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THE POSTMENOPAUSAL WOMEN

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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 with consistently low circulating estradiol and elevated gonadotropins. Estrogen is the most efficacious therapy for bothersome vasomotor symptoms and is the recommended first line treatment for women who do not have a contraindication to its use. 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 in post-menopausal women. Estrogen is not usually a first line agent for bone preservation in women unless there are concurrent menopausal symptoms, despite its antiresorptive effects. Non-hormonal alternatives to estrogen use are also available to treat common menopausal symptoms, including a new class of agents that are specific neurokinin receptor antagonists, which may have comparable efficacy to hormones though may have risks for some patients.

Note: In this article, the word 'woman' is used to refer to individuals who are assigned female at birth (AFAB) and who have ovaries. The available medical literature is deficient in knowledge about the experience, risks, and benefits of hormone therapy in transmasculine individuals and how the menopausal process impacts those who are concurrently using cross-gender hormone therapy.

INTRODUCTION

Menopause is associated with a constellation of physical changes. Although many of these changes are viewed negatively by society, when surveyed, American women, especially African American women, have positive associations with menopause that include freedom from worry about unwanted pregnancy and absence of menstrual bleeding (1). Some of the changes associated with menopause 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. The menopause transition is associated with distinct changes in a number of risk factors for chronic disease, some of

This review will address the menopausal transition, its common symptoms and associations with future disease risk, and the risks and benefits of Hormone Therapy (HT), specifically, estrogen therapy with or without progestin, raloxifene, tamoxifen and bazedoxifene, and non-hormonal therapies.

DEFINITIONS

The Menopausal Transition

In 2001 (2) and again in 2012 (3), 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 cycle and hormone changes of the early transition are best explained by a critical reduction of the follicle cohort. This decrease in the available pool of growing follicles leads to a decrease in inhibin B production (4). Reduced inhibin B removes the physiologic restraint on follicle-stimulating hormone (FSH) that controls the process of folliculogenesis, and thus increased FSH secretion is observed, most notably in the early follicular phase of the menstrual

which ‘reset’ back to the premenopausal trajectory after the transition is completed and others which remain elevated.

cycle. FSH levels may vary considerably from month to month as the growing follicle cohort itself varies month to month. The follicular phase often shortens and estradiol (E2) production is variable and even elevated at times (5). 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’ (6). A sharp drop-off in the proportion of ovulatory cycles begins at about 5 years before the final menstrual period (FMP) and luteal progesterone production declines. Gonadotropins rise sharply beginning at 3 years prior to the FMP (5). This early phase of the menopausal 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. Although the median duration of the transition is about 4 years, its duration is longer in women with onset at an earlier age and can persist as long as 10 years or more in some cases (8).

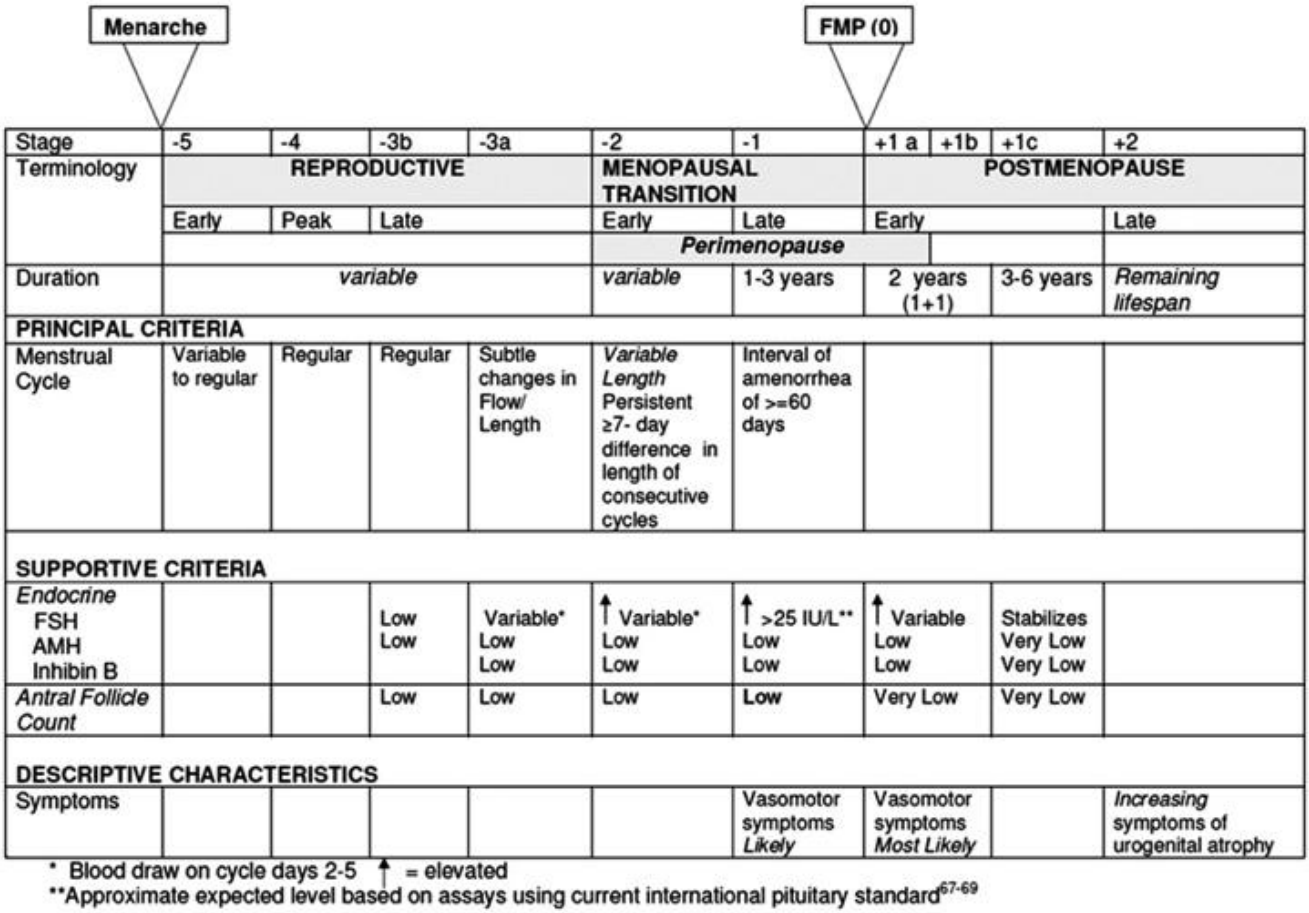

Figure 1. The Stages of Reproductive Aging Workshop +10 staging system for reproductive aging in women (3).

