After reading these slides and notes, physicians and other health care providers will be able to:

- Define QOL.
- Describe the fundamental principles involved in the evaluation and measurement of menopause-related QOL, and list validated measures for its assessment.
- Describe the physiological changes associated with estrogen loss at menopause and the effects of these changes on QOL.
- List the most common menopause-related symptoms prompting women to seek treatment.
- Evaluate the efficacy of HT, including low-dose and topical therapy for treating menopausal symptoms, and examine the efficacy of alternative therapies.
- Review the specific physiological effects of HT on urogenital tissue and describe how urogenital health may influence sexual function and QOL in postmenopausal women.
- Examine how the presence of menopausal symptoms, such as vasomotor symptoms, mood and sleep disturbances, urogenital and sexual complaints may contribute to the risk/benefit profile of HT for individual patients.
- Summarize currently available data on the effects of menopause-related changes and the use of HT on QOL in postmenopausal women.
Quality of Life, Menopausal Changes, and Hormone Therapy

Section 1: Quality of Life Definition and Assessment

Section 2: Menopause-Related Changes
2a. Vasomotor Symptoms
2b. Sleep Quality
2c. Urogenital Changes
2d. Sexual Well-Being
2e. Skin Changes
2f. Bone

Section 3: Recent Evidence and Critical Review of QOL in Menopause

Section 4: Summary and Conclusions
Quality of Life, Menopausal Changes, and Hormone Therapy

Section 1:
Quality of Life Definition and Assessment
Menopausal Changes and Quality of Life

Definition of QOL

◆ Global sense of self-satisfaction
◆ Sense of well-being
◆ Patient’s perception of her interest in life
◆ Maintaining satisfactory interpersonal relationships
◆ Perception of physical and psychological wellness
◆ Satisfaction with position in life in the context of culture and value systems


• Quality of life, as it relates to menopausal women, is best described as health-related QOL that includes physical health and functioning, emotional functioning, role limitations, and social functioning.

• Unfortunately, menopause-related QOL is commonly used to refer to only symptoms, such as severe hot flushes, night sweats, and vaginal dryness or pain. While these symptoms may negatively affect QOL and are improved with use of HT, it is important to recognize other more global aspects of QOL, including health status, life satisfaction, coping, and psychological functioning.

• Instruments that measure menopause-related QOL should be modern, reliable, and comparable to other validated instruments, and be responsive to changes in clinical symptoms or with different interventions. Simple use of a symptom checklist can introduce bias since patients may respond positively to symptoms on a checklist, but report declines if frequency or degree of bother is queried. Failure to use adequately validated assessment tools has been a common problem in menopause research.
Global and Health-Related QOL

- **Global QOL**
  - “Sense of well-being” that is impacted by experience of symptoms but not solely determined by symptoms
  - Patient’s own subjective appraisal of overall life satisfaction/sense of well-being

- **Health-related QOL**
  - Patient’s perceptions of their physical, cognitive, and mental health


• In discussing the topic of QOL, a distinction needs to be made between *global* QOL and *health-related* QOL.
  - Global QOL refers to a sense of well-being that is impacted by the experience of symptoms, but is not solely determined by them; it is a subjective appraisal of life satisfaction.
    - For example, one person may objectively be experiencing severe symptoms but perceive their life as having excellent quality, while another person may be symptom-free but perceive their life to have poor quality.
  - Health-related QOL, on the other hand, specifically refers to a patient’s perceived physical and mental health over time.
Menopausal Changes and Quality of Life

Menopause-Related QOL

- Validated tools for assessment
  - Utian Menopause QOL Score
  - Menopause Rating Scale
  - Greene Climacteric Scale
  - Women’s Health Questionnaire
  - Menopausal Symptom List

According to Schneider, menopause-specific instruments should satisfy the following criteria:
- Factor analysis
- Sound psychometric properties
- Subscales measuring different aspects of symptomatology
- Standardized across populations of women

