**CHAPTER 17 – THE POSTMENOPAUSAL WOMAN**

**Zain Al-Safi, M.D.** Instructor, University of Colorado Denver. Division of Reproductive Endocrinology and Infertility, 12631 East 17th Avenue, Mail Stop B-198, Aurora, CO 80045

**Nanette Santoro M.D.** Professor and E Stewart Taylor Chair of Obstetrics and Gynecology, University of Colorado at Denver, 12631 East 17th Avenue, Mail Stop B-198, Room 4010, Aurora, CO 80045

**Updated September 2015**

**ABSTRACT**

The menopausal transition marks a time of great variability in reproductive hormones, and this variability can be responsible for specific symptoms, such as hot flashes and mood disturbances. Once a woman who is more than 45 years old has gone for 12 months without a menstrual period, she is considered to be menopausal and has consistently low circulating estradiol and elevated gonadotropins.

Although estrogen exerts clear-cut protective effects on the cardiovascular system in premenopausal women, medical evidence does not support its use for the prevention of cardiovascular disease. Also, estrogen is generally not a first line agent for bone preservation in women without concurrent menopausal symptoms, despite its antiresorptive effects.

Non-hormonal alternatives to estrogen and new, tissue specific estrogen complexes (TSECs) are now FDA approved and available for clinical use to treat common menopausal symptoms.

# INTRODUCTION

Menopause is associated with a constellation of physical changes. Some of these changes are directly attributable to the loss of estrogen, including hot flashes, bone demineralization and vaginal dryness. Though a matter of controversy, an increased incidence of cardiovascular disease and dementia seem to be associated with both menopause and aging. Furthermore, other conditions, such as breast, ovarian and endometrial cancer, are associated primarily with aging but certainly are impacted by ovarian hormones.

This review will address the menopausal transition, its common symptoms, and the risks and benefits of Menopausal Hormone Therapy (MHT), specifically, estrogen therapy, the selective estrogen receptor modulators (SERMs): raloxifene, tamoxifen and bazedoxifene, and other non-hormonal therapies. For complete coverage of this and related aspects of Endocrinology, please visit our FREE web-book, [www.endotext.org](http://www.endotext.org).

# DEFINITIONS

## The Menopausal Transition

In 2001 (1) and again in 2012 (2), a Stages of Reproductive Aging Workshop (STRAW) was held to describe and define the various stages of the menopausal transition (Figure 1). On average, the menopausal transition lasts 4 years in duration and is divided into early and late phases. It begins when menstrual irregularity first appears, classically defined as either a “skipped” period or by an increase in variability of cycle length by more than 7 days. The menstrual irregularity that characterizes the menopausal transition occurs as the overall ovarian follicular complement decreases. However the menstrual cycle and hormone changes of the early transition are best explained by a loss of the follicle cohort, rather than insufficient follicles to result in a single ovulation. This decrease in the available pool of growing follicles leads to a decrease in inhibin B production (3). Reduced inhibin B removes the physiologic restraint on FSH that controls the process of folliculogenesis, and an increase in follicle-stimulating hormone (FSH) secretion is observed. Early in the transition period, FSH levels are not consistently elevated, and may often vary considerably from month to month as the growing follicle cohort itself varies month to month. The follicular phase becomes notably shorter, and as a result, estradiol (E2) production is variable and even elevated at times. Follicle growth is more rapid, but ovulation may occur at smaller follicle diameters (4). There is evidence that follicles may grow relatively rapidly in the preceding luteal phase, causing very short follicular phases, a phenomenon that has been named ‘luteal out of phase events’ (5). Anovulatory cycles become more prevalent, and luteal progesterone production declines (6). This early phase of the transition is associated with an increase in menopausal symptoms such as hot flashes, though initially, the increase may be relatively small as there may not necessarily be a reduction in the amount of circulating E2. By the late transition, prolonged amenorrhea (defined as > 60 days) occurs, and is associated with a persistently reduced follicle pool and failure of folliculogenesis. At this point in the transition, estrogen deficiency begins to dominate, bone mineral density loss begins (7) and menopausal symptoms including hot flashes and vaginal dryness increase sharply in prevalence.



**Figure 1:** The Stages of Reproductive Aging Workshop +10 staging system for reproductive aging in women (2).

## Menopause

Menopause is defined as the cessation of menstruation for 12 months in a woman over age 45 and occurs at a median age of 52 years (8). This event represents permanent failure of ovarian function secondary to depletion of the follicular pool. As such, supporting granulosa cells cease to produce estrogen and theca cells cease to produce androgens, and subsequently, ovarian estrogen and progesterone production stops. There is no established relationship between a woman's age at menarche and her age at menopause. However, it is well established that a woman's age at menopause is reflective of her mother's age at menopause (9). Although few specific linked genes have been identified, there is heritability for age of menopause, and thus, several genes are likely involved in ovarian aging (10). Menopause is known to occur approximately 1-2 years earlier in tobacco users (8).

## Primary ovarian insufficiency

Primary ovarian insufficiency (POI), or premature ovarian failure (POF) has been defined as 3-6 months of amenorrhea accompanied by FSH levels greater than 40 IU/L on two separate occasions, at least one month apart in a woman less than 40 years old. POI is diagnosed in 5-10% of women who are evaluated for amenorrhea and the overall prevalence in the general population is thought to be around 1.1% (11). The designation of “premature menopause” for such patients implies that menses will never happen again and this term should not be used. Rather, many recommend the use of the term “premature ovarian insufficiency (POI)” to describe the syndrome. POI and POF are more neutral terms, as young women with prolonged hypergonadotropic amenorrhea, unlike their older counterparts, are far more likely to have some intermittent ovarian function after the diagnosis has been made.

The treatment for POI usually consists of combined estrogen and progestin replacement. It is important to recognize that the risk to benefit equation of MHT for women under age 40 who have ovarian failure differs from that for menopausal women aged 50-79. A preventive cardiovascular benefit for MHT appears to be more likely in younger women. Women with early loss of ovarian function are likely to spend more years of their lives exposed to the risk of bone demineralization, and therefore this important protective benefit of hormones is more likely to be realized. There are no current, evidence-based criteria to determine how to best provide hormone therapy to women with POI/POF, but it is widely assumed that hormone treatment up to the mean age at natural menopause should be considered in most cases, with a re-evaluation of risk to benefit once a woman attains the age associated with natural menopause in the population.

# PHYSIOLOGIC CHANGES ASSOCIATED WITH AGING AND MENOPAUSE

## Cardiovascular system

The largest health threat to women over age 50 is cardiovascular disease (Figure 2) (12). In women age 45-49, the incidence of cardiovascular disease is 3 times lower than men of matched age. However, data from the Framingham study have shown that by age 75-79, a woman's risk of heart disease increases and equals a man's risk for her age (13). Women are less likely to be diagnosed correctly, less likely to undergo the correct revascularization procedure, and less likely to survive a major cardiac event than are men. It is critical to develop new ways to identify preclinical disease amendable to intervention and prevention. Moreover, women appear to have risk factors that differ substantially from men, and include more social/emotional and autoimmune/inflammatory risks, along with more microvascular disease (14).

Carotid intimal medial thickness (CIMT) has emerged as a strong predictor of subsequent disease and serves as a non-invasive marker of subclinical cardiovascular disease. El Khoudary, et al, have found associations between low endogenous SHBG and estradiol and elevated FSH with increased CIMT in perimenopausal women (15).

MHT for the secondary prevention of coronary heart disease (CHD) was evaluated in The Heart and Estrogen/Progestin Replacement study (HERS). This trial included 2763 post-menopausal women with pre-existing CHD and followed over 4 years. The objective of this study was to see if initiating MHT would alter a woman's risk of future events. All participants were post-menopausal, younger than age 80 with a uterus and established CHD. Women were prescribed conjugated equine estrogen (CEE) 0.625 mg with medroxyprogesterone acetate (MPA) 2.5mg daily or placebo. The primary outcome was the occurrence of fatal or nonfatal myocardial infarction (MI). Secondary outcomes were other cardiovascular events: coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack and peripheral arterial disease. The results showed no significant differences in the occurrence of fatal or nonfatal myocardial infarctions by treatment. However, in the first year of the study, there were significantly more CHD events in the MHT group, as well as a higher incidence of thromboembolic events (both deep venous thrombosis (DVT) and pulmonary embolus) and gallbladder disease when compared to placebo. The incidence of diabetes mellitus decreased by 3.5% over 4 years in the MHT group. Similar to the results of the PEPI Study on intermediate cardiovascular markers (17), the MHT group had a decrease in LDL cholesterol and an increase in HDL cholesterol when compared to placebo. These investigators concluded that MHT did not reduce the risk of future cardiac events in post-menopausal women with established CHD. In addition, because of the increased incidence of adverse cardiac events in the first year of treatment, initiating MHT in women with established CHD is not recommended. Based on the findings of the HERS Study, MHT should not be initiated for secondary prevention of cardiovascular disease.



**Figure 2**: Beneficial effects of estrogen on the endothelium may be limited to the earlier stages of atherogenesis (left panel), when elasticity is relatively preserved. In later stages (right panel), the endothelium becomes dysfunctional, and estrogen is no longer beneficial. From Mendelsohn ME and Karas RH Science 2005; 308: 1583 (reprinted with permission).

Similarly, the Women’s Health Initiative hormone therapy clinical trial did not find primary protection against cardiovascular disease in women treated for a mean of 5-7 years with either conjugated equine estrogen alone (women with a hysterectomy) (18) or estrogen plus the progestin, medroxyprogesterone acetate (19). Recently, the hypothesis that early intervention with estrogen, using a regimen of either conjugated equine estrogen or transdermal estradiol, both with cyclic administration of oral, micronized progesterone for 12 days each month, was tested in the Kronos Early Estrogen Prevention Study (KEEPS). KEEPS did not demonstrate any between-group differences in CIMT or coronary calcium scores (20). The rationale that hormones are protective of the vascular system when vessels are less affected by atherogenesis is depicted in Figure 2.

