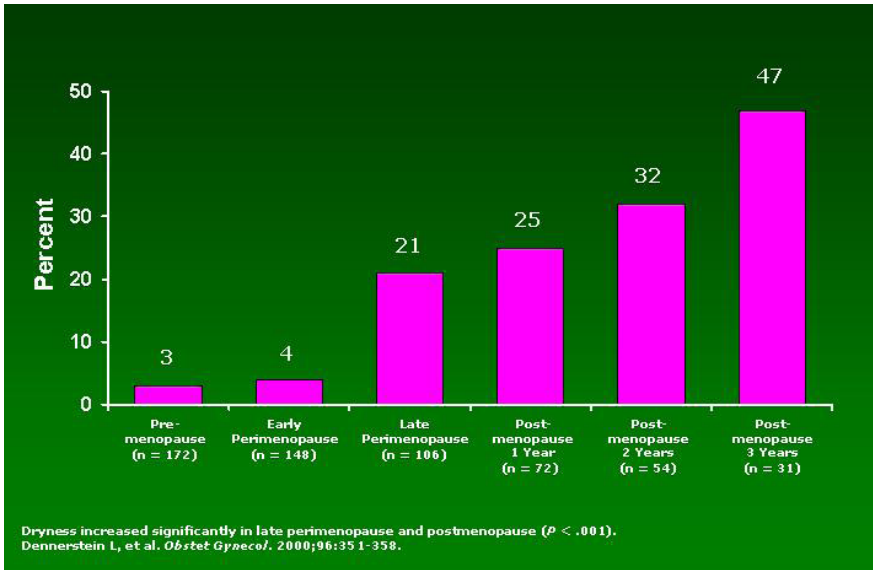
Although there are a number of therapies available for the treatment of vasomotor symptoms, none are as effective as estrogen. In fact, for patients suffering with moderate-to-severe vasomotor symptoms (defined as more than 2 or 3 hot flushes, respectively, with night sweats and sleep disruption), hormone therapy is the only treatment approved by the FDA.[12]

Roberta is also suffering from other menopausal symptoms, including vaginal dryness, dysuria, dyspareunia, and sleep disturbances.

The urogenital symptoms that Roberta reports are not uncommon. Many postmenopausal women complain of symptoms that are a consequence of vaginal atrophy (eg, vaginal dryness, vulvovaginal irritation and itching, and dyspareunia). The term vaginal atrophy describes vaginal walls that are thin, pale, dry, and sometimes inflamed (ie, atrophic vaginitis). In contrast to vasomotor symptoms, which often gradually diminish with time, urogenital symptoms can worsen and are not likely to resolve without medical intervention (Figure 2).[13,14]

Figure 1. Hot Flushes: Years of Continuance Following Menopause[11]

Figure 2. Increase in Vaginal Dryness With Menopause Over Time[14]

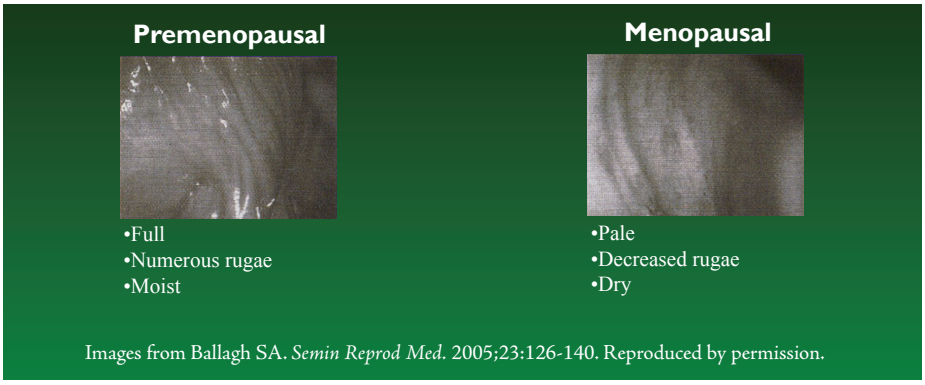


Vaginal atrophy is a frequent consequence of urogenital aging, affecting 10% to 40% of postmenopausal women.[13] The signs of atrophy that are observed during the physical evaluation of the vulva and vagina vary with its degree of severity. As an adjunct to the physical examination, the vaginal pH can be measured either by cytology or wet mount smears to substantiate the diagnosis. In patients with vaginal atrophy, the vaginal pH is typically greater than 5.0.[13] Without treatment, vaginal atrophy can result in years of urogenital discomfort and impact quality of life significantly.

The therapeutic gold standard for the treatment of moderate to severe vaginal atrophy is estrogen therapy, administered either systemically or vaginally at a low dose (Figure 3).[13,15,16]

Figure 3 shows, on the left, the full vaginal wall of a premenopausal woman, which has numerous rugae and is moistened by vaginal secretions. In contrast, the vaginal wall of a menopausal woman, shown on the right, is pale and smooth, with decreased rugae, and is dry because of decreased vaginal secretions.

Figure 3. Difference in Appearance of Vaginal Walls of Premenopausal and Menopausal Women[17]



Images from Ballagh SA. *Semin Reprod Med.* 2005;23:126-140. Reproduced by permission.

Clinical Consideration

Given these considerations, what would you now offer this patient?

Case Resolution: The Intervention

Roberta was prescribed an oral combination regimen (0.3 mg [CEE]/1.5 mg medroxyprogesterone [MPA], which is FDA-approved/indicated for both vasomotor symptoms and for vaginal atrophy.[18]

Hormone therapy is a reasonable short-term option for the management of most symptomatic postmenopausal women.[19] Table 4 includes some other systemic hormonal options. Exceptions include women with a history of breast cancer, coronary heart disease, a prior venous thromboembolic event or stroke, or those at high risk for these complications (see Tables 8 and 9). Short-term therapy is considered to range from 6 months to less than 5 years.

In women who still have an intact uterus, like Roberta, combination hormone therapy should be prescribed because of the association of unopposed estrogen and endometrial hyperplasia and cancer.

The FDA and the clinical guidelines developed by numerous organizations, including the North American Menopause Society (NAMS), American College of Obstetricians and Gynecologists (ACOG), and Society of Obstetricians and Gynaecologists of Canada (SOGC), recommend prescribing hormone therapy at the lowest effective dose.[20-24] The FDA also recommends that the treatment be used for the shortest duration consistent with treatment goals.[25] The NAMS position is congruent with that of the FDA, but it also notes that, provided the patient is aware of risks/benefits of hormone therapy, she may remain on treatment under specific circumstances, such as if symptom relief outweighs the risks of continuation of therapy, there is a high risk for fracture, or the therapy is considered a viable option for prevention of osteoporosis.[26] However, attempts should be made over time to lower the dose or cease hormone therapy and introduce alternate bone-sparing therapy.[25] Table 5 provides a list of the risk/benefits associated with hormone therapy.[27,28]

PRACTICE RECOMMENDATION #1

Prescription systemic estrogen-containing products remain the therapeutic standard for moderate to severe menopause-related hot flashes.

Sources:
•NAMS. *Menopause.* 2004;11:11-33.
•Speroff L, Haney AF, et al. *Menopause.* 2006;13:442-450.
See Appendix for evidence.