Five instruments fulfill these criteria:
- The Utian Menopause QOL Score
  - Development was based on a 2-stage process of a principle component analysis followed by a factor analysis using 40 symptoms from a sample of women in the US; the final scale consists of 23 items, each rated on a 5-point Likert scale.
- Menopause Rating Scale
  - Development was based on factor analysis of somatic, psychological, and urogenital symptoms from a sample of German women; the final scale consists of 11 symptoms, each rated for severity on a 5-point scale.
- Greene Climacteric Scale
  - This scale was developed from factor analysis that categorized symptoms into 3 factors: vasomotor, somatic, and psychological; the scale includes 21 symptoms, each rated on a 4-point scale of severity.
- Women’s Health Questionnaire
  - This questionnaire is based on factor analysis of 36 symptoms reported by a sample from southeast England; the instrument contains 32 symptoms, each rated on a binary scale 0/1.
- Menopausal Symptom List
  - Development of this tool was based on factor analysis of 56 symptoms reported by a sample of Australian women; the instrument has 25 symptoms and 3 subscales: vaso-somatic, general somatic, and psychological.
Importance of QOL Measurement

Accurate Appraisal of QOL

- Critical to enhancing treatment adherence
- Enhances clinician interactions with patients
- Helps assess and optimize treatment effectiveness
- Improves overall patient satisfaction with treatment


- Measuring QOL provides valuable information to help the practitioner make the best choices in patient care.
- An accurate appraisal of QOL can improve treatment adherence, patient-clinician interactions, treatment effectiveness, and patient satisfaction.
Utian Quality of Life (UQOL) Scale

- Measures QOL during the climacteric years
- 23-item questionnaire
- 4 domains
  - Occupational QOL
  - Health QOL
  - Sexual QOL
  - Emotional QOL


- The Utian Quality of Life (UQOL) Scale is a 23-item questionnaire with a stable factor structure that demonstrates 4 separate, intercorrelated domains
  - Occupational QOL (eg, "I feel challenged by my work.")
  - Health QOL (eg, "My diet is not nutritionally sound.")
  - Sexual QOL (eg, "I am content with my romantic life.")
  - Emotional QOL (eg, "My mood is generally depressed."

- The items in the UQOL scale were constructed to tap a broad array of topics relevant to QOL and well-being in menopausal women. Women rate each item according to the degree to which it applies to them in the past month using a 5-point, Likert-type scale (1 = "not true of me," 5 = "very true of me"). Domain scores are derived by the sum of responses in each domain. An overall score is derived from the sum of the domain scores.

- Following are the 23 items that comprise the UQOL questionnaire:
  1. I am able to control things in my life that are important to me.
  2. I feel challenged by my work.
  3. I believe my work benefits society.
  4. I am not content with my sexual life.
  5. I am content with my romantic life.
  6. I have gained a lot of personal recognition within my community or at my job.
  7. I am unhappy with my appearance.
  8. My diet is not nutritionally sound.
  9. I feel in control of my eating behavior.
  10. Routinely, I engage in active exercise three or more times each week.
  11. My mood is generally depressed.
  12. I frequently experience anxiety.
  13. Most things that happen to me are outside my control.
  14. I am content with the frequency of my sexual interactions with a partner.
  15. I currently experience physical discomfort or pain during sexual activity.
  16. I believe I have no control over my physical health.
  17. I am proud of my occupational accomplishments.
  18. I consider my life stimulating.
  19. I continue to set new personal goals for myself.
  20. I expect that good things will happen in my life.
  21. I feel physically well.
  22. I feel physically fit.
  23. I continue to set new professional goals for myself.
Purpose of UQOL

- Assess QOL
- Gather data about the woman’s perception of the overall quality of her life
- Follow progress in clinical practice
- Evaluate drug responses in clinical trials


- The UQOL was created to meet the need for an instrument with the following characteristics
  1. Measures the specific domains of functioning that have been found to affect the QOL of peri- and postmenopausal women.
  2. Not a symptom inventory, per se, but is capable of being combined with one to give an overall outcome/response to therapy.
  3. Reliable and valid.
  4. Practical to administer and easy to score.
  5. Sensitive to changes in QOL status and, as such, is useful as a repeated measure to evaluate menopause-related QOL status over time.
Menopausal Changes and Quality of Life

Greene Climacteric Scale

- 21-item symptom questionnaire
- Patients assign score to each symptom using 4-point scale
- 3 subscales
  - Psychological (anxiety and depression)
  - Somatic
  - Vasomotor


The Greene Climacteric Scale evaluates 21 symptoms and is divided into subscales. Anxiety and depression together constitute the psychological subscale.