## Lipoprotein Changes

The role of menopause in contributing to dyslipidemia has long been hypothesized. In women, total and low-density lipoprotein (LDL) cholesterol increase with age, and this increase is accelerated by menopause whereas cardioprotective, high density lipoprotein (HDL) decreases. Moreover, the protective effect of HDL cholesterol appears to be diminished as women progress through menopause—possibly related to denser subparticle size (21). A rise in LDL has specifically been associated with the latter part of the menopausal transition and appears to be related to the loss of estrogen at this time of life (22). In agreement with this finding is the relatively sharp upturn in CIMT observed in association with the late menopausal transition (23). Through exercise, a low-fat diet, and cholesterol-lowering drugs, patients with high total and LDL cholesterol levels are able to significantly lower these lipoprotein levels and their subsequent risk for heart disease (24).

## Lipoprotein Changes, Cardiovascular Risk and MHT

The Womens Health Initiative (WHI) trials describes a group of randomized, placebo controlled, clinical primary prevention trials that were designed to test the effects of MHT, diet modification, and calcium and vitamin D supplements on cardiovascular disease, fracture risk, and breast and colorectal cancer. The WHI had three overlapping clinical trials. One was to test the effects of a low fat diet on breast cancer and cardiovascular disease outcomes; one was to test the effect of calcium plus vitamin D on fracture outcomes, and one was to test the effects of hormone therapy in cardiovascular disease outcomes. The hormone therapy trial consisted of three study arms: the Estrogen + Progestin arm (conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) was administered to women with a uterus, the estrogen-alone arm (CEE) was administrated to women without a uterus, and a placebo arm involved both women with or without a uterus. The WHI findings suggest that administration of MHT does not protect the heart and may even increase the risk of CHD. In the final analyses, CEE + MPA use was associated with a 24% overall increase in the risk of CHD (6 more heart attacks annually per 10,000 women using CEE + MPA) and an 81% increased risk of CHD in the first year alone after starting therapy. Neither of these differences was statistically significant. Women who had higher baseline LDL cholesterol levels at the beginning of the study were at particularly high risk of CHD with MHT use (25). Although the expected changes in lipoproteins were observed with hormone therapy (decreased LDL and increased HDL), there was no associated reduction in CHD risk.

The estrogen alone arm (CEE) differed from the CEE + MPA study in that it enrolled women who did not have a uterus, and who therefore did not need progestin. In this trial, 10,739 women with a prior hysterectomy, aged 50-79 years, were assigned to CEE 0.625 mg daily or to placebo. The study was stopped ahead of schedule in February 2004 for ‘futility’. During 7.1 years of follow up, estrogen provided no overall protection against heart attack or CAD in healthy post-menopausal women, most of whom were more than 10 years past menopause when they entered the study. In women 50-59 years of age at study entry, there was a suggestion of lower rates of heart attacks or procedures to revascularize thrombosed coronary arteries; however, these findings could be due to chance (18). The KEEPS results suggest that initiation of MHT in overall healthy, nonsmoking women within 3 years of their final menstrual period does not result in demonstrable cardioprotection within 4 years based on CIMT and coronary calcium outcomes.

Data from the WHI estrogen-alone arm (CEE) supports the notion that coronary calcium accrual is prevented by early intervention with estrogen. The WHI evaluated the presence of CAC burden to determine whether or not it differed based on treatment assignment. The WHI Coronary-Artery Calcium Study (WHI-CACS)evaluated 1,064 womenaged 50 to 59 years after a mean of 7.4 years. CAC was evaluated by cardiac CT scans, which were performed blindly on patients to measure the CAC in these estrogen-alone participants. CAC scores were lower in women in the (CEE) alone group compared to those in the placebo group. The mean CAC score was 83.1 for (CEE) and 123.1 for placebo. After taking into account other heart disease risk factors, the risk of having mild-to-moderate CAC was 20-30% lower and the risk of severe CAC was 40% lower in the (CEE) group compared to placebo. After the trial ended, the calcium plaque build-up in the coronary arteries was lower in women randomized to estrogen compared to placebo (26).

In conclusion, studies show that most women have minimal CAC and minimal increases in carotid IMT prior to menopause. The findings imply strongly that ovarian hormones exert a protective effect on the cardiovascular system in premenopausal women, even though they do not appear to maintain a protective role after menopause. Despite these data, and secondary findings suggestive that early intervention with hormones may delay the onset of clinical heart disease, prescribing hormones for this purpose cannot be recommended based on the available data. These studies are unlikely to be the last word in this controversial field.

## Coagulation

After menopause, there are noted changes in clotting parameters. There is an increase in procoagulation factors including fibrinogen, plasminogen activator inhibitor-1 (PAI-1) and factor VII, all of which cause a relatively hypercoagulable state. These increases are thought to be another contributor to the increase in cardiovascular and cerebrovascular disease in older women. With the administration of oral estrogen therapy, many procoagulation parameters improve, as evidenced by a decrease in fibrinogen and plasminogen levels; however, there is an increased risk for venous thromboembolism (VTE) (27). MHT in currently used doses is associated with an approximately 3-fold increase in VTE events. Transdermal estrogen preparations may offer an advantage, and in one non-randomized study, were not associated with an increased risk of VTE (28). Tamoxifen increases VTE risk in a manner similar to oral estrogen, whereas raloxifene is associated with fewer VTE events than tamoxifen or estrogen (29,30). Bazedoxifene, a new SERM marketed in combination with conjugated equine estrogen, has a VTE profile similar to estrogen, based on limited available data (31).

## Skeletal System

Osteoporosis is a major concern for postmenopausal women, leading to substantial morbidity and mortality. Fifty percent of women over age 65 have a compression fracture. Maintenance of bone mass is critical to prevent the development of osteoporosis. Height loss, up to several inches, and postural changes including kyphosis and lordosis are also caused by vertebral fractures. The mortality rate of women with hip fractures is 20% within the year following the fracture (32).

After peak bone mass is attained, usually around age 30, there is a slow, steady decline during the reproductive years, when approximately 0.7% of total bone is lost per year. At menopause, there is an accelerated rate of bone loss; 5% trabecular and 1.5% of total bone mass, on average, is lost per year. In the first 20 years after menopause, there is a 50% reduction in trabecular bone and 30% reduction in cortical bone, primarily due to the lack of estrogen (33).

Estrogen is responsible for promoting osteoblast (bone-forming cell) activity. It also inhibits bone remodeling and balances osteoblast and osteoclast (bone-resorbing cell) activity. As levels of serum estrogen decline in menopause, there is an increase in the rate of bone loss.. As such, increased bone turnover increases serum calcium. This increase in serum calcium, in turn, causes a decrease in parathyroid hormone (PTH) secretion, followed by calciuria and decreased renal production of 1,25 dihydroxy-vitamin D. Vitamin D is responsible for intestinal calcium absorption and kidney tubular reabsorption. This domino effect causes a postmenopausal woman to lose 20 to 60 mg of calcium daily (34).

## Osteoporosis Screening

It is a challenging public health problem to provide a cost-effective approach to identify women who are most likely to fracture, and to preferentially target them for screening and therapy.

An important and sensitive test to identify bone loss is a Dual Energy X ray Absorptimetry (DEXA) scan. Usually two sites are analyzed-- the lumbar spine and the femoral neck (occasionally the radius is also checked). Scoring systems for evaluating Bone Mineral Density (BMD) are based on the T-score and Z-score. The T-score compares the patient's BMD to young women at peak bone mass whereas the Z-score compares the patient to women her own age. It is the T-score that is used to make a diagnosis.

The World Health Organization (WHO) has established the following definitions:

1. normal BMD as a T-score => -1 standard deviation (SD) of the mean
2. osteopenia as BMD between -1 and -2.5 SD
3. osteoporosis as a T-score =< -2.5 SD

However, BMD via DEXA scan has a precision error of 2 to 6% depending on the site, which can amount to almost 1 t-score unit(35).

Bone density screening is useful, but does not provide all of the desired information about true fracture risk. Low bone density alone will not cause a fracture, unless it is so low that activities of daily living cause bones to break. Rather, women must have a combination of low bone density and a predisposition to falling that increases their risk. In order to attempt to address the factors beyond bone density that can be used to predict fractures, the World Health Organization (WHO) developed the Fracture Risk Assessment Tool (FRAX), to identify those women who are at the greatest risk for fracture. FRAX was developed to calculate the 10-year probability of a hip fracture and the 10-year probability of a major osteoporotic fracture (defined as a clinical vertebral, hip, forearm or humerus fracture) taking into account femoral neck BMD and the risk factors listed below in (Box 1). Clinicians can use the FRAX tool to make clinical decisions regarding BMD. (<http://www.shef.ac.uk/FRAX/index.aspx>).

|  |
| --- |
| **Box 1**WHO Technical Report: Fracture Risk Assessment Model |
| **Risk Factors Included in the Fracture Risk Assessment (FRAX) Model** |
| • Current age  |
| • Rheumatoid arthritis |
| • Gender |
| • Secondary osteoporosis |
| • A prior osteoporotic fracture |
| • Parental history of hip fracture |
| • Femoral neck BMD  |
| • Current smoking |
| • Low body mass index (kg/m2)  |
| • Alcohol intake (3 or more drinks/day) |
| • Oral glucocorticoids ≥5 mg/d of prednisone for ≥ 3 month |

All major current guidelines state that BMD screening should begin at age 65 years for women of ‘average risk’ (36). The rationale for waiting until age 65 to screen is that for most women, therapy will not need to be initiated before this time. Most guidelines also agree that BMD screening can and should be used selectively for women younger than 65 years if they are postmenopausal and have other risk factors for fracture (Box 2). Alternatively, FRAX can be used in women younger than 65 years to determine which women should have a BMD scan (37). Those women with a FRAX 10-year risk of major osteoporotic fracture of 9.3% could justifiably be referred for DXA because that is the risk of fracture found in a 65-year-old Caucasian woman with no risk factors. It is important to note that FRAX does not provide data on fracture risk for women aged 40 or under.