Table 4. Examples of Available Systemic Estrogen Therapies (ETs)/Hormone Therapies (HTs)[19]

Drug	Available Strengths
Oral estrogens*	
Estradiol†	
Estrace® (Warner Chillcott)	0.5, 1, 2 mg
Gynodiol® (Novavax)	0.5, 1, 1.5, 2 mg
Esterified estrogens	
Menest® (Monarch)	0.3, 0.625, 1.25, 2.5 mg
Estropipate†	
Ogen® (Pharmacia)	0.75, 1.5, 3 mg
Ortho-est® (Women First Healthcare)	0.78, 1.5 mg
Conjugated equine estrogens (CEE)	
Premarin® (Wyeth-Ayerst)	0.3, 0.45, 0.625, 0.9, 1.25 mg
Conjugated synthetic estrogens	
Cenestin™ (Elan)	0.3, 0.45, 0.625, 0.9, 1.25 mg
Enjuvia™ (Elan)	0.625, 1.25 mg
Estrogen-progestin combinations	
Prempro™ (Wyeth-Ayerst)▲	0.3 mg CEE/1.5 mg medroxyprogesterone, 0.45/1.5 mg, 0.625/2.5 mg, 0.625/5 mg
Ortho-Pretest® (Monarch)	
Activella® (Pharmacia)	1 mg estradiol/0.9 mg norgestimate
FemHRT® (Warner Chilcott)	5 mcg ethinyl estradiol/ 1 mg norethindrone acetate
Angeliq® (Berlex)	1 mg estradiol/0.5 mg drosperinone

Drug	Available Strengths
Transdermal estrogens*	
Estradiol patches†	
Alora® (Watson)	0.025, 0.05, 0.075, 0.1 mg/d
Climara® (Beriax)	0.025, 0.05, 0.06, 0.075, 0.1 mg/d
Esclim® (Women First)	0.025, 0.0375, 0.05, 0.075, 0.1 mg/d
Vivelle® (Novartis)	0.05, 0.1 mg/d
Estrogen-progestin patches	
CombiPatch® (Novartis)	0.05 mg estradiol/0.14 mg norethindrone, 0.05 mg/0.25 mg
Climara Pro® (Berlex)	0.045 mg estradiol/0.015 mg levonorgestrel
Gel	
EstroGel® (Solvay)	1.25 mg (0.75 mg estradiol)
Emulsion	
Estrasorb® (Novavax)	0.025 mg estradiol/pouch
Intravaginal rings*	
Femring® (Warner-Chilcott)	0.05 mg estradiol/day over 3 months

* For women with an intact uterus, a progestin must be added to estrogen therapy.
† Available generically.
▲ Also available as Premphase which contains both combination tablets and estrogen alone.
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Table 5. Attributable Risk Summary for Estrogen + Progestin Versus Estrogen Monotherapy: Women's Health Initiative[27,28]

Per 10,000 Women per Year on Estrogen+Progestin

Risks:
- 7 more women with CHD
- 8 more women with stroke
- 8 more women with pulmonary embolism
- 8 more women with breast cancer

Benefits:
- 6 fewer women with colorectal cancer
- 5 fewer women with hip fractures

Net Effect:
- 19-20 extra adverse events

Per 10,000 Women per Year on Estrogen-Alone

Risk:
- 12 more women with stroke

Benefit:
- 6 fewer women with hip fracture

Null (not statistically significant):
- CHD, pulmonary embolism, breast cancer, colorectal cancer

Net Effect:
- 2 extra adverse events

Sources: Writing Group for the WHI Investigators, *JAMA*. 2002;288:321-333.
The Women's Health Initiative Steering Committee. *JAMA*. 2004;291:1701-1712.

Note the net effects per 10,000 women per year depicted in Table 5: no significant increase in mortality rate in either arm was observed.[27,28]

Roberta was also provided with information on how she might relieve some of her menopausal symptoms (Table 6).

Table 6. How Do I Manage My Menopausal Symptoms Effectively? A Patient Handout[29]

Here are some helpful strategies for relieving some of your menopausal symptoms:

Hot Flashes

- Sleep in a cool room
- Dress in layers
- Wear "breathable fabrics" such as cotton or CoolMax™
- Drink cool beverages
- Avoid alcohol

Sleep

- Get at least 30 minutes of exercise most days of the week
- Don't exercise close to bedtime
- Avoid large meals and alcohol close to bedtime
- Limit your work close to bedtime
- Keep your bedroom dark, cool, and quiet
- Try to go to bed and wake up the same time each day
- Avoid napping during the day
- If you wake up at night and can't fall back to sleep, get up and read until you become sleepy again
- Keep your bed for sleeping and for sex

Sexual Relations

- Thinning of your vagina and vulva during menopause can make sexual relations less comfortable.
  Try—
- A water-based over-the-counter vaginal lubricant such as KY Jelly™ can be helpful
- Estrogen cream can be prescribed to help you with vaginal dryness

Case Clinical Question

Roberta returns 2 months later for a follow-up appointment and states that although her vasomotor symptoms have improved considerably, she is still experiencing moderate urogenital discomfort. What would you do now?

A. Increase the dosages of the combination hormone therapy regimen?
B. Add on a low-dose local estrogen therapy?
C. Recommend use of nonprescription vaginal lubricants?

What would you do?

Case Resolution at 3-Month Follow-up Appointment

To avoid any potential side effects that might be associated with an increase in the dosages of her oral combination hormone therapy, a low-dose local estrogen therapy is added to her established oral regimen.[13]

PRACTICE RECOMMENDATION #2

Although nonprescription vaginal lubricants and moisturizers may provide some relief for vaginal dryness, estrogens are far superior, and local treatment of these symptoms with estrogen (with an intravaginal ring, tablet, or cream) is preferred. Vaginal estrogens also significantly reduce the rate of recurrent urinary tract infections compared with placebo.

Source: Institute for Clinical Systems Improvement. *Menopause and Hormone Therapy*. 8th ed. October 2005.
See Appendix for strength of evidence.

Case Resolution at 6-Month Follow-up Appointment

Roberta reports that her vasomotor symptoms are greatly improved and her urogenital discomfort has almost disappeared. While local vaginal hormone therapy is generally more effective for urogenital atrophy than systemic estrogen, with less potential side effects, local vaginal estrogen therapy does not provide relief of vasomotor symptoms. The risks and benefits of her treatment are re-evaluated and both Roberta and her clinician agree that it is appropriate for her to continue treatment.

PRACTICE RECOMMENDATION #3

Vaginal hormone therapy should be continued for women as long as the distressing symptoms remain.

Sources:
NAMS. *Menopause*. 2007;14(3 Pt 1):355-369.
Lobo RA, Bélisle S, Creasman WT, et al. *MedGenMed*. 2006;8:40.
See Appendix for evidence.

