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Review

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Review

Hormone Therapy in Menopause: Concepts, Controversies, and Approach to Treatment

Valerie A. Flores,[1] Lubna Pal,[1] and JoAnn E. Manson[2]

[1]Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, New Haven, Connecticut 06520, USA; and [2]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02215, USA

INTRODUCTION

- The use of hormone therapy (HT) in menopausal women has, in recent decades, been one of the most contentious topics in women's health.

OBSERVATIONAL STUDIES

- decreased CHD risk in postmenopausal women using HT compared to nonusers of HT.
- This seemed plausible because:
  - low risk of CHD in premenopausal compared to postmenopausal women.
  - estrogens increase HDL-C and decrease LDL-C, thus potentially slowing the risk of atherosclerosis.
- Meta-analyses of observational studies demonstrated 40% to 50% reductions in CHD comparing HT users to nonusers.

RCTs

- However, as RCTs of HT were conducted, some of the previously purported long-term health benefits of HT were called into question.

- the large-scale WHI trials:
  - did not confirm the cardiovascular and all-cause mortality benefits
  - benefits for fracture reduction were confirmed
  - increase the risk of stroke and venous thromboembolic disease.
  - Was discontinued prematurely because of evidence of net harm in the absence of evidence of benefit for CHD

Table 1. Women's Health Initiative estrogen-progestin and estrogen-alone trials, intervention phase[a] (62, 63)

Outcome	Estrogen + progestin HR (95% CI)	Estrogen alone HR (95% CI)
CVD		
Coronary heart disease[b]	1.18 (0.95-1.45)	0.94 (0.78-1.14)
Myocardial infarction	1.24 (0.98-1.56)	0.97 (0.79-1.21)
Coronary revascularization[c]	0.95 (0.78-1.16)	1.00 (0.83-1.19)
Stroke	1.37 (1.07-1.76)	1.35 (1.07-1.70)
Pulmonary embolism	1.98 (1.36-2.87)	1.35 (0.89-2.05)
Deep vein thrombosis	1.87 (1.37-2.54)	1.48 (1.06-2.07)
Cardiovascular mortality	1.08 (0.78-1.48)	1.01 (0.78-1.31)
All cardiovascular events[d]	1.13 (1.02-1.25)	1.11 (1.01-1.22)
Cancer		
Breast cancer	1.24 (1.01-1.53)	0.79 (0.61-1.02)
Colorectal cancer	0.62 (0.43-0.89)	1.15 (0.81-1.64)
Endometrial cancer	0.83 (0.49-1.40)	NA
Cancer mortality	1.10 (0.86-1.42)	0.96 (0.75-1.22)
All cancer types[e]	1.02 (0.91-1.15)	0.93 (0.81-1.07)
Other outcomes		
Hip fracture	0.67 (0.47-0.95)	0.67 (0.46-0.96)
All fracture	0.76 (0.69-0.83)	0.72 (0.64-0.80)
Diabetes	0.81 (0.70-0.94)	0.86 (0.76-0.98)
Gallbladder disease	1.57 (1.36-1.80)	1.55 (1.34-1.79)
Probable dementia[f]	2.01 (1.19-3.42)	1.47 (0.85-2.52)
Other (non-CVD, noncancer) mortality[g]	0.59 (0.39-0.90)	1.34 (0.93-1.94)
All-cause mortality	0.97 (0.81-1.16)	1.03 (0.88-1.21)
Global index[h]	1.12 (1.02-1.24)	1.03 (0.93-1.13)

Secondary Prevention Trials

- HERS:
  - Increased risk of CHD during the first year of the HT in preexisting coronary disease
  - Increased risk of VTEs
- WELLHART, The Estrogen Replacement and Atherosclerosis trial
  - No difference in atherosclerosis progression across treatment groups

Meta-Analyses of RCTs of HT in Relation to CVD, VTE, Breast Cancer, Fx, and All-Cause Mortality

- CVD/VTE:
  - the effects of HT on CHD varied by the woman's age and/or time since onset of menopause.
  - HT initiated < 10 years from the onset of menopause was associated with a 32% reduction of CHD
  - HT initiated > 10 year since menopause onset did not reduce CHD risk.
  - There was no association between HT and cardiac death or stroke.
  - VTE risk was increased in postmenopausal women using oral HT (ET or EPT); however, there was no significant excess risk in women using nonoral HT.

Meta-Analyses of RCTs of HT in Relation to CVD, VTE, Breast Cancer, Fx, and All-Cause Mortality

- Breast Cancer:
  - In some meta-analysis (CGHFBC): increased risk of B.C in HT users particularly EPT users
  - In another meta-analysis: increase in B.C mortality in EPT users; however, there was no increase in breast cancer risk with ET use alone.
  - However, a major limitation of the prior studies was the lack of assessment of the effect of underlying breast cancer risk on attributable risk.

Meta-Analyses of RCTs of HT in Relation to CVD, VTE, Breast Cancer, Fx, and All-Cause Mortality

- So the CGHFBC data was recently reassessed based on the effect of underlying risk of breast cancer on attributable risk. women were divided into low (1.5%), intermediate (3%), and high (6%) underlying risk of breast cancer over 5 years. The attributable risk in ET users was lower in less underlying risk groups.
- These results highlight the importance of examining the innate risk of breast cancer for each woman.
- it is important to recognize that many of the analyzed studies were observational studies with the potential for residual confounding

Meta-Analyses of RCTs of HT in Relation to CVD, VTE, Breast Cancer, Fx, and All-Cause Mortality

- Bone Health:
  - in oral CEEs, transdermal, or oral E2 (with or without the addition of a progestin) there was a 20% to 37% reduced risk of hip, vertebral, and total fracture. E2 resulted in a slightly greater decrease in risk.
  - more pronounced reduced risk of fracture in those using HT before age 60 years
  - There was some attenuation of protection following cessation of HT
  - There was no increased risk of rebound fractures.

