VMS TREATMENT LANDSCAPE

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Table of Contents

Introduction

This internal training is for the VEOZA™ TEAM. The objective of this training is to provide an overview of vasomotor symptoms (VMS), the most common symptoms of menopause. This training provides background information on women's health as it relates to VMS due to menopause. This training is not for external distribution or promotional use.

Vasomotor symptoms (VMS), characterized by **hot flashes** and **night sweats** (hot flashes that occur at night), are the most commonly reported symptoms during the **menopause** transition.[1,2] VMS is experienced to some degree by most postmenopausal women.[1]

This module will review the different therapies that may be used for the treatment of VMS as well as discuss the outcomes of several long-term studies that had an impact on the use of **hormone** therapy. This module will conclude with a summary of key established clinical practice guidelines.

1: Hormone Therapy for Treatment of VMS

Introduction

Hormone therapy is the most effective treatment currently available for women who experience the hot flashes and night sweats associated with moderate to severe VMS.[1] This section will describe the evolution of hormone therapy for the treatment of menopausal symptoms, including VMS. This section will then describe the results of the Women's Health Initiative (WHI), WHI Memory Study (WHIMS), and the Million Women Study. It will also describe the different types of hormone therapy used to treat VMS.

Learning Objectives

Upon completion of this section, you should be able to:

- Describe hormone therapy and its use for menopause-related VMS
- Summarize the key results of the WHI, WHIMS, and Million Women clinical trials
- Differentiate among different types of hormone therapy, including **estrogen**-only, estrogen plus **progestin**, and estrogen plus SERM

1.1: How Is Hormone Therapy Used for Treatment of Menopause-Associated Symptoms?

Hormone therapy—or menopausal hormone therapy (MHT)—is a general term that encompasses estrogens, progestins, and combined estrogen plus progestin therapies used to treat various symptoms of menopause, including VMS.[3] During hormone therapy, a patient receives estrogen or a combination of estrogen plus progestin to replace the natural hormones secreted previously by the ovaries.[2] MHT is currently the most effective therapy for VMS.[2,3]

The combination of estrogen and bazedoxifene also may be used to treat VMS.[4] Note that bazedoxifene is an estrogen receptor agonist/antagonist, also referred to as a **selective estrogen receptor modulator (SERM)**.[3] Bazedoxifene alone does not alleviate VMS associated with menopause.[3] However, in a clinical study, estrogen plus bazedoxifene significantly reduced the number and severity of moderate to severe hot flashes compared with placebo.[4]

Key Facts
Estrogen, Progesterone, and Progestin
Endogenous estrogens (e.g., estradiol, estrone, and estriol) are natural hormones produced in the body.[5] Synthetic estrogens are available, such as those used to treat moderate to severe VMS.[5] Progestins are synthetic forms of the body's naturally occurring hormone progesterone that cause progesterone-like effects.[5]

You will learn more about the products that contain either estrogen or estrogen plus progestin and their different uses and effects later in this section. First, let us review some well-known studies that investigated the effects of hormone therapy on long-term health outcomes in postmenopausal women.

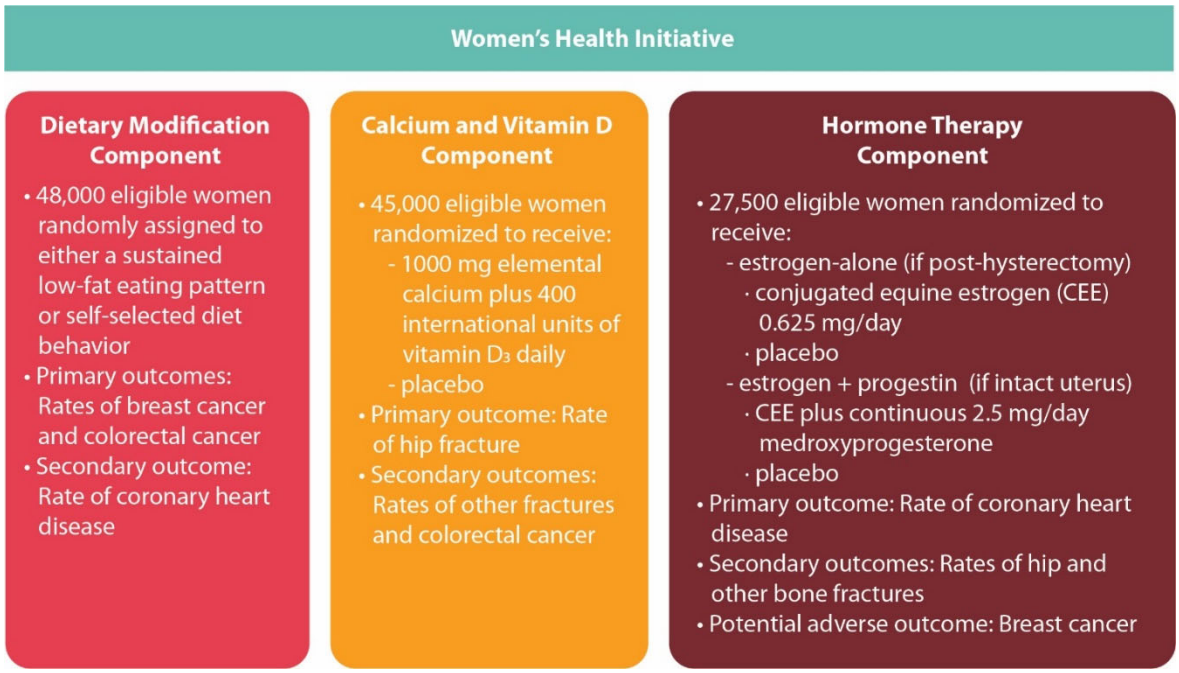
1.2: WHI and the WHIMS

WHI

The WHI is a long-term study funded by the National Heart, Lung, and Blood Institute (NHLBI) that focused on defining risks and benefits of different strategies that could potentially reduce the incidence of heart disease, breast and colorectal cancer, and bone fractures in postmenopausal women.[6,7]

Between 1993 and 1998, the WHI enrolled 161,809 postmenopausal women in the age range of 50 to 79 years in a set of clinical trials, 2 of which involved postmenopausal hormone use.[7]
The study design of the WHI is summarized in the figure below.

Figure 1.1: WHI Study Design[8]



Postmenopausal women who were screened for enrollment in the WHI but who were either ineligible or unwilling to be randomized were offered the opportunity to be 1 of 100,000 women enrolled into an observational study. The goal of the observational study was to provide additional knowledge about risk factors for a range of diseases, including cancer, cardiovascular disease, and fractures, with an emphasis on biological markers of disease risk and risk factor changes as modifiers of risk.[8]

Historical Insights

WHI Extension Studies

The original WHI study began in the early 1990s and concluded in 2005.[6] Since 2005, the WHI has continued as Extension Studies, which are annual collections of health updates and outcomes in active participants. The second Extension Study enrolled 93,500 women in 2010, and follow-up of these women continues annually.[6]

Although the WHI consisted of 3 different components, this module will only focus on outcomes from the hormone therapy component.