Case 2: Perimenopausal Patient With Moderate to Severe Vasomotor Symptoms, Depression, and a Family History of Breast Cancer Who Requests Treatment With "Bioidenticals"

Case Presentation

Jennifer Moore is a 44-year-old, married Caucasian woman who presents with symptoms of the perimenopause. Her primary complaints include frequent hot flushes (at least 8/day) with drenching night sweats, difficulty falling/staying asleep, and decreased libido, all progressing over the past 3 months. She states that her periods used to be very regular, but for the past 6 months have become increasingly irregular/variable, occurring approximately every 3 to 4 weeks and lasting about 7 days, with a heavier flow the first 2 days. She also says that she suffers severe symptoms of premenstrual bloating and cramping, and is frequently depressed and irritable. She feels that her premenstrual and vasomotor symptoms, decreased libido, depression, and irritability are making her unbearable to live with. She sums up the impact of her current health status, in remarking that "If I don't start feeling better soon, I am afraid that I will seriously jeopardize my relationship with my husband, perhaps even lose him." She has no other mood-related symptoms and denies any suicidal ideations. Jennifer says because of her family history of breast cancer, she would prefer to try bioidentical hormone therapy based on the results of salivary hormone testing she is requesting. She states that she has done enough research in the area of menopause and its treatment to be comfortable with this choice.

Past Medical History

Jennifer's past medical history is unremarkable. She has no history or family history of clinical depression. The onset of her mood-related symptoms correlates temporally with the onset of her vasomotor symptoms and menstrual changes. She has had no other significant life event. Her Pap smears and mammograms are up to date and have always been normal.

Medications

Jennifer does not take any prescription medications or supplements. She has been taking ibuprofen for her premenstrual symptoms with only limited relief.

Family History

- Postmenopausal breast cancer – mother at age 60
- Stroke, diabetes mellitus, hypertension – father
- Hip fracture – mother

Social History

Jennifer has been married for 20 years. Her only child is 12 years of age. Up until this period of her life, the marital relationship was solid. Jennifer does not smoke but has an occasional glass of wine with dinner. For exercise, she walks at least 15 minutes each day.

Physical/Laboratory Findings

- Height: 5'5"
- Weight: 145 lbs
- BMI: 26
- Blood pressure: 115/75 mm Hg
- Total cholesterol : 190
  - HDL: 83
  - LDL: 76
  - TG: 150
- Pap smear: normal

Physical examination is unremarkable. Speculum examination reveals slight thinning of the vaginal mucosa. The bimanual examination reveals no abnormal masses or tenderness. The clinical breast examination is unremarkable.

Case Clinical Question

Given Jennifer's case, what would you offer her?

A. Lifestyle changes
B. Combination oral hormone therapy
C. Low-dose oral contraceptives
D. Low-dose estrogen/combination transdermal patch
E. Local vaginal hormone therapy
F. Antidepressants
G. Bioidentical hormones

What would you do?

Case Discussion: Therapeutic Targets

Jennifer Moore is a 44-year-old woman now in the perimenopause. The perimenopause begins in the early stage of the menopausal transition (stage -2) and ends 12 months after the last menstrual period. Ovulation occurs irregularly during this transitional period, and menstruation may become sporadic, with increasing variability in cycles.

Usually, vasomotor symptoms (hot flushes, night sweats), sleep disturbances, and irritability begin late in the menopausal transition stage and early postmenopause but can also occur in the earlier stage of transition (see Table 3).[10]

Jennifer has several problems that need to be addressed. She is experiencing irregular bleeding characteristic of perimenopausal menstrual cycles and symptoms of premenstrual syndrome. She also has hot flushes as well as night sweats that are disturbing her sleep. Jennifer may still be ovulating, even though irregularly; therefore, contraception may still be an important issue. She also reports depression that may or may not be menopause-related.

Hormone Therapy

Hormone therapy to alleviate symptoms is the mainstay of treatment for the vasomotor symptoms.[19]

PRACTICE RECOMMENDATION #4

When prescribing hormone therapy, use the lowest effective dose possible for the individual patient.

Sources:

- Grimes DA, Lobo RA. Perspectives on the Women's Health Initiative trial of hormone replacement therapy. *Obstet Gynecol.* 2002;100:1344-1353.
- North American Menopause Society. Estrogen and progestogen use in peri- and postmenopausal women: March 2007 position statement of The North American Menopause Society. *Menopause.*2007;14;1-17.

See Appendix for evidence.

For women who still require contraception, low-dose oral contraceptives ([LOCs] ≤35 micrograms of ethinyl estradiol) are considered the optimal treatment because they not only relieve symptoms but also help regulate cycles and prevent pregnancy (see Table 4).[19] LOCs should be prescribed at the smallest dose needed to regulate the menses and avoid intermenstrual bleeding (see Table 4).[19]

All OCs are contraindicated in women aged 35 years and older who smoke, because of the increased risk of cardiovascular or cerebrovascular events. These therapies are also contraindicated in women who have histories of deep-vein thrombosis or undiagnosed abnormal genital bleeding (see Tables 8 and 9). Progestin-only contraceptives may provide treatment alternatives for these women. However, they are not as likely to alleviate Jennifer's vasomotor symptoms. Some of these therapies such as Depo Provera are thought to have a negative effect on bone. (See revised label and black box warning at http://www.fda.gov/medwatch/SAFETY/2004/DepoProvera_Label.pdf.) The benefits of any therapy should always be weighed against its risks.

The low-dose transdermal hormonal contraceptive patch is also an effective alternative for treating perimenopausal symptoms. Because this route of administration avoids first-pass metabolism in the liver, it results in fewer adverse hepatic events.

PRACTICE RECOMMENDATION #5

Clarifying whether a woman is perimenopausal is usually a clinical diagnosis, and laboratory testing is not required. Serum levels of follicle-stimulating hormone (FSH) do not correlate with either intensity or frequency of hot flashes; it is fluctuation in estrogen levels that seems to be of greater significance.

For women with apparent menopausal symptoms who are younger than average (ie, less than age 35), or who continue to have apparently regular menses, testing may be useful. Measure both FSH and estradiol (E2).

Testing may be most useful for the older woman (ie, over age 50) still on oral contraceptives who is interested in confirming that oral contraceptives can be discontinued. FSH levels can fluctuate during the early perimenopause; therefore, an isolated FSH level, particularly if only borderline elevated, is not totally confirmatory. Alternatively, although estradiol levels can occasionally remain elevated after discontinuation of OCPs, a low estradiol level is a reliable confirmation of menopause.

Source: Institute for Clinical Systems Improvement. *Menopause and Hormone Therapy.* 8th ed. October 2005.