- Anxiety: 1–6
- Depression: 7–11
- Somatic: 12–18
- Vasomotor: 19–20
- Sexual Dysfunction*: 21

*Single item added in recent years; not included in subscales.

To complete the evaluation, the participant assigns a score to each symptom using a 4-point scale:
0 = not at all; 1 = a little; 2 = quite a bit; and 3 = extremely. The total score on the Greene Climacteric Scale is the sum of all 21 scores.

Following are the 21 symptoms women are asked to evaluate.

1. Heart beating quickly or strongly
2. Feeling tense or nervous
3. Difficulty in sleeping
4. Excitable
5. Attacks of panic
6. Difficulty in concentrating
7. Feeling tired or lacking in energy
8. Loss of interest in most things
9. Feeling unhappy or depressed
10. Crying spells
11. Irritability
12. Feeling dizzy or faint
13. Pressure or tightness in head or body
14. Parts of body feel numb or tingling
15. Headaches
16. Muscle and joint pains
17. Loss of feeling in hands or feet
18. Breathing difficulties
19. Hot flushes
20. Sweating at night
21. Loss of interest in sex

Menopausal Changes and Quality of Life

HT Use After the WHI

- Telephone interviews with 670 of 1000 randomly selected female HMO members aged 50 to 69 years (mean age, 58.9 ± 5.1 years) who had been using HT for ≥1 year before July 2002

- Reasons for starting HT
  - Symptom relief (57%)
  - Health promotion (23%)
  - Hysterectomy (11%)

- 56% reported trying to stop HT between July 2002 and March 2003


Following publication of preliminary findings from the Women’s Health Initiative (WHI), Grady et al randomly selected 1000 women from a computerized pharmacy database of women aged 50 to 69 years (mean 58.9 ± 5.1 years) to describe the experiences of postmenopausal women who attempted to stop HT and to identify characteristics associated with inability to stop.

- All of the women in this database were told to stop HT.
- 670 of the 1000 completed the interview.
- Using records from the computerized database, the investigators indicated that the mean age, HT regimen, and HT prescriber type were similar in both groups of women—those who agreed to be interviewed and those who declined.

- Most women (57%) had started HT for symptom relief; other reasons provided were health promotion (23%) and hysterectomy (11%).

- Three hundred seventy-seven (56%) had regularly used HT for at least 1 year before July 1, 2002 and had attempted to stop between July 2002 and March 2003.
  - % who had used HT 1–4 years = 23%
  - % who had used HT 5–9 years = 31%
  - % who had used HT 10+ years = 46%

Of the 377 women who had attempted stopping HT, 74% were not using HT at time of interview (had been off HT a median of 5.7 months)
  – 26% had resumed HT

After stopping HT, 30% reported troublesome symptoms
  – Flashes (88%)
  – Excessive sweating (76%)
  – Difficulty sleeping (54%)
  – Fatigue (39%)
  – Depression (38%)
  – Vaginal dryness (38%)


• Three hundred seventy-seven of the 670 women interviewed reported that they had attempted to stop using HT. At the time of the interview, 280 (74%) were not taking HT and had been off of HT for a median of 5.7 months.
• After stopping HT, 30% reported the troublesome withdrawal symptoms detailed on this slide.
  – Troublesome symptoms began a median of 1 week (interquartile range, 0–4 weeks) after stopping HT, and were more common among women who had started HT for the relief of symptoms than those who had not (37% vs 26%; \( P = .01 \)).
  – Women who resumed HT were more likely to have troublesome symptoms than those who had not resumed HT at the time of the interview (62% vs 19%).
  – Among those women who had experienced troublesome symptoms after quitting HT and had not resumed HT, 73% reported that their symptoms were still troublesome at the time of the interview.

Factors Associated With Restarting HT After Attempt to Stop

<table>
<thead>
<tr>
<th></th>
<th>Multivariate OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troublesome symptoms after stopping HT</td>
<td>8.8 (4.9–16.0)</td>
</tr>
<tr>
<td>HT prescribed by non-gynecologist</td>
<td>2.2 (1.2–4.0)</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>1.9 (1.1–3.6)</td>
</tr>
<tr>
<td>Perceived high risk of hip or spine fracture</td>
<td>1.4 (1.1–1.8)</td>
</tr>
</tbody>
</table>