Hormone Therapy Component Outcomes: Estrogen-Alone Arm

Overall, 10,739 women were randomized into the estrogen-alone arm of the WHI hormone therapy component, 5310 who received estrogen alone and 5429 who received placebo.[9] Outcomes of the estrogen-alone arm of the WHI hormone therapy component are shown in the following figures.

Figure 1.2: Outcomes in the Estrogen-Alone Arm[8,9]

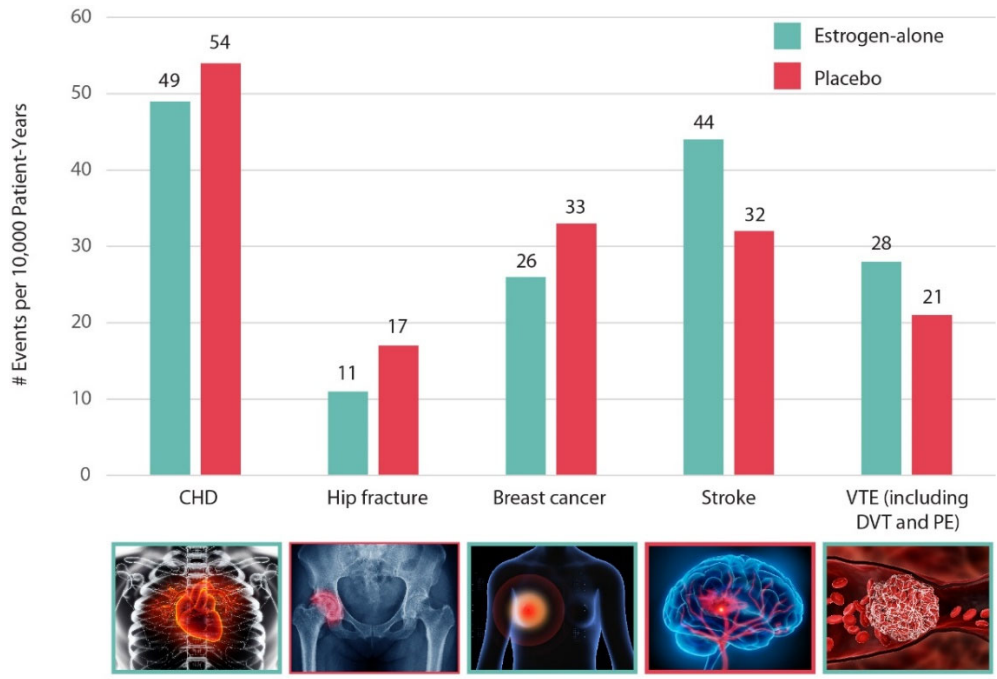
Outcome Measure	Results
Primary outcome measure: Rate of coronary heart disease	• No significant effect of estrogen-alone therapy on the rate of coronary heart disease compared with placebo (49 versus 54 events per 10,000 person-years)
Secondary outcome measures: Rates of hip and other bone fractures	• Estrogen-alone therapy reduced the overall rate of fracture by 30% to 39% compared with placebo • Rates of hip fractures (11 versus 17 per 10,000 person-years), vertebral fractures (11 versus 17 per 10,000 person-years), and total osteoporotic fractures (139 versus 195 per 10,000 person-years) were lower in women who received estrogen alone versus placebo
Primary safety outcome: Rate of breast cancer occurrence	• Invasive breast cancer was diagnosed at a 23% lower rate in women who received estrogen alone compared with placebo (26 versus 33 per 10,000 person-years)
Other safety outcomes: Rates of colorectal cancer or total cancer	• No significant differences were found between women who received estrogen alone and those who received placebo for rates of colorectal cancer (17 versus 16 per 10,000 person-years) or total cancer (103 versus 110 per 10,000 person-years)

Positive effects of estrogen

No significant effects of estrogen

The incidence of stroke was 39% higher in women who received estrogen-alone therapy compared with those who received placebo (44 vs 32 per 10,000 **person-years**).[9] The risk of **venous thromboembolism (VTE)** was also increased 33% for women receiving estrogen-alone therapy (28 vs 21 per 10,000 person-years).[9] These outcomes are highlighted in the figure below. In addition, total cardiovascular disease events, including stroke, were 12% higher in women receiving estrogen-alone therapy compared with placebo.[9]

Figure 1.3: Clinical Outcomes in the WHI Estrogen-Alone Arm[9]



CHD = coronary heart disease; DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

Deeper Dive

Hypercoagulable States

Hypercoagulable states, or thrombophilias, are a group of inherited or acquired conditions that are associated with an increased risk for thrombosis.[10] Two of these hypercoagulable states are[10]:

- protein S deficiency
  - loss of fibrin (a protein involved in blood clot formation) regulation, leading to clot formation[10]
  - estimated to occur in approximately 1 in 500 of the general population[10]
  - found in approximately 1% to 3% of patients evaluated for VTE[10]
- factor V Leiden
  - causes resistance to activated protein C, resulting in unregulated fibrin generation and clot formation[10]
  - estimated to occur in 3% to 8% of healthy white populations of European ancestry[10]
  - found in approximately 10% to 64% of patients evaluated for VTE[10]

Treatment guidelines from the International Menopause Society (IMS) and North American Menopause Society (NAMS) recommend that certain hormone therapies not be used in women at high risk of thrombosis because they increase the risk of VTE.[3,11]

Termination of the estrogen-alone arm was planned for March 2005; however, in February 2004, the National Institutes of Health stopped the study early due to estrogen-alone therapy appearing to have no effect on **coronary heart disease** but having increased risk of stroke.[9]

Therapy Component Outcomes: Estrogen Plus Progestin Arm

Overall, 16,608 women were randomized into the estrogen plus progestin arm of the WHI hormone therapy component, 8506 who received estrogen plus progestin and 8102 who received placebo.[7] Outcomes of the estrogen plus progestin arm of the WHI hormone therapy component are listed in the following table.

Figure 1.4: Outcomes in the Estrogen Plus Progestin Arm[7]

Outcome Measure	Results
Primary outcome measure: Rate of coronary heart disease	• Estrogen plus progestin therapy increased the rate of women experiencing coronary heart disease events by 29% compared with placebo (37 versus 30 per 10,000 person-years)
Secondary outcome measures: Rates of hip and other bone fractures	• Estrogen plus progestin reduced hip and clinical vertebral fractures by approximately 33% compared with placebo (hip fractures, 10 versus 15 per 10,000 person-years) – osteoporotic fractures and total fractures were reduced by 23% and 24%, respectively, in the estrogen plus progestin group
Primary safety outcome: Rate of breast cancer occurrence	• Invasive breast cancer was diagnosed at a 26% higher rate in the estrogen plus progestin group (38 versus 30 per 10,000 person-years)
Other safety outcomes: Rate colorectal cancer	• Rate of colorectal cancer was decreased by 37% in women who received estrogen plus progestin (10 versus 16 per 10,000 person-years)
Other safety outcomes: Rates of endometrial cancer, lung cancer, or total cancer	• No differences were found between groups for the rates of endometrial cancer, lung cancer, or total cancer