|  |
| --- |
| **Box 2** When to Screen for Bone Density Before Age 65 Years  |
| Bone density should be screened in postmenopausal women younger than 65 years if any of the following risk factors are noted:* Medical history of a fragility fracture
* Body weight less than 127lb
* Medical causes of bone loss (medications or diseases)
* Parental medical history of hip fracture
* Current smoker
* Alcoholism
* Premature ovarian failure
* Rheumatoid arthritis
 |

Other considerations for BMD testing include:

• Estrogen deficient women of any age at clinical risk for osteoporosis

• Individuals with vertebral abnormalities

• Individuals with primary hyperparathyroidism

## AVOIDING BONE LOSS

Exercise, calcium and vitamin D supplementation can help protect women from bone loss. By engaging in regular weight-bearing exercise, women lose less bone than they would if they remained sedentary (38). Supplementing a woman's diet with at least 1200 mg of calcium daily can also help protect her from menopausal bone loss. Adequate vitamin D levels are also crucial for calcium homeostasis. Cholecalciferol (vitamin D3) 1000 IU or more can be taken daily to assure adequate vitamin D stores. This is particularly important for women who do not have sufficient sunlight exposure (at least 15 minutes per day to non-sunscreened skin) and women over 60 years of age (39). Recent concerns have been raised about dietary calcium supplementation and increased risk of cardiovascular events. Data from several large clinical trials indicate that a small but statistically significant risk exists. This risk does not exist if a woman takes in calcium through dietary sources. It has been speculated that higher serum calcium levels are achieved with supplements but not when calcium is absorbed through consumption of calcium-rich foods, and that this transient, high circulating calcium can cause tissue calcification and dysfunction.

However, subsequent analyses of several additional samples of women (Table 1) do not support this notion. Practically speaking, patients should be encouraged to eat as many calcium rich foods as they can through their diet, and to supplement only if necessary and only up to the recommended daily allowances (1000mg per day for menopausal women taking hormones and 1200-1500mg per day for menopausal women not taking estrogen).

|  |
| --- |
| Table 1. Calcium supplementation and risk of heart disease. |
| **Author** | **Study** | **N** | **Findings** |
| Bostick (40) | Iowa Women’s Health Study | 34,486 | Decreased risk HR 0.66 |
| Michaelsson (41) | Swedish Cohort Study | 61,433 | >1400mg/day increased risk HR 2.57 |
| Chung (42) | Meta-analysis | 200 articles | No association |
| Bolland (43) | WHI—CT ONLY | 36,282 | >1000mg/day Increased risk  |
| Prentice (44) | WHI—CT +OS | >100,000 | No association |
| Xiao (45) | NIH-AARP diet and health study | 388,229 | No increased risk with supplements |
| Paik (46) | Nurse’s Health Study | 74,245 | No increased risk with supplements |

|  |
| --- |
| **Table 2** Treatments For Osteoporosis |
| Bisphosphonates | * **Alendronate** (Fosamax) 10 mg daily tablet, 70 mg weekly tablet or liquid formulation
* **Risedronate** (Actonel) 5 mg daily tablet, 35 mg weekly tablet or 150 mg monthly (75 mg tablet on 2 consecutive days)
* **Ibandronate** (Boniva) 2.5 mg daily tablet, 150 mg monthly tablet or 3 mg IV therapy every 3 months
* **Zoledronic Acid** (Reclast) 5 mg IV therapy yearly
 |
| SERMs  | * **Raloxifene HCl** (Evista) 60 mg daily
* Bazedoxifene/conjugated equine estrogens (Duavee) (20mg/0.45mg)
 |
| Calcitonin  | * **Calcitonin** **Salmon** (Miacalcin or Fortical) 200 IU intranasal spray daily
 |
| MHT | * **Estrogen** (see table 8 for detailed information)
 |
| PTH  | * **Recombinant PTH** (1-34) **Teriparatide** (Forteo) 20 µg SQ daily
 |
| RANK-L ligand inhibitor | * **Denosumab (Prolia) 60mg SC q6months**
 |

## Treatment for osteopenia and osteoporosis includes weight-bearing exercise, dietary modification, assuring adequate calcium and vitamin D intake, and the introduction of other medications. There are several different types of medications that can be used to treat low BMD: bisphosphonates, SERMs, calcitonin, hormones, and denosumab are all clinically-proven anti-resorptives (Table 2).

## TREATING OSTEOPOROSIS

|  |
| --- |
|  |

Although most fracture occur in women with bone density in the osteopenic range, it is not recommended to treat osteopenia without additional features that carry a more worrisome prognosis for fracture (47). For younger postmenopausal women, menopausal hormone therapy (when symptoms are present) or bazedoxifene/conjugated equine estrogens and raloxifene are appropriate agents (47). Raloxifene acts like a pro-estrogen on bone, lipids and liver and acts as an anti-estrogen on both the uterus and the breast. This makes its effects more favorable than tamoxifen, which acts like a pro-estrogen on the uterus. Bazedoxifene has a similar profile to raloxifene, and thus, when combined with estrogen, appears to exert a neutral effect on the endometrium and can therefore be given without a concomitant progestin. This confers a significant advantage over MHT for women with a uterus.

The landmark MORE (Multiple Outcomes of Raloxifene Evaluation) trial evaluated the ability of raloxifene to prevent fractures in women with established osteoporosis. 7705 post-menopausal women were randomized to either 60 or 120 mg of raloxifene versus placebo. The risk of both vertebral and non-vertebral fractures was reduced in the groups treated with raloxifene, and BMD increased in both the hip and the spine in raloxifene treated patients(48). Furthermore, a substantial decrease in the incidence of breast cancer was noted in raloxifene treated women, and the risk of having estrogen receptor positive invasive breast cancer was decreased when compared to placebo (49). There was no difference between treatment groups with respect to the development of endometrial cancer.

Bazedoxifene has a similar profile to raloxifene but has not yet been tested in a large clinical trial for outcomes related to breast cancer (50).

For older postmenopausal women without menopausal symptoms, bisphosphonates have been a mainstay of therapy for many years. Although they have a long track record of efficacy and safety, prolonged and high-dose usage has been associated with the rare side effects of osteonecrosis of the jaw and atypical femoral fracture (47). Recent research indicates that bone density is maintained for several years after discontinuation of treatment, and ‘drug holidays’ may help reduce the risk of developing adynamic bone.

Menopausal women with significant symptoms who are also osteopenic or osteoporotic can be treated with MHT. A disadvantage of MHT compared to bisphosphonates is the abrupt decrease in bone density that occurs when MHT is stopped.

Finally, denosumab, is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density. Denosumab can be given subcutaneously twice yearly to reduce the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis (51).

Once a patient has been started on therapy, markers of bone turnover can be used to assess a patient's response. Urinary calcium, deoxypyridinoline, pyridinoline, hydroxyproline and N-telopeptides can be checked after 1-3 months of initiating treatment in selected cases (51). DEXA scans, although they are currently the best method for determining BMD, should not be repeated too frequently, such as yearly, since errors in interpretation of trends can occur and lead to inappropriate therapy (53). It is recommended that DEXA scans be repeated no more frequently than every 2 years.

## CENTRAL NERVOUS SYSTEM

Vasomotor symptoms and “hot flashes” adversely affect the quality of life and functional status of most women during the menopausal transition. Hot flashes can occur in up to 85% of menopausal women. Col et al. estimated the duration of vasomotor symptoms in a longitudinal study on 438 women from the population-based Melbourne Women's Midlife Health Project. The onset and cessation of vasomotor symptoms were reported, and stratified according to whether or not MHT was used. They found that the mean (SD) duration of bothersome menopausal symptoms for women who never used MHT was 5.2 (3.8) years (54). A meta-analysis of 35,445 women taken from 10 different studies appeared to confirm a median 4-year duration of hot flashes, with the most bothersome symptoms beginning about 1 year before the final menstrual period and declining thereafter (55). However, two newer studies that have examined women longitudinally over a longer time frame indicate that the duration of vasomotor symptoms may be far longer than previously appreciated (56, 57). These studies have found that hot flashes may last as long as 10 years in up to one quarter of women who report them. The earlier in life that they appear, the longer they may last, and among all racial/ethnic groups studied, African-American women appear particularly vulnerable to long duration, bothersome vasomotor symptoms.

The exact etiology of the hot flash has not been elucidated but a resetting and narrowing of the thermoregulatory system is believed to occur. In the past, hot flashes were thought to be related to a withdrawal of estrogen; however, there is no acute change in serum estradiol during a hot flash. Others have related hot flashes to variability in both estradiol and FSH. It is thought that decreased estrogen levels may reduce serotonin levels and thus upregulate the 5-HT2A receptor in the hypothalamus. As such, additional serotonin is then released which can cause activation of the 5-HT2a receptor itself. This activation changes the set point temperature and results in hot flashes (58). Regardless of the exact etiology behind the hot flash, both hormone therapy and non-hormonal regimens can help to relieve vasomotor symptoms.

**Mood**

Significantly higher odds of depressive symptoms are reported by women who reach the late perimenopause in the Study of Women’s Health Across the Nation (SWAN) (59), as well as 2 other longitudinal studies of the menopausal transition (60, 61), risk for depression was most pronounced in women who began the study with a low Center for Epidemiologic Studies Depression Scale score (59), indicating that the depressive symptoms were of new onset and appeared to be directly related to the menopausal transition. Follow up studies using a Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) confirmed that the late perimenopause is a vulnerable window for new-onset major depression (62). The late perimenopause is also associated with a higher prevalence of sleep difficulty (63), which in turn is associated with depressive symptoms. Recent examination of anxiety symptoms in perimenopausal women indicate that, similar to depression, those with lower anxiety scores prior to the onset of the menopause transition are most vulnerable to a sudden escalation of anxiety and experience the greatest negative impact from their symptoms (64). Not surprisingly, women with a lifetime history of anxiety and depressive symptoms during their menopausal transition report the lowest health related quality of life (HRQOL) (65), and poor sleep exacerbates these associations.