- The major predictor of resuming HT was the development of troublesome withdrawal symptoms (OR in a multivariate model, 8.8; 95% CI, 4.9–16.0).
- Report of hysterectomy, HT prescribed by a nongynecologist, and perception of high risk of hip or spine fracture were also associated in the multivariate model with a higher likelihood of resuming HT.
- Development of either troublesome vasomotor symptoms (OR, 2.2; 95% CI, 1.2–4.0) or other troublesome symptoms (OR, 2.4; 95% CI, 1.3–4.6) was independently associated with the resumption of HT following an attempt to stop.
- These results may be helpful to clinicians in identifying women who may be most likely to experience moderate-to-severe symptoms following cessation of HT. Continued use of HT, if appropriate based on the patient’s individualized risk/benefit profile, may be considered and discussed in these cases.

The authors of this study hypothesized that the abrupt discontinuation of HT after the publication of the WHI results in July 2002 would be associated with an increase in antidepressant usage.

This figure appears to confirm their hypothesis—there was a significant decrease in the number of HT prescriptions dispensed in Ontario (shown by the solid line) after July 2002. This decrease was associated with a statistically significant increase in prescriptions for serotonergic antidepressants (shown by the dotted line; eg, citalopram, fluoxetine, sertraline, fluvoxamine, paroxetine, venlafaxine, nefazadone, and trazadone).

The authors suggest that the simultaneous increase in prescriptions for antidepressants may indicate that they are being prescribed for symptoms (psychological and/or physical) previously controlled with the use of HT.

Duration of HT Use

**FDA 2003**

- Recommends shortest duration and lowest dose consistent with treatment goals

**NAMS 2004**

- Recommends duration and dose consistent with treatment goals
- Extended use recommended under specific circumstances provided patient is aware of risks/benefits
  - Patient perceives benefit of symptom relief outweighs risks
  - Symptomatic women at high risk for fracture
  - Viable option for prevention of osteoporosis

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- On January 8, 2003, the US Food and Drug Administration (FDA) approved new labels for HT for postmenopausal women following review of WHI data. In the labeling, the FDA recommends that estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.\(^1\)

- On September 17, 2003, the North American Menopause Society (NAMS) released a position statement on estrogen and progestogen use in peri- and postmenopausal women.\(^2\)
  - This was a follow-up to an October 2002 position statement.\(^3\)

- The 2003 HT Advisory Panel agreed that extended use of HT was acceptable under certain circumstances, provided the woman is aware of risks and there is strict clinical supervision.
  - For the woman for whom, in her opinion, benefits of symptom relief outweigh risks, notably after failing an attempt to withdraw HT. Attempts should be made over time to reduce and cease HT.
    - As noted in a survey conducted by Grady et al,\(^4\) 30% of women who stop HT reported troublesome withdrawal symptoms. In addition, 73% of women who had stopped HT still experienced troublesome symptoms at the time of their interview, which was a median of 5.7 months after they had stopped HT.
  - For women with moderate-to-severe menopause symptoms who are at high risk for osteoporotic fracture. Attempts should be made over time to lower the dose or cease HT and introduce alternate bone-sparing therapy.
  - For prevention of osteoporosis in a high-risk woman when alternate therapies are not appropriate.

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Quality of Life, Menopausal Changes, and Hormone Therapy

Section 2: Menopause-Related Changes
Menopausal Changes and Quality of Life

Menopause-Related Changes

- Vasomotor symptoms
- Sleep quality
- Sexual well-being
- Urogenital symptoms
- Skin changes
- Bone loss

The three FDA-approved indications for estrogen use are for treatment of vasomotor symptoms, osteoporosis, and vaginal atrophy. All of these factors can affect QOL for menopausal women. However, the WHI study did not address vasomotor symptoms or vaginal atrophy.

In addition to the well-reported effects of HT on vasomotor symptoms, studies have also shown that HT can have a positive influence on other menopause-related QOL factors, such as sleep quality, mood, sexual function, urogenital symptoms, and skin changes.

This section of the presentation will discuss some of the QOL issues that can be influenced by HT. We will begin with a discussion of vasomotor symptoms and mood changes.
Quality of Life, Menopausal Changes, and Hormone Therapy

Section 2a:
Vasomotor Symptoms
Hot flushes occur in the vast majority of menopausal women, with estimates ranging from 68% to 93% of women. Hot flushes often begin before menopause, tend to peak within 2 to 3 years after menopause, and lessen thereafter. But the range of patterns among menopausal women is quite diverse.