Positive effects of estrogen plus progestin

Negative effects of estrogen plus progestin

Rates of stroke were 41% higher in women receiving estrogen plus progestin compared with those receiving placebo (29 vs 21 per 10,000 patient years).[7] Additionally, women receiving estrogen plus progestin had a 2-fold greater rate of experiencing VTE (34 vs 16 per 10,000 person-years).[7] These outcomes are highlighted in the figure below. In addition, total cardiovascular disease was increased by 22% in the estrogen plus progestin group compared with placebo.[7]

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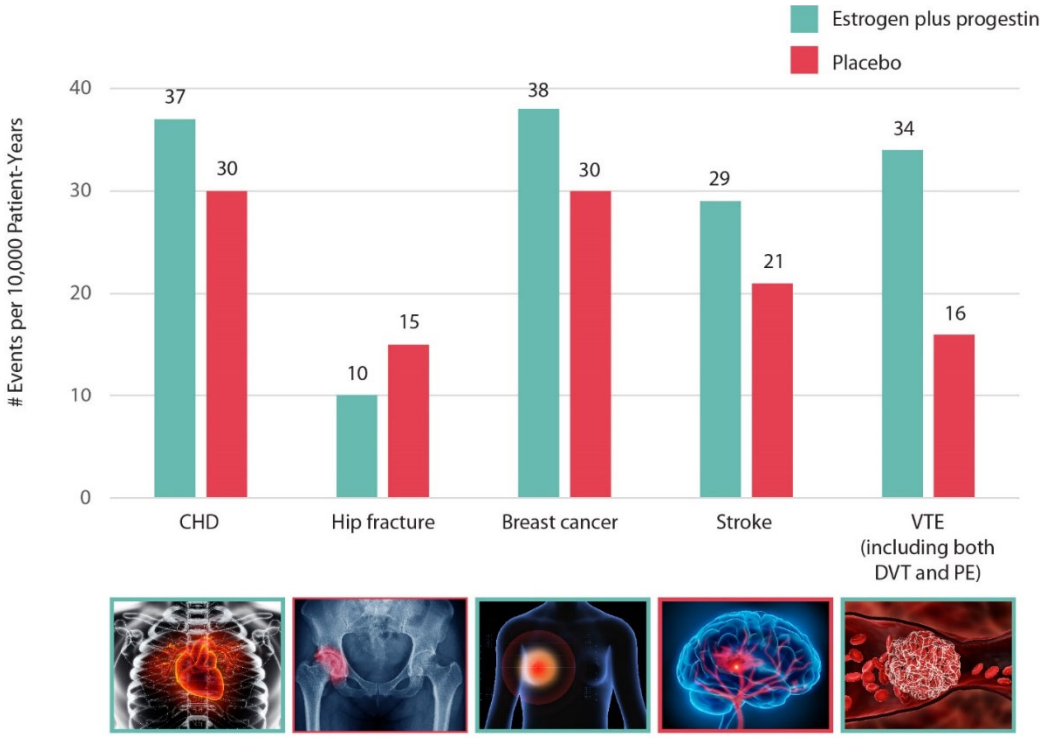
Figure 1.5: Clinical Outcomes in the WHI Estrogen Plus Progestin Arm[7]



CHD = coronary heart disease; DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

Final analysis was planned for 2005; however, in July 2002, the data and safety monitoring board stopped the study early based on evidence of breast cancer harm and increases in coronary heart disease, stroke, and VTE in the estrogen plus progestin arm that outweighed any benefits for fractures or colorectal cancer.[5,7]

WHIMS

WHIMS, an ancillary study to the WHI, examined whether postmenopausal estrogen supplementation (either alone or with progestin) reduced the risk of all-cause dementia and mild cognitive impairment in healthy women aged 65 years or older.[12] Overall, the WHIMS found that estrogen therapy (either alone or with progestin) increased the risk for dementia or mild cognitive impairment.[13]

Limitations and Subsequent Analyses of WHI and WHIMS Data

Limitations

It is important to note that the population studied in the WHI and WHIMS clinical trials included older women (50 to 79 years), and all participants received the standard of care at the time, which was estrogen (oral conjugated equine estrogen [CEE], dosed at 0.625 mg/day) and

progestin (medroxyprogesterone acetate [MPA], dosed at 2.5 mg/day) administered orally.[8,14-16] These parameters limit the results of the WHI and WHIMS studies, and they are not generalizable to other hormone preparations, routes of administration, dose, length of treatment, etc.[15]

Subgroup Analysis by Age

Using combined estrogen-alone and estrogen plus progestin data from the WHI hormone therapy component, a secondary analysis published in 2007 stratified women by age at enrollment (i.e., 50 to 59 years; 60 to 69 years; 70 to 79 years) or years since menopause (i.e., <10 years; 10 to 19 years; ≥20 years) and analyzed these subgroups for rates of coronary heart disease and stroke.[17]

Subgroup analysis by age noted an increased risk for both coronary heart disease and stroke in older subgroups (60 to 69 years; 70 to 79 years) due to hormone therapy use.[17] When looking at women grouped by years since menopause, hormone therapy increased the risk of coronary heart disease in women with 20 or more years since menopause.[17] The effect of hormone therapy on stroke when accounting for years since menopause was similar across all groups.[17]

18-Year Follow-up of WHI Participants

Although the original WHI found increased risk of some adverse outcomes, subsequent 18-year follow-up of WHI participants found that neither CEE alone nor conjugated equine estrogen plus medroxyprogesterone acetate (CEE plus MPA) increased or decreased all-cause, cardiovascular, or total cancer mortality.[16] Previous analyses of WHI data focused on incident diagnoses, such as coronary heart disease, stroke, and breast cancer, which were serious outcomes but predominantly nonfatal, leading to fewer than one-half of the deaths observed in the study cohort.[16] During 18 years of WHI participant follow-up, a large number of deaths occurred; however, no elevations in all-cause mortality due to hormone therapy were found.[16]

1.3: Million Women Study and Breast Cancer

From 1996 to 2001, the Million Women Study collected data from 1,084,110 women aged 50 to 64 years via questionnaires sent out from the United Kingdom National Health Service Breast Screening Program.[18] About one-half of the women enrolled had used MHT at some point in their lives.[18] The women were followed to determine cancer incidence and death.[18] No increase in risk of breast cancer was measured in past users of any hormone preparation, regardless of length of time since discontinuation, from less than five years to 10 or more years (with the exception of discontinuation in the year previous to diagnosis), and regardless of duration of use.[1,18] Based on an average follow-up of 2.6 years (breast cancers were diagnosed an average of 1.2 years after the study began), the relative risk for invasive breast cancer in current users of estrogen only was 1.30 (confidence interval [CI] = 1.22 to 1.38) and for current users of estrogen plus progestin, the relative risk was 2.00 (CI = 1.91 to 2.09).[18]

There are some criticisms of the Million Women Study; for example[1]:

- the study reported a lower risk of breast cancer for perimenopausal and postmenopausal women compared with premenopausal women despite the established fact that breast cancer increases with aging
- there were many differences comparing users and nonusers, requiring multiple adjustments of the data
- validation of the questionnaire data was based on information obtained from only 570 women