## Cognition

Women routinely complain of cognitive deficits around the time of menopause. Certain aspects of cognition appear to be related to a decline in estrogen, but many are simply related to the aging process itself. While some studies have demonstrated improved short term and verbal memory in postmenopausal women taking estrogen (66),others have not found such beneficial effects (67). Greendale et. al. observed a subcohort of 2,362 SWAN participants longitudinally over 4 years to determined the effects of the menopausal transition and MHT use on cognitive performance in midlife women. The outcomes analyzed were longitudinal performance in 3 separate areas: processing speed, verbal memory and working memory. The results of the study showed that, consistent with transitioning women's perceived memory difficulties, perimenopause was associated with a decrement in cognitive performance, characterized by women not being able to learn as well as they had during premenopause. Improvement rebounded to near-premenopausal levels once the transition was completed, suggesting that menopause transition-related cognitive difficulties may be time-limited. The initiation of MHT prior to the final menstrual period had a beneficial effect, whereas initiation after the final menstrual period had a detrimental effect, on cognitive performance (68).

## Dementia and Alzheimer's disease

The most common form of dementia is Alzheimer's disease (AD), which is 3 times more common in women than in men. Women with preexisting dementia or AD have been noted to have lower serum estradiol levels than women without dementia (69). In observational studies, less AD has been observed in postmenopausal women who use estrogen and the effect was greater with increasing duration of use (70, 71). In some trials, women with mild to moderate AD who were given estrogen had improvement in their dementia (72, 73) but this was not observed in all clinical trials (74, 75). Estrogen has been believed to help prevent AD by regulating synapse formation in the hippocampus and by inducing acetycholinesterase and choline acetyltransferase, both of which are important in memory (76). Estrogen may also improve cognitive function because of protection against neuronal toxicity caused by oxidation and increasing metabolism of serum amyloid P (77). However, these molecular findings do not appear to translate into clinical benefits, as the WHI’s Mental Status (WHIMS) Trial demonstrated that hormone treatment with either (CCE+MPA) or (CCE) alone doubled the risk of AD and mild cognitive impairment. These clinical trial findings do not support a long- term role of estrogen in the prevention or treatment of AD. However, considerable controversy remains, as the sensitivity of the testing used in the WHI may not have been adequate to detect early disease. The KEEPS Cognitive and Affective Study did not demonstrate any differences in cognitive performance between early postmenopausal women randomized to 2 forms of estrogen plus progestin compared to placebo (78). This is notable because KEEPS used a very detailed cognitive battery of tests.

## LIBIDO

Loss of libido is a prevalent complaint in women of all ages and is present in approximately 9% of postmenopausal women (79). Causes for a menopause-related decline in sexual interest may relate partly to a drop in both estrogen and testosterone as ovarian function wanes. It is very important to consider the medication history and to screen for depression when clinically evaluating women with a complaint of diminished libido. In a survey of 35,381 women (the PRESIDE Study) (80), 10% reported decreased sexual desire; when women without concomitant depression or antidepressant medication were accounted for, the prevalence of desire disorder decreased to 6.3%.

Testosterone has long been considered as an agent that might promote libido in women. Several well-conducted,double-blind, randomized trials of testosterone in menopausal with decreased libido have demonstrated small, but clinically and statistically improved symptoms (81). Testosterone has been used as a transdermal formulation in most of these studies and demonstrates efficacy with or without concurrent use of estrogen, in women with and without their ovaries. The APHRODITE study examined transdermal testosterone in 814 menopausal women over 52 weeks. Women were randomly assigned to receive either a patch delivering 150 or300 µg of testosterone per day or placebo. Evaluation at week 24 demonstrated that the women on the 300 µg testosterone patch noted a significantly greater increase in their 4-week frequency ofsatisfying sexual episodes in comparison to placebo, but this was not observed in the group receiving 150 µg per day. Both doses of testosterone patcheswere associated with significant increases in desire compared with placebo. Androgenic adverse events were greater in the groupreceiving 300 µg of testosterone per day. Breast cancer was diagnosed in 4women who received testosterone (as compared with none who receivedplacebo) (82). The excess cases of breast cancer in women treatedwith testosterone may be due to chance. However, the possibilityof a causal relationship must be considered as several published studies have shown that higher levels of endogenous and administration of exogenous testosteroneis associated with the risk of breast cancer (83,84). Clearly, long-term data fromlarge clinical trials using testosterone are lacking and are needed (81). Of note, a recent trial of a testosterone gel for female libido was discontinued because of lack of efficacy. There are no FDA-approved testosterone preparations available for women. As of this writing, filbanserin, a centrally-acting agent that increases female sexual motivation, is not yet marketed. Its effect size appears similar to that of testosterone (small, but statistically and probably clinically significant) (85).

## BREAST

After menopause and with aging, breast tissue is gradually replaced with increasing amounts of adipose tissue. This causes an age associated decrease in breast density, which makes mammography more effective in detecting breast disease. Breast cancer becomes more prevalent with advancing age with a lifetime risk of breast cancer in 1:8 women (86).

## Breast Cancer and MHT

Combined estrogen and progesterone treatment increases a woman's risk of developing breast cancer. The WHI trials demonstrated a detectably increased risk of developing invasive breast cancer after 3 years of combined MHT use, with an unadjusted hazard ratio of 1.26 over 5.2 years of average follow-up (87). Technically, the 95% confidence interval included 1.00, thus, the data could be considered ‘not significant’; however, this level of risk is biologically plausible, as it is similar to that seen in many observational studies, and similar to the small, incremental risk for breast cancer that is seen with later onset of menopause. The only risk factor identified in WHI patients for the development of invasive breast cancer was the duration of MHT use. Patients taking hormones for 10 or more years were at greatest risk followed by patients using MHT for 5 to 10 years. Women who took MHT for less than 5 years had only a slight increase in risk. No correlation was noted between other risk factors--a patient's age, ethnicity, the 5-year Gail model risk score, body mass index (BMI) or family history--and the development of breast cancer. In women who had undergone hysterectomy and were randomized to CEE alone, no increase in breast cancer risk was observed; in fact, a decreased risk was observed in this group (88).

One of the ways in which MHT might increase breast cancer is by increasing breast density. It has been noted that estrogen with cyclic micronized progesterone resulted in 16.4% more women with increased breast density (89). A subset of 307 women in The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial was studied to examine the effect of MHT on mammograms. Of the group of women taking unopposed estrogen, 3.5% had an increase in breast density. Of the women taking both estrogen with progestin therapy, a 19.4-23.5% increase in breast density on mammography was noted, depending upon whether they took cyclic versus continuous MPA. Increased mammographic breast density is a strong independent risk factor (6-fold) for the development of breast cancer (90).

Case series and case-controls studies have suggested that patients taking MHT who are diagnosed with breast cancer have a better prognosis than women not taking hormones, even when matched for stage of disease (91). It has also been suggested that women who develop breast cancer while taking MHT have their cancers detected at a more favorable stage and have less malignant disease (92). These notions were disproven by the WHI Clinical Trial. Women randomized to combined MHT with (MPA + CEE) had a higher risk of invasive breast cancer and mortality from breast cancer. Tumors in the women taking combined MHT were comparable in histology and grade to the placebo group but were at a more advanced stage (87).

In contrast to combined E+P MHT, E alone MHT given to women without a uterus in the WHI, led to a decrease in breast cancer risk, which persisted after discontinuation of treatment and became statistically significant in the post-trial follow up study. After a median follow-up of 11.8 years, E alone treated women still had a lower incidence of invasive breast cancer (151 cases, 0·27% per year) compared with placebo (199 cases, 0·35% per year; HR 0·77, 95% CI 0·62—0·95; p=0·02 (93).

**Screening for breast cancer**

The U.S. Preventive Services Task Force (USPSTF) recommends biennial screening mammography for women aged 50 to 74 years (94), while the American College of Obstetricians and Gynecologists (ACOG) recommends that women aged 40 years and older be offered screening mammography annually (95).

## Assessing breast cancer risk

The Gail Model was developed to help clinicians determine if a patient was at higher risk than the general female population for the development of breast cancer (96).

The Gail Model takes into account the following characteristics:

1. age
2. age at menarche
3. age at first live birth
4. number of first degree relatives with breast cancer
5. number of previous breast biopsies
6. number of breast biopsies that were hyperplastic

This model provides an individualized risk for developing breast cancer over the next 5 years and over a lifetime. Other prospective scoring systems have been developed, but as of this writing there is no other dominant system that has proven to be superior to the Gail Model. By calculating a woman's risk of breast cancer with this model, a clinician can use the information to determine if a woman should consider chemoprophylaxis with a SERM (i.e., tamoxifen or raloxifene) to reduce her risk of breast cancer..Note that the Gail model does not factor into account breast density or MHT use. It also does not account for mutations, such as BRCA1 or 2, which have a profound effect on a woman’s risk of contracting breast cancer.

## Chemoprevention

Tamoxifen is indicated as adjuvant treatment for breast cancer. It is also prescribed for chemoprevention of breast cancer in high-risk women. Because tamoxifen is a SERM, it has both estrogenic and anti-estrogen actions. In the breast, it acts as an anti-estrogen. In the bone, on lipids and in the uterus, it acts like estrogen.