Kronenberg showed that women can have hot flushes for more than 20 years. In this survey of 501 self-selected postmenopausal women (ages 29 to 82 years), the total duration of flushing ranged from a few months to 44 years after menopause.

Fifty percent of the women in this survey began experiencing hot flushes before menopause, when the menstrual cycle was still regular or just becoming irregular. Most of the remaining women began having episodes within 1 year of menopause, and a small percentage did not begin having them until >2 years after menopause.

Although the majority (60%) of these women experienced hot flushes for <7 years, 15% had hot flushes for >15 years.

The symptoms that can accompany hot flushes (including perspiration and palpitations) contribute to the discomfort, inconvenience, and anxiety associated with vasomotor symptoms, particularly when these episodes occur very frequently and during the night. Thus, the effect of hot flushes on QOL can be quite significant.

Kronenberg reported that, for women in Western societies, hot flushes are a chief menopausal complaint that leads women to seek medical treatment, supporting the belief that this symptom represents a significant disruption in QOL.

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3Kronenberg F. Ann NY Acad Sci. 1990;592:52-86.
The Study of Women’s Health Across the Nation (SWAN) was conducted to investigate the relationships among a number of factors associated with menopausal symptoms reported by women in the United States. These factors included age; race/ethnicity; educational attainment; lifestyle factors (smoking, physical activity); and menopausal status.1

Participants responded to a survey regarding physical, psychological, and vasomotor symptoms.

The statistical analysis included 12,425 women aged 40 to 55 years. The majority of these women (12,357) reported hot flushes and night sweats. Data were collected by administering a brief series of closed-ended questions to women in seven regions of the US between 1995 and 1997.

Most of the women were premenopausal or early perimenopausal.

Vasomotor symptoms were reported most commonly among African American women (45.5%), followed by Hispanic (35.4%) and Caucasian women (31.2%). Less than 25% of Chinese and Japanese women reported vasomotor symptoms (20.5% and 17.6%, respectively).

Late perimenopausal women and surgically menopausal women were more likely to report vasomotor symptoms than were premenopausal or naturally menopausal women.

Sociodemographic variables also affected reporting of vasomotor symptoms. Lower educational attainment and greater difficulty paying for basic needs were associated with increased reporting of vasomotor symptoms. Further, prevalence of vasomotor symptoms increased as difficulty paying for basic needs became greater.1

Cultural variations may affect reporting of vasomotor symptoms by women.2

In certain cultures, it is possible that women are not expected to report vasomotor symptoms, so they tend not to.

Other cultural factors, like diet, may also affect frequency and severity of vasomotor symptoms.

Hot Flush Mechanisms

- Hot flushes and shivering may result from small fluctuations in core body temperature superimposed on an extremely narrow thermoneutral zone*
- Hot flushes occur when core body temperature rises above the upper (sweating) threshold
- Shivering occurs when core body temperature falls from the elevated level to a level below the lower threshold of the thermoneutral zone

*Zone in which neither sweating nor shivering occurs.

• Hot flushes may be triggered by small elevations in core body temperature within a narrowed thermoneutral zone. (The thermoneutral zone is the range of temperatures between an upper sweating threshold and a lower shivering threshold.)
  – This reduced thermoneutral zone occurs primarily because of a lowering of the threshold for sweating.
• The onset of hot flushes may be the result of the increase in sympathetic activation that occurs with aging combined with decreasing estrogen levels.
Menopausal Changes and Quality of Life

**Body Temperature and Time to Reach Sweating Threshold in Symptomatic and Asymptomatic Postmenopausal Women**

<table>
<thead>
<tr>
<th>Substance Administered</th>
<th>Symptomatic (n = 12)</th>
<th>Asymptomatic (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core body temperature (°C)</td>
<td>Placebo 37.1 ± 0.07*</td>
<td>37.4 ± 0.05†</td>
</tr>
<tr>
<td></td>
<td>Clonidine 37.3 ± 0.09</td>
<td>37.2 ± 0.03</td>
</tr>
<tr>
<td>Skin temperature (°C)</td>
<td>Placebo 36.0 ± 0.2</td>
<td>36.5 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>Clonidine 36.2 ± 0.2</td>
<td>36.5 ± 0.2</td>
</tr>
<tr>
<td>Time to sweating threshold (min)</td>
<td>Placebo 84.7 ± 9.1*</td>
<td>130.4 ± 9.9</td>
</tr>
<tr>
<td></td>
<td>Clonidine 132.0 ± 10.6*</td>
<td>149.4 ± 10.2</td>
</tr>
</tbody>
</table>

*P < .05 vs asymptomatic women; †P < .05 vs clonidine.