The menopause transition is also associated with a variety of non-reproductive changes, some of which are subtle and revert to their premenopausal rate of change and some of which remain on an accelerated trajectory. For this reason, the menopause transition is truly an ideal stage of life for an accounting of health status and for planning medical surveillance. Many of the diseases that will appear later in life and threaten a woman's health, such as cardiometabolic disease, will present some early warning signals during the transition. The late transition, when menstrual cycles become more than 60 days' apart, appears to be a particularly vulnerable time point (Figure 2). Although weight change is small with the onset of menopause, an acute increase in fat mass is seen within a two year period of time surrounding the final menses. Fat accrual appears to stabilize thereafter (10), as does progression of carotid intima-medial thickness (11). Visceral adipose tissue accumulates rapidly in the two years surrounding the transition, after which the rate of accumulation goes down, but not back to premenopausal levels (12). Depressive symptoms follow a pattern similar to visceral adipose tissue accumulation (13). The trajectory for prevalent metabolic syndrome appears to be increased permanently by the late transition (14).

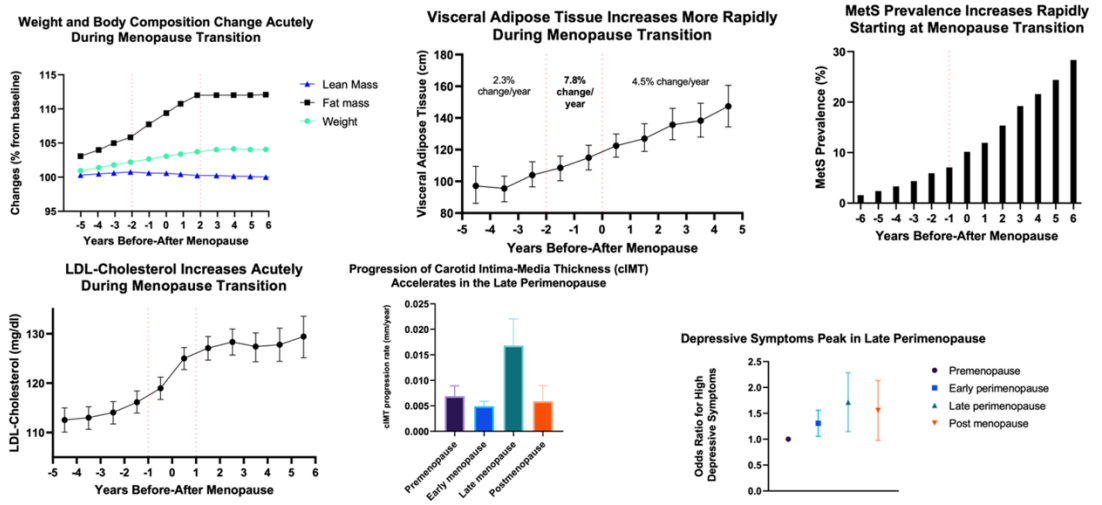

Figure 2. Pattern of change in body weight and fat mass, visceral adipose tissue, metabolic syndrome, LDL-cholesterol, carotid intima-medial thickness, and depressive symptoms in relation to the final menstrual period. Note the different patterns of change in these key cardiometabolic risk factors. While some, such as fat mass, stabilize after acutely increasing in the years surrounding the menopause transition, others, such as metabolic syndrome, appear permanently altered in rate of change in association with the transition (adapted from references 9-14).

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 (15). 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 (16). The heritability of age at menopause suggest genetic linkages for genes are involved in ovarian aging (17). Interestingly, genes that are responsible for predicting the age at menopause regulate DNA damage response and are also predictive of premature menopause, or primary ovarian insufficiency (18; see below). Menopause is known to occur approximately 1-2 years earlier in tobacco users (16).

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% (19). 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 HT for

women under age 40 who have ovarian failure differs from that for menopausal women aged 50-79. A preventive cardiovascular benefit for HT 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 (20).

PHYSIOLOGIC CHANGES ASSOCIATED WITH AGING AND MENOPAUSE

Cardiovascular System

The largest health threat to women over age 50 is cardiovascular disease (CVD) (14). In women aged 45-49, the incidence of CVD 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 (21). 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 amenable to intervention and prevention. 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 (22,23). Further, vascular dysfunction and future cardiovascular events are associated with more bothersome menopausal vasomotor symptoms (24,25). The direction of any possible causation, however, is not known.

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 (26). Endothelial function is also a predictor for CVD and has been shown to decrease during the menopause transition in relation to changes in estradiol and increased oxidative stress (27). Due to the strong association of adverse cardiovascular changes with diminishing ovarian function, researchers have long studied the use of hormone therapy to prevent the rise in CVD risk associated with menopause.

The Heart and Estrogen/Progestin Replacement study (HERS) evaluated the role of estrogen in secondary prevention (28). This trial included 2763 post-menopausal women with pre-existing coronary heart disease (CHD) followed over 4 years. The objective was to see if initiating HT would alter a woman's risk of future events. All participants were post-menopausal, younger than age 80 with a uterus and had 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 HT 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. Incidentally, the incidence of diabetes mellitus was noted to decrease by 3.5% over 4 years in the HT group. Similar to the results of the placebo-controlled, randomized Postmenopausal Estrogen/Progestin Interventions (or PEPI) Study, which evaluated intermediate cardiovascular markers (29), the HT group had a

decrease in LDL cholesterol and an increase in HDL cholesterol when compared to placebo. These investigators concluded that HT 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 HT in women with established CHD is not recommended. Based on the findings of the HERS Study, HT should not be initiated for secondary prevention of cardiovascular disease.