Tamoxifen was found to be effective in breast cancer prevention in a trial that included 13,388 women who were at high risk for developing breast cancer because of 1) advancing age (>60 years old), 2) increased risk based on a Gail Model predicted risk of 1.66% over the next 5 years and age 35-59, or 3) a history of lobular carcinoma in situ. Women who were randomly assigned to tamoxifen experienced a 49% decrease in the incidence of invasive breast cancer compared to those who received a placebo. In addition, there was a decrease in the risk of estrogen receptor positive breast cancer and nodal involvement in those with breast cancer. Women randomized to t[amoxifen](http://imaginis.com/breasthealth/tamoxifen.asp) also had fewer diagnoses of non-invasive breast cancer, such as ductal carcinoma *in situ* ([DCIS](http://imaginis.com/breasthealth/dcis.asp)) (97).

The STAR trial investigated the ability of t[amoxifen](http://imaginis.com/breasthealth/tamoxifen.asp) compared to [raloxifene](http://imaginis.com/osteoporosis/osteo_treatment.asp#raloxifene) in preventing breast cancer in women at high risk for disease. All participants received either tamoxifen or raloxifene and took the drug for 5 years. In 2006, the results of STAR showed that both raloxifene and tamoxifen were equally effective in reducing breast cancer risk in post-menopausal women at increased risk of the disease. Women in the tamoxifen group and women in the raloxifene group had statistically equivalent numbers of invasive breast cancers (163 cases in 9,726 women in the tamoxifen group versus 167 cases in 9,745 women in the raloxifene group). Tamoxifen is known to be able to reduce breast cancer risk by 49%, and this study showed that raloxifene can also reduce breast cancer risk by half as well. As a result of this study, the FDA approved raloxifene as a second agent to help prevent invasive breast cancer in high-risk, post-menopausal women (98). On an update of STAR trial, The risk ratio (RR; raloxifene:tamoxifen) for invasive breast cancer was 1.24 (95% confidence interval [CI], 1.05**–**1.47) and for noninvasive disease, 1.22 (95% CI, 0.95**–**1.59). Compared with initial results, the RRs widened for invasive and narrowed for noninvasive breast cancer. Toxicity RRs (raloxifene:tamoxifen) were 0.55 (95% CI, 0.36**–**0.83; P = 0.003) for endometrial cancer (this difference was not significant in the initial results), 0.19 (95% CI, 0.12**–**0.29) for uterine hyperplasia, and 0.75 (95% CI, 0.60**–**0.93) for thromboembolic events. There were no significant mortality differences (99).

To become active, tamoxifen must be metabolized by the hepatic cytochromeP450 enzyme system, specifically cytochromeP450 2D6 (CYP2D6), to its active metabolite, endoxifen. Consequently, therapywith drugs that inhibit CYP2D6 may reduce the clinical benefitof tamoxifen by interfering with its bioactivation, particularlywhen these drugs are used for an extended period. A significant percentage of patients with breast cancer experience a depressivedisorder and are prescribed an anti-depressant, most commonly one in the selective serotonin reuptake inhibitor(SSRI) category. This is clinically relevant in the contextof tamoxifen therapy, because SSRIs inhibit CYP2D6 to varying degrees. Paroxetine is an irreversible inhibitor of CYP2D6, and therefore has the greatest potential to disrupt the biological activity of tamoxifen. A population based cohort study was performed on 2430 women treated with tamoxifen and a single SSRI from 1993-2005. Of the group studied, 374 (15.4%) women died of breast cancer during follow-up. After adjustment for age, duration oftamoxifen treatment, and other potential confounders, absoluteincreases of 25%, 50%, and 75% in the proportion of time ontamoxifen with overlapping use of paroxetine were associated with 24%, 54%, and 91%increases in the risk of death from breast cancer, respectively(P<0.05 for each comparison). No such risk wasseen with other anti-depressants (100).

## THYROID GLAND

As women age, the cumulative risk of hypothyroidism increases. Frequently, symptoms are ignored or misattributed to other causes, making the diagnosis difficult. It is recommended by ACOG that all women, even asymptomatic females, have a thyroid stimulating hormone (TSH) level measured beginning at age 50 years and every 5 years thereafter (101). The American College of Physicians (ACP) also recommends periodic screening beginning at age 50 (102), while the American Thyroid Association (ATA) recommends that screening begin at age 35 (103).

## LOWER REPRODUCTIVE TRACT

The entire gynecologic tract contains estrogen receptors. As women become menopausal, the pelvic organs may be affected by the loss of estrogen resulting in vaginal atrophy, narrowing and shortening of the vagina and uterine prolapse, leading to high rates of dysparuenia. Furthermore, the urinary tract contains estrogen receptors in the urethra and bladder, and as the loss of estrogen becomes evident, patients may experience urinary incontinence (UI). Collectively, these symptoms, previously called vulvovaginal atrophy, have recently been renamed ‘genitourinary syndrome of menopause’ (GSM) (104). While MHT is effective in reversing changes associated with GSM (105,106), it does not consistently help with symptoms of UI. The WHI Clinical Trial found that women who received MHT and who were continent at baseline demonstrated an increase in the incidenceof all types of UI at 1 year. The risk was highest for women in the CEE alone arm. Among women experiencing UI at baseline, the frequencyof symptoms worsened in both arms and these women reported that UI limited theirdaily activities. This clinical trial evidence strongly suggests that MHT should not be prescribed as part of a regimen for UI alone (107). However, MHT is highly effective in the treatment of vaginal dryness. Systemic or vaginal estrogen can be used for GSM, though locally applied estrogen is preferable is there are no systemic symptoms that need to be treated. Very low doses can be used for this purpose. These low doses are believed to be safe for the uterus, even without concomitant use of a progestin. The data are currently insufficient to define the minimum effective dose, but vaginal rings, creams, and tablets have all been tested and demonstrated to reduce vaginal symptoms (108). Ospemifene is a new SERM that has recently been FDA approved for the treatment of GSM symptoms (109). It has a track record of endometrial safety (110) and in pre-clinical testing, was an effective antiresportive agent for bone and may even have breast-protective effects (111). These latter benefits remain to be proven in clinical trials.

## ADRENAL GLAND

The adrenal gland is responsible for producing androstenedione, dehydroepiandrosterone sulfate (DHEA-S) and, indirectly, total testosterone. After the menopausal years, androstenedione levels decrease by 62%, DHEA-S levels decline by 74% and testosterone, produced by the peripheral conversion of androstenedione, decreases by up to 25%. Circulating estrone, which is produced from the peripheral conversion of androstenedione, increases after menopause, whereas estradiol, which is produced from the peripheral conversion of estrone, declines. The menopause-associated drop in estrogen is related to a significant decline in sex hormone binding globulin (SHBG), resulting in a higher free testosterone level (112). This increase in free androgens may be responsible for the clinical problem of increased facial hair and androgenetic alopecia that accompanies the postmenopausal years for some some women.

# TREATMENT

## Figure 3: The Hormone Health Network has developed a self-administered algorithm for women to help them determine whether or not menopausal hormone therapy is a reasonable option for them. http://www.hormone.org/MenopauseMap/#.

## NON-HORMONAL TREATMENT

## Selective Serotonin Reuptake Inhibitors (SSRIs)

When MHT is contraindicated, (i.e., history of breast cancer), women with hot flashes may be treated with non-hormonal prescription drugs; one such class is the SSRIs (113,114). Once initiated, the relief of vasomotor symptoms usually occurs within a week, more rapidly than the relief of depressive symptoms, which usually takes 6 weeks or longer. The most common side effects of these drugs are nausea and sexual dysfunction but use of the lowest dose may minimize these effects.

Though not as drastic of a reduction when compared to MHT, the SSRIs result in a modest improvement in symptoms. A long-acting mesylate salt of paroxetine, 7.5mg, has been FDA-approved to treat hot flashes (115). Non-approved SSRIs that have been tested and have clinical efficacy include paroxetine (non-mesylate), escitalopram, citalopram, fluoxetine and sertraline (113).

## Serotonin–norepinephrine reuptake inhibitors (SNRIs)

Venlafaxine is a combined serotonin and norepinephrine reuptake inhibitor that has shown promise in reducing the severity of hot flashes in symptomatic women. A randomized trial was conducted in 229 women for 4 weeks where women with breast cancer received either varying doses of venlafaxine (37.5, 75 or 150 mg/day) versus placebo. There was a significant reduction in hot flashes in women receiving all doses of venlafaxine in comparison to placebo. Common side effects included nausea or vomiting, which are usually limited to the first 1 to 2 weeks of treatment. Other side effects include lethargy, dizziness, constipation and sexual dysfunction (116).

## Gabapentin

.A randomized, double-blind, placebo-controlled trial was conducted on 197 women aged 45-65 years, who were menopausal and having at least 14 hot flashes per week. These women were randomized to receive either gabapentin 900 mg daily or placebo for 4 weeks. Of women assigned to receive gabapentin, hot flash scores decreased by 51% as compared with a 26% reduction in the placebo group, from baseline to week 4. These women reported greater dizziness, unsteadiness and drowsiness at week 1 compared with those taking placebo; however, these symptoms improved by week 2 and returned to baseline levels by week 4 (117). A 2009 meta-analysis confirmed consistency across several clinical studies (118). The dose range of gabapentin is broad, and although many clinical trials use doses of 900mg, less may work well for individual patients. The chief limiting side effects of gabapentin are drowsiness, dizziness (which can present a hazard for falls), and weight gain.

**HORMONAL TREATMENT**

MHT is a mainstay of treatment for many women. As outlined above, there are specific risks and benefits associated with MHT that may not make it suitable for some women. Moreover, many women have a tendency to shun MHT because the level of discourse about its true benefits and risks are so fraught with drama! It is important for the menopause care provider to be knowledgeable about the benefits and potential risks of hormonal therapies and to have some facility with non-hormonal alternatives. This approach allows the clinician to engage the patient in truly shared decision making. It is important to maintain clear lines of communication with menopausal patients who are struggling with bothersome symptoms, because their subjective improvement is frequently the sole arbiter of success of treatment, and it is what all risks must be balanced against.