- This study sought to determine the effects of clonidine on the sweating threshold in postmenopausal women with and without hot flushes.
  - The study included 12 healthy postmenopausal women having at least 5 hot flushes per day and 7 postmenopausal women who had never had a hot flush.
- Two separate sessions were conducted 1 week apart, in which participants received either intravenous clonidine HCl (2 µg/kg of body weight) or placebo, followed by body heating (room temperature was first maintained at 23°C for 30 minutes, then was raised to 26°C and two 40 × 60 cm circulating water pads at 42°C were placed on the subject’s torso).
- This slide shows data obtained at the sweating threshold.
  - With placebo, core body temperature at the sweating threshold was significantly lower in the symptomatic women than in the asymptomatic women (P < .05).
  - Clonidine significantly increased the sweating threshold in the symptomatic women (P < .01) but decreased it in the asymptomatic women (P < .05).
  - No significant effects were seen on skin temperature.
  - With placebo, the sweating threshold was reached more rapidly (P < .01) in the symptomatic women compared with the asymptomatic women. Clonidine prolonged the time to the sweating threshold in all women; however, this prolongation was only statistically significant (P < .001) in the symptomatic women.
- These findings support the hypothesis that elevated brain levels of norepinephrine decrease the sweating threshold in symptomatic postmenopausal women (but not in asymptomatic women), thereby contributing to the initiation of hot flushes.

Sweat Rates in Symptomatic and Asymptomatic Postmenopausal Women During Body Heating*

- Room temperature increased from 23°C to 26°C and subjects' torsos were covered with 2 circulating water pads at 42°C.
- *P < .05.

- The previous slide showed a lower sweating threshold in symptomatic women compared with asymptomatic women, which may contribute to the initiation of hot flushes.
- These data from the same study further illustrate the difference between symptomatic and asymptomatic women. During the 10-minute period after subjects reached the sweating threshold, sweat rates were significantly higher in the symptomatic women than the asymptomatic women from minutes 2 through 4 (*P < .05*).
Menopausal Changes and Quality of Life

Reduction in Mean Daily Number of Hot Flushes with HT

Women’s HOPE Study (n = 241†)

*Adjusted for baseline.
Mean hot flushes at baseline = 12.3 (range 11.3–13.8); †Efficacy-evaluable population included women who recorded taking study medication and had at least 7 moderate-to-severe flushes/week or at least 50 flushes per week at baseline.

- These data are from the Women’s HOPE study, a randomized, double-blind, placebo-controlled trial that evaluated the safety and efficacy of standard and lower-than-standard doses of CEE and CEE/MPA.
- The 241 postmenopausal women included in this efficacy-evaluable analysis had reported at least 7 moderate-to-severe hot flushes on each of the last 7 days of baseline screening or at least 50 total hot flushes during the last 7 days of baseline screening.
- This graph depicts mean number of hot flushes over a 12-week period for women given unopposed CEE (0.625, 0.45, or 0.3 mg/d), CEE with MPA (0.625/2.5, 0.45/2.5, 0.45/1.5, or 0.3/1.5 mg/d), or placebo. Data for unopposed CEE groups are shown on the left, and CEE/MPA data are shown on the right.
- All groups, including placebo, experienced a statistically significant decrease from baseline in mean number of hot flushes (P < .01). This effect was seen in the first week in all active treatment groups, except the CEE 0.3/MPA 1.5 group, which experienced a significant decrease (P < .001) by the end of the second week. By the second or third week, the mean daily number of hot flushes in each of the CEE and CEE/MPA groups was significantly lower than the mean daily number of hot flushes in the placebo group (P < .001).
- Thus, all of the doses of CEE alone or CEE/MPA examined in this study provided significant symptom relief within the first few weeks of use.
- The graph on the right also shows that the reduction in number of hot flushes was comparable in all CEE/MPA groups.
- The results also suggest that the addition of MPA to lower doses of CEE may enhance the relief of vasomotor symptoms seen with CEE alone.