In particular, the Million Women Study calculated their risk of mortality by dividing deaths from breast cancer by the total number of users or nonusers of hormone therapy and, although the risk of mortality was increased, it did not reach statistical significance (1.22; CI = 1.00 to 1.48).[1] However, when the data were recalculated appropriately by dividing deaths from breast cancer by the total number of cases in the user and nonuser groups, then the risk of mortality was reduced about 27% in the hormone users (which is consistent with most published studies).[1]

1.4: Addition of Safety Information to Product Labeling for Products Containing Estrogen With or Without Progestins

Based on the outcomes of the hormone therapy component of the WHI and other studies, government agencies require certain safety information to be included in the labels of all products containing estrogen with or without progestins.[5] These key warnings include:

- for initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used[19]
- increased risks of endometrial cancer in women with a uterus who use unopposed estrogen; adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer[5,19]
- the overall evidence shows an increased risk of breast cancer in women taking combined estrogen plus progestin or estrogen only, that is dependent on the duration of taking hormone therapy.[19] The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer.[19] The WHI trial found no increase in the risk of breast cancer in hysterectomized women using estrogen only[19]
- MHT is associated with a 1.3- to 3-fold risk in developing VTE, i.e., deep vein thrombosis (DVT) or pulmonary embolism (PE)[5,19]
- combined estrogen plus progestin and estrogen-only therapies are associated with an up to 1.5-fold increase in risk of ischemic stroke.[19] In the WHI estrogen-alone substudy, a statistically significant risk of stroke was reported in women 50 to 79 years of age receiving estrogen alone compared to women receiving placebo.[19] However, subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving estrogen alone versus those receiving placebo (18 vs 21 per 10,000 women-years)[19]
- estrogen-alone and estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia[5,19]

- in the absence of comparable data, these risks should be assumed to be similar for other doses of estrogen and other dosage forms of estrogens, as well as other doses of estrogen and MPA and other combinations and dosage forms of estrogens and progestins[5]

During clinical decision making, the potential adverse outcomes of hormone therapy must be weighed against evidence that links untreated VMS with impaired health and quality of life, disrupted sleep, reduced work productivity, and increased healthcare expenditures.[16] Systemic hormone therapy with either estrogen alone or in combination with progestin is recommended as the most effective therapy for VMS related to menopause.[20]

Historical Insights
WHI Extension Studies
Initial publication in 2002 of findings from the WHI reported increased risks of cardiovascular disease, VTE, and breast cancer associated with hormone therapy used to treat symptoms of menopause.[21] These findings caused a drastic and immediate decline in the overall use of hormone therapy.[21] Since that time, different methods of analyzing the data and information from other trials have reduced some of these concerns. In addition, lower-dose hormone therapy products are available that may offer similar benefits with fewer risks.[5] Leading healthcare organizations and medical societies support the use of hormone therapy in appropriate situations.[5] Still, confusion about menopause and proven treatments for VMS are persistent problems for healthcare providers.[14]

The rest of this section will introduce the different estrogen-containing products that are available.

1.5: Estrogen-Only Products

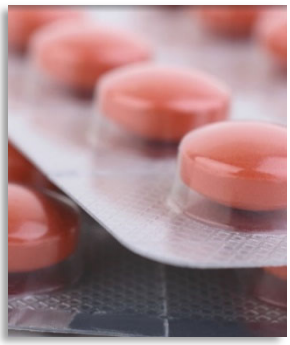
The different type of estrogens that may be used in hormone therapy are summarized in the following table. It is important to review these different types of estrogens as you will learn later in this section about the different products in which they are incorporated.

Estrogens Used in Hormone Therapy[5]	
Animal-derived conjugated estrogens (CEs)	• A mixture of estrogens extracted from the urine of pregnant mares (CEE)
Synthetic conjugated estrogens	• A mixture of estrogens synthetically created in a laboratory
17β-estradiol (i.e., **estradiol**; micronized estrogen)	• A powder form of estradiol reduced to micron-size particles
Esterified estrogens (i.e., estradiol acetate)	• Salt forms of synthetic estrogens that are estradiol **esters**
Estropipate	• An oral form of **estrone** sulfate, a salt form of estrone, that is stabilized by piperazine, a cyclical, nitrogen-containing compound

Exogenous estrogen can be delivered to the body through several routes of administration, depending on the symptoms that are being targeted for treatment.[5]

Estrogen Routes of Administration[5,20]

Oral



- Results in estrone being the predominant estrogen in the circulation due to metabolism in the liver and uptake in the gastrointestinal tract[5]
- Can result in fluctuating estrogen levels[5]

Transdermal Patch

- Used as systemic therapy but can be prescribed in lower doses than oral products because the estrogen delivered is not dependent on liver metabolism and gastrointestinal absorption[5]
- Associated with relatively stable serum estrogen levels[5]
- Transdermal estrogen has less of an effect than oral estrogen preparations on triglyceride levels, gallbladder disease, and coagulation factors[5]

Topical Gel, Lotion, Spray

- Like transdermal patches, can be prescribed in lower doses than oral products[5]
- May be less likely to cause skin irritation than transdermal patches, but skin-to-skin contact within 2 hours after application can lead to person-to-person transfer of small amounts of hormone[5]
- Variation in absorption depending on how the products are applied[5]
- Topically administered estrogen has less of an effect than oral estrogen preparations on triglyceride levels, gallbladder disease, and coagulation factors[5]

Vaginal Ring

- Except for the estradiol acetate vaginal ring (Femring®), vaginal estrogens are not used for systemic effects (e.g., hot flashes)[5]
- In general, estradiol levels vary according to the dose of the product but are all in the postmenopause range[5]

Local Vaginal Therapy

- Delivered as creams, tablets, or inserts[5]
- Delivers small amount of estrogen locally to relieve vaginal symptoms, such as vaginal atrophy, when use of systemic estrogen is unneeded or unwanted[5,20]
- Labeling for vaginal estrogen products often includes the same warnings, contraindications, and adverse effects as labeling for systemic estrogen products despite local vaginal therapy typically not resulting in significant systemic estrogen levels[5]

The choice of administration route for exogenous estrogen should be based on a woman's individual needs and preferences.[5] Some medical conditions, such as high triglyceride levels, may come into play when choosing the route of administration (e.g., transdermal and topically administered estrogen have less of an effect than oral estrogen preparations on triglyceride levels, gallbladder disease, and coagulation factors), while other factors, such as cost and insurance coverage, also need to be considered.[5]

1.6: Estrogen Plus Progestin Products

You learned earlier that the benefits for VMS from products that contain both estrogen and progestin are almost exclusively from the effects of estrogen, but the addition of progestin reduces the risk of endometrial hyperplasia and endometrial cancer in women with a uterus that may occur when exogenous estrogen is used alone.[5]