MHT is the most effective treatment for vasomotor symptoms and vaginal dryness caused by the loss of endogenous estrogen production. In addition, it acts like an anti-resorptive and is therefore osteoprotective and also has been shown to reduce the incidence of colon cancer by almost 40%. As mentioned earlier in this review, it is well established that MHT changes the lipoprotein profile favorably, although these latter changes do not translate into reduced cardiovascular morbidity.

However, unopposed estrogen use in women who have a uterus creates a risk for developing endometrial hyperplasia and cancer. Therefore, estrogen replacement must be accompanied by a progestin. In patients with a uterus who were given estrogen alone in The Postmenopausal Estrogen/Progestin Intervention (PEPI) Trial, 62% developed endometrial hyperplasia over 3 years. By identifying this pathology early, patients were medically treated with high doses of progestins so that no patients developed endometrial cancer (119). It is the standard of care to give women estrogen with a progestin when they have a uterus.

The decision to prescribe MHT must be based on each individual patient, taking into account the risk factors involved and creating a favorable benefit:risk ratio. To date, acceptable reasons to prescribe MHT include relief of severe vasomotor symptoms and to address GSM. There is sufficient medical evidence to consider a trial of MHT for women with adverse mood or sleep symptoms in association with their menopause (120). At present, there is no indication for using MHT for the prevention of cardiovascular disease, dementia/AD or osteoporosis or for the prevention of colon cancer, as the risks outweigh any potential benefits, although as mentioned earlier in this review, there are suggestions that premenopausal MHT may have protective effects in some cases.

A key factor in the decision tree for the initiation of MHT is the individual risk of breast cancer, which is a real and serious concern. It is contraindicated to prescribe MHT to patients with a history of breast cancer and it is not recommended to give MHT to those with a high risk profile. The adverse events demonstrated in patients taking combined estrogen-progestin MHT included a 26% increase of invasive breast cancer, with the excess risk starting to be observed after 3 years of combined MHT use. It is important to note that estrogen alone treatment of women without a uterus did not increase the risk of breast cancer.

Recommendations for prescribing MHT should be based upon the randomized, clinical trial results of the WHI, as highlighted throughout this review, as they currently constitute the best available medical evidence. Although the WHI studied the Prempro® formulation only, it is biologically plausible that other systemic formulations, including the transdermal patch, will carry similar risks and benefits and it should not be assumed that switching MHT formulations protects a patient from adverse events.

However, The Estrogen and Thromboembolism Risk study, a multicenter case-control study of thromboembolism among postmenopausal women aged 45-70 years, demonstrated an odds ratio for venous thromboembolism in users of oral and transdermal estrogen to be 4.2 (95% CI, 1.5-11.6) and 0.9 (95% CI, 0.4-2.1), respectively, when compared with nonusers28 (28). This has led ACOG, NAMS and the Endocrine Society to recommend that clinicians take into consideration the possible thrombosis-sparing properties of transdermal forms of estrogen therapy (113,114,121).

Women with vasomotor symptoms may consider short-term MHT use at the lowest effective dose. Women who are currently taking MHT and are asymptomatic, should be encouraged to periodically discontinue MHT use to see whether or not symptoms return. Finally, women who desire long-term MHT use for quality of life reasons (after appropriate counseling) should be evaluated regularly and their decision to continue MHT periodically reassessed.

## MHT regimens: continuous combined and cyclic regimens

There are many ways to prescribe MHT: oral tablets, patches, creams, sprays (Table 3). Considering the importance of including a progestin, there are several different modalities of administering these medications as well. This includes continuous combined and cyclical administrations. The continuous combined formulation administers both the estrogen and progestin hormones every day. Cyclical administration means that hormones are given in a cycle: 1) unopposed estrogen is given continuously 2) progestin is added. This regimen can be a cycle every 3 days (e.g. Ortho Prefest), every 14 days (e.g. Premphase), or at the discretion of the prescribing physician (e.g. every 3 months). Although generally believed to be safe, if progestins are given less frequently than monthly, the potential for hyperplasia exists and endometrial monitoring should be considered (122).

In women just entering menopause, the cyclical administration of the estrogen and progestin is usually the simplest choice. These patients can easily make the transition from taking a low dose oral contraceptive pill in the menopausal transition (frequently prescribed to control the irregular vaginal bleeding during that time) to the cyclical form of MHT. At the onset of MHT, most women will experience a withdrawal bleed at the end of the treatment month. Gradually, as the endometrium thins and becomes atrophic, some women will become amenorrheic on this regimen. Although irregular vaginal bleeding is uncommon, any abnormal uterine bleeding should be investigated. Another advantage of cyclical administration is that women will know when to expect bleeding.

Advantages of giving continuous combined therapy is that a lower dose of progestin can be used and patients should not expect a withdrawal flow at the end of the treatment month. Eventually, most women become amenorrheic on this regimen. Some women also develop irregular and inconvenient vaginal spotting or bleeding. This most frequently occurs in women who have recently entered menopause and still have an endometrial lining.

Besides oral preparations, MHT can be administered in a variety of other ways. Estrogen can be delivered through a vaginal ring that delivers either 0.05 or 0.1 mg/day of estradiol acetate over a three month period. It may also be given transdermally as 17β-estradiol with norethindrone acetate or levonorgestrel. Progesterone can be administered through a levonorgestrel-releasing IUD which can be left in place for up to10 years. Finally, vaginal preparations of progesterone are also available. More recently, transdermal estradiol sprays and gels have been FDA approved (Evamist ®, Divigel, and Elestrin). These preparations are relatively short acting and sometimes need to be used more than once a day. All are FDA approved for the treatment of hot flashes.

|  |
| --- |
| **Table 3**. MHT FORMULATIONS |
|  **Trade Name** |  **Estrogen** |  **Progestin** |  **Dose** |
| **Premarin** | Conjugated Estrogen | - | 0.3 to 1.25 mg PO daily  |
| **Cenestin** | Synthetic Conjugated Estrogen | - | 0.3 to 1.25 mg PO daily |
| **Menest** | Esterified Estrogen | -  | 0.3 to 1.25 mg PO daily |
| **Estrace**  | 17 β-estradiol | - | 1-2 mg PO daily |
| **Estinyl**  |  Ethinyl estradiol  | - | 0.02 to 0.05 mg PO 1-3 x daily  |
| **Evamist** | 17 β-estradiol  | - | 1-3 sprays daily |
| **Alora, Climara, Esclim, Menostar, Vivelle, Vivelle Dot, Estraderm** | 17 β-estradiol | - | 1 patch weekly-twice weekly |
| **Estrogel** | 17 β-estradiol  | - | 1.25 g daily transdermal gel (equivalent 0.75 mg estradiol) |
| **Estrasorb** | 17 β-estradiol | - | 2 foil pouches daily of transdermal topical emulsion  |
| **Activella** | Estradiol 1 mg  | Norethindrone Acetate 0.5mg  | 1 tab PO daily |
| **FemHRT** | Ethinyl Estradiol 5 mcg | Norethindrone Acetate 1 mg  | 1 tab PO daily |
| **Ortho Prefest** | 17 β-estradiol 1 mg  | Norgestimate 0.09 mg  | First 3 tablets contain estrogen, next 3 contain both hormones; alternate pills every 3 days |
| **Premphase** | Conjugated Estrogen 0.625 mg  | Medroxyprogesterone Acetate 5 mg  | First 14 tablets contain estrogen only and remaining 14 tablets contain both hormones.1 tab PO daily |
| **Prempro** | Conjugated Estrogen 0.625 mg  | Medroxyprogesterone Acetate 2.5 or 5 mg  | 1 tab PO daily |
| **Combipatch**  | 17 β-estradiol | Norethindrone acetate | 1 patch transdermal twice weekly |
| **Climara-Pro** | 17 β-estradiol | Levonorgestrel | 1 patch weekly |
| **Estrace**  | 17 β-estradiol vaginal cream  |  | 2-4 g daily x 1 week, then 1 g three times weekly  |
| **Premarin** | 17 β-estradiol vaginal cream |  | 0.5 g daily for 21 days on, 7 days off or twice weekly |
| **Vagifem** | 17 β-estradiol vaginal tablet |  | 10 mcg per vagina daily x 2 weeks, then 2 times per week |
| **Estring** | Estradiol vaginal ring |  | 1 ring inserted vaginally every 3 months |
| **Duavee** | Bazedoxifene 20mg Conjugated equine estrogen 0.45mg | None needed | 20/0.45mg daily |

**TSECs—Tissue Specific Estrogen Complexes**

The newest drug to market is bazedoxifene/conjugated equine estrogens, and represents yet another novel approach to hormone therapy. The combination of bazedoxifene, a SERM, with estrogen allows the clinician to apply estrogen where it is most beneficial—reducing or eliminating hot flashes, while the SERM bazedoxifene exerts anti-estrogenic effects at the target tissues where estrogen action is unwelcome—the endometrium and the breast (50). Thus, the combination of bazedoxifene and conjugated equine estrogens is effective as an antiresorptive agent in bone and does not cause endometrial stimulation. With the basedoxifene/conjugated equine estrogen combination, the clinician can avoid having to give progestin and avoid irregular or breakthrough bleeding.

# SUMMARY

In conclusion, this review has highlighted the major health concerns faced by the post-menopausal woman. Cardiovascular disease becomes more prevalent with the loss of estrogen and the decrease in endothelial function and HDL cholesterol levels that occur concurrent with menopause. Osteoporosis is another serious potential problem that the aging woman faces, and can be prevented by careful screening and early treatment. Cognitive decline and memory changes occur as aging ensues and AD becomes more prevalent, making it more difficult for aging women to maintain an independent lifestyle. Finally, breast cancer becomes more prevalent with advancing age. The increased risk of breast cancer needs to be considered when choosing a treatment plan for the post-menopausal woman.