Studies have also focused on the possibility that use of HT during an optimal 'window of opportunity' in the early postmenopausal period could be effective for primary prevention of cardiovascular disease. The Women's Health Initiative hormone therapy clinical trial did not find primary protection against CVD in women treated for a mean of 5-7 years with either conjugated equine estrogen alone (women with a hysterectomy) (30) or estrogen plus the progestin, medroxyprogesterone acetate (31), and these results were consistent in cumulative 18-year follow-up (32). When subgroup analyses were performed by age, women in the youngest age group (50-59 at enrollment), did not demonstrate significant benefit from HT. The Kronos Early Estrogen Prevention Study (KEEPS) tested the hypothesis that early intervention with estrogen delays the onset of atherosclerosis as measured by carotid intima medial thickness and coronary calcium accrual using a regimen of either conjugated equine estrogen or transdermal estradiol, both with cyclic administration of oral, micronized progesterone for 12 days each month. KEEPS did not demonstrate any between-group differences in CIMT or coronary calcium scores (33). The rationale that hormones are protective of the vascular system when initiated early in menopause was supported, however, by the Early versus Late Intervention Trial with Estradiol (ELITE). The ELITE study found that oral estradiol treatment initiated within 6 years of menopause reduced the rate of CIMT compared to placebo, and this effect was not seen in women who initiated estrogen 10 or more years after menopause (34). The long-term effect of time of HT initiation on CVD is therefore not established, and HT is not currently recommended for primary prevention of CVD, regardless of age at initiation.

LIPOPROTEIN CHANGES, CARDIOVASCULAR RISK, AND HT

The role of menopause in contributing to dyslipidemia has also 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 (35). Moreover, the protective effect of HDL cholesterol appears to be diminished as women progress through menopause—possibly related to denser sub-particle size (36). 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 (37). In agreement with this finding is the relatively sharp upturn in CIMT observed in association with the late menopausal transition (11). 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 (38).

The Womens' Health Initiative (WHI) trials describe a group of randomized, placebo controlled, clinical primary prevention trials that were designed to test the effects of HT, diet modification, and calcium and vitamin D supplements on CVD, 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 administered to women without a uterus, and a placebo arm involved both women with or without a uterus. The WHI findings

suggest that administration of HT does not protect the heart. While the initial analysis showed that 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, 18-year cumulative follow-up showed no difference in CHD and CVD-related mortality (31,32). Women who had higher baseline LDL cholesterol levels at the beginning of the study were at particularly high risk of CHD with HT use (39). 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 (30).

Some 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 coronary artery calcium (CAC) burden to determine whether or not it differed based on treatment assignment. The WHI Coronary-Artery Calcium Study (WHI-CACS) evaluated 1,064 women aged 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 (40).

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 because they are not consistent and randomized clinical trial data are lacking. 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 a higher risk for venous thromboembolism (VTE) due to increased liver metabolism of estrogen given orally (41).

HT in currently used doses is associated with an approximately 3-fold increase in VTE events.

Transdermal estrogen preparations bypass liver metabolism and may be associated with the lowest VTE risk. Multiple observational studies have demonstrated fewer VTE and ischemic events with transdermal estrogen preparations compared to oral (42-45). There is some observational evidence that oral estradiol may also carry a lower risk of VTE than conjugated equine estrogen (46). SERM preparations also increase VTE risk. Tamoxifen increases VTE risk in a manner similar to oral estrogen, whereas raloxifene is associated with fewer VTE events than tamoxifen or estrogen (47,48). Bazedoxifene showed similar VTE risk compared to raloxifene in a randomized placebo-controlled trial (49)

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 (50).

After peak bone mass is attained in the 4th decade of life, 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. Almost all of this loss occurs in a 5–7-year period of the 'transmenopause' (51,52). 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 (51).

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 calcinuria 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 (53).

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 Absorptiometry (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 (54). It is therefore important to avoid errors in clinical decision making by overinterpreting DEXA scans that are performed too close together in time. When the measurement error exceeds the likely change in bone density that might

be expected to influence clinical decision making, repeat testing should be deferred in most cases.

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. Current clinical guidelines recommend BMD screening at age 65 years for women of 'average risk' (55). The rationale for waiting until age 65 to screen is that for most women, therapy will not need to be initiated before this time. However, most clinical guidelines also agree that BMD screening can and should be used selectively for women younger than 65 years if they are postmenopausal and/or have other risk factors for fracture (Table 1). Other considerations for BMD screening include estrogen deficient women of any age, vertebral anomalies, and primary hyperparathyroidism.

Table 1. Conditions and Medications to Consider When Deciding Whether to Screen For Bone Density Before Age 65 Years (from reference 56)
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 (commonly used medications include SSRIs/SNRIs, proton pump inhibitors, SGLT2 inhibitors, glucocorticoids and other immunosuppressive agents, GnRH agonists or antagonists, excess thyroid hormone and aromatase inhibitors)
Medical conditions (hyperthyroidism, hypercortisolism, nutritional deficiencies due to lack of intake or malabsorption, type 1 and type 2 diabetes mellitus, primary hyperparathyroidism, obesity, inflammatory bowel disease and chronic liver disease)
Parental medical history of hip fracture
Current smoker
Alcoholism
Primary ovarian insufficiency
Rheumatoid arthritis, other rheumatological diseases
Frailty

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 Table 2. Clinicians can use the FRAX tool to make clinical decisions regarding BMD testing (http://www.shef.ac.uk/FRAX/index.aspx). FRAX can be used in women younger than 65 years to determine which women should have a BMD scan (56). 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. Ultimately, it is important for clinicians to take into account not only age, but also presence of risk factors and the expected rate of bone loss when using screening tools and deciding whom to screen for BMD testing.