Meta-Analyses of RCTs of HT in Relation to CVD, VTE, Breast Cancer, Fx, and All-Cause Mortality

- All Cause Mortality:
  - HT in younger postmenopausal women (mean age < 60 years) demonstrated a 25% reduction in mortality in women taking HT compared to placebo.
  - Age at HT initiation is an important factor to consider when balancing risks and benefits of HT use in postmenopausal women,

TIMING HYPOTHESIS

- First proposed by Thomas Clarkson in the 1990s in animal model and Human studies have demonstrated similar findings.

- The mechanism by which early initiation of estrogen has favorable cardiovascular and neurological effects is felt to relate to its ability to play an anti-inflammatory/ protective role only prior to an inflammatory insult, and prior to a prolonged hypoestrogenic state.

Table 2. Health outcomes in the Women's Health Initiative estrogen-progestin and estrogen-alone trials, according to age at study entry, intervention phase[a] (62)

	Estrogen + progestin		Estrogen alone	
Outcome	HR (95% CI)	*P*, trend by age	HR (95% CI)	*P*, trend by age
CVD				
Coronary heart disease[b]				
50-59 y	1.34 (0.82-2.19)	.81	0.60 (0.35-1.04)	.08
60-69 y	1.01 (0.73-1.39)		0.95 (0.72-1.24)	
70-79 y	1.31 (0.93-1.84)		1.09 (0.80-1.49)	
Myocardial infarction				
50-59 y	1.32 (0.77-2.25)	.55	0.55 (0.31-1.00)	.02
60-69 y	1.05 (0.74-1.47)		0.95 (0.69-1.30)	
70-79 y	1.46 (1.00-2.15)		1.24 (0.88-1.75)	
Coronary revascularization[c]				
50-59 y	1.03 (0.63-1.68)	.67	0.56 (0.35-0.88)	.06
60-69 y	0.85 (0.64-1.13)		1.13 (0.88-1.46)	
70-79 y	1.08 (0.77-1.51)		1.07 (0.79-1.43)	

Table 2. Health outcomes in the Women's Health Initiative estrogen-progestin and estrogen-alone trials, according to age at study entry, intervention phase[a] (62)

	Estrogen + progestin		Estrogen alone	
Outcome	HR (95% CI)	*P*, trend by age	HR (95% CI)	*P*, trend by age
Stroke				
50-59 y	1.51 (0.81-–2.82)	.50	0.99 (0.53-1.85)	.77
60-69 y	1.45 (1.00-2.11)		1.55 (1.10-2.16)	
70-79 y	1.22 (0.84-1.79)		1.29 (0.90-1.86)	
Pulmonary embolism				
50-59 y	2.05 (0.89-4.71)	.61	1.53 (0.63-3.75)	.28
60-69 y	1.69 (1.01-2.85)		1.72 (0.94-3.14)	
70-79 y	2.54 (1.27-5.09)		0.85 (0.39-1.84)	
Cancer				
Breast cancer				
50-59 y	1.21 (0.81-1.80)	.68	0.82 (0.50-1.34)	.89
60-69 y	1.20 (0.89-1.62)		0.73 (0.51-1.07)	
70-79 y	1.37 (0.90-2.07)		0.86 (0.52-1.43)	
Colorectal cancer				
50-59 y	0.79 (0.29-2.18)	.66	0.71 (0.30-1.67)	.02
60-69 y	0.61 (0.37-0.99)		0.88 (0.53-1.47)	
70-79 y	0.58 (0.31-1.08)		2.24 (1.16-4.30)	

Table 2. Health outcomes in the Women's Health Initiative estrogen-progestin and estrogen-alone trials, according to age at study entry, intervention phase[a] (62)

	Estrogen + progestin		Estrogen alone	
Outcome	HR (95% CI)	*P*, trend by age	HR (95% CI)	*P*, trend by age
Cancer mortality				
50-59 y	0.71 (0.38-1.33)	.37	0.78 (0.43-1.40)	.06
60-69 y	1.26 (0.88-1.80)		0.77 (0.53-1.12)	
70-79 y	1.13 (0.73-1.75)		1.34 (0.90-1.97)	
All cancer[d]				
50-59 y	0.97 (0.76-1.23)	.77	0.89 (0.66-1.19)	.39
60-69 y	1.11 (0.93-1.31)		0.89 (0.73-1.08)	
70-79 y	0.94 (0.75-1.17)		1.04 (0.81-1.33)	
Other outcomes				
All fracture				
50-59 y	0.82 (0.68-1.00)	.83	0.90 (0.72-1.11)	.33
60-69 y	0.70 (0.61-0.81)		0.63 (0.53-0.75)	
70-79 y	0.79 (0.66-0.95)		0.71 (0.58-0.87)	
Diabetes				
50-59 y	0.85 (0.66-1.09)	.10	0.83 (0.67-1.04)	.99
60-69 y	0.61 (0.49-0.77)		0.91 (0.76-1.09)	
70-79 y	1.35 (0.98-1.88)		0.82 (0.62-1.07)	
Other (non-CVD, noncancer) mortality[e]				
50-59 y	0.53 (0.22-1.27)	.65	0.51 (0.20-1.26)	.002
60-69 y	0.55 (0.27-1.13)		1.15 (0.65-2.03)	

Table 2. Continued

Outcome	Estrogen + progestin		Estrogen alone	
	HR (95% CI)	*P*, trend by age	HR (95% CI)	*P*, trend by age
All-cause mortality				
50-59 y	0.67 (0.43-1.04)	.20	0.70 (0.46-1.09)	.04
60-69 y	1.07 (0.81-1.41)		1.01 (0.79-1.29)	
70-79 y	1.03 (0.78-1.36)		1.21 (0.95-1.56)	
Global index[f]				
50-59 y	1.12 (0.89-1.40)	> .99	0.84 (0.66-1.07)	.02
60-69 y	1.13 (0.97-1.31)		0.99 (0.85-1.15)	
70-79 y	1.12 (0.95-1.32)		1.17 (0.99-1.39)	

- Overall, the evidence suggests that, while HT does not reduce the risk of cardiac disease/events in the secondary prevention setting or in late menopause, earlier initiation (with respect to time since menopause and age younger than 60 may provide cardioprotective effects.