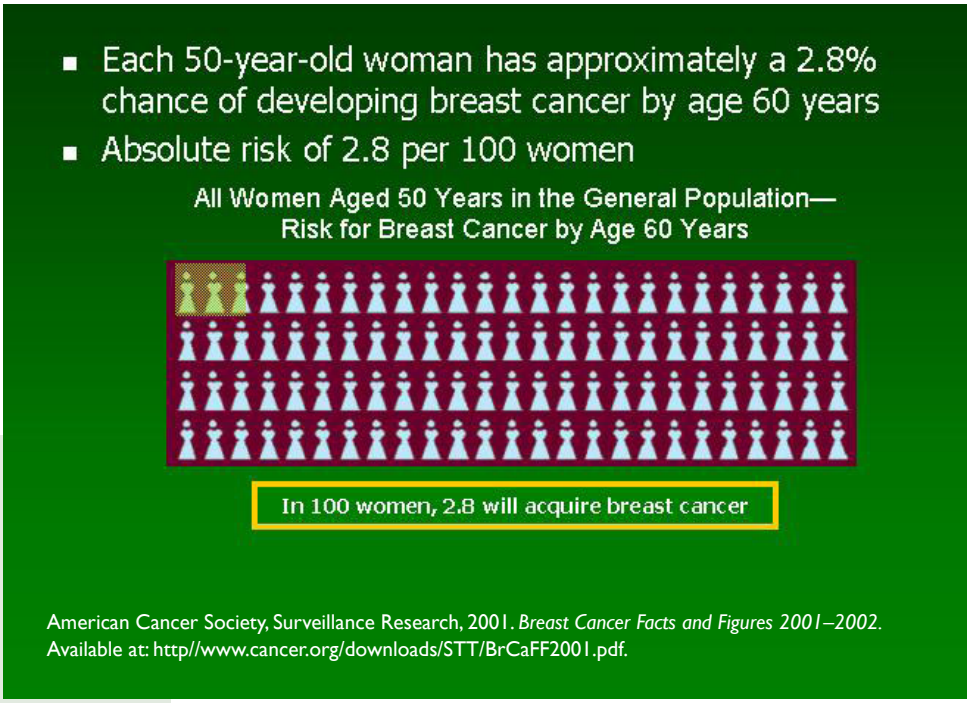
See Appendix for strength of evidence.

Clinicians discussing hormone therapy use with perimenopausal patients should be prepared to address concerns regarding the risk of breast cancer because of the publicity surrounding results from the WHI. Any concerns patients may have about using hormone therapy may be further heightened if there is a family history of breast cancer.[30]

The association between hormone therapy and breast cancer remains somewhat controversial. Generalizing the results of the WHI to a population of healthy postmenopausal women presenting with menopausal symptoms is difficult. As has been observed, the WHI study protocol itself appears problematic due to the age of the study participants (ie, mean age, 63; the average patient being 12 years postmenopause) and the study selection criteria, which excluded women more characteristic of those seen in daily practice (eg, typically younger, less obese, and healthier than the women recruited for the study). Also, the study did not evaluate the efficacy of hormonal treatment in managing menopausal symptoms and vaginal atrophy, symptoms which, according to the WHI, constitute the major reason women choose and remain on treatment.[1-5]

There is, however, an association between hormone therapy and breast cancer, albeit small.[31] In terms of absolute risk, a 50-year-old woman has a 2.8% chance of developing breast cancer, with or without hormone therapy (Figure 4).[32]

Figure 4. Absolute Risk of Breast Cancer: General Population[32]



With hormone therapy, according to the WHI, the relative risk of breast cancer is 1.26, or a 26% increase in the risk of breast cancer versus no hormone therapy.[31]

The absolute risk of breast cancer by age 60 among 50-year-old women receiving hormone therapy for 5.2 years is 3.5 per 100 users, an increase of only 0.7% (Figure 5).[31]

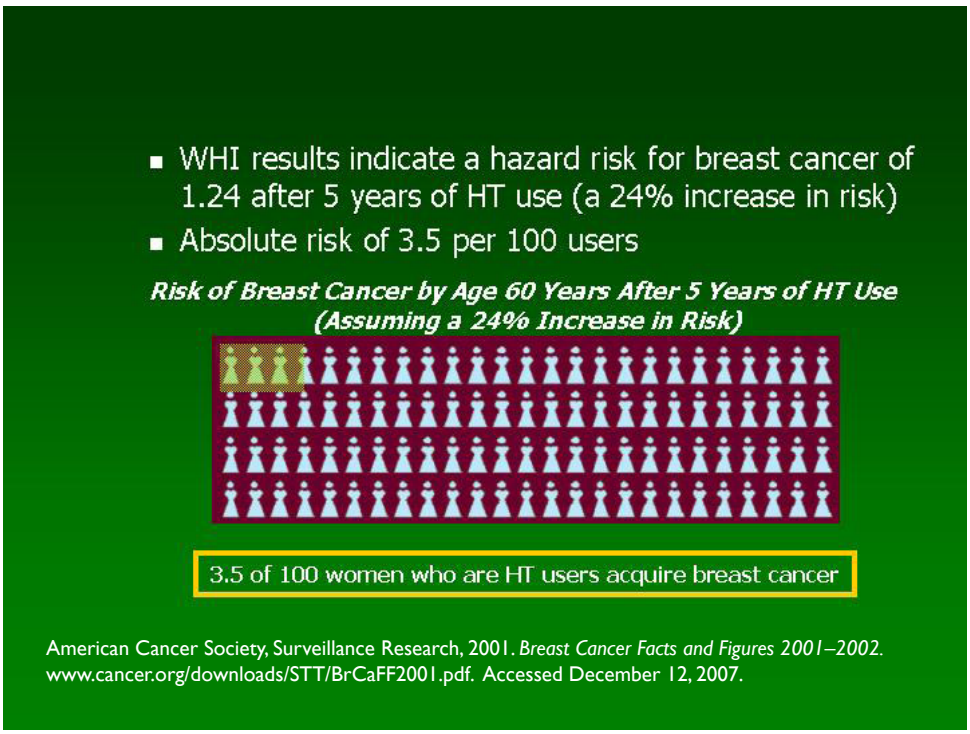
Alternatives to Hormone Therapy

For patients who are either unwilling or unable to take hormone therapy, there are a number of other alternatives on the market that include phytoestrogens, black cohosh, and the so-called "bioidentical" hormones.[32-40] These treatments are not approved by the FDA but are often prescribed by clinicians. Other available alternatives include antidepressants, anticonvulsants, and antihypertensives.[38-41]

Phytoestrogens. Phytoestrogens are compounds similar in structure to estradiol that are found in many edible plants and plant-based foods, such as yams, flax seeds, sesame seeds, and tofu and other soy products. The efficacy of these produces was investigated in a review that included 25 trials that compared phytoestrogens with placebo or control groups involving 2,348 participants. The review concluded mixed results, most of which were negative. The trials were grouped into categories according to type of phytoestrogen: soy foods, beverages, or powders (n=11); soy extracts (n=9); and red clover extracts (n=5). Seven of the 8 soy food trials reporting hot flush frequency outcomes showed negative results. Five soy trials that provided information to calculate effect sizes were in the small-to-medium range, with placebo in 3 trials and soy in 2. Three of the 5 soy extract trials reporting hot flush frequency, including the 2 largest trials were negative. No improvement in hot flush frequency was seen in the red clover trials. Adverse effects were primarily gastrointestinal and taste intolerance in the soy food and beverage trials.[34]

The evidence to date suggests that phytoestrogens do not ameliorate hot flushes or other menopausal symptoms. In addition, there are

Figure 5. Absolute Risk of Breast Cancer: 5 Years of Hormone Therapy[31]



combined (biestrogens/triestrogens), and the dosage is tailored to the individual. One of the disadvantages of bioidenticals is their expense.[36] Many insurance companies do not cover these products. These same hormones are used in several less expensive, FDA-approved commercial products. Some compounded products actually contain higher doses of estrogen than conventional FDA-approved estrogen products.[37] There is also a concern regarding consistency of dosing, since these compounded products are unregulated. Several studies have documented dosing variability/inconsistencies of compounded hormonal products.