There are a variety of treatments available to protect women from developing serious health problems. First and foremost, a healthy lifestyle is the best preventive medicine. MHT will control a patient's vasomotor symptoms, prevent bone loss, maintain a favorable lipoprotein profile and help prevent vaginal and urogenital atrophy. Other benefits of MHT include the reduction in the incidence of colon cancer. The SERM, raloxifene, also can be used to treat osteoporosis in menopausal women. The advantage of a SERM compared to MHT is its lack of endometrial stimulation and reduction in the risk of breast cancer. The prevention of bone loss and the beneficial effects on lipoprotein levels with SERMs are similar to those seen with MHT.

The role of MHT has changed over the years as its risks and benefits have been clarified through carefully designed randomized trials, most notably, the WHI. For a low-risk woman with moderate to severe vasomotor symptoms, the introduction of MHT is an effective option and patients will improve. However, the clinician needs to evaluate each patient independently and take into account the individual risk profile, including family history, in order to determine which form of treatment is most appropriate. The ability to modulate estrogen action via the development of SERMs provides the hope that a 'perfect' SERM can be produced, which will relieve vasomotor symptoms, protect the bone and the heart, maintain a favorable lipoprotein profile and be anti-estrogenic to the endometrium and the breast. Until then, non-hormonal alternatives are available for women who cannot or do not wish to take MHT. Prudent clinical judgment and an individualized assessment of risks and benefits for patients using the currently available medical evidence remains the most appropriate approach.

# REFERENCES

1. Soules MR, Sherman S, Parrott E, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). Fertility and sterility 2001;76:874-8.

2. Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. The Journal of clinical endocrinology and metabolism 2012;97:1159-68.

3. Burger HG, Hale GE, Robertson DM, Dennerstein L. A review of hormonal changes during the menopausal transition: focus on findings from the Melbourne Women's Midlife Health Project. Human reproduction update 2007;13:559-65.

4. Santoro N, Isaac B, Neal-Perry G, et al. Impaired folliculogenesis and ovulation in older reproductive aged women. The Journal of clinical endocrinology and metabolism 2003;88:5502-9.

5. Hale GE, Hughes CL, Burger HG, Robertson DM, Fraser IS. Atypical estradiol secretion and ovulation patterns caused by luteal out-of-phase (LOOP) events underlying irregular ovulatory menstrual cycles in the menopausal transition. Menopause 2009;16:50-9.

6. Santoro N, Crawford SL, Lasley WL, et al. Factors related to declining luteal function in women during the menopausal transition. The Journal of clinical endocrinology and metabolism 2008;93:1711-21.

7. Finkelstein JS, Brockwell SE, Mehta V, et al. Bone mineral density changes during the menopause transition in a multiethnic cohort of women. The Journal of clinical endocrinology and metabolism 2008;93:861-8.

8. Gold EB, Crawford SL, Avis NE, et al. Factors related to age at natural menopause: longitudinal analyses from SWAN. American journal of epidemiology 2013;178:70-83.

9. Torgerson DJ, Thomas RE, Reid DM. Mothers and daughters menopausal ages: is there a link? European journal of obstetrics, gynecology, and reproductive biology 1997;74:63-6.

10. He C, Murabito JM. Genome-wide association studies of age at menarche and age at natural menopause. Molecular and cellular endocrinology 2014;382:767-79.

11. Luborsky JL, Meyer P, Sowers MF, Gold EB, Santoro N. Premature menopause in a multi-ethnic population study of the menopause transition. Hum Reprod 2003;18:199-206.

12. Minino AM, Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2008. National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System 2011;59:1-126.

13. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: the Framingham study. Annals of internal medicine 1976;85:447-52.

14. Chae CU, Derby CA. The menopausal transition and cardiovascular risk. Obstetrics and gynecology clinics of North America 2011;38:477-88.

15. El Khoudary SR, Wildman RP, Matthews K, Thurston RC, Bromberger JT, Sutton-Tyrrell K. Endogenous sex hormones impact the progression of subclinical atherosclerosis in women during the menopausal transition. Atherosclerosis 2012;225:180-6.

16. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Jama 1998;280:605-13.

17. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. Jama 1995;273:199-208.

18. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. Jama 2004;291:1701-12.

19. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. Jama 2002;288:321-33.

20. Harman SM, Black DM, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. Annals of internal medicine 2014;161:249-60.

21. Woodard GA, Brooks MM, Barinas-Mitchell E, Mackey RH, Matthews KA, Sutton-Tyrrell K. Lipids, menopause, and early atherosclerosis in Study of Women's Health Across the Nation Heart women. Menopause 2011;18:376-84.

22. Matthews KA, Crawford SL, Chae CU, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? Journal of the American College of Cardiology 2009;54:2366-73.

23. El Khoudary SR, Wildman RP, Matthews K, Thurston RC, Bromberger JT, Sutton-Tyrrell K. Progression rates of carotid intima-media thickness and adventitial diameter during the menopausal transition. Menopause 2013;20:8-14.

24. Stefanick ML, Mackey S, Sheehan M, Ellsworth N, Haskell WL, Wood PD. Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. The New England journal of medicine 1998;339:12-20.

25. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. The New England journal of medicine 2003;349:523-34.

26. Manson JE, Allison MA, Rossouw JE, et al. Estrogen therapy and coronary-artery calcification. The New England journal of medicine 2007;356:2591-602.

27. Wu O. Postmenopausal hormone replacement therapy and venous thromboembolism. Gender medicine 2005;2 Suppl A:S18-27.

28. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation 2007;115:840-5.

29. Adomaityte J, Farooq M, Qayyum R. Effect of raloxifene therapy on venous thromboembolism in postmenopausal women. A meta-analysis. Thrombosis and haemostasis 2008;99:338-42.

30. Hernandez RK, Sorensen HT, Pedersen L, Jacobsen J, Lash TL. Tamoxifen treatment and risk of deep venous thrombosis and pulmonary embolism: a Danish population-based cohort study. Cancer 2009;115:4442-9.

31. Kawate H, Takayanagi R. Efficacy and safety of bazedoxifene for postmenopausal osteoporosis. Clinical interventions in aging 2011;6:151-60.

32. Cummings SR, Kelsey JL, Nevitt MC, O'Dowd KJ. Epidemiology of osteoporosis and osteoporotic fractures. Epidemiologic reviews 1985;7:178-208.

33. Riggs BL, Wahner HW, Melton LJ, 3rd, Richelson LS, Judd HL, Offord KP. Rates of bone loss in the appendicular and axial skeletons of women. Evidence of substantial vertebral bone loss before menopause. The Journal of clinical investigation 1986;77:1487-91.

34. Shoback D, Marcus R, Bickle D, Strewler G, eds. Mineral metabolism and bone disease. New York: Lange Medical Books/McGraw Hill; 2001.

35. Blake GM, Fogelman I. How important are BMD accuracy errors for the clinical interpretation of DXA scans? Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2008;23:457-62.

36. Force USPST. Screening for osteoporosis: U.S. preventive services task force recommendation statement. Annals of internal medicine 2011;154:356-64.

37. Watts NB, Bilezikian JP, Camacho PM, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis: executive summary of recommendations. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2010;16:1016-9.

38. Puntila E, Kroger H, Lakka T, Tuppurainen M, Jurvelin J, Honkanen R. Leisure-time physical activity and rate of bone loss among peri- and postmenopausal women: a longitudinal study. Bone 2001;29:442-6.

39. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. The New England journal of medicine 1997;337:670-6.

40. Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. American journal of epidemiology 1999;149:151-61.

41. Michaelsson K, Melhus H, Warensjo Lemming E, Wolk A, Byberg L. Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. Bmj 2013;346:f228.

42. Chung M, Balk EM, Brendel M, et al. Vitamin D and calcium: a systematic review of health outcomes. Evidence report/technology assessment 2009:1-420.

43. Bolland MJ, Grey A, Gamble GD, Reid IR. Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. The American journal of clinical nutrition 2011;94:1144-9.

44. Prentice RL, Pettinger MB, Jackson RD, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporosis International 2013;24:567-80.

45. Xiao Q, Murphy RA, Houston DK, Harris TB, Chow WH, Park Y. Dietary and supplemental calcium intake and cardiovascular disease mortality: the National Institutes of Health-AARP diet and health study. JAMA internal medicine 2013;173:639-46.

46. Paik JM, Curhan GC, Sun Q, et al. Calcium supplement intake and risk of cardiovascular disease in women. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2014;25:2047-56.

47. Eriksen EF. Treatment of osteopenia. Reviews in endocrine & metabolic disorders 2012;13:209-23.

48. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. Jama 1999;282:637-45.

49. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. Jama 1999;281:2189-97.

50. Smith CL, Santen RJ, Komm B, Mirkin S. Breast-related effects of selective estrogen receptor modulators and tissue-selective estrogen complexes. Breast cancer research : BCR 2014;16:212.

51. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. The New England journal of medicine 2009;361:756-65.

52. Eastell R, Hannon RA, eds. Biochemical markers of bone turnover. St. Louis, MO: Elsevier Academic Press; 2007.

53. Cummings SR, Palermo L, Browner W, et al. Monitoring osteoporosis therapy with bone densitometry: misleading changes and regression to the mean. Fracture Intervention Trial Research Group. Jama 2000;283:1318-21.

54. Col NF, Guthrie JR, Politi M, Dennerstein L. Duration of vasomotor symptoms in middle-aged women: a longitudinal study. Menopause 2009;16:453-7.

55. Politi MC, Schleinitz MD, Col NF. Revisiting the duration of vasomotor symptoms of menopause: a meta-analysis. J Gen Intern Med 2008;23:1507-13.

56. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA internal medicine 2015;175:531-9.