Do Hormone Therapy Effects Differ by Formulation, Dose, or Route of Administration?

ESTROGEN FORMULATIONS

- The available estrogen formulations for HT include:
  - CEEs
  - 17β- E2
  - Esterified Estrogens (EEs)

ESTROGEN FORMULATIONS

- VMS: all forms are similarly effective in treating VMS
- Cardiovascular effects: have not been different with oral CEEs vs oral E2
- VTE: CEEs have a slightly higher risk compared to oral E2
- Fracture risk: All estrogen formulations were effective in reducing fx risk
- Cognition: oral CEEs and oral E2 had Neutral results

ESTROGEN FORMULATIONS

- CEE formulations contain more than 10 estrogens that can
  - bind with differential affinity for the 2 estrogen receptor types (ERα and ERβ)
  - can have differential actions on the target tissue, similar to SERMs

- Certain estrogens in CEEs can activate ERβ, which serves to inhibit ERα-mediated cell proliferation.

PROGESTOGEN FORMULATIONS

- The most common progestogen formulations include:
  - micronized progesterone(MP)
  - MPA
  - norethindrone acetate (NETA).

PROGESTOGEN FORMULATIONS

- Cardiovascular system:
  - From a CVD risk perspective, an ideal progestogen is one that does not counteract the positive effects of estrogens on lipids.
  - progestogens without androgenic effects (progesterone and 19-norprogesterone derivatives) did not counteract estrogen's beneficial effects on the lipid profile
  - conversely, progestogens with androgenic activity (19-nortestoterone derivates and MPA) can blunt some of the beneficial effects on lipids
  - HT regimens using NETA have not shown any adverse effect on lipid parameters
  - vasodilation induced by estrogens was not attenuated by the addition of MPA or NETA

PROGESTOGEN FORMULATIONS

- Cardiovascular system:
  - **Drospirenone**, a third-generation progestin that possesses both antiandrogenic and antimineralocorticoid properties, may confer benefits against **CVD risk**
  - **VTE** risk is, however, increased with the inclusion of pregnane derivatives (ie, **MPA**) and norpregnane derivative progestogens (**nomegestrol acetate** and **promegestone**) in the HT regimen
  - The addition of MP or NETA (ie, nortestosterone derivatives) to estrogen did not increase VTE risk

PROGESTOGEN FORMULATIONS

- Cognition risk:
  - Studies on the effects of progestogens on cognition are limited
  - CEEs alone did not affect cognitive test scores, CEEs/MPA decreased delayed verbal memory scores, and CEEs/MP significantly improved working memory
  - While progesterone is a neuroactive steroid, its potential for clinically relevant neuroprotective effects requires further research

PROGESTOGEN FORMULATIONS

- Fracture Risk:
  - CEEs plus MPA and CEEs alone similarly reduced hip fracture risk by one-third
  - MPA and NETA alone both have been shown to prevent bone resorption in postmenopausal women.
  - Other progestogen formulations have been studied for effects on BMD but have not been tested in large RCTs for fracture reduction.

PROGESTOGEN FORMULATIONS

- Endometrial Safety:
  - Because unopposed estrogens in postmenopausal women increase the risk of endometrial hyperplasia/cancer, a progestogen is indicated in women with a uterus.
  - The LNG IUDs are an alternative method for endometrial protection in women taking estrogen-based HT who are sensitive to the bothersome systemic side effects of progestogens, although this is considered off-label use

DOSE of ESTROGEN or PROGESTOGEN

- The dose of E in an HT regimen should be the lowest effective dose needed for the menopausal symptoms being treated.
- the progestogen dose should be one that provides adequate endometrial protection in postmenopausal women with a uterus.
- The initial standard oral doses of various E formulations:
  - 0.625 mg of CEEs
  - 1 to 2 mg of E2
  - 0.625 mg EE
- the standard transdermal E2 dose: 50 μg.

DOSE of ESTROGEN or PROGESTOGEN

- lower doses of estrogens reduce hot flashes by 65% (twice as effective than placebo) although the time needed to achieve this rate was 8 to 12 weeks, compared to 4 weeks for standard doses.
- However, the lower doses of estrogen are associated with fewer unwanted side effects (50% lower rates of irregular bleeding and less breast tenderness).
- In addition, when lower doses of estrogen are prescribed, less progestogen can be used.
- In appropriately selected individuals, MPA in daily doses as low as 1.5 mg, or in intermittent doses as infrequent as an only twice-yearly regimen of 10 mg for 14 days, has been shown to be both safe and associated with less breakthrough bleeding.

DOSE of ESTROGEN or PROGESTOGEN

- In a 2-year prospective study using low (0.3 mg), standard (0.625 mg), and high (1.25 mg) doses of esterified estrogens compared to placebo:
  - Endometrial hyperplasia/thickened endometrium was a cause of termination of ET only in women using standard and high-dose EE.
  - Lipid levels were significantly favorable (decreased LDL and increased HDL) across all 3 doses of EE.
  - BMD was increased across all 3 doses at the lumbar spine, total hip, and whole body.
  - VMS were relieved at all doses (though greater with increasing doses of CEEs)
  - breakthrough bleeding was less frequent with the lower-dose regimens

DOSE of ESTROGEN or PROGESTOGEN

- In studies assessing the effects of low-dose transdermal E2 administration, hot flashes were relieved at all doses; however, the ultra-low dose (0.014 mg) improved hot flashes less when compared to the low dose (41% decrease in VMS).
- favorable lipid effects (decreased total cholesterol and LDL) remain notable with low-dose transdermal E2 administration

DOSE of ESTROGEN or PROGESTOGEN

- When assessing risks/concerns related to higher doses of estrogen, much of the rationale for avoiding higher doses of estrogen comes from literature on cardiovascular outcomes with various estrogen doses.
- Low- and standard-dose CEEs had a similar reduced risk of coronary events, while the risk (including risk of stroke) was increased with higher doses.
- VTE risk is also dose dependent.

DOSE of ESTROGEN or PROGESTOGEN

- Transdermal estrogens, because they avoid first-pass metabolism, allow for lower doses of estrogen to be used for management of menopausal symptoms.