Salivary hormone levels, specifically estrogen, are commonly used in compounding to evaluate hormone levels. The rationale for this testing is that saliva is an ultrafiltrate of plasma, and as such, salivary levels should reflect the unbound, bioavailable hormone concentrations. There are some concerns about this approach. First, there are no established norms to correlate serum and salivary levels; and second, there are no available guidelines for dose adjustment based on levels. There is also significant variability in these results. These levels do not even correlate with/reflect what is going on in the target tissue/organs (breast, uterus, bone, etc.). Therefore, the measure is of questionable reliability.[39] Hormonal dose adjustments should be based primarily on patient's symptoms, using the lowest possible dose to address the individual goals.

The safety and efficacy of compounded hormone therapies have not been evaluated in controlled clinical trials. The data available provide no evidence that they are safer or more efficacious than FDA-approved hormonal options/therapies, and there is inadequate evidence to support their use. Clinical trials are unlikely to be conducted because of the lack of patent protection and high cost associated with these studies. These products are neither approved nor controlled by the FDA.[39]

no data to support the safety of long-term therapy with phytoestrogens and other herbal medications.[34]

Black cohosh. Preliminary data on black cohosh from a 2-year, randomized, prospective ongoing trial funded by the National Institutes of Health failed to show any binding to estrogen receptors, although binding to serotonin receptors was observed. In addition, in a review of 14 trials, including 4 randomized trials using a placebo and/or estrogen treatment arm, 3 of 4 trials found black cohosh to be beneficial (only 1 of these 3 used placebo as a control), and 12 of 14 reported some benefit. The longest trial currently has run for 6 months. Black cohosh is approved in Germany for a 6-month treatment period, and there is controversy regarding long-term safety issues.[34,35]

Bioidenticals. Bioidentical hormones are preparations compounded by a professional for an individual according to a healthcare provider's prescription. Estradiol (produced by the ovaries, most common estrogen in the premenopausal women), estriol (a relatively weak placental estrogen), and estrone sulfate (quantitatively the most important circulating estrogen), are examples of bioidentical hormones, because they are found in the human body. Compounded hormone therapy is marketed as being more "natural" because only bioidentical hormones are used, multiple estrogens are

Depression: Clinical or Situational (Menopause-Related)?

In addition to her vasomotor symptoms, Jennifer also complains of depression and irritability. Observational studies report that the perimenopause may be associated with an increased risk of significant depressive illness, even for someone without a prior history of depression.[41] Because the symptoms of menopause may overlap with those of depression, differentiating between the two can be difficult. (Figure 6.)[39,40]

When considering depression, it is important to determine whether the depression is a climacteric symptom that may resolve with treatment of other climacteric symptoms, or whether the depression is a pre-existing psychological condition that needs to be addressed as a separate issue. Depression can be assessed during the history taking or with an office questionnaire. Women with a prior history of depression are the most vulnerable during the perimenopause.

The antidepressants venlafaxine, paroxetine, and fluoxetine and the anticonvulsant gabapentin have shown some efficacy for treating hot flushes and are well tolerated.[38] Mirtazapine is a new addition to the list. Available data suggest that mirtazapine is a reasonable treatment for patients with hot flushes, particularly those with sleep disturbances.[38] Clonidine and methyldopa are antihypertensive agents with modest efficacy but relatively high rates of adverse effects.[38]

Jennifer also has a family history of hip fracture, a factor that increases her risk for osteoporosis, which, as is well known, increases as estrogen levels decline.[42] Preventive measures will be required.

Case Resolution: The Intervention

Because of her heightened sensitivity and awareness of physical changes that are occurring in her body, this period of life presents a woman with the opportunity to assess her overall health and evaluate what can be done to improve it. For the clinician, it can be an opportunity to advise patients about good health practices, such as exercising and eating healthy food, and a simultaneous decrease in risky health behaviors such as smoking or excess alcohol intake.

Jennifer was advised by her clinician about the importance of maintaining a healthy low fat diet, continuing her exercise program, and taking adequate amounts of calcium (adults under age 50: 1000 mg dietary Ca++/day; Patients older than age 50 years should be advised to take 1500 mg per day of elemental calcium). Adding vitamin D (400-800 IU/day) and a multivitamin (without iron) to her regimen was also recommended.

Jennifer and her clinician then reviewed the various treatment options. After a discussion, they agreed that compounding products are not a good choice because they have not been tested and they are not government-approved treatments. Instead, they decided that LOCs are the best choice to fit her needs. Her clinician advised her that this treatment would alleviate her menopausal symptoms, including depression if it was related to her hormonal state, help her premenstrual discomfort, help regulate her cycles, and prevent pregnancy.

PRACTICE RECOMMENDATION #6

Younger perimenopausal women with irregular menstrual cycles and hot flushes may still be occasionally ovulating.

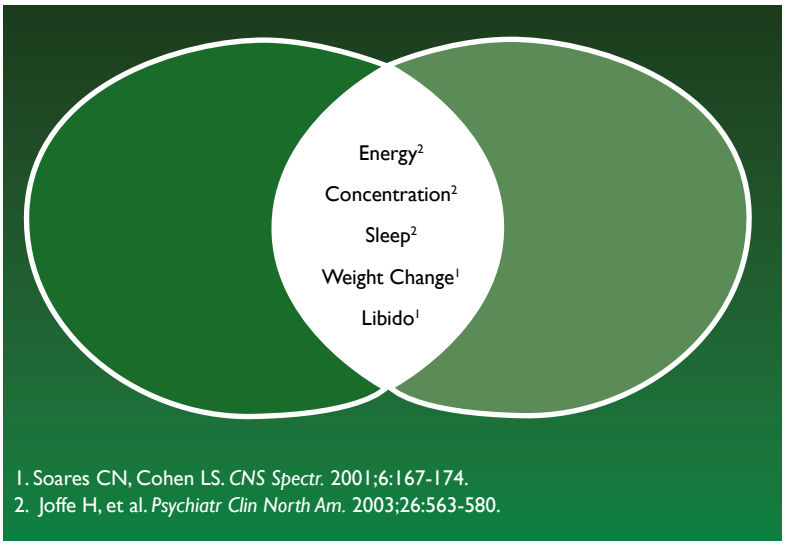
- Consider low-dose oral contraceptives (LOCs) rather than hormone therapy to control symptoms and minimize irregular bleeding while providing still-needed contraception
- Prescribe LOCs to minimize any risk of thromboembolic events
- Oral contraceptives are contraindicated in women over age 35 who smoke

Testing may be most useful for the older woman (over age 50) still on oral contraceptives who is interested in confirming that OCs can be discontinued.

- FSH levels can fluctuate during the early perimenopause; therefore, an isolated FSH level, particularly if only borderline elevated, is not totally confirmatory
- For accurate levels, FSH/LH should be checked while not on OCs – stop for several cycles using backup contraceptive methods in the meantime
- Alternatively, although estradiol levels can occasionally remain elevated after discontinuation of OCs, a low estradiol level is a reliable confirmation of menopause

Source: Institute for Clinical Systems Improvement. *Menopause and Hormone Therapy*. 8th ed. October 2005.
See Appendix for strength of evidence.