Making the Connection
Estrogen, Progesterone, and Progestin
Initial publication in 2002 of findings from the WHI reported increased risks of cardiovascular disease, VTE, and breast cancer associated with hormone therapy used to treat symptoms of menopause.[21] These findings caused a drastic and immediate decline in the overall use of hormone therapy.[21] Since that time, different methods of analyzing the data and information from other trials have reduced some of these concerns. In addition, lower-dose hormone therapy products are available that may offer similar benefits with fewer risks.[5] Leading healthcare organizations and medical societies support the use of hormone therapy in appropriate situations.[5] Still, confusion about menopause and proven treatments for VMS are persistent problems for healthcare providers.[14]

Both estrogen and **progesterone** have effects on the endometrial lining. Use of estrogen-alone products for hormone therapy can lead to increased and potentially harmful growth of the endometrial lining, the risk of which can be reduced with the use of estrogen plus progestin products.[5]

As with estrogen, there can also be different progestins used in hormone therapy.[5] The table below reviews some of the progestins that may be used in estrogen plus progestin products. It is important to review these progestins as you will later learn about the products in which they are incorporated. These are available in different dosing regimens, which are prescribed for the needs of different patients.[5]

Progestins Used in Estrogen Plus Progestin Products[5]	
MPA	• A progestin structurally related to progesterone • The most commonly used progesterone formulation for endometrial protection and postmenopause use
Progesterone	• A micronized powder form of progesterone
Norethindrone acetate (NETA)	• A derivative of 19-nortestosterone, a **steroid** hormone
Drospirenone	• A progestin structurally related to **testosterone**
Norgestimate	• A progestin structurally related to testosterone
Levonorgestrel (LNG)	• A progestin structurally related to testosterone

Estrogen plus progestin products are available in either oral or transdermal preparations, and the choice between products is typically made to provide uterine protection and maintain estrogen benefits while minimizing adverse effects, such as breakthrough uterine bleeding (i.e., irregular uterine bleeding that may occur with regimens that use continuous progestin).[5]

Although progestin is added to estrogen products in an effort to stop endometrial hyperplasia, some progestins may negatively affect mood, particularly in women with a history of mood disorders.[5]

As an alternative to estrogen plus progestin therapy that may still protect against endometrial hyperplasia, women may use estrogen combined with a SERM, which you will learn about next.[5]

1.7: Estrogen Paired With a SERM

A SERM is a drug that allows estrogen to act on some tissues but blocks the effect of estrogen on other tissues, such as the uterus.[22] A SERM can reduce the risk of endometrial hyperplasia that can occur with the use of estrogen alone while still allowing for the beneficial effects of estrogen on VMS.[4]

CE/BZA (Duavive®) is a medication known as a tissue-selective estrogen complex.[4] The SERM BZA is paired with CEs and is indicated for the treatment of VMS in women who have a uterus.[4] The rest of this section will briefly summarize the dosing regimen, clinical efficacy, and safety profile of CE/BZA.

Dosing Regimen

When taken for the treatment of VMS, CE/BZA is taken as one tablet (CE 0.45 mg/BZA 20 mg) daily, with or without a meal.[4]

Clinical Efficacy

CE/BZA was evaluated in 4868 postmenopausal women who participated in five phase 3 trials. Among these, 1585 women were treated with CE 0.45 mg/BZA 20 mg and 1241 received placebo. Long-term exposure to CE/BZA for up to two years was evaluated; 3322 women were exposed to CE/BZA for at least one year, and 1999 women were exposed for two years.[4]

Relief of menopausal symptoms was achieved during the first few weeks of treatment. In a 12-week study, CE/BZA significantly reduced the number and severity of hot flashes compared to placebo at weeks 4 and 12.[4]

Safety Profile

The most commonly reported adverse reaction associated with CE/BZA is abdominal pain, occurring in more than 10% of patients in clinical trials.[4]

Serious VTE events may occur rarely (less than one case per 1000 patients).[4]

The following table lists the adverse reactions observed with CE/BZA (n = 3168) in placebo-controlled clinical trials. Adverse reactions were categorized as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), or rare (≥1/10,000 to <1/1000).[4]

Frequency of Occurrence of Adverse Reactions[4]				
System Organ Class	**Very Common**	**Common**	**Uncommon**	**Rare**
Infections and infestations		Vulvovaginal candidiasis		
Vascular disorders				VTE (including pulmonary embolism, retinal vein thrombosis, and thrombophlebitis)
Gastrointestinal disorders	Abdominal pain	Constipation, diarrhea, nausea		
Hepatobiliary disorders			Cholecystitis	
Musculoskeletal and connective tissue disorders		Muscle spasms		
Investigations		Blood triglycerides increased		

1.8: Bioidentical Hormone Therapy

Bioidentical hormone therapy is a vague term used to describe compounded hormone preparations, which contain mixtures of various hormones, including estradiol, estrone, estriol, progesterone, testosterone, and DHEA. They are usually prepared by compounding pharmacies, but they are not governed by the same rigorous manufacturing standards, quality control, and regulatory oversight as pharmaceutical-grade registered products.[3] Bioidentical hormones are not natural. They are synthesized in laboratories from plant-based precursors in the same way that regulated hormones are prepared.[3] Advertising and promotional claims made about the safety and efficacy of compounded bioidentical hormones are not validated by medical evidence.[3]

Marketers of compounded bioidentical hormones often claim that their preparations are made to meet the needs of individual women based on blood or salivary hormone levels.[3] These claims are erroneous as the ratios of estrone and estriol to the parent estradiol remain relatively constant, depending on the enzyme activity within cells, and it is futile for physicians to write prescriptions for all three hormones in an attempt to do what the body does naturally.[3]

Bioidentical compounded hormone therapy offers no proven advantages over similar regulated products and lacks the protection to the patient offered by strict regulation and oversight.[3] All mainstream scientific, clinical, and regulatory bodies in women's health advise against the use of these products.[3]

Knowledge Check

1.1 Which of the following statements about hormone therapy is **incorrect**?[2]

A The benefits to VMS from products that contain both estrogen and progestin are almost exclusively from the effects of estrogen.

B The addition of progestin to hormone therapy reduces the risk of endometrial cancer in women with a uterus that may occur when estrogen is used alone.

C Hormone therapy is used to decrease levels of natural hormones when the body produces them at a high level, such as during menopause.

D The hormones used as hormone therapy for menopause are similar to those produced by a woman's body and can be natural or synthetic.