- Overall, while the lowest effective dose is recommended, in those with inadequate relief of symptoms with lower doses, consideration should be given to increasing to standard dose regimens to alleviate clinical symptoms.

DOSE of ESTROGEN or PROGESTOGEN

- In a review of randomized trials, although lower doses of CEE, E2, and EE were effective at treating VMS, low-dose CEEs plus MPA tended to be more effective than low-dose CEEs alone.
- Continuous combined regimens of low-dose E plus progestogen allow for amenorrhea/low breakthrough bleeding risk, and maintain the reduced risk of endometrial hyperplasia/cancer.
- Breast cancer risk was not significantly different by estrogen dose, although RCT data are lacking

DOSE of ESTROGEN or PROGESTOGEN

- Progestogens can be administered continuously or sequentially (12-14 days per month).
- the recommended dose of progestogen is higher in sequential compared to continuous E+P regimens
- Oral MPA at 10 mg, MP at 300 mg, or megestrol acetate at 20 mg daily are also effective at treating VMS, although long-term safety data are not available.

ROUTE OF ADMINISTRATION
ORAL Vs. TRANSDERMAL

- Cardiometabolic biomarkers:
  - Oral and transdermal estrogens reduce total cholesterol, LDL-C and insulin resistance.
  - Oral CEEs were associated with increase in HDL-C, triglycerides, and CRP levels
  - Transdermal E2 reduced triglyceride levels
  - Overall, endothelial function did not differ between regimens

ROUTE OF ADMINISTRATION
ORAL Vs. TRANSDERMAL

- Venous thromboembolism:
  - Risk of venous thrombosis is different between oral vs transdermal estrogen.
  - Because oral estrogens undergo first-pass hepatic metabolism, there is activation of the coagulation system, and an increased risk of VTE.
  - Transdermal estrogens avoid first pass hepatic metabolism, and do not increase risk of venous thrombosis.

ROUTE OF ADMINISTRATION
ORAL Vs. TRANSDERMAL

- Breast cancer:
  - No RCT has compared effects of oral vs transdermal estrogens effect on breast cancer risk.
  - observational studies have found no significant difference in breast cancer risk by E route of administration

ROUTE OF ADMINISTRATION
ORAL Vs. TRANSDERMAL

- Fracture:
  - Oral and transdermal formulations both are effective for fracture prevention, without appreciable differences by regimen.

ROUTE OF ADMINISTRATION
ORAL Vs. TRANSDERMAL

- Cognition and mood:
  - No clear difference in HT's effects on cognition has been demonstrated by route of administration.

ROUTE OF ADMINISTRATION
ORAL Vs. TRANSDERMAL

- Sexual function:
  - both routes were associated with improvement in vaginal dryness and dyspareunia
  - only transdermal E2 was associated with significant improved sexual function (ie, libido and sexual satisfaction).
  - The lack of effect of transdermal E2 on SHBG levels (as compared with increased levels with oral estrogens) results in increased free testosterone, likely explaining the improvement in sexual function.

- Oral and transdermal formulations of estrogens both are effective for treatment of VMS.

ROUTE OF ADMINISTRATION
PROGESTOGENS

- Progestogens administered in combination with estrogens in a transdermal patch are able to provide endometrial protection.
- Transdermal cream application of progestogens is not effective given the lack of adequate systemic levels achieved
- oral progestogens—unlike vaginal progesterone—are effective for VMS.

ROUTE OF ADMINISTRATION
PROGESTOGENS

- For women on systemic estrogen therapy, vaginal progesterone gel (used off-label) can be administered every other day, twice weekly, or sequentially, although there are no long-term studies on endometrial protection in the latter regimen.

ROUTE OF ADMINISTRATION
PROGESTOGENS

- There are also 3 available progestin-based IUDs, each with different doses of LNG—52 mg, 19.5 mg, and 13.5 mg.

- The LNG devices are effective at preventing endometrial hyperplasia/cancer, and the localized intrauterine effect of the device may avoid the bothersome side effects of oral and transdermal progestogens.

ROUTE OF ADMINISTRATION
VAGINAL ESTROGEN

- Low-dose vaginal estrogen is the most effective treatment available for GSM.
- Vaginal estrogen can be administered as a ring, tablet, suppository, or cream, all with equal effectiveness.
- Creams are more readily absorbed in atrophic vaginal mucosa; however, as the mucosa matures, absorption decreases.
- As most studies were no longer than 2 years, it is difficult to draw definitive conclusions regarding long-term endometrial safety.

ROUTE OF ADMINISTRATION
VAGINAL ESTROGEN

- In general the addition of a progestogen is not indicated with low-dose vaginal estrogen therapy.
- vaginal bleeding or spotting on low-dose vaginal estrogen therapy requires an evaluation.
- There is also a vaginal E2 ring that is a standard dose HT (Femring; Estradiol acetate vaginal ring). The ring relieves GSM symptoms as well as VMS; it likely also improves bone health. Given the systemic levels with this formulation, a progestogen is indicated in postmenopausal women with a uterus.

SERMs

- SERMs are able to exert agonist or antagonist actions on the ER in various estrogen-target tissues.
- Raloxifene
  - proven efficacy in the prevention of osteoporosis-related spine fractures
  - neutral on the endometrium
  - chemoprophylactic efficacy against breast cancer risk
  - favorable effects on lipids
  - does not modify CHD events/risks.
  - does have a VTE risk similar to that of oral estrogen
  - unlike E, can lead to an increased incidence of hot flushes.

SERMs

- Raloxifen:
  - No reported adverse effects on cognitive function.
  - 80% reduction in ER-positive breast cancers in postmenopausal women.
  - is approved for:
    - preventing osteoporosis-related spinal fractures (however, it does not reduce hip or wrist fractures)
    - preventing breast cancer in women with osteoporosis and those at high risk of breast cancer
  - For women deemed at elevated risk for hip fracture, bisphosphonates or other fracture-reducing medications should be considered.