Figure 6. Menopause and Depression: Symptom Overlap[39,40]



Her clinician also remarked that if her LOC treatment did not alleviate her depression, Jennifer should then try a course of antidepressant medicine. The decision could be made at the time of a follow-up visit.

Jennifer was also provided a patient hand-out with suggestions on how to manage her symptoms (see Table 6).

Case Clinical Question

Jennifer returns 6 weeks later for her follow-up visit. She tells her clinician that her vasomotor symptoms have subsided considerably, but she still complains of depression.
What do you do?

A. Add SSRI
B. Refer to psychiatrist
C. Encourage to schedule date night with husband

What would you do?

Case Resolution at 2-Month Follow-up Appointment

Jennifer's clinician prescribes a course of SSRIs to treat her depression. The risks and benefits of her LOC treatment are re-evaluated, and both Jennifer and her clinician agree that it is appropriate for her to continue with this therapy. The patient was cautioned that St. Johns wort can decrease the efficacy of OCs.

Case 3: Early Menopausal Woman With Vasomotor Symptoms, Mild Hypertension, Hyperlipidemia, and Family History of CAD

Case Presentation

Lena Gordon is a 50-year old woman who presents with symptoms of the early menopause. Within the last 6 months, she has missed 4 periods, the last one occurring about 3 months ago. At that time, she started to experience hot flushes about 4 to 5 times daily, and 2 to 3 times nightly with accompanying night sweats. Lena says that her symptoms are causing her mild anxiety, are interfering with sleep, and are affecting her quality of life. Lena has an abiding fear of breast cancer and of cardiovascular disease.

Past Medical History

Lena has mild hypertension and mild intermittent asthma, rarely requiring an inhaler. She had an ASCUS Pap 10 years ago, but colposcopic biopsies were all normal/benign; all of her annual Pap smear results have been normal ever since. She has some occasional mild low back pain and stiffness. She has no previous history of insomnia. She has no history of diabetes or any other medical problems.

Medications

Lena takes HCTZ, allergy shots, albuterol sulfate, and an occasional ibuprofen for her back pain. She has never used hormone-derived contraceptives.

Family History

- Mother: died aged 68 years of lung cancer; a smoker of many years; history of coronary artery disease
- Father: died in 70s of heart attack secondary to coronary artery disease; history of high blood pressure, high cholesterol with no therapy; diabetes, type 2; smoked and drank heavily
- Sister: aged 56 years, healthy, married, with 2 children
- Maternal grandparents: died in old age (80s)
- Paternal grandparents: no information

Social History

Lena is employed in the computer technology field as a systems analyst. She has never been married and has no children. She is involved in a serious relationship with a man for the past 3 years. She is sexually active, and uses condoms and over-the-counter jellies for contraception. She notes some vaginal dryness with intercourse, improved with water-based lubricants. Lena says that her diet is healthful and, in her words, she "eats well." She says that she frequently has spinach salad, yogurt, fish, and meat. Her carbohydrate intake includes occasional pasta for dinner and, infrequently, a bagel for breakfast. Lena does not smoke but has one beer or a glass of wine daily; occasionally, she has a mixed drink. Lena exercises several times a week. Her program consists of the elliptical trainer or walking, 20 minutes, 4 days each week, but no weight training. She does not take any calcium or vitamin D supplements.

Physical/Laboratory Findings

- Height: 5'3"
- Weight: 142 lbs (stable)
- BMI: 26
- Blood pressure: 150/100 mm Hg
  Repeat 130/75 mm Hg
- Total cholesterol: 225 mg/dL
  - HDL: 81
  - LDL: 124
  - TG: 101
  - Cholesterol/HDL ratio: 2.8 (average cardiovascular risk)
- Fasting glucose: 83
- Pap smear: normal

The physical examination is normal. Speculum examination reveals very slight thinning of the vaginal mucosa. The bimanual examination reveals no abnormal masses or tenderness. The clinical breast examination is unremarkable.

Case Discussion: Therapeutic Targets

Lena Gordon is a 50-year-old woman with symptoms that indicate she is in the early stages of menopause. In particular, Lena is experiencing daily and nightly hot flushes and night sweats which, she says, are a source of great distress for her. Lena has a family history of cardiovascular disease and she is noted to have an elevated blood pressure. Although her total cholesterol level is high, her cholesterol/HDL ratio is low (ie, 2.8, a good indicator of reduced cardiovascular risk). In fact, according to the Framingham risk calculator, Lena is at low risk of heart disease (see Table 7 for Helpful Physician Web Sites and Tools).

Hormone therapy to alleviate symptoms and regulate menstrual cycles is the mainstay of treatment for the vasomotor symptoms Lena is experiencing (Table 4).[19] In fact, for patients suffering with moderate to severe vasomotor symptoms (defined as more than 2 or 3 hot flushes, respectively, with night sweats and sleep disruption), hormone therapy is the only treatment approved by the FDA.[12] Hot flushes are reportedly the most uncomfortable of symptoms related to this stage of life and, far from abating like some of the others do as the menopause progresses from early to late stage, may continue well on into the postmenopause (Figure 1).[11] However, Lena has stated somewhat emphatically that she is afraid of hormone therapy because of its association with an increase in breast cancer and cardiovascular events, all of which have been publicized by coverage of the WHI (see Table 5 for risks and benefits of hormone therapy).[27,28]

What would you do?

Case Clinical Question

Given Lena's case history, what would you prescribe for her menopausal symptoms?

A. Lifestyle changes only
B. Combination hormone therapy
C. Transdermal estrogen
D. Systemic estrogen therapy
E. Nonhormonal pharmacologic treatment

Patients should be educated about the effects of hormone therapy on different risk factors so that they are able to make an informed decision. Statistical information from the WHI about the absolute risk for breast cancer in women not using hormone therapy compared with women using it (2.8% versus 3.5%, respectively) can be used to alleviate fears about developing breast cancer (Figures 4 and 5).[32]

In terms of increased cardiovascular risk associated with hormone therapy, data from a primate model and an observational study in postmenopausal women

Table 7. Helpful Physician Web Sites and Tools

North American Menopause Society
- www.menopause.org

American College of Obstetricians and Gynecologists
- http://www.acog.org

American Society of Reproductive Medicine
- http://www.asrm.org

Framingham Cardiovascular Risk Factor Calculator
- http://www.americanheart.org/presenter.jhtml?identifier=3003499

Breast Cancer Risk Factor Calculator
- http://www.cancer.gov/bcrisktool/

suggest that the timing of exposure to hormone therapy may be an important factor in determining subsequent cardiovascular risk.[42,24] The increased risk of these events may be confined to older women. As noted in the introduction, the WHI study patients who experienced increased incidences of cerebro-cardiovascular events were an older population (a mean age of 63 years) when compared with women enrolled in most observational studies.[1] Older age at the time of instituting hormone therapy might well be associated with more subclinical atherosclerosis at baseline and, therefore, a greater number of subsequent atherosclerotic-related events might be expected. In contrast, women with presumably normal endothelium who start estrogen earlier may derive cardiovascular benefit because advanced, unstable atherosclerotic plaques have not yet formed (see Figure 7).[44]