Table 2. WHO Technical Report: Fracture Risk Assessment Model
Risk Factors Included in the Fracture Risk Assessment (FRAX) Model
• Current age
• Rheumatoid arthritis
• Sex
• 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

AVOIDING BONE LOSS

Exercise, calcium, and vitamin D supplementation have long been recommended to help protect women from bone loss, but the evidence for this recommendation is poor and neither supplement is endorsed by the USPSTF for primary prevention of fracture (57). Supplementation with calcium and vitamin D if dietary levels cannot be achieved has been recommended. However, concerns have been raised about excess calcium supplementation including increased risk of renal stones and cardiovascular events. A recent meta-analysis of 13 RCTs supports an increased risk of cardiovascular disease (RR 1.15, 95% CI 1.06-1.25) and coronary heart disease (RR 1.16, 95% CI 1.05-1.28) in women with a dietary calcium intake above 700-1000mg per day or a supplementary intake of more than 1000mg per day. 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 transient high circulating calcium can cause tissue calcification and dysfunction. Cardiovascular risk has not been demonstrated in association with vitamin D intake (61, 62). Practically speaking, patients should be encouraged to eat calcium and vitamin-D rich foods through their diet. Those who have documented vitamin D deficiency should be given supplements (56). Lifestyle is also important for preventing bone loss. By engaging in regular weight-bearing exercise, women lose less bone than they would if they remained sedentary (59).

TREATING OSTEOPOROSIS

Treatment for osteopenia and osteoporosis includes weight-bearing exercise, dietary modification, ensuring adequate calcium and vitamin D intake, and the introduction of other medications. There are several types of medications that can be used to treat low BMD: bisphosphonates, SERMs, calcitonin, hormones, and denosumab are all clinically proven anti-resorptives (Table 3).

Table 3. Treatments For Osteoporosis	
Treatment and Prevention	
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
SERM	**Raloxifene HCl** (Evista) 60 mg daily
Treatment Only	
Calcitonin	**Calcitonin Salmon** (Miacalcin or Fortical) 200 IU daily intranasal spray or 100 IU daily IM or SQ
PTH	**Teriparatide** (Forteo) 20 µg SQ daily **Abalopartide** (Tymlos) 80 µg SQ daily
RANK-L ligand inhibitor	**Denosumab (Prolia)** 60mg SC q6months
Sclerostin inhibitor	**Romosozumab (Evenity)** 210mg SC monthly
Prevention Only	
HT	**Estrogen** (see table 6 for detailed information)
TSEC	**Conjugated estrogen + bazedoxifene** (Duavee) 0.045mg/20mg daily tablet

Although most fractures 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 (60). The approved medications for both treatment and prevention of osteoporosis include bisphosphonates and the SERM, raloxifene. Bisphosphonates have been a mainstay of therapy for many years, and act by inhibiting bone resorption. 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 (61). 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. Recent guidelines recommend risk assessment 3-5 years after initiation and those at low-moderate risk attempt a bisphosphonate holiday (discontinuation up to 5 years)(62,63). Fracture risk assessment should be made every 2-4 years during a drug holiday. Worsening risk should trigger resumption of treatment (56). Bisphosphonates should be avoided in women of child-bearing potential as they deposit in the bone, have a very long half-life, and can accumulate in fetal bone if they have been given to the mother, even preconceptually.

Denosumab is a 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. This drug is approved for treatment, but not prevention, of osteoporosis. Denosumab can be given subcutaneously twice yearly to reduce the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis (64). A drug holiday is not recommended for denosumab since reversal of its effects occur within 6 months if dosing is interrupted.

Drug holidays for denosumab can be considered after 5-10 years, and consideration for switching to an antiresorptive agent should be made.

Parathyroid hormone (PTH) acts as an anabolic metabolite to stimulate bone production from osteoblasts and is approved for treatment of osteoporosis. PTH decreases the incidence of new fractures and increases bone density and thus is recommended in patients at high fracture risk. However, adverse side effects include hypercalcemia and gastrointestinal symptoms. Early rodent studies were associated with possible osteosarcoma; however, post-marketing studies have not observed an increased risk in humans. It remains that its approved use in humans is only for 24 months (65).

Romosozumab is a human monoclonal antibody that inhibits sclerostin, resulting in increased Wnt signaling with both anabolic and resorptive effects on bone. This is the newest FDA-approved medication for treatment of osteoporosis and has shown significant reduction in fracture risk (66). The ARCH trial (Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk) demonstrated significantly lower fracture risk in patients who took romosozumab for 12 months followed by alendronate, compared to alendronate alone (67). Increased incidence of cardiovascular events including myocardial infarction and stroke were observed, so initiation is recommended in those with low risk factors. A 5-year post-marketing observational study, required by the FDA, is underway to better assess cardiovascular events.

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 mixed estrogen agonist on the 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 (68). 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 (69). There was no difference between treatment groups with respect to the development of endometrial cancer. Raloxifene may be considered for patients with osteoporosis at high risk of fracture and with increased risk of breast cancer. Raloxifene increases thrombotic events so is best reserved for those with low DVT risk.

For prevention of osteoporosis in postmenopausal or hypoestrogenic women, menopausal hormone therapy or bazedoxifene/conjugated equine estrogens are appropriate agents (56). Bisphosphonates or denosumab are preferred, but HT can also be considered if menopausal symptoms are present and the timing is not more than 10 years from the last period (70). A disadvantage of HT compared to bisphosphonates is the abrupt decrease in bone density that occurs when HT is stopped. Bazedoxifene is a SERM that 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 HT for women with a uterus. This combination of SERM with estrogen, such as bazedoxifene with estrogen, is termed a tissue selective estrogen complex (TSEC). Bazedoxifene has a similar profile to raloxifene but has not yet been tested in a large clinical trial for outcomes related to breast cancer. Thus far, clinical studies demonstrate no reports of breast concerns or benefits. Studies of bazedoxifene alone have demonstrated improvement in BMD and reduced vertebral fractures in a subset of high-risk women over placebo, though no reduced risk was demonstrated in the general postmenopausal population. Likewise, a reduction in fractures with the combination of bazedoxifene and conjugated estrogen has not yet been demonstrated.

Calcitonin inhibits bone resorption, though not as effectively as other osteoporotic therapies. It is only available in intranasal or injectable forms as no effectiveness has been shown from oral formulations (71). This is not generally considered first-line therapy and is a useful alternative only when other medications are contraindicated.