SERMs

- Ospemifene:
  - has been approved for the treatment of vulvovaginal atrophy.
  - acts as an ER agonist at the level of the urogenital tissues, reducing symptoms of dyspareunia, as well as improves urge incontinence, and sexual function.
  - in a preclinical model it suppressed breast cancer development (human studies are needed)
  - Like raloxifene, hot flashes can worsen.
  - VTE risk is increased, likely with a similar risk profile to oral ET and other SERMs

TISSUE SELECTIVE ESTROGEN COMPLEX (TSEC)

- builds on pairing an estrogen with a SERM
- estrogenic component offers benefit against menopausal symptoms whereas the SERM component, by acting as an antiestrogen, negates the proliferative effects of E on the endometrium and/or breast.
- both the E and SERM components hold antiresorptive effects on the skeleton.
- The only TSEC approved for menopause management in women with a uterus is a combination of bazedoxifene (BZA, a SERM) and CEEs
- TSEC represents a novel treatment option for VMS management while also having positive effects on the bone and genitourinary tissue, without the need for a progestin to protect the endometrium

BIOIDENTICAL HORMONES

- Despite subsequent analyses of the WHI Trials demonstrating safety of HT in those younger than 60 years or less than 10 years since menopause, there remained an increased interest in compounded bioidentical hormone therapy (cBHT).
- A common misconception with cBHT is that bioidentical hormones equate to “natural” or are structurally identical to endogenous hormones. However, bioidentical hormones still require biochemical synthesis.
- cBHT increased rate of endometrial cancer.

BIOIDENTICAL HORMONES

- not FDA-approved
- Recently, the NASEM provided recommendations regarding the clinical utility of cBHT.
- Their key message is that cBHT use should be restricted to those with a documented allergy to an active pharmaceutical ingredient in an FDA-approved HT formulation.

Clinical Guide for Treatment of Menopausal Symptoms

Assessment of Comorbid Conditions/ Contraindications to HT

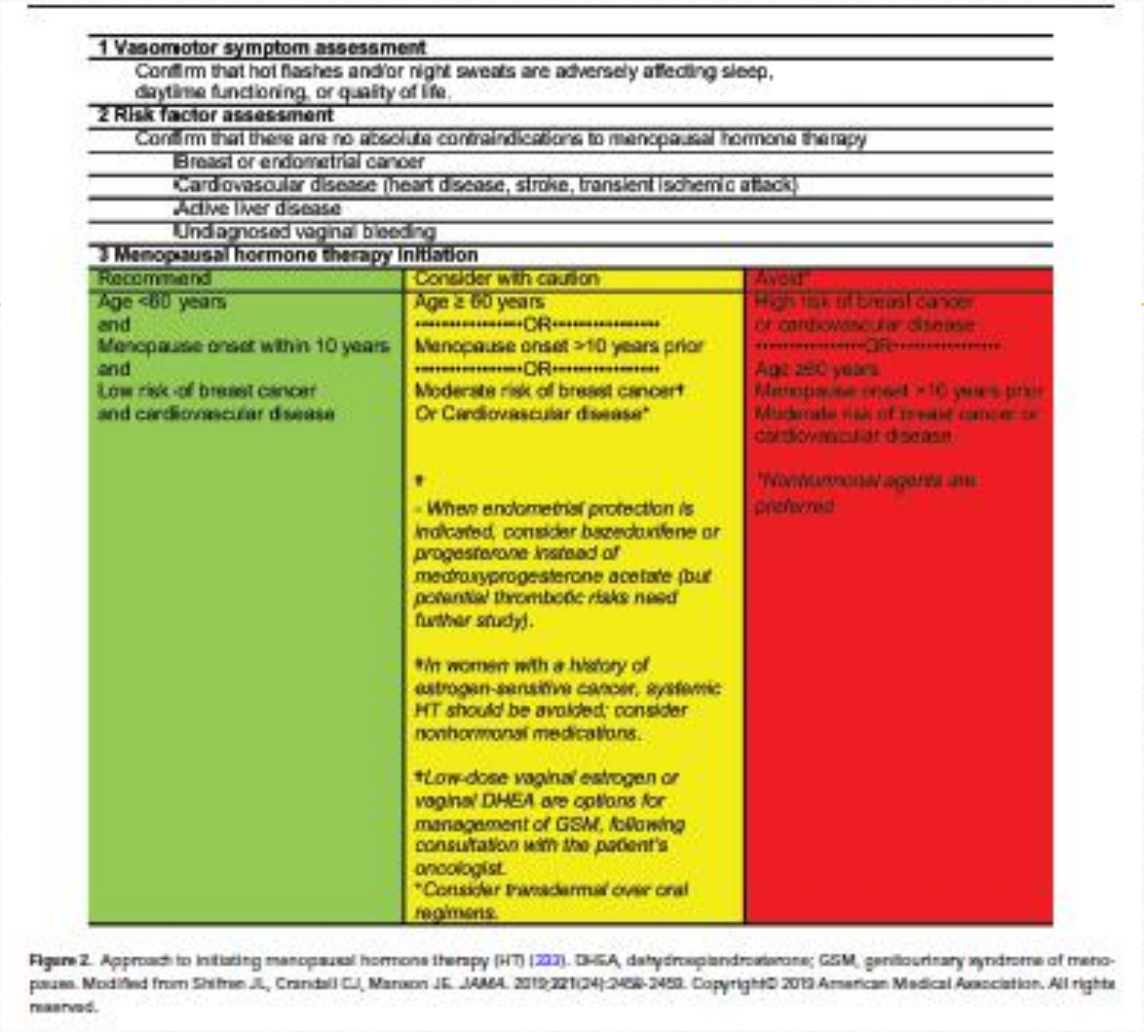
- **Risk stratification:**
  - Careful assessment of absolute contraindications and medical comorbidities is necessary prior to considering start of HT.
  - Contraindications include:
    - a personal history of CHD, VTE, stroke, TIA, active liver disease, breast cancer, high-risk endometrial cancer, or unexplained vaginal bleeding.
  - Relatively young age (≤ 60 years) and/or less than 10 years since menopause onset, are predictors of relative safety of HT in otherwise healthy menopausal women.

