The 2017 NAMS Hormone Therapy Position Statement has been endorsed by:

- Academy of Women’s Health
- American Association of Clinical Endocrinologists
- American Association of Nurse Practitioners
- American Medical Women’s Association
- American Society for Reproductive Medicine
- Asociación Mexicana para el Estudio del Climaterio
- Association of Reproductive Health Professionals
- Australasian Menopause Society
- Chinese Menopause Society
- Colegio Mexicano de Especialistas en Ginecología y Obstetricia
- Czech Menopause and Andropause Society
- Dominican Menopause Society
- European Menopause and Andropause Society
- German Menopause Society
- Groupe d’études de la ménopause et du remaniement hormonal
- HealthyWomen
- Indian Menopause Society
- International Menopause Society
- International Osteoporosis Foundation
- International Society for the Study of Women’s Sexual Health
- Israel Menopause Society
- Japan Society of Menopause and Women’s Health
- Korean Society of Menopause
- Menopause Research Society of Singapore
- National Association of Nurse Practitioners in Women’s Health
- SDBA Canadian Menopause Society
- SOBRAF and FEBRASGO
- Società Italiana della Menopausa
- Society of Obstetricians and Gynecologists of Canada
- South African Menopause Society
- Thai Menopause Society
- The American College of Obstetricians and Gynecologists supports the value of this clinical document as an educational tool, June 2017.
- The British Menopause Society supports this Position Statement.

The 2017 NAMS Hormone Therapy Position Panel:

Chair, JoAnn V. Pinkerton, MD, FACOG, NCMP
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Howard N. Hodis, MD
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Robert L. Reid, MD
Philip M. Sarrel, MD
Jan L. Shifren, MD, NCMP
Wulf H. Utian, MD, PhD, DSc (Med), NCMP

Recommendation grading categories (where provided):

- Level I: Based on good and consistent scientific evidence
- Level II: Based on limited or inconsistent scientific evidence
- Level III: Based on primarily on consensus and expert opinion
Misperceptions about Hormone Therapy
• Despite the fact that published evidence from the WHI suggests that hormone therapy is a relatively safe, viable solution for symptomatic menopausal women under age 60 or who are within 10 years postmenopause, the number of women being prescribed and using hormones continues to decline.

The 2017 NAMS Hormone Therapy Position Statement published in July 2017 issue of Menopause
• Hormone therapy remains the most effective treatment for vasomotor symptoms and the genitourinary syndrome of menopause and has been shown to prevent bone loss and fracture,” says Dr. JoAnn V. Pinkerton, NAMS Executive Director and Chair of the Position Statement Advisory Panel.

Women’s Health Initiative study 2002
Breast cancer
Heart disease
Probable Dementia

Fear has been driving the conversation about hormone therapy

FDA-approved indications for hormone therapy
• First-line therapy-relieve VMS in appropriate candidates
• Prevent bone loss and reduce fractures in PM women at elevated risk of osteoporosis or fractures
• For women with hypogonadism, primary ovarian insufficiency, or premature surgical menopause without contraindication, until the average age of menopause
• Low-dose vaginal estrogen therapy first line for isolated GMS to treat symptoms of VVA

Age and Time Since Menopause “Timing Hypothesis”
– The effects of HT on CHD may vary depending on a woman’s age and time since menopause
– There are data that show reduced CHD in women who initiate HT before age 60 and/or within 10 years of menopause
– There is concern of increased risk of CHD in women who initiate HT more than 10 or 20 years from menopause

Risks appear different for ET vs EPT
• The risks of HT in the Women’s Health Initiative (WHI) and other studies differ overall for
  – Estrogen Therapy (ET)
  – Estrogen-Progestin therapy (EPT)
• Potentially more favorable safety profile for longer use of ET

HT & Breast
• The effect of HT on breast cancer risk is complex and conflicting
• The effect of HT on breast cancer risk may depend on
  – Type of HT (Less risk estrogen alone)
  – Dose, duration of use
  – Regimen, route of administration
  – Prior exposure to HT
  – Individual characteristics

Women’s Health Initiative Hormone Therapy and Breast Cancer
• Increased risk of invasive breast cancer after 3 to 5 years of EPT (Premarin-MPA) - <1/1000 RARE Risk
• No increased risk of breast cancer with 7 years of Estrogen only (CEE)
• 7 fewer cases of breast cancer
• Allows for more flexibility in duration of ET alone
Meta-analysis of CHD in RCTs

- HT initiated < 10 years after the menopause in postmenopausal women reduced CHD
  - RR of 0.52 (CI 0.29 to 0.96)
- Significant increased risk of VTE
  - RR 1.74 (1.11 to 2.73)
- Death was significantly reduced
  - RR 0.70 (0.52 to 0.95)