Once a patient has been started on therapy, markers of bone turnover can be used to assess a patient's response. Serum C-terminal crosslinking telopeptide or procollagen type 1 N-telopeptides can be checked after 1-3 months of initiating treatment in selected cases using anti-resorptive or anabolic therapies, respectively (56,70). DEXA scans, although they are currently the best method for determining BMD, should not be repeated too frequently since errors in interpretation of trends can occur and lead to inappropriate therapy (72). 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 HT was used. They found that the mean (SD) duration of bothersome menopausal symptoms for women who never used HT was 5.2 (3.8) years (73). 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 (74). However, more recent, longitudinal analyses over a longer time frame indicate that the duration of vasomotor symptoms is twice as long on average and may last for 10 years or more in up to one quarter of women who report them (75,76). The earlier in life that they appear, the longer they last, and among all racial/ethnic groups studied, African-American women appear particularly likely to experience longer duration and more bothersome vasomotor symptoms.

In the past, hot flashes were thought to be related to the 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. More recent work has focused on the kisspeptin-neurokinin B-dynorphin neurons of the hypothalamus, the so-called KNDy neurons. KNDy neurons innervate the hypothalamic regions involved in temperature regulation, and estradiol decreases signaling. Menopause results in a lowering of estrogen and subsequent rise in NKB overstimulation thought to result in vasomotor symptoms. Ablation of the tachykinin 3 receptor (NK3R) has been shown to abolish cutaneous vasodilatation in oophorectomized rats (77), and use of compounds that selectively block the NK3R have been shown to be effective in humans (78). Genetic variation in the NK3R gene has also been associated with vasomotor symptoms (79). These exciting findings bring us closer to an understanding of the etiology of hot flashes and indicate the potential for novel treatments (discussed below). Genetics studies have identified variants in CYP1B1, a gene involved in estrogen metabolism, that may be associated with vasomotor symptoms, which may be more pronounced in smokers compared to nonsmokers (79).

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) (80), as well as 2 other longitudinal studies of the menopausal transition (81,82), risk for depression was most pronounced in women who began the study with a low Center for Epidemiologic Studies Depression Scale score (80), 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 (83). The late perimenopause is also associated with a higher prevalence of sleep difficulty (84), which in turn is associated with depressive symptoms. A recent secondary analysis of SWAN demonstrated higher reporting of depressive symptoms during postmenopause than during premenopause, particularly in patients with depression prior to the final menstrual period (85). 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 (83). 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) (86), and poor sleep exacerbates these associations (87). The Women Living Better Survey included over 2,000 participants ages 35-55 and showed anxiety during the menopausal transition was associated with additional life stressors including health and job stress and worry about covering basic living costs (88).

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 (89), others have not found such beneficial effects (90). Greendale et. al. observed a sub-cohort of 2,362 SWAN participants longitudinally over 4 years to determine the effects of the menopausal transition and HT 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 decline 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 (91). More recently, the Cognitive Affective Study of the Kronos Early Estrogen Prevention Study (KEEPS-Cog) evaluated the impact of 4 years of HT on mood and cognition in early postmenopausal women. Various cognitive factors were not influenced by HT over 4 years, though a slightly positive effect on mood was observed in patients receiving oral conjugated equine estrogens. Mood and cognition did not differ between women receiving transdermal estrogen or placebo (92).

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 (93). In observational studies, less AD has been observed in postmenopausal women who use estrogen and the effect was greater with increasing duration of use (94,95). In some trials, women with mild to moderate AD who were given estrogen had improvement in their dementia (96,97), but this was not observed in all clinical trials (98,99). Estrogen is believed to help prevent AD by regulating synapse formation in the hippocampus and by inducing acetycholinesterasel and choline acetyltransferase, both of which are important in memory (100). Estrogen may also improve cognitive function because of protection against neuronal toxicity caused by oxidation and increasing metabolism of serum amyloid P (101). 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 (90). 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. A recent publication from the European Prevention of Alzheimer Dementia (EPAD) Trial indicates that a benefit in memory and brain volume associated with hormone therapy was only seen in women with the APOE4 genotype, the apolipoprotein E genotype that confers the highest risk for development of Alzheimer's Disease (102). As stated above, the KEEPS Trial did not note cognitive differences among women randomized to 2 types of estrogen plus progesterone or to placebo (92). This is noteworthy because KEEPS used a very detailed cognitive battery of tests. Ongoing studies of the KEEPS cohort are anticipated to yield more definitive data.

LIBIDO

Loss of libido is a prevalent complaint in women of all ages and is present in approximately 9% of postmenopausal women (103). Causes for a menopause-related decline in sexual interest may relate partly to a drop in both estrogen and testosterone with ovarian decline and aging. 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) (104), 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, but its use and efficacy remains debatable. Circulating testosterone does not correlate with sexual desire, and long-term safety is not established (105). Routine administration of androgen therapy for low testosterone levels is discouraged, though there may be some women within the menopause transition or beyond who could benefit. Several double-blind, randomized trials of testosterone in menopausal women with decreased libido have demonstrated a small effect but clinically and statistically improved symptoms (105, 106). 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. Testosterone can be converted to estrogen in women by aromatization just as estrogen can be metabolized from testosterone further complicating study interpretation. Androgenic side effects are greater in those receiving higher doses, and the relationship with breast cancer remains a biologic concern (105, 107, 108). Clearly, long-term data from large clinical trials using testosterone are lacking and are needed (105). If testosterone is administered, it should be for short duration and titrated to upper physiologic levels, and patients should be closely monitored for androgenic signs and symptoms. There are no FDA-approved testosterone preparations available for women. Compounded bioidentical hormones are not endorsed and raise safety concerns due to lack of oversight and monitoring and potential contamination (109).