Assessment of Comorbid Conditions/ Contraindications to HT

- **Risk stratification:**
  - In **postmenopausal women with comorbidities** such as CHD and those with a history of VTE, stroke, or TIA, the risks of HT are greater; **nonhormonal strategies** should be considered as the first-line approach for the management of menopausal symptoms in such "at-risk" populations.
  - In general, for women who **are within 10 years of menopause** and are deemed **at low risk for CVD**, **HT** can be safely considered.
  - For those who are **less than 10 years since menopause** onset but **with risk factors for CVD**, if HT is considered for symptom control, **a transdermal rather than oral route** of HT should be considered.
  - HT does not adversely affect glucose levels, and HT is not contraindicated in women with diabetes; however, careful assessment of associated comorbidities is warranted to minimize risks.

Assessment of Comorbid Conditions/ Contraindications to HT

- **Risk stratification:**
  - For women who are **considered high risk for VTE**, such as obese women, or those who are smokers, if HT is being considered, then a **transdermal route** would be preferred given the higher risk of thrombosis with oral route of estrogen therapy.
  - for women who are **more than 10 years past FMP**, **nonhormonal approaches** should be preferentially considered as the first-line approach even in those deemed at low or moderate risk for CVD.



1 Vasomotor symptom assessment

Confirm that hot flashes and/or night sweats are adversely affecting sleep, daytime functioning, or quality of life.

2 Risk factor assessment

Confirm that there are no absolute contraindications to menopausal hormone therapy

- Breast or endometrial cancer
- Cardiovascular disease (heart disease, stroke, transient ischemic attack)
- Active liver disease
- Undiagnosed vaginal bleeding

3 Menopausal hormone therapy initiation

Recommend	Consider with caution	Avoid
Age <60 years and Menopause onset within 10 years and Low risk of breast cancer and cardiovascular disease	Age ≥ 60 years ----------OR---------- Menopause onset >10 years prior ----------OR---------- Moderate risk of breast cancer† Or Cardiovascular disease* † - *Where endometrial protection is indicated, consider bazedoxifene or progesterone instead of medroxyprogesterone acetate (but potential thrombotic risks need further study).* *†In women with a history of estrogen-sensitive cancer, systemic HT should be avoided; consider nonhormonal medications.* *†Low-dose vaginal estrogen or vaginal DHEA are options for management of GSM, following consultation with the patient's oncologist.* **Consider transdermal over oral regimens.*	High risk of breast cancer or cardiovascular disease ----------OR---------- Age ≥60 years Menopause onset >10 years prior Moderate risk of breast cancer or cardiovascular disease **Nonhormonal agents are preferred*

Figure 2. Approach to initiating menopausal hormone therapy (HT) (203). DHEA, dehydroepiandrosterone; GSM, genitourinary syndrome of menopause. Modified from Shifren JL, Crandall CJ, Manson JE. JAMA. 2019;321(24):2458-2459.

Available nonhormonal agents for those with contraindications to, or who prefer, nonhormonal therapy

- Paroxetine (a SSRI)
  - is the only FDA-approved nonhormonal treatment available for managing hot flashes, at a dosage of 7.5 mg daily.
  - While improvements in hot flashes are significantly greater than placebo, paroxetine is less effective than HT.
  - Paroxetine should be reserved for women with contraindications to HT.
- .

Available nonhormonal agents for those with contraindications to, or who prefer, nonhormonal therapy

- Other SSRIs and SNRIs have also demonstrated reduction in VMS, although some have no greater effect than placebo.

- When choosing a nonhormonal regimen, consideration should be given to use the lowest effective dose to avoid the unwanted side effect of decreased libido, as well as potential nausea, constipation, and dry mouth

Available nonhormonal agents for those with contraindications to, or who prefer, nonhormonal therapy

- in women taking tamoxifen as an adjuvant therapy in the management of breast cancer, The following SSRIs (paroxetine, fluoxetine, sertraline) should be avoided because they can inhibit tamoxifen's active metabolite.

Available nonhormonal agents for those with contraindications to, or who prefer, nonhormonal therapy

- Gabapentin and pregabalin:
  - reduce VMS; however, side effects limit their use at high doses.
  - Gabapentin and pregabalin both can cause drowsiness and dizziness.
  - pregabalin can also decrease libido.

Available nonhormonal agents for those with contraindications to, or who prefer, nonhormonal therapy

- Oxybutynin:
  - In a phase 2 trial, it was more effective than placebo (73% vs 26%) at relieving moderate-to-severe VMS
  - dry mouth was the most common side effect

Available nonhormonal agents for those with contraindications to, or who prefer, nonhormonal therapy

- NK3R antagonists:
  - As the neurokinin B/neurokinin 3 receptor (NK3R) signaling pathway has recently been implicated in the initiation of a hot flash, recent work has focused on blocking this pathway.
  - In 2 randomized, placebo controlled studies, it was found that these nonhormonal agents reduced hot flashes in symptomatic postmenopausal women by 45%.
  - While these results are promising, additional studies are needed to assess safety of NK3R antagonists.

Available nonhormonal agents for those with contraindications to, or who prefer, nonhormonal therapy

- GSM is best treated by low-dose vaginal estrogen, intravaginal DHEA, or ospemifene (SERM) administration.
- Alternative nonhormonal therapies for GSM include vaginal lubricants and moisturizers.
- Lubricants provide immediate, short-term relief of vaginal dryness and related pain during sex.
- There are no published studies on the irritation potential of various types of lubricants, so it is recommended that women first test on their skin prior to using intravaginally. If no skin irritation occurs, they can proceed with a given product.
- Moisturizers serve to hydrate dry mucosal tissue and, because they adhere to the vaginal lining, they can mimic normal vaginal secretions and may be helpful for GSM.

TREATMENT BY INDICATION
VSM & GSM

- the lowest effective E dose needed for symptom relief is recommended.
- In those with VMS + GSM, the addition of low-dose vaginal estrogen, intravaginal DHEA, or ospemifene can be considered if focal symptoms persist despite improvement in VMS with systemic HT.
- A variety of vaginal E formulations are available to address GSM (creams, tablets, rings).
- vaginal DHEA and vaginal estrogens, both are equally effective at improving vulvovaginal symptoms.
- Whether vaginally administered DHEA has any effect on the bone or breast is unknown.