Risks which increase with age or time from menopause

- In meta-analysis of RCTS, absolute risks which increased with age or time from menopause included stroke, venous thromboembolism and pulmonary embolism

Transdermal HT

- Based on observational data only, the use of lower doses and transdermal therapy appear to be associated with lower VTE and stroke risk
- But…. the lack of comparative RCT data limit recommendations

Lowering doses or transdermal

- May be appropriate as women age
- For those with metabolic syndrome
  - Hypertriglyceridemia with risk of pancreatitis
  - Fatty liver (Level III)
Endometrial protection

- For systemic estrogen, endometrial protection requires an adequate dose and duration of a progestogen or use of the combination CEE with bazedoxifene (TSEC) (Level I)

- Progestogen therapy is not recommended with low-dose vaginal estrogen—1-year safety data

- Appropriate evaluation of the endometrium for vaginal bleeding (Level I)

Concerns about compounded bioidentical hormone therapy

- Unique concerns about safety surround use of compounded bioidentical hormone therapy
  - Lack of regulation and monitoring
  - Possibility of overdosing or underdosing
  - Lack of scientific efficacy and safety data
  - Lack of a label outlining risks

- No evidence to support use of routine serum or salivary hormone testing

Compounded bioidentical hormone therapy should be avoided

- Prescribers of compounded bioidentical hormone therapy should identify and document the medical indication for compounded hormone therapy over government-approved therapies

- Such indications include allergy or the need for different dosing, formulation, or preparation

Bothersome GMS (VVA) and HT

- Low-dose vaginal estrogen preparations are safe and effective

- Minimal systemic absorption

- Advised when ET is considered only for symptoms of the genitourinary syndrome of menopause
HT & Sexual Function

• Both systemic HT and low-dose vaginal ET provide effective treatment for increasing lubrication, blood flow and sensation of vaginal tissues
• HT increases sexual function scores primarily in symptomatic, but not asymptomatic women
• HT not recommended as the sole treatment of other sexual function problems (e.g., diminished libido) but may be an adjunct

Hormone Therapy and Specific Areas

Vasomotor symptoms
Sleep
Bone and joints
Cognition and mood
Diabetes mellitus
Gallbladder and liver
Quality of life

HT, VMS & Sleep

- Hormone therapy is the most effective treatment for hot flashes
- During the menopause transition, women with hot flashes are more likely to report reduced sleep
- Hormone therapy improves sleep in women with bothersome nighttime hot flashes
  - Reduces nighttime awakenings
  - Improves duration, disruption, latency, and sleep cycles

HT & Bone & Joints

- Hormone therapy effectively prevents postmenopause osteoporosis and fractures
- Women in the estrogen-alone and estrogen-progestogen therapy overall cohorts in the WHI had significant 33% reductions in hip fracture
- After treatment discontinuation in the WHI, beneficial effects on bone dissipated rapidly, but no rebound was seen
- Women in the WHI showed less joint pain or stiffness
HT & Cognition
- HT not recommended at any age to prevent or treat cognition or dementia.
- CEE/MPA initiated >65 – rare increase in risk for dementia (WHI)
- ET may have positive cognitive benefits if initiated immediately after early surgical menopause
- Early postmenopause period - neutral effects
- Tentative support (observational critical window hypothesis of HT in Alzheimer disease prevention

NAMS position statement. Menopause 2017

HT & Mood
- Evidence is insufficient to support HT in the treatment of clinical depression
- In small RCTs, ET improved clinical depression in perimenopausal, but not postmenopausal women
- Progestins may contribute to mood disturbance
- If depression improves with HT, more likely to experience a worsening of mood after estrogen withdrawal

Hormone therapy & diabetes mellitus
- HT significantly reduces the diagnosis of new-onset type 2 DM but not FDA approved for this purpose
- HT may help attenuate abdominal adipose accumulation and the weight gain that is often associated with the menopause transition

HT & gallbladder & liver
- Risk of gallstones, cholecystitis, and cholecystectomy increased with oral ET and EPT
- Lower risk with transdermal HT than with oral and with oral estradiol vs CEE (lacking RCT data)
- Association of HT with slower fibrosis progression in hepatitis C and with fatty liver observed, but no RCTs benefits/risks of HT in postmenopausal women with liver disease


Menopause. 2017;24(7):728-753.
Hormone Therapy and Cancer

Breast
Lung (neutral)
Ovarian
Colon

Observational evidence shows use of HT does not alter risk for breast cancer in women with a FH of breast cancer

FH is one risk among many that should be assessed when counseling women on the use of HT (Level II)


HT & Ovarian Cancer

• If an association between hormone therapy and ovarian cancer exists, the absolute risk is likely to be rare (< 1/1,000) and possibly only with long duration of use