Transdermal estrogen, according to research, has more favorable effects than oral estrogen on markers for cardiovascular risk, may be less thrombogenic, and may be associated with a lower risk of thromboembolism than oral estrogens.[27,28,45,46]

In one study, 255 postmenopausal women with ischemic heart disease were randomly assigned to transdermal preparations (estrogen alone or combined with progestin) versus placebo. After an average of 31 months of follow-up, investigators found a nonsignificant increase in coronary disease-related events in the transdermal hormone therapy group when compared with the placebo group.[46]

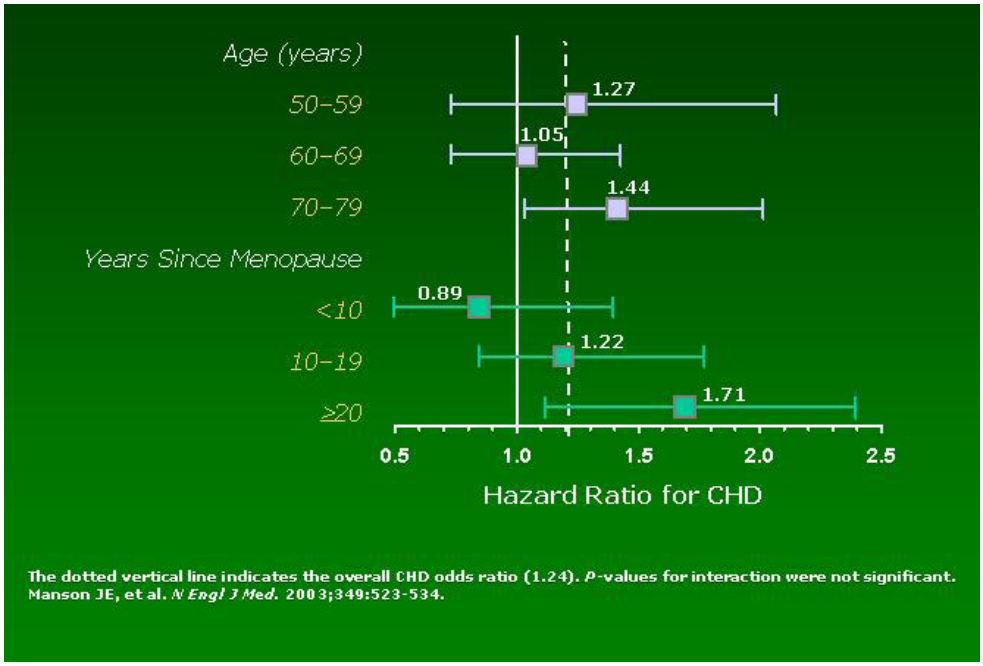
The use of hormone therapy for young postmenopausal women with moderate to severe symptoms appears to be safe.[26] Candidates for this therapy include peri- or postmenopausal women with moderate to severe menopausal symptoms and no contraindications to hormone therapy (see Table 9). The lowest estrogen dose that relieves symptoms should be used and the therapy is generally stopped before 5 years. Postmenopausal hormone therapy should not be prescribed to postmenopausal women of any age for primary or secondary prevention of coronary heart disease. In women taking hormone therapy for menopausal symptoms, treatment should be discontinued if an acute cardiovascular event occurs, and should not be resumed as a secondary prevention strategy.[27,28,43,45,46]

Case Resolution: The Intervention

No tests measuring FSH or estradiol were ordered, given the patient's symptoms and age.

Because of Lena's concerns about hormone therapy and her

Figure 7. WHI CEE/MPA Analyses: Time Since Menopause May Be a Better Predictor of CHD Risk Than Age[44]



family history of cardiovascular disease on both maternal and paternal sides, Lena's clinician decided to offer her treatment with transdermal estrogen gel (2.50 grams 2x daily) for 3 months. Lena was also advised by her clinician about the benefits of a healthy low-fat diet, the importance of exercise – aerobic for cardiovascular benefit and weight training for strengthening bone – and vitamin and mineral supplementation (ie, vitamin D and calcium).

Lena's clinician discussed her overall diet. Lena then admitted that her diet probably had more carbohydrate content than was previously disclosed during initial visit. She agreed to do a 2-3 day food diary, including alcohol intake, to assess any need for modification. They also scheduled a bone density test.

Lena was provided a patient handout with suggestions on how to manage her symptoms and requested to make an appointment in 5 weeks for follow-up (see Table 6).

Clinical Case Resolution at 5-Week Follow-up Visit

Lena returned for a follow-up visit 5 weeks later. At that time, the patient reported that she decreased the transdermal estrogen herself a few weeks ago (1.25 grams per day). She stated that she was feeling better. Her hot flashes and night sweats had decreased steadily over the past several weeks. Her sleep has much improved, and she now has no night-time awakening. Her anxiety symptoms have also resolved. Her clinician changed the preparation to include progesterone. Lena expressed gratification at the therapeutic response.

PRACTICE RECOMMENDATION #7

Hormone therapy is ***not*** contraindicated in clinical settings where many practitioners have often been reluctant to recommend oral contraceptives.* These conditions include:

- endometriosis
- fibrocystic breast changes
- hypertension
- mastalgia
- migraine headaches
- obesity
- tobacco use
- uterine leiomyomata (fibroids)

*Oral contraceptives have much more potent estrogenic effects than hormone therapy.Source: Institute for Clinical Systems Improvement. *Menopause and Hormone Therapy*. 8th ed. October 2005.
See Appendix for strength of evidence.

Summary

In general, current thought indicates that the benefits of hormone therapy outweigh the risks in healthy menopausal women for short-term treatment of menopausal symptoms and prevention of osteoporosis.

Hormone therapy is associated with small increased early risks of heart attack, stroke, thrombosis in legs or lungs, and a small increased long-term risk of breast cancer. It should not be used for prevention of any disease.

ET/HT should be employed for the shortest time consistent with treatment goals and risks, and periodically re-evaluated. Also, therapeutic decisions should be based on the needs and goals of the individual patient. Communication in this area is critical.

The treatment decision is a complex but important one in primary care practice.

Table 8. Who Can Receive Hormone Therapy[39]

FDA-approved indications:

- Treatment of moderate to severe vasomotor symptoms associated with the menopause
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause
- Prevention of postmenopausal osteoporosis (only for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate)
- Women with heart disease risk factors (hypertension, diabetes, smoking)
- Women with family history of breast cancer

Table 9. Who Should Not Receive Hormone Therapy[39]

Contraindications

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of cancer of the breast
- Known or suspected estrogen-dependent neoplasia
- Active deep-vein thrombosis, pulmonary embolism, or a history of these conditions
- Active or recent (within past year) arterial thromboembolic disease (eg, stroke, myocardial infarction)
- Liver dysfunction or disease
- Pregnancy

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Appendix: Practice Recommendations, Sources, and Strength of Evidence

PRACTICE RECOMMENDATION #1

Prescription systemic estrogen-containing products remain the therapeutic standard for moderate to severe menopause-related hot flashes.

Sources:
•NAMS. *Menopause.* 2004;11:11-33.
•Speroff L, Haney AF, et al. *Menopause.* 2006;13:442-450.