There are two FDA approved medications for treatment of hyposexual desire disorder: bremelanotide and flibanserin. Flibanserin, marketed as Addyi, is a centrally acting serotonin agonist/antagonist that increases female sexual desire and number of sexual acts (110). These effects have been observed in the postmenopausal population, although it is not FDA-approved for this group of women. Adverse effects are generally mild and short-lived, except for a risk for hypotension and sedation if it is taken concurrently with alcohol, a problem that resulted in a black box warning and a need for prescribing clinicians to complete a risk evaluation and management strategy (REMS) certification before prescribing the drug (111). Its effect size appears similar to that of testosterone (small, but statistically and probably clinically significant) (106). Bremelanotide, sold under the brand name Vyleesi, is a melanocortin receptor agonist that induces nitric oxide and dopamine release to modulate sexual

desire pathways (112). Two randomized controlled trials (RECONNECT) found that 1.75mg subcutaneous administration vs placebo did not increase the number of satisfying sexual events over the 24-week study period, but post-hoc analysis showed improved desire and lowered sexual desire-related distress (113). The most common side effects included nausea, flushing, and headache. Bremelanotide was FDA-approved for treatment of hyposexual desire disorder in premenopausal women in 2019. Its safety and efficacy in postmenopausal women remains to be studied.

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 of 1 in 8 women in the USA (114).

BREAST CANCER AND HORMONE THERAPY

Combined estrogen and progesterone treatment increase a woman's risk of developing breast cancer. The WHI trials demonstrated an increased risk of developing invasive breast cancer after 3 years of combined HT use, with an unadjusted hazard ratio of 1.26 over 5.2 years of average follow-up (115). As the 95% confidence interval included 1.00, the data could be considered ‘not significant’; however, this level of risk is biologically plausible given that 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 HT use. Patients taking hormones for 10 or more years were at greatest risk followed by patients using HT for 5 to 10 years. Women who took HT 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 continued to be observed in this group after 20-year follow-up (32, 116).

One of the ways by which HT might increase breast cancer incidence 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 (117). A subset of 307 women in The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial was studied to examine the effect of HT 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 (118).

Case series and case-control studies have suggested that patients taking HT who are diagnosed with breast cancer have a better prognosis than women not taking hormones, even when matched for stage of disease (119). It has also been suggested that women who develop breast cancer while taking HT have their cancers detected at a more favorable stage and have less malignant disease (120). These notions were disproven by the WHI Clinical Trial. Women randomized to combination HT with (MPA + CEE) had a higher risk of invasive breast cancer and mortality from breast cancer. Tumors in the women taking combined HT were comparable in histology and grade to the placebo group but were at a more advanced stage (115).

In contrast to combined E+P HT, E alone HT 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 over 20 years, E alone treated women still had a lower incidence of invasive breast cancer (151 cases, 0·27% per year) compared with placebo (0.30% vs 0.37% per year; HR 0.78, 95% CI 0 65—0.93; p=0.005 (116).

SCREENING FOR BREAST CANCER

The lifetime risk of developing breast cancer is 12%. Various organizations recommend breast cancer screening for average-risk women (Table 4). These guidelines all suggest an individualized approach with patients that includes consideration of a patient's risk factors, as well as shared decision making based on a discussion of risks and benefits of screening. For average-risk women, mammography is the recommended screening modality.

Table 4. Breast Cancer Screening Guidelines*	
ACOG (121)	Offer annual or biennial mammogram starting at age 40, start no later than age 50. Consider biennial mammogram starting age 55. Continue until age 75.
ACS (122)	Offer annual mammogram starting at 40, start no later than age 45. Can offer biennial mammogram at age 55. Continue until within 10-years of life expectancy.
USPSTF (123)	Biennial mammogram starting at age 50. Continue until age 75.
*For average-risk females ACOG = American College of Obstetricians and Gynecologists; ACS = American Cancer Society; USPSTF = United States Preventative Services Task Force	

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 over the next 5 years and over a lifetime (124). The Tyrer-Cuzick model takes into account both personal and family history including BRCA mutations to help determine lifetime risk and is a more sensitive model for determining risk (125).

Table 5. Tools for Assessing Breast Cancer Risk		
	Gail Model	Tyrer Cusick
Age	x	x
Age at menarche	x	x
Age at first live birth	x	x
Age at menopause		x
Number of first-degree relatives with breast cancer	x	x
Number of previous breast biopsies	x	
Number of breast biopsies that were hyperplastic	x	x
Hormone replacement therapy		x
Race/ethnicity	x	x
Detailed Family history		x
BRCA1/2 gene mutations		x

Other prospective scoring systems have been developed, but these remain the dominant ones in use as of now. By calculating a woman's risk of breast cancer with these models one can use the information to determine if a woman should consider annual screening MRI and/or chemoprophylaxis to reduce her risk of breast cancer. Note that the Gail model does not factor into account breast density or HT 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. The Tyrer Cusick model takes into account a more extensive family history as well as BRCA1 or 2 status.

CHEMOPREVENTION

In women who are considered high risk for breast cancer, chemoprevention therapies are approved to reduce breast cancer incidence. These therapies include SERMs (Tamoxifen and Raloxifene) as well as aromatase inhibitors (Exemastane and Anastrazole) (126).

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-estrogenic actions. In the breast, it acts as an anti-estrogen. In the bone, on lipids and in the uterus, it acts like estrogen. Raloxifene is also a SERM but has the advantage of acting as an anti-estrogen at the level of the uterus. 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 diagnosed with breast cancer. Women randomized to tamoxifen also had fewer diagnoses of non-invasive breast cancer, such as ductal carcinoma *in situ* (DCIS) (127).

The STAR trial investigated the ability of tamoxifen compared to 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. 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 (128). On an update of STAR trial, the RRs widened for invasive and narrowed for noninvasive breast cancer compared with initial results (129).

To become active, tamoxifen must be metabolized by the hepatic cytochrome P450 enzyme system, specifically cytochrome P450 2D6 (CYP2D6), to its active metabolite, endoxifen. Consequently, therapy with drugs that inhibit CYP2D6 may reduce the clinical benefit of tamoxifen by interfering with its bioactivation, particularly when these drugs are used for an extended period. This is clinically relevant in the context of 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 showed absolute increases of 25%, 50%, and 75% in the proportion of time on tamoxifen 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 was seen with other anti-depressants (130).