TREATMENT BY INDICATION
Bone Health

- HT has been shown to effectively improve BMD and reduce fracture risk.
- Some systemic E-alone, E+P, or BZA/CEEs (TSEC) are approved for postmenopausal osteoporosis and fracture prevention.
- The ideal candidates for HT use for skeletal benefit are recently menopausal women (within 10 years of FMP and younger than 60 years) who in addition to having an elevated lifetime risk for fracture, are also experiencing bothersome VMS, and have no contraindications to HT use.

TREATMENT BY INDICATION
Bone Health

- For older postmenopausal women or in those with contraindications to HT, a number of nonhormonal treatment options should be considered:
  - antiresorptive agents, bone-forming agents, Romosozumab
- available nonhormonal agents are more effective at reducing fractures.
- raloxifene (a SERM) is effective only for the prevention of spine fractures.

TREATMENT BY INDICATION
hypoestrogenism in perimenopausal women

- For the younger perimenopausal population of women presenting with VMS who are seeking contraception and/or are experiencing irregular menses (with negative workup for other causes), low-dose combined oral contraceptives (COCs; 10-20 µg EE) can offer relief as well as ensure reliable contraception, provided there are no contraindications to the use of COCs.
- The decision to transition from COCs to HT should be an ongoing discussion with women, and usually can occur near the average age of menopause (around age 52 years), or based on individualized family reproductive history and personal profile.

SPECIAL POPULATIONS
Early Menopause

- Early menopause is defined as cessation of ovarian function between ages 40 and 45 years
- if this occurs before age 40, it is considered premature.
- For those with early menopause, consideration for initiation of HT is advisable not only to mitigate the symptoms resulting from hypoestrogenism, but also to prevent the long-term health consequences (increased lifetime risk of osteoporosis and fragility fractures, CVD, cognitive deficits, mood disorders, and increased all-cause mortality).

SPECIAL POPULATIONS
Early Menopause

- For this particular group of women, HT is highly recommended at least until the average age of natural menopause.
- HT dosing should be so that E2 levels reach 100 pg/mL which is the usual serum level in premenopausal women, attainable with consistent use of:
  - transdermal 0.1 mg E2 patch
  - 0.1 mg vaginal ring
  - oral dose equivalents being daily 1.25 mg CEEs and 2 mg E2

SPECIAL POPULATIONS
Early Menopause

- Estrogen replacement can be administered orally (as oral HT or COCs), transdermally, or vaginally, and should be individualized based on patient preference.
- In women with a uterus, the addition of a progestogen to estrogen regimen is indicated: 5 to 10 mg MPA, 200 mg natural MP, NETA 5 mg.
  - alternatively, vaginal and intrauterine routes of progestogen administration—while off-label—can be used based on individualized needs and preferences.

SPECIAL POPULATIONS
Early Menopause

- Progestogen inclusion in an HT regimen can be cyclical or continuous.

- While COCs can offer symptom relief (and contraception in those with POI), they are not ideal for reducing the risk of long-term health consequences of these conditions

SPECIAL POPULATIONS
Hysterectomy with bilateral oophorectomy

- bilateral oophorectomy renders women abruptly hypoestrogenic and severely symptomatic.
- often require HT to ensure quality of life and minimize long-term health consequences.
- E-alone regimens suffice for the vast majority. The only exceptions: endometriosis
- They experience an abrupt and profound drop in circulating levels of both ovarian estrogens and ovarian androgens. Systemic estrogen therapy will treat symptoms resulting from hypoestrogenemia. Women who experience hypoactive sexual desire following surgical menopause may benefit from the addition of androgen (testosterone) to ET.
- testosterone use is off-label and it is contraindicated in women with breast or uterine cancer, CVD, or liver disease.

SPECIAL POPULATIONS
PH or FH of VTE or Other CVD

- In women with a PH of idiopathic VTE, or FH of VTE, an evaluation is warranted prior to considering HT:
  - CBC (malignancy), activated protein C, factor V Leiden mutation, prothrombin gene mutation, protein S and C, and antithrombin III mutation
- While a PH of VTE is an absolute contraindication to HT, in rare cases of intractable VMS unresponsive to alternatives, a very low-dose transdermal E regimen may be considered, possibly concomitant with anticoagulation, but only after thorough counseling. a consideration of transdermal HT can be examined on an individualized basis for those with a personal or family history of VTE.

SPECIAL POPULATIONS
PH or FH of VTE or Other CVD

- Postmenopausal women with SLE who have stable disease without high antiphospholipid antibodies or renal disease can also consider transdermal HT in consultation with their rheumatologist.

SPECIAL POPULATIONS

Women with a PH of estrogen-sensitive cancer/strong FH of cancer/BRCA positivity

- In women with a PH of early stage and surgically treated endometrial cancer, combined E plus progestogen HT can be used following consultation with their oncologist.
- those with advanced disease should use nonhormonal treatment options for menopause.
- At this time, systemic HT is not recommended for women with a history of breast cancer.

SPECIAL POPULATIONS

Women with a PH of estrogen-sensitive cancer/strong FH of cancer/BRCA positivity

- In B.C, those presenting with GSM, consideration of low-dose vaginal estrogen, in consultation with their oncologist, is a potential therapeutic option.
- Alternatively, vaginal DHEA can be considered
- In women with a FH of breast cancer, HT does not affect the risk of subsequent breast cancer development

Duration of Treatment and Importance of Shared Decision Making

- In women with a history of ovarian cancer, an increased risk of cancer recurrence when using HT has not been found, although data come primarily from observational studies.
- There is concern that hormone-responsive ovarian cancers may reactivate, but studies are limited.
- HT use and cervical cancer has not been well studied; however, existing studies do not demonstrate an increased risk of cervical cancer or cervical cancer recurrence in postmenopausal women using HT.
- While data on lung cancer are limited, the overall data do not clearly support an increased risk with HT use.