Evidence:

- The North American Menopause Society (NAMS) enlisted clinicians and researchers acknowledged to be experts in the field of menopause-associated vasomotor symptoms to review the evidence obtained from the medical literature and develop a document for final approval by the NAMS Board of Trustees
- Speroff, et al. conducted separate 12-week studies in postmenopausal women with moderate to severe vasomotor symptoms. In the first study, women were randomly assigned to EA 0.9 mg/day, EA 1.8 mg/day, or placebo (study 1; N=293), and in the second study to oral EA 0.45 mg/day or placebo (study 2; N=259). Women recorded the frequency and severity of vasomotor symptoms daily and urogenital symptoms weekly on diary cards. Investigators assessed signs of vaginal atrophy

PRACTICE RECOMMENDATION #2

Although nonprescription vaginal lubricants and moisturizers may provide some relief for vaginal dryness, estrogens are far superior, and local treatment of these symptoms with estrogen (with an intravaginal ring, tablet, or cream) is preferred. Vaginal estrogens also significantly reduce the rate of recurrent urinary tract infections compared with placebo.

Source: Institute for Clinical Systems Improvement. *Menopause and Hormone Therapy*. 8th ed. October 2005.

Strength of Evidence: Vaginal dryness – Classes A, C, D, M, R

Class A: Randomized, controlled study

Class C: Nonrandomized trial with concurrent or historical controls; Case-control study; Study of sensitivity and specificity of a diagnostic test; Population–based descriptive study

Class D: Cross-sectional study; Case series; Case report

Class M: Meta-analysis; Systematic review; Decision analysis; Cost-effectiveness analysis

Class R: Consensus statement; Consensus report; Narrative review

PRACTICE RECOMMENDATION #3

Vaginal hormone therapy should be continued for women as long as the distressing symptoms remain.

Sources:
NAMS. *Menopause*. 2007;14(3 Pt 1):355-369.
Lobo RA, Bélisle S, Creasman WT, et al. *MedGenMed.* 2006;8:40.

Evidence:

- NAMS followed the general principles established for evidence-based guidelines to create this document. A panel of clinicians and researchers acknowledged to be experts in the field of genitourinary disease was enlisted to review, synthesize, and interpret the current evidence on vaginal ET for vaginal atrophy, develop conclusions, and make recommendations. Their advice was used to assist the NAMS Board of Trustees in publishing this position statement
- Randomized, controlled trials, albeit limited, have shown that low-dose, local vaginal estrogen delivery is effective and well tolerated for treating vaginal atrophy. All of the low-dose vaginal estrogen products approved in the United States for treatment of vaginal atrophy are equally effective at the doses recommended in labeling

PRACTICE RECOMMENDATION #4

When prescribing hormone therapy, use the lowest effective dose possible for the individual patient.

Sources:
- Grimes DA, Lobo RA. Perspectives on the Women's Health Initiative trial of hormone replacement therapy. *Obstet Gynecol.* 2002;100:1344-353.
- North American Menopause Society. Estrogen and progestogen use in peri- and postmenopausal women: March 2007 position statement of The North American Menopause Society. *Menopause*. 2007;14;1-17.

Evidence:

- Grimes: Review of Women's Health Initiative results and observational studies
- NAMS followed the general principles established for evidence-based guidelines to create this updated document. An Advisory Panel of clinicians and researchers expert in the field of women`s health was enlisted to review the 2004 NAMS position statement, compile supporting statements, and reach consensus on recommendations
- Level of evidence for both references is A: Clinical Trials

PRACTICE RECOMMENDATION #5

Clarifying whether a woman is perimenopausal is usually a clinical diagnosis, and laboratory testing is not required. Serum levels of follicle-stimulating hormone (FSH) do not correlate with either intensity or frequency of hot flashes; it is fluctuation in estrogen levels that seems to be of greater significance.

For women with apparent menopausal symptoms who are younger than average (ie, less than age 35), or who continue to have apparently regular menses, testing may be useful. Measure both FSH and estradiol (E2).

Testing may be most useful for the older woman (ie, over age 50) still on oral contraceptives who is interested in confirming that oral contraceptives can be discontinued. FSH levels can fluctuate during the early perimenopause; therefore, an isolated FSH level, particularly if only borderline elevated, is not totally confirmatory. Alternatively, although estradiol levels can occasionally remain elevated after discontinuation of OCPs, a low estradiol level is a reliable confirmation of menopause.

Source: Institute for Clinical Systems Improvement. *Menopause and Hormone Therapy*. 8th ed. October 2005.

Strength of Evidence: Laboratory testing is usually not necessary to establish menopausal status.
Classes A, C, D, R

Class A: Randomized, controlled study

Class C: Nonrandomized trial with concurrent or historical controls; Case-control study; Study of sensitivity and specificity of a diagnostic test; Population–based descriptive study

Class D: Cross-sectional study; Case series; Case report

Class R: Consensus statement; Consensus report; Narrative review

PRACTICE RECOMMENDATION #6

Younger perimenopausal women with irregular menstrual cycles and hot flushes may still be occasionally ovulating.

- Consider low-dose oral contraceptives (LOCs) rather than hormone therapy to control symptoms and minimize irregular bleeding while providing still-needed contraception.
- Prescribe LOCs to minimize any risk of thromboembolic events
- Oral contraceptives are contraindicated in women over age 35 who smoke.

Testing may be most useful for the older woman (over age 50) still on oral contraceptives who is interested in confirming that OCs can be discontinued.

- FSH levels can fluctuate during the early perimenopause; therefore, an isolated FSH level, particularly if only borderline elevated, is not totally confirmatory.
- For accurate levels, FSH/LH should be checked while not on OCs – stop for several cycles using backup contraceptive methods in the meantime.
- Alternatively, although estradiol levels can occasionally remain elevated after discontinuation of OCs, a low estradiol level is a reliable confirmation of menopause.

Source: Institute for Clinical Systems Improvement. *Menopause and Hormone Therapy*. 8th ed. October 2005.

Strength of Evidence: Women who may still need contraception – Classes A, C, M

Class A: Randomized, controlled study

Class C: Nonrandomized trial with concurrent or historical controls; Case-control study; Study of sensitivity and specificity of a diagnostic test; Population-based descriptive study

Class M: Meta-analysis; Systematic review; Decision analysis; Cost-effectiveness analysis

PRACTICE RECOMMENDATION #7

Hormone therapy is not contraindicated in clinical settings where many practitioners have often been reluctant to recommend oral contraceptives.* These conditions include:

- endometriosis
- fibrocystic breast changes
- hypertension
- mastalgia
- migraine headaches
- obesity
- tobacco use
- uterine leiomyomata (fibroids)

Source: Institute for Clinical Systems Improvement. *Menopause and Hormone Therapy*. 8th ed. October 2005.*Oral contraceptives have much more potent estrogenic effects than hormone therapy.

Strength of Evidence: Vaginal dryness – Classes A, C, D, M, R

Class A: Randomized, controlled study

Class C: Nonrandomized trial with concurrent or historical controls; Case-control study; Study of sensitivity and specificity of a diagnostic test; Population-based descriptive study

Class D: Cross-sectional study; Case series; Case report

Class M: Meta-analysis; Systematic review; Decision analysis; Cost-effectiveness analysis

Class R: Consensus statement; Consensus report; Narrative review

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