57. Freeman EW, Sammel MD, Sanders RJ. Risk of long-term hot flashes after natural menopause: evidence from the Penn Ovarian Aging Study cohort. Menopause 2014;21:924-32.

58. Freedman RR. Menopausal hot flashes: mechanisms, endocrinology, treatment. The Journal of steroid biochemistry and molecular biology 2014;142:115-20.

59. Bromberger JT. The menopausal transition increases the risk of depressive symptoms and depression diagnosis in women without a history of depression. Evidence-based mental health 2006;9:110.

60. Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Archives of general psychiatry 2006;63:385-90.

61. Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Archives of general psychiatry 2006;63:375-82.

62. Bromberger JT, Kravitz HM, Chang YF, Cyranowski JM, Brown C, Matthews KA. Major depression during and after the menopausal transition: Study of Women's Health Across the Nation (SWAN). Psychological medicine 2011;41:1879-88.

63. Kravitz HM, Joffe H. Sleep during the perimenopause: a SWAN story. Obstetrics and gynecology clinics of North America 2011;38:567-86.

64. Bromberger JT, Kravitz HM, Chang Y, et al. Does risk for anxiety increase during the menopausal transition? Study of women's health across the nation. Menopause 2013;20:488-95.

65. Joffe H, Chang Y, Dhaliwal S, et al. Lifetime history of depression and anxiety disorders as a predictor of quality of life in midlife women in the absence of current illness episodes. Archives of general psychiatry 2012;69:484-92.

66. Kimura D. Estrogen replacement therapy may protect against intellectual decline in postmenopausal women. Hormones and behavior 1995;29:312-21.

67. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. Jama 2004;291:2947-58.

68. Greendale GA, Huang MH, Wight RG, et al. Effects of the menopause transition and hormone use on cognitive performance in midlife women. Neurology 2009;72:1850-7.

69. Manly JJ, Merchant CA, Jacobs DM, et al. Endogenous estrogen levels and Alzheimer's disease among postmenopausal women. Neurology 2000;54:833-7.

70. Kawas C, Resnick S, Morrison A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 1997;48:1517-21.

71. Tang MX, Jacobs D, Stern Y, et al. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet 1996;348:429-32.

72. Asthana S, Baker LD, Craft S, et al. High-dose estradiol improves cognition for women with AD: results of a randomized study. Neurology 2001;57:605-12.

73. Henderson VW, Paganini-Hill A, Emanuel CK, Dunn ME, Buckwalter JG. Estrogen replacement therapy in older women. Comparisons between Alzheimer's disease cases and nondemented control subjects. Archives of neurology 1994;51:896-900.

74. Henderson VW, Paganini-Hill A, Miller BL, et al. Estrogen for Alzheimer's disease in women: randomized, double-blind, placebo-controlled trial. Neurology 2000;54:295-301.

75. Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. Jama 2000;283:1007-15.

76. McEwen BS, Alves SE, Bulloch K, Weiland NG. Ovarian steroids and the brain: implications for cognition and aging. Neurology 1997;48:S8-15.

77. Gandy S, Duff K. Post-menopausal estrogen deprivation and Alzheimer's disease. Experimental gerontology 2000;35:503-11.

78. Gleason CE, Dowling NM, Wharton W, et al. Effects of Hormone Therapy on Cognition and Mood in Recently Postmenopausal Women: Findings from the Randomized, Controlled KEEPS-Cognitive and Affective Study. PLoS medicine 2015;12:e1001833; discussion e.

79. Leiblum SR, Koochaki PE, Rodenberg CA, Barton IP, Rosen RC. Hypoactive sexual desire disorder in postmenopausal women: US results from the Women's International Study of Health and Sexuality (WISHeS). Menopause 2006;13:46-56.

80. Johannes CB, Clayton AH, Odom DM, et al. Distressing sexual problems in United States women revisited: prevalence after accounting for depression. The Journal of clinical psychiatry 2009;70:1698-706.

81. Wierman ME, Arlt W, Basson R, et al. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. The Journal of clinical endocrinology and metabolism 2014;99:3489-510.

82. Davis SR, Moreau M, Kroll R, et al. Testosterone for low libido in postmenopausal women not taking estrogen. The New England journal of medicine 2008;359:2005-17.

83. Somboonporn W, Davis SR, National H, Medical Research C. Testosterone effects on the breast: implications for testosterone therapy for women. Endocrine reviews 2004;25:374-88.

84. Hankinson SE, Eliassen AH. Endogenous estrogen, testosterone and progesterone levels in relation to breast cancer risk. The Journal of steroid biochemistry and molecular biology 2007;106:24-30.

85. Simon JA, Kingsberg SA, Shumel B, Hanes V, Garcia M, Jr., Sand M. Efficacy and safety of flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the SNOWDROP trial. Menopause 2014;21:633-40.

86. Sakorafas GH, Krespis E, Pavlakis G. Risk estimation for breast cancer development; a clinical perspective. Surgical oncology 2002;10:183-92.

87. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. Jama 2003;289:3243-53.

88. Stefanick ML, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. Jama 2006;295:1647-57.

89. Greendale GA, Reboussin BA, Sie A, et al. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators. Annals of internal medicine 1999;130:262-9.

90. Huo CW, Chew GL, Britt KL, et al. Mammographic density-a review on the current understanding of its association with breast cancer. Breast cancer research and treatment 2014;144:479-502.

91. Bonnier P, Romain S, Giacalone PL, Laffargue F, Martin PM, Piana L. Clinical and biologic prognostic factors in breast cancer diagnosed during postmenopausal hormone replacement therapy. Obstetrics and gynecology 1995;85:11-7.

92. Delgado RC, Lubian Lopez DM. Prognosis of breast cancers detected in women receiving hormone replacement therapy. Maturitas 2001;38:147-56.

93. Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. The Lancet Oncology 2012;13:476-86.

94. Force USPST. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Annals of internal medicine 2009;151:716-26, W-236.

95. American College of O-G. Practice bulletin no. 122: Breast cancer screening. Obstetrics and gynecology 2011;118:372-82.

96. Spiegelman D, Colditz GA, Hunter D, Hertzmark E. Validation of the Gail et al. model for predicting individual breast cancer risk. Journal of the National Cancer Institute 1994;86:600-7.

97. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. Journal of the National Cancer Institute 1998;90:1371-88.

98. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. Jama 2006;295:2727-41.

99. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. Cancer prevention research 2010;3:696-706.

100. Kelly CM, Juurlink DN, Gomes T, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. Bmj 2010;340:c693.

101. American College of O, Gynecologists Committee on Gynecologic P. ACOG Committee Opinion No. 483: Primary and preventive care: periodic assessments. Obstetrics and gynecology 2011;117:1008-15.

102. Helfand M, Redfern CC. Clinical guideline, part 2. Screening for thyroid disease: an update. American College of Physicians. Annals of internal medicine 1998;129:144-58.

103. Ladenson PW, Singer PA, Ain KB, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. Archives of internal medicine 2000;160:1573-5.

104. Portman DJ, Gass ML, Vulvovaginal Atrophy Terminology Consensus Conference P. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. Menopause 2014;21:1063-8.

105. Leiblum S, Bachmann G, Kemmann E, Colburn D, Swartzman L. Vaginal atrophy in the postmenopausal woman. The importance of sexual activity and hormones. Jama 1983;249:2195-8.

106. Rioux JE, Devlin C, Gelfand MM, Steinberg WM, Hepburn DS. 17beta-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. Menopause 2000;7:156-61.

107. Hendrix SL, Cochrane BB, Nygaard IE, et al. Effects of estrogen with and without progestin on urinary incontinence. Jama 2005;293:935-48.

108. Henriksson L, Stjernquist M, Boquist L, Cedergren I, Selinus I. A one-year multicenter study of efficacy and safety of a continuous, low-dose, estradiol-releasing vaginal ring (Estring) in postmenopausal women with symptoms and signs of urogenital aging. American journal of obstetrics and gynecology 1996;174:85-92.

109. Constantine G, Graham S, Portman DJ, Rosen RC, Kingsberg SA. Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. Climacteric : the journal of the International Menopause Society 2015;18:226-32.

110. Constantine GD, Goldstein SR, Archer DF. Endometrial safety of ospemifene: results of the phase 2/3 clinical development program. Menopause 2015;22:36-43.

111. Kangas L, Unkila M. Tissue selectivity of ospemifene: pharmacologic profile and clinical implications. Steroids 2013;78:1273-80.

112. Labrie F, Belanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. The Journal of clinical endocrinology and metabolism 1997;82:2396-402.

113. ACOG Practice Bulletin No. 141: management of menopausal symptoms. Obstetrics and gynecology 2014;123:202-16.

114. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. Menopause 2004;11:11-33.

115. Weber L, Thacker HL. Paroxetine: a first for selective serotonin reuptake inhibitors - a new use: approved for vasomotor symptoms in postmenopausal women. Women's health (London, England) 2014;10:147-54.

116. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356:2059-63.

117. Butt DA, Lock M, Lewis JE, Ross S, Moineddin R. Gabapentin for the treatment of menopausal hot flashes: a randomized controlled trial. Menopause 2008;15:310-8.

118. Toulis KA, Tzellos T, Kouvelas D, Goulis DG. Gabapentin for the treatment of hot flashes in women with natural or tamoxifen-induced menopause: a systematic review and meta-analysis. Clinical therapeutics 2009;31:221-35.

119. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. Jama 1996;275:370-5.

120. National Institutes of H. National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. Annals of internal medicine 2005;142:1003-13.

121. Santen RJ, Allred DC, Ardoin SP, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. The Journal of clinical endocrinology and metabolism 2010;95:s1-s66.

122. Ettinger B, Selby J, Citron JT, Vangessel A, Ettinger VM, Hendrickson MR. Cyclic hormone replacement therapy using quarterly progestin. Obstetrics and gynecology 1994;83:693-700.