1.2 Which of the following correctly describes the patient population of the WHI clinical study?[8] (*Select all that apply.*)

A Received CEE 0.625 mg/day if in the estrogen-alone arm

B Age 70 to 85 years

C Premenopausal

D Received CEE 0.625 mg/day plus MPA 2.5 mg/day if in the estrogen plus progestin arm

1.3 Which of the following formulations is used as systemic therapy but can be prescribed in lower doses than oral products because the estrogen delivered is not dependent on liver metabolism and gastrointestinal absorption?[5]

A Transdermal

B Injectable

C Topical gel

D Vaginal ring

1.4 Estrogen plus progestin products are available in which types of preparations?[5] *(Select all that apply.)*

A Vaginal ring

B Vaginal cream

C Oral

D Transdermal

1.5 **True** or **False**? A SERM is a drug that allows estrogen to act on some tissues but blocks the effect of estrogen on other tissues, such as the uterus.[22]

A True

B False

Answers

1.1 C (Section 1.1)

1.2 A, D (Section 1.2)

1.3 A (Section 1.3)

1.4 C, D (Section 1.4)

1.5 A (Section 1.5)

2: Nonhormonal Therapies for Treatment of VMS

Introduction

Hormone therapy is the most effective treatment for moderate to severe VMS; however, hormone therapy may be contraindicated in some women.[3] A variety of nonhormonal pharmacological agents have been shown to decrease the frequency and severity of VMS; however, head-to-head comparisons with hormone therapy or between nonhormonal agents are limited.[3] In this section, we will identify the following types of nonhormonal products that have been shown to have some efficacy in the treatment of VMS[3,14]:

- selective **serotonin** reuptake inhibitors (SSRIs)
- serotonin-norepinephrine reuptake inhibitors (SNRIs)
- gabapentin
- clonidine
- oxybutynin

Learning Objective

Upon completion of this section, you should be able to:

- Identify the nonhormonal pharmacological therapies that are not indicated for the treatment of VMS but have shown efficacy in some clinical trials and may be used to treat some patients with VMS

2.1: SSRIs and SNRIs

Increasing evidence from the results of randomized controlled trials of SSRIs and SNRIs support their use for the treatment of VMS in healthy, nondepressed women.[20] Although available evidence suggests that SSRIs and SNRIs appear to be less effective than hormone therapy for the

treatment of VMS, direct comparisons with estrogen are limited and make it difficult to draw definitive conclusions.[20]

Comparisons of trials of the SSRIs paroxetine, citalopram, and escitalopram and the SNRIs venlafaxine and desvenlafaxine suggest that these agents have similar efficacy for the treatment of VMS.[3] SSRIs and SNRIs decrease hot flashes by up to 50% in women with a history of breast cancer, which is acceptable in most cases.[3]

Sertraline and fluoxetine are not associated with significant reductions in hot flashes in placebo-controlled studies, and are therefore not recommended for treatment of VMS.[3]

Common side effects of SSRIs and SNRIs include nausea, dizziness, dry mouth, nervousness, constipation, sleepiness, sweating, and sexual dysfunction, although these generally resolve with time or dose adjustment.[20]

2.2: Other Nonhormonal Agents

Clonidine

Clonidine is an antihypertensive agent that is sometimes used to treat VMS.[20] There is limited clinical data on the use of clonidine for the management of VMS, although a few studies have reported clonidine to have a small benefit compared with placebo but less benefit compared with hormone therapy.[20] Transdermal preparations may be superior to oral ones due to more stable blood levels and may help to increase compliance.[3]

Common side effects of clonidine include dry mouth, insomnia, constipation, hypotension, and drowsiness.[3,20]

Gabapentin

Gabapentin is an anticonvulsant agent that has been shown in several studies to reduce VMS.[20] Studies have shown that gabapentin reduces both the frequency and severity of hot flashes, although comparisons with estrogen have shown that estrogen is more effective.[20]

Common side effects of gabapentin include dizziness, sleepiness, and peripheral edema.[20]

Oxybutynin

Oxybutynin is an anticholinergic and antimuscarinic agent used to treat overactive bladder.[14] In one study, oxybutynin was effective in reducing the frequency and severity of VMS after one week of treatment and through the end of 12 weeks of treatment.[14] However, more than 50% of treated women reported dry mouth.[14]

Knowledge Check Questions

2.1 Results of randomized controlled trials support the use of which classes of agents for the treatment of VMS in healthy, nondepressed women?[2]

A SSRIs only

B SNRIs only

C Neither SSRIs nor SNRIs

D Both SSRIs and SNRIs

2.2 Which of the following is an antihypertensive that is not US Food and Drug Administration (FDA)-approved for the treatment of VMS but is sometimes used in clinical practice?[2]

A Gabapentin

B Paroxetine

C Bazedoxifene

D Clonidine

Answers

2.1 D (Section 2.1)

2.2 D (Section 2.2)

3: Lifestyle Changes and Alternative Therapies

Introduction

Women may choose to incorporate lifestyle and alternative therapies into their VMS management.[14] Lifestyle changes and alternative therapies for the treatment of VMS range from dressing in layers and incorporating exercise into a daily routine to supplements and herbal therapies.[14] This section will describe the alternative and/or nonprescription therapies that some women may use to help alleviate the symptoms of VMS.

Learning Objectives

Upon completion of this section, you should be able to:

- Describe the lifestyle changes women may use to help alleviate VMS
- Describe the uses of common alternative therapies women may use to help alleviate VMS

3.1: Lifestyle Changes

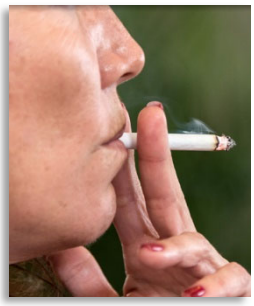
Women who experience VMS may try different lifestyle changes to manage their symptoms

Lifestyle Changes to Potentially Alleviate VMS[3,11,14,20,23]

Keeping Core Body Temperature Cool

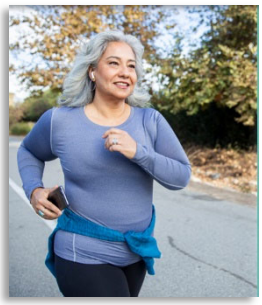
- Cooling techniques may be implemented, including[14,20,23]:
  - dressing in layers
  - using breathable, natural fiber clothing
  - using fans or cold packs
  - sleeping in a cool room
  - drinking cool non-alcoholic drinks

Refraining From Smoking



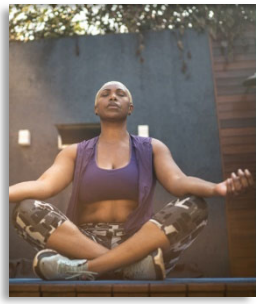
- Smoking has been suggested as a risk factor for VMS[20]
  - refraining from smoking may provide relief from VMS[11]

Exercising Regularly



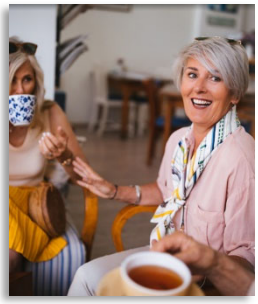
- Exercising regularly may help relieve VMS by[11,14,23]:
  - maintaining a healthy body weight
  - promoting weight loss

Relaxation Techniques



- Relaxation techniques, such as those below, may help with VMS stress management and mindfulness[3,14]:
  - cognitive-behavioral therapy
  - clinical hypnosis
  - yoga
  - stretching

Avoiding Perceived VMS Triggers



- Women may avoid dietary triggers of their VMS, including[20,23]:
  - hot drinks
  - spicy foods
  - alcohol
  - caffeine

Although these lifestyle modifications may improve VMS in some women, there are limited data from clinical trials that support their efficacy.[3,20]

3.2: Complementary Therapies

The role of complementary therapies in the management of menopause, both for symptomatic relief and avoidance of long-term complications, remains controversial.[3] Studies have not consistently supported the efficacy of complementary or over-the-counter (OTC) therapies in reducing the frequency or severity of VMS.[3]