SPECIAL POPULATIONS

Women with a PH of estrogen-sensitive cancer/strong FH of cancer/BRCA positivity

- In women who are *BRCA*1/2 positive, HT (including estrogen alone) has not negated the risk reduction in cancer following prophylactic bilateral oophorectomy in cohort studies.
- In a case-control study of *BRCA*1-positive women using estrogen-alone or estrogen plus progestogen-based HT, there was no increased risk of breast cancer.
- While RCTs are limited, available evidence demonstrates the relative safety of HT in women who are *BRCA* positive, although these women may benefit particularly from BZA/CEEs given the neutral effect of BZA on the breast.

Duration of Treatment and Importance of Shared Decision Making

- The decision regarding duration of treatment and when to stop HT must be considered in the context of the individualized risk/benefit profile, as well as the personal preferences of the patient.
- It is not known if ongoing use of HT by women who initiated treatment early but are now older than 60 years carries the same risks as initiating HT in women older than 60 or those who are more than 10 years since menopause onset.
- VMS can continue on average for 7 years (and for some beyond 10 years). For otherwise healthy women with persistent VMS, continuing HT is a reasonable option provided counseling and shared decision making are taken into account.

Duration of Treatment and Importance of Shared Decision Making

- In women at high risk for osteoporosis who also experience persistent VMS, HT may also be considered beyond age 65 years in select women who are deemed to remain at low risk for CVD despite advancing age.
- With discontinuation of HT, the beneficial effect on the skeleton dissipates; GSM and VMS can also reappear. Therefore, the preferred approach to HT duration is to consistently assess symptoms and changes to patients' medical history so as to ensure that risks of continued therapy do not outweigh the benefits for each individual woman treated with HT.
- The choice of transdermal estrogen with or without MP (depending on the presence or absence of a uterus) with periodic E dose reduction offers benefits of symptom control and long-term fracture risk reduction while minimizing some risks (such as VTE) and thus may be a safer strategy for long-term HT

Table 3. Systemic hormone therapy formulations

Route and formulation	Available doses	Considerations
Oral formulations		
CEEs		
	0.3, 0.45 mg	Low dose
	0.625 mg	Standard dose
	0.9 mg, 1.25 mg	High dose
CEE + BZA	0.45 mg CEE/20 mg BZA	No need for addition of progestin in women with uteri
Esterified estrogen		
	0.3 mg	Low dose
	0.625 mg	Standard dose
	1.25 mg	High dose
Estradiol		
	0.5 mg	Low dose
	1 mg	Standard dose
	2 mg	High dose
Transdermal formulations		
Patch		
Estrogen-progestin	0.05 mg estradiol/0.14 or 0.25 mg norethindrone	Apply twice weekly
Estrogen-progestin	0.045 mg estradiol/0.015 mg levonorgestrel	Apply twice weekly
Estradiol	0.025 mg	Low dose
	0.05, 0.075 mg	Standard dose
	0.1 mg	High dose
		Apply twice weekly
Estradiol	0.025, 0.0375 mg	Low dose
	0.05, 0.06, 0.075 mg	Standard dose
	0.1 mg	High dose
		Apply weekly
Estradiol	0.014 mg	Lowest approved dose
		Apply weekly
Gel		
Estradiol	0.52, 0.75 mg	Per pump, daily
Estradiol	0.25, 0.5, 1 mg	Per pouch, daily
Spray		
Estradiol	1.53 mg	Per spray, daily

Abbreviations: BZA, bazedoxifene; CEE, conjugated equine estrogen.

Table 4. Progestogen formulations

Progestogen class	Formulation	Comparable dose	Dosing regimens
Oral			
Progesterone	MP	100 mg (when used as single tab of 1 mg E$_2$/100 mg MP, no peanut oil in tablet)	Daily, sequential
		200 mg	
		300 mg (VMS)	
21-Carbon derivatives	Medroxyprogesterone	2.5 mg	Daily
	Acetate	5 mg	Sequential
		10 mg for VMS	
	Megesterol acetate	5 mg	Daily
		20 mg for VMS	
	Cyproterone acetate	1 mg	Daily, sequential
	Dydrogesterone	10 mg	Daily, sequential
	Chormadinone acetate	5-10 mg	Daily, sequential
	Medrogestone	10 mg	Daily, sequential
19-Norpregnanes	Trimegestone	0.0625-0.5 mg	Daily, sequential
	Promegestone	0.5 mg	Daily, sequential
	Nomegestrol	5 mg	Daily, sequential
	Nomegestrol acetate	3.75–5 mg	Daily, sequential
19-Nortestosterone	Norethindrone	0.35 mg	Daily
		0.7 mg	Sequential
Ethinylated	Norethindrone acetate	1 mg	Daily, sequential
Nonethinylated	Levonorgestrel	0.075 mg	Daily, sequential
		52 mg	5-7 y
		19.5 mg	5 y
		13.5 mg	3 y
	Desogestrel	0.15 mg	Daily, sequential
	Norgestrimate	0.09 mg	Daily, sequential
	Gestodene	0.2 mg	Daily, sequential
	Dienogest	2 mg	Daily, sequential
Spironolactone derivative	Drosperinone	2 mg	Daily, sequential
Vaginal			
Progesterone off-label use	4% gel	45 mg	Twice weekly, every other day, sequential
	Suppository	100 mg	Twice weekly, every other day, sequential
Intrauterine			
Levonorgestrel off-label use	Intrauterine device	52 mg	5-7 y
		19.5 mg	5 y
		13.5 mg	3 y

Table 5. Hormone therapy formulations for symptoms of genitourinary syndrome of menopause

Vaginal		
Estradiol tablet	10 mcg	Daily for 2 wk, followed by twice weekly
Estradiol suppository	4 mcg	Per suppository, daily
	10 mcg	followed by twice weekly
Prasterone suppository	6.5 mg	Daily
Estradiol ring	7.5 mcg	Per 3 mo
	0.05 mg	Standard dose
	0.1 mg	High dose
		Per 3 mo
		Progestogen required because of systemic levels
Oral		
Ospemiphene tablet	60 mg	Daily