The effectiveness of aromatase inhibitors for reduction of breast cancer incidence has also been demonstrated. The MAP3 trial investigated the incidence of invasive breast cancer with exemestane versus placebo in 5,560 high-risk postmenopausal women for up to 5 years (131). Exemestane significantly reduced invasive breast cancer by 65% compared to placebo (95% CI, 0.18-0.70). There were no cardiovascular or thromboembolic side effects. However, follow-up study demonstrated that BMD worsened after 2 years in the treatment group regardless of calcium and vitamin D supplementation (132). Thus, for women receiving this therapy, close BMD screening is important. Anastrazole for prevention of breast cancer in high-risk postmenopausal women was studied in the IBIS-II trial (133). One thousand nine hundred twenty women were randomized to anastrozole vs placebo for 5 years. A 53% reduction in invasive cancer was seen in the anastrazole group (95% CI, 0.32-0.68). Women who were concurrently treated with a bisphosphonate did not have significant bone loss, but the anastrazole-only group demonstrated worsened BMD after 3 years (134).

The American Society of Clinical Oncology recommends tamoxifen for chemoprevention in women for 5 years who are at least 35 years old and have completed childbearing who are at increased risk (126). This remains the only recommended chemoprevention in premenopausal women. In postmenopausal women at increased risk, either tamoxifen, raloxifene, exemastane or anastrazole can be considered. Due to effects on bone density, anastrazole use is advised with concurrent assessment of bone density and bisphosphonate or denosumab in moderate bone density loss.

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 60 or earlier in those who have family history, autoimmune disease, or younger women desiring pregnancy (135). USPSTF does not recommend routine thyroid screening for asymptomatic, non-pregnant adults (136), while the American Thyroid Association (ATA) recommends that screening begin at age 35 (137).

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 dyspareunia. 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) (138). While HT is effective in reversing changes associated with GSM (139, 140), it does not consistently help with symptoms of UI. The WHI Clinical Trial found that women who received HT and who were continent at baseline demonstrated an increase in the incidence of 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 frequency of symptoms worsened in both arms and these women reported that UI limited their daily activities. This clinical trial evidence strongly suggests that systemic HT should not be prescribed as part of a regimen for UI alone (141).

HT is highly effective in the treatment of vaginal dryness. Systemic or vaginal estrogen can be used for GSM, though locally applied estrogen is preferable if there are no systemic symptoms that need to be treated. Very low doses can be used for this purpose. Of note, a vaginal estradiol tablet was recently shown not to be superior to a hydroxyethylcellulose gel in a randomized controlled trial of 302 women (142). Low

estradiol doses are believed to be safe for the uterus, even without concomitant use of a progestin when administered vaginally. Long term data from the WHI Observational Study confirm safety of vaginal estrogen use (143), and a recent publication indicates minimal increases in circulating estradiol in women using a variety of currently available preparations (144). 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 (140,145). Ospemifene is a SERM that is FDA approved for the treatment of GSM symptoms (146). It has a track record of endometrial safety (147). In 2016, prasterone, a formulation of dehydroepiandrosterone (DHEA), was FDA approved for the treatment of dyspareunia related to vulvar and vaginal atrophy. In a randomized controlled trial, 12-weeks of daily vaginal prasterone significantly alleviated dyspareunia compared to placebo (148). The trial also demonstrated a significant drop in the vaginal pH, as well as improvement in vaginal dryness. Carbon dioxide laser therapy has also been suggested as an alternative treatment for GSM, but a double-blind, randomized, sham-controlled trial of 85 patients with 12-month follow-up showed no benefit of the treatment when compared to sham laser (149).

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 (150). 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 women. Adrenal androgens known as 11-oxyandrogens with tissue-level effects similar to testosterone rise steadily as women age, and as opposed to men, levels do not seem to decline with aging and menopause. These may also contribute to androgenic changes in postmenopausal women (151).

TREATMENT OF MENOPAUSAL SYMPTOMS

Non-Pharmacologic

Non-pharmacologic options for treatment of menopausal symptoms have yet to show proven benefit in large clinical trials. There are mixed results from trials evaluating the benefits of acupuncture for treatment of menopausal symptoms including vasomotor symptoms, insomnia, and mood. As acupuncture is a generally low-risk therapy, it is at the discretion of the patient to pursue this treatment modality, but effectiveness in large trials is lacking. Phytoestrogens, which are estrogen-like compounds found in products such as soy, have no proven benefit in treatment of menopausal symptoms. Chinese herbal remedies likewise have not been shown to significantly alleviate symptoms, with or without acupuncture. The MsFLASH trial is a randomized controlled trial that showed reduction of insomnia in peri- and post-menopausal women with hot flashes who were treated with cognitive behavioral therapy for insomnia (CBT-I) compared to menopause education control (152). Women who practiced CBT-I had significant reduction of insomnia after the 8-week intervention, and these results persisted at 24-week follow-up despite having no effect on daily hot flash frequency. Practical daily lifestyle habits including exercise, dressing in layers, consuming cold drinks, and avoiding caffeine and alcohol may help alleviate symptoms (153,154).

Pharmacologic

NON-HORMONAL TREATMENT

Selective Serotonin Reuptake Inhibitors (SSRIs)

When HT is contraindicated (i.e., personal history of breast cancer), women with hot flashes may be treated with non-hormonal prescription drugs; and one such class is the SSRIs (155). 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 HT, 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 (155). Non-approved SSRIs that have been tested and have clinical efficacy include paroxetine (non-mesylate), escitalopram, citalopram, fluoxetine, and sertraline (153,154).

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) or placebo. There was a significant reduction in hot flashes in women receiving all doses of venlafaxine in comparison to placebo (156). 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 (156).

Gabapentin

A randomized, double-blind, placebo-controlled trial of gabapentin to treat hot flashes 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. The women taking gabapentin 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 (157). A 2009 meta-analysis confirmed consistency across several clinical studies (158). The dose range of gabapentin is broad, and although many clinical trials use doses of 900 mg, lower doses 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.

Neurokinin B Receptor (NK3R) Inhibitors

Neurokinin B acting on its receptor, NK3R, at the level of the hypothalamus induces vasomotor symptoms typical of menopause. It is hypothesized that variable expression of NK3-R and interaction with its ligand is responsible for the differences in reported hot flashes experienced by menopausal women. The TACR3 gene codes for NK3R. Genome-wide association studies performed on 17,695 women from the WHI trial and observational studies demonstrated significant genetic variation in TACR3 in women who reported vasomotor symptoms (159).