Randomized clinical trials of **acupuncture** have not consistently shown a beneficial effect in reducing VMS, although some meta-analyses suggest a small benefit.[3]

Isoflavone preparations derived from soy and red clover and traditional Chinese medicines have shown variable efficacy compared to placebo in small randomized trials.[3] Therapies such as Black cohosh and St. John's Wort have been associated with adverse effects and interactions with medications and should therefore be used with caution and appropriate medical guidance.[3]

Further data from larger randomized trials are required to confirm the efficacy and safety of complementary therapies.[3]

Key Facts
Some herbal products may affect the metabolism of drugs or increase bleeding; therefore, NAMS recommends that healthcare providers ask midlife women about their use of herbal remedies and supplements, particularly if a medical procedure or drug therapy is planned.[11]

Although complementary therapies represent a large market of healthcare spending, multiple studies of these alternative treatments have shown that they produce results similar to placebo and are unlikely to alleviate VMS.[14] Studies have shown that complementary therapies for VMS are not as effective for relief of VMS as conventional treatments and that hormonal treatment is still the most effective therapy.[11,20,23]

Knowledge Check Questions

3.1 Which of the following are lifestyle changes that a woman may use to potentially alleviate VMS?[11,14,20,23] *(Select all that apply.)*

A Using breathable, natural fiber clothing

B Refraining from smoking

C Dressing in layers

D Increasing caffeine consumption

3.2 **True** or **False**? In addition to herbal therapies, other complementary therapies used by some women to alleviate VMS include acupuncture and yoga.[14]

A True

B False

Answers

3.1 A, B, C (Section 3.1)

3.2 A (Section 3.2)

4: Guidelines for the Treatment of Menopause Symptoms

Introduction

Several organizations provide recommendations and practice guidelines to guide the treatment of women during their menopausal transition. This section will describe some of these organizations and summarize their key recommendations for the management of VMS. The guidelines summarized in this section are from the:

- American College of Obstetricians and Gynecologists (ACOG)
- North American Menopause Society (NAMS)
- Endocrine Society (ENDO)
- International Menopause Society (IMS)
- National Institute for Health and Care Excellence (NICE)
- Society of Obstetricians and Gynecologists of Canada (SOGC)

Learning Objective

Upon completion of this section, you should be able to:

- Describe the clinical guidelines for management of menopausal symptoms developed by ACOG, NAMS, ENDO, IMS, NICE, and SOGC

4.1: American College of Obstetricians and Gynecologists (ACOG) Guidelines

ACOG is a professional organization for obstetrician-gynecologists.[24] With roots dating back to 1951, ACOG's activities include[24]:

- producing practice guidelines for providers and educational materials for patients
- providing practice management and career support
- facilitating programs and initiatives aimed at improving women's health
- advocating on behalf of members and patients

ACOG provides guideline recommendations for the management of menopausal symptoms. A summary of the ACOG treatment guidelines for menopause-related VMS is provided in the table below.

Key Points From the ACOG Guidelines on the Use of Hormone Therapy for the Treatment of Menopause-Related VMS[20]
• Systemic hormone therapy with estrogen alone or in combination with progestin is the most effective therapy for VMS related to menopause – clinical evidence does not support the use of progestin-only medications, testosterone, or compounded bioidentical hormones for the treatment of VMS
• SSRIs, SNRIs, clonidine, and gabapentin are effective alternatives to hormonal therapy for the treatment of VMS related to menopause
• Systemic hormone therapy should be given in the lowest dose and for the shortest period possible to decrease the risk of serious adverse events, such as thromboembolic disease and breast cancer

4.2: North American Menopause Society (NAMS) Guidelines

NAMS is North America's leading nonprofit organization dedicated to promoting the health and quality of life of all women during midlife and beyond through an understanding of menopause and healthy aging.[25] NAMS maintains a multidisciplinary membership of approximately 2900 leaders in the field—including clinical and basic science experts from medicine, nursing, sociology, psychology, nutrition, anthropology, epidemiology, pharmacy, and education—allowing NAMS to be uniquely qualified to provide information that is both accurate and unbiased, not for or against any point of view.[25]

NAMS publishes *Menopause Practice: A Clinician's Guide*, which is a comprehensive overview of the field of menopause and includes treatment recommendations.[25] Additionally, NAMS publishes position statements of the Society's recommendations about select topics of considerable interest to help guide clinicians in their treatment decisions.[25]

Key points from the NAMS position statement on the use of hormone therapy as treatment for menoapuse-related VMS are listed in the following table.

Key Points From the NAMS Position Statement on the Use of Hormone Therapy as Treatment for Menopause-Related VMS[26]
• Hormone therapy remains the gold standard for relief of VMS due to menopause
• Estrogen-alone therapy can be used for symptomatic women after hysterectomy
• For symptomatic women with a uterus requesting hormone therapy, combination therapy protects against endometrial hyperplasia, either with a progestin or as a combination of CEE and BZA
• For menopause symptom control, the lowest dose that offers relief should be used – dosing and need for ongoing therapy for relief of menopause symptoms should be assessed periodically
• Hormone therapy improves sleep in women with bothersome nighttime VMS by reducing nighttime awakenings

4.3: Endocrine Society (ENDO) Guidelines

ENDO is dedicated to providing the field of endocrinology with timely, evidence-based recommendations for clinical care and practice.[27] ENDO continually creates new guidelines and updates existing guidelines to reflect evolving clinical science and meet the needs of practicing physicians.[27]

Key points from ENDO clinical practice guidelines on the treatment of VMS are listed in the following table.

Key Points From ENDO Clinical Practice Guidelines on the Use of Hormone Therapy for the Treatment of Menopause-Related VMS[23]
• For women in postmenopause with mild or less bothersome hot flashes, we suggest a series of steps that do not involve medication, such as turning down the thermostat, dressing in layers, avoiding alcohol and spicy foods, and reducing obesity and stress
• For menopausal women <60 years of age or <10 years past menopause with bothersome VMS (with or without additional climacteric symptoms) who do not have contraindications or excess cardiovascular or breast cancer risks and are willing to take hormone therapy, we suggest initiating estrogen therapy for those without a uterus and estrogen plus progestin for those with a uterus
• Transdermal estrogen therapy by patch, gel, or spray is recommended for women who request MHT and have a moderate risk of cardiovascular disease or an increased risk of VTE
• For women seeking pharmacological management for moderate to severe VMS for whom hormone therapy is contraindicated, or who choose not to take hormone therapy, SSRIs, SNRIs, gabapentin, or pregabalin are recommended if there are no contraindications
• For women seeking relief of VMS with OTC or complementary medicine therapies, we suggest counseling regarding the lack of consistent evidence for benefit for botanicals, black cohosh, omega-3-fatty acids, red clover, vitamin E, and mind/body alternatives including anxiety control, acupuncture, paced breathing, and hypnosis
• Healthcare providers and patients should choose an individualized hormone therapy approach using shared decision making

4.4: International Menopause Society (IMS)

The IMS works globally to promote and support access to best practice healthcare for women through their menopause transition and post-reproductive years, enabling them to achieve optimal health and well-being.[28] The IMS conducts the following activities related to evidence-based medicine[28]:

- disseminating evidence-based knowledge to healthcare providers globally through multilingual and multicultural education resources, programs, and events, including the World Menopause Congress
- facilitating collaboration and information exchange between healthcare professionals, medical societies, and organizations with shared interests and goals
- developing evidence-based guidelines and position statements on issues related to menopause and post-reproductive health

Key points from the IMS clinical practice guidelines on the treatment of VMS and MHT are listed in the following table.