• Based on limited observational data – no increased risk of ovarian cancer in women with a FH or a BRCA mutation using EPT

North American Menopause Society Position statement HT. 2017

HT & Colon Cancer

• Observational studies suggest a preventive benefit of HT on colorectal cancer incidence, particularly if initiated early in menopause

• WHI data and post intervention data found no strong evidence of a protective effect of either estrogen-progestin therapy or estrogen therapy on risk of colorectal cancer
HT & Endometrial Cancer

- Use of HT may be considered in symptomatic women with surgically treated, early stage endometrial cancer (low risk) if other options are not effective
  - particularly in early surgical menopause due to higher risk of health consequences related to estrogen loss
- Tested and effective non-hormone therapies are recommended for women with higher stages or those with intermediate- or high-risk endometrial cancer

Low-dose vaginal estrogen therapy & survivors of endometrial cancer

- Consideration may be given for low-dose vaginal estrogen therapy for relief of the GSM
- early endometrial cancer who have completed successful treatment, including hysterectomy
- If nonhormone options are not successful
- On the basis of limited short-term safety trials (Level II)

HT& survivors of breast cancer

- Systemic hormone therapy is not recommended for survivors of breast cancer
  - Selected cases with compelling reasons may be discussed in conjunction with an oncologist
  - After nonhormone options have been unsuccessful
Breast Cancer Survivors & GSM—low dose vaginal ET

• Minimal systemic absorption
  • Blood levels in postmenopause range
  • Based on limited data, minimal risk for recurrence of breast cancer (Level II)

• Decisions should involve the woman’s oncologist

• Concern raised for those on aromatase inhibitors with lowered overall estradiol levels (Level III)

Special Populations

Early menopause
Primary ovarian insufficiency
BRCA after oophorectomy
Age older than 65 years

HT & Premature Menopause & POI

• Don’t extrapolate WHI Data to younger postmenopausal women

• Observational studies benefits on bone, heart, cognition, GSM, sexual function, and mood

• HT recommended until at least the median age of menopause (51.4 y)

• Higher doses of estrogen with adequate endometrial protection may be needed to protect bone

BRCA-positive women without breast cancer

– Higher genetic risk of breast cancer, primarily estrogen-receptor negative.

– If surgical menopause, consider benefits of estrogen to decrease health risks caused by premature loss of estrogen (Level II)

– Systemic HT may be offered until at least the median age of menopause (52 y)
  • Based on limited observational studies
  • Discussions about longer use should be individualized. (Level II)
Prolonged duration- no good data

- Prolonged Duration- there is a lack of good quality information about prolonged duration with lower doses, transdermal products, in women who initiate hormone therapy at younger ages or closer to menopause

- Observational data is positive including recent Finnish Database (less heart disease, no increase breast cancer, but may include “healthy user bias”)

No general rule to discontinue HT >65

- The recommendation to routinely discontinue systemic HT after age 65 is **NOT** supported by data
- Decisions regarding whether to continue HT beyond the age of 60 should be individualized
  - After appropriate evaluation
  - Counseling about potential benefits/risks
  - Ongoing surveillance (Level III)

Conclusion—
OVERALL BENEFIT-TO-RISK RATIO

The Experts Agree About Hormone Therapy

- Benefits are likely to outweigh risks for symptomatic women who initiate HT when aged younger than 60 years and within 10 years of menopause
The Experts Agree about who SHOULDN’T TAKE Hormone Therapy

• For women who initiate HT > than 10 or 20 years from menopause or 60 yrs or older, the benefit-risk ratio appears less favorable than for younger women
• Greater absolute risks
  • CHD, stroke, VTE, & dementia

NAMS Guidelines

• No evidence to discontinue HT after age 65 if indication to continue remains & no contraindications
• Breast cancer risk does not increase appreciably with short term use of EPT and may be decreased with estrogen alone (CEE in WHI)
• No increased risk of breast ca in BRCA+ women on HT after RRBSO (observational studies)

Change the message about Hormone Therapy

• Post WHI “Lowest dose for shortest period of time”
• Change “Appropriate hormone therapy to meet treatment objectives (goals)
  • Type, dose and formulation
  • Route of administration
  • Duration

KEY TAKE HOME
Differing risks of HT for women

• Depending on type, dose, duration, route of administration, and timing of initiation and whether a progestogen is needed.
• Individualize treatment- use best available evidence
  – Maximize benefits and minimize risks
  – Appropriate Dose, Duration, Type
• Periodic reevaluation about benefits and risks of continuing or discontinuing HT.
The North American Menopause Society
2018 Annual Meeting
October 3 - 6
Hilton San Diego Bayfront, California

Gloria A Richard-Davis, MD, FACOG, NCMP
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