An oral NK3R antagonist, pavinetant (MLE4901) completed phase II clinical trials and demonstrated a 45% decrease in the number of hot flashes per week as compared with placebo (160). However, further development of this compound was halted due to concerns about liver toxicity. Another NK3R antagonist, fezolinetant (ESN364), has been evaluated in several clinical trials, with consistent evidence for a significant reduction in severity and frequency of vasomotor symptoms when compared to placebo (78). More recently, another phase II trial was performed to assess the efficacy and safety of elinzanetant (NT814), which is a dual antagonist

targeting both NK-1 and NK-3 receptors (161). When compared to placebo, it showed significant reduction in vasomotor symptoms, as well as improvements in measures of sleep and quality of life. There were sporadic mild increases in transaminases during treatment, but these were of equal frequency and magnitude in placebo- and elinzanetant-treated participants and were not considered clinically relevant.

These agents may represent a promising new approach in treating menopausal symptoms.
Recently fezolinetant has been FDA approved for treatment of vasomotor symptoms in women though rare hepatotoxicity in post marketing reports has resulted in inclusion of a black box warning and recommendations for increased frequency of liver testing in patients on fezolinetant. Elinzanetant is in an extended review period by the FDA and awaiting initial approval.

HORMONAL TREATMENT

HT is utilized by many women for treatment of bothersome menopausal symptoms. As outlined above, there are specific risks and benefits associated with HT that may not make it suitable for some women. Moreover, many women have a tendency to shun HT because the level of discourse about its true benefits and risks are so fraught with drama (162). 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.

HT is the most effective treatment for vasomotor symptoms and vaginal dryness caused by the loss of endogenous estrogen production. In addition, it acts as 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 HT 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 (29). It is the standard of care to give women estrogen with a progestin when they have a uterus.

The decision to prescribe HT must be based on each individual patient, taking into account the risk factors involved and creating a favorable benefit to risk ratio. To date, acceptable reasons to prescribe HT include relief of severe vasomotor symptoms and to address GSM. There is sufficient medical evidence to consider a trial of HT for women with adverse mood or sleep symptoms in association with their menopause (163). At present, there is no indication for using HT 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 early menopausal HT may have protective effects in some cases.

A key factor in the decision tree for the initiation of HT is the individual risk of breast cancer, which is a real and serious concern. It is contraindicated to prescribe HT to patients with a personal history of breast cancer, and it is not recommended to give HT to those with a high-risk profile. The adverse events demonstrated in patients taking combined estrogen-progestin HT

included a 26% increase of invasive breast cancer, with the excess risk starting to be observed after 3-4 years of combined HT use. It is important to note that estrogen treatment alone in women without a uterus did not increase the risk of breast cancer.

Recommendations for prescribing HT 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 HT 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 nonusers (42). 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 (153, 154, 164).

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

HT Regimens: Continuous Combined and Cyclic Regimens

There are many ways to prescribe HT: oral tablets, patches, creams, sprays (Table 6). Considering the importance of including a progestin, there are several different modalities of administering these medications as well. This includes continuous combined and cyclical administration. The continuous combined formulation administers both the estrogen and progestin hormones every day. Cyclical administration means that hormones are given in a cycle: 1) 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). If progestins are given less frequently than monthly, the potential for hyperplasia exists and endometrial monitoring should be considered (165).

In women just entering menopause or who have not yet experienced their final menstrual period, cyclical administration of estrogen and progestin is often 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 HT. At the onset of HT, 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 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. Eventually, most women become amenorrheic on this regimen. Some women also develop irregular and inconvenient vaginal spotting or bleeding.

Besides oral preparations, HT 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. Progestins can be administered through a

levonorgestrel-releasing IUD which can be left in place for up to 8 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 6. HORMONE THERAPY FORMULATIONS

Trade Name	Estrogen	Progestin	Dose
Vasomotor Symptom Therapies			
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	1tab PO daily
FemHRT	Ethinyl Estradiol 5 mcg	Norethindrone Acetate 1 mg	1tab 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. 1tab PO daily

Prempro	Conjugated Estrogen 0.625 mg	Medroxyprogesterone Acetate 2.5 or 5 mg	1tab PO daily
Combipatch	17 β-estradiol	Norethindrone acetate	1 patch transdermal twice weekly
Climara-Pro	17 β-estradiol	Levonorgestrel	1 patch weekly
Angeliq	17 β-estradiol	Drosperinone	1tab PO daily
Genitourinary Symptom Therapies			
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	-	20/0.45mg daily
Ospemiphene	-	-	60mg PO daily
Prasterone	-	-	DHEA 6.5mg inserted vaginally daily

TSECs—Tissue Specific Estrogen Complexes

The combination of bazedoxifene, a SERM, with estrogen allows the clinician to apply estrogen where it is most beneficial—reducing or eliminating hot flashes and reducing bone resorption--while the SERM bazedoxifene exerts anti-estrogenic effects at the target tissues where estrogen action is unwelcome—the endometrium and the breast (166). 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 bazedoxifene/conjugated equine estrogen combination, the clinician may avoid having to give progestin and avoid irregular or breakthrough bleeding. Risks of VTE with bazedoxifene appear similar to what is seen with other SERMs (166). Long term data on the potential of this compound to reduce the risk of clinical fractures and breast and endometrial cancer are pending.

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, the decrease in endothelial function, and the relative dyslipidemia that occurs 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. HT 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 HT include the reduction in the incidence of colon cancer. However, risks of HT accrue over time and the benefits of HT need to be re-assessed periodically to ensure that they continue to outweigh risks. The SERM, raloxifene, also can be used to treat osteoporosis in menopausal women. The advantage of a SERM compared to HT 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 HT.

The role of HT 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 HT 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 HT, with some promising new treatments on the horizon. Prudent clinical judgment and an individualized assessment of risks and benefits for patients using the currently available medical evidence remains the most appropriate approach.

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