Key Points From the IMS Governing Principles on MHT[3]
• MHT remains the most effective therapy for VMS and urogenital atrophy
• Other menopause-related complaints, such as joint and muscle pains, mood swings, sleep disturbances, and sexual function (including reduced libido) may improve during MHT
• Quality of life and sexual function may also improve
• The administration of individualized MHT (including androgenic preparations when appropriate) may improve both sexuality and overall quality of life
• Consideration of MHT should be part of an overall strategy including lifestyle recommendations regarding diet, exercise, smoking cessation, and safe levels of alcohol consumption for maintaining the health of peri- and post-menopausal women
• MHT must be individualized and tailored according to symptoms and the need for prevention, as well as personal and family history, results of relevant investigations, and the woman's preferences and expectations
• The risks and benefits of MHT differ for women during the menopause transition compared to those for older women

4.5: National Institute for Health and Care Excellence (NICE)

Key functions of NICE include[29]:

- providing rigorous, independent assessment of complex evidence to produce guidance and advice for healthcare professionals
- developing recommendations that provide healthcare professionals with innovative solutions for their patients
- encouraging the uptake of best practices to improve patient outcomes

The following table summarizes key points regarding treatment of VMS provided in the NICE guidelines on the diagnosis and management of menopause.

Key Points from the NICE Guidelines for the Treatment of VMS[30]
• Offer women MHT for VMS after discussing with them the short-term (up to five years) and longer-term benefits and risks. Offer a choice of preparations as follows: – estrogen and progestin to women with a uterus – estrogen alone to women without a uterus
• Do not routinely offer SSRIs, SNRIs, or clonidine as first-line treatment for VMS alone
• Explain to women that there is some evidence that isoflavones or black cohosh may relieve VMS. However, explain that: – multiple preparations are available and their safety is uncertain – different preparations may vary – interactions with other medicines have been reported

4.6: Society of Obstetricians and Gynecologists of Canada (SOGC)

Established in 1944, the mission of the SOGC is to lead the advancement of women's health through excellence and collaborative professional practice.[31] The SOGC is comprised of obstetricians, gynecologists, family physicians, nurses, midwives, and allied health professionals working in the field of women's sexual and reproductive health.[31]

Knowledge Check Questions

4.1 **True** or **False**? According to ACOG guidelines for the management of menopausal symptoms, systemic hormone therapy with estrogen alone or in combination with progestin is the most effective therapy for VMS related to menopause.[20]

A True

B False

4.2 **True** or **False**? According to the NAMS position statement on the use of hormone therapy as treatment for VMS, for symptomatic women with a uterus requesting hormone therapy, combination therapy protects against endometrial hyperplasia, either with a progestin or as a combination of CEE and bazedoxifene.[26]

A True

B False

4.3 Which guideline states that menopausal hormone therapy must be individualized and tailored according to symptoms and the need for prevention, as well as personal and family history, results of relevant investigations, and the woman's preferences and expectations?[3]

A ENDO

B IMS

C NAMS

D NICE

Answers

4.1 A (Section 4.1)

4.2 A (Section 4.2)

4.3 B (Section 4.3)

Glossary

acupuncture

a method of producing analgesia or altering the function of a body system by inserting fine, wire-thin needles into the skin at specific body sites along a series of lines, or channels, called meridians[32]

coronary heart disease

a disease in which there is narrowing or blockage of the coronary arteries (blood vessels that carry blood and oxygen to the heart); may cause chest pain, shortness of breath during exercise, and heart attacks[33]

esters

a class of chemical compounds formed by the bonding of an alcohol and one or more organic acids, with the loss of a water molecule for each ester group formed[32]

estradiol

the principal estrogen secreted in the ovaries and also the most biologically active; among the human estrogens, only estradiol is available in a government-approved single estrogen product; estradiol levels steeply decline during the first year of menopause, followed by a more gradual decline[1,5]

estrogen

one of a group of hormonal steroid compounds that promote the development of female secondary sex characteristics; the estrogens produced in the human body are estradiol, estrone, and estriol[5,32]

estrone

estrone is metabolized from estradiol; it is also 50% to 70% less biologically active than estradiol; in postmenopause, the dominant circulating type of estrogen is estrone[2,5]

exogenous

originating outside the body or an organ of the body or produced from external causes[32]

hormone

one of many substances made by glands in the body that circulates in the bloodstream and controls the actions of certain cells or organs; some hormones can also be made in the laboratory[34]

hot flashes

a sudden, temporary onset of body warmth, flushing, and sweating; often associated with menopause[34]

hyperplasia

an increase in the number of cells in an organ or tissue; the cells appear normal under a microscope and are not cancer, but may become cancer[34]

menopause

the permanent end of menstruation; a woman is diagnosed as having entered menopause after she has not had a menstrual cycle for 12 consecutive months[1,2]

night sweats

nocturnal sweating by a woman as an effect of menopause or perimenopause (hot flashes that occur at night); may be mild or profuse enough to disrupt sleep[32]

person-years

a statistical measure representing one person at risk of development of a disease during a period of one year[32]

progesterone

a type of hormone made by the body that plays a role in the menstrual cycle and pregnancy[35]

progestin

any natural or laboratory-made substance that has some or all of the biologic effects of progesterone[35]

selective estrogen receptor modulator (SERM)

a drug that acts like estrogen on some tissues but blocks the effect of estrogen on other tissues[22]

serotonin

a hormone found in the brain, platelets, digestive tract, and pineal gland that acts as both a neurotransmitter and a vasoconstrictor[22]

steroid

any of a group of fats that have a certain chemical structure; examples include sex hormones, cholesterol, bile acids, and some drugs[22]

testosterone

a hormone made mainly in the testes and needed to develop and maintain male sex characteristics, such as facial hair, deep voice, and muscle growth[36]

venous thromboembolism (VTE)

a condition in which a blood clot forms within a vein[32]

Acronyms

ACOG	American College of Obstetricians and Gynecologists
CAM	complementary or alternative medicine
CE	synthetic conjugated estrogens
CEE	conjugated equine estrogen
DSHEA	Dietary Supplement Health and Education Act
ENDO	ENDO Endocrine Society
FDA	Food and Drug Administration
IMS	International Menopause Society
LNG	levonorgestrel
MPA	medroxyprogesterone acetate
NAMS	North American Menopause Society
NETA	norethindrone acetate
NHLBI	National Heart, Lung, and Blood Institute
NICE	National Institute for Health and Care Excellence
SERM	selective estrogen receptor modulator
SOGC	Society of Obstetrician and Gynecologists of Canada
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
VMS	vasomotor symptoms
WHI	Women's Health Initiative
WHIMS	WHI Memory Study

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