In this study, highly symptomatic women (N = 281) were randomized to treatment for 12 weeks with three different doses of 10-component synthetic conjugated estrogens (0.3, 0.625, and 1.25 mg) or placebo.

- All of the women were experiencing at least 7 moderate-to-severe hot flushes per day, or 50 moderate-to-severe hot flushes per week.
- Patients ranged in age from 26 to 65 years, with a mean age of 51.1 years.

At each of the time points, there were significant reductions in the frequency and severity of hot flushes with all 3 different dosages compared with placebo ($P < .05$ for all).

Treatment with 10-component synthetic conjugated estrogens were well tolerated, with no difference in the incidence of treatment-related adverse events between active treatment and placebo.
Position Statement on Treatment of Vasomotor Symptoms

North American Menopause Society

- The gold standard for moderate-to-severe vasomotor symptoms remains HT
- For mild vasomotor symptoms, lifestyle changes alone or combined with a nonprescription remedy can be considered
  - However, due to inconclusive efficacy data, this was not a consensus recommendation


- In response to the need to define standards of clinical practice in North America, the North American Menopause Society published an evidence-based position statement regarding the treatment of vasomotor symptoms.
- Recommendations for moderate-to-severe vasomotor symptoms
  - Systemic HT remains the gold standard in women without contraindications.
  - Oral contraceptives are an option for perimenopausal women, especially those needing contraception.
- Recommendations for mild vasomotor symptoms
  - Lifestyle changes alone or combined with a nonprescription remedy (eg, dietary isoflavones, black cohosh, or vitamin E) can be considered.
    - However, due to inconclusive efficacy data, this was not a consensus recommendation.
  - It is not known if isoflavones can be safely consumed by women with breast cancer.
Quality of Life, Menopausal Changes, and Hormone Therapy

Section 2b:
Sleep Quality
Menopausal Changes and Quality of Life

Unopposed Estrogen Improves Sleep

- Decreases the frequency of
  - Night sweats\(^1-4\)
  - Periods of wakefulness during the night\(^3,4\)
- Reduces sleep latency\(^1,2\)
- Improves sleep in menopausal women with insomnia, even in the absence of vasomotor symptoms\(^4\)
- Increases the percentage of REM sleep\(^1,5\)


- Studies have shown that unopposed E improves sleep quality\(^1-5\)
- Not only is there an increase in REM sleep with unopposed E,\(^1,5\) but night sweats\(^1,4\), sleep disturbances (waking episodes)\(^3,4\), and sleep latency (the time required to fall asleep)\(^1,2\) are also reduced.
- Unopposed E also improved sleep for women who did not report vasomotor symptoms\(^4\).
Effect of Unopposed Estrogen on Sleep Quality
Ages 45 to 60 Years

Mean Number of Occurrences

Mean Number of Hot Flushes per 24 Hours
Mean Number of Hot Flushes With Awakenings per Night

*P < .01 compared with baseline.
n = 7; treatment was CEE 0.625 mg for 27 days.

- Seven postmenopausal women complaining of sleep disruptions and/or hot flushes participated in this single-blind (investigators were aware of treatment group, but participants were not) pilot study.
- Participants were given estrogen for 4 weeks; their sleep was monitored in a sleep laboratory. Pretreatment baseline measurements provided placebo data.
- Unopposed E decreased the mean number of hot flushes and also decreased the number of hot flushes associated with awakenings.
- Unopposed E also reduced cyclic alternating patterns of sleep (CAPS), and improved sleep efficiency. The CAPS rate reduction indicates an overall improvement in sleep quality.
Menopausal Changes and Quality of Life

Percentage of Women Using Alternative Therapies to Improve Sleep

<table>
<thead>
<tr>
<th>Trouble Sleeping</th>
<th>Any Alternative Therapy</th>
<th>Body Work (Massage)</th>
<th>Soy Products</th>
<th>Herbal or Homeopathic</th>
<th>Stress Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>20%</td>
<td>2%</td>
<td>9%</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>Moderate</td>
<td>27%</td>
<td>5%</td>
<td>9%</td>
<td>17%</td>
<td>11%</td>
</tr>
<tr>
<td>Severe</td>
<td>33%</td>
<td>7%</td>
<td>8%</td>
<td>21%</td>
<td>16%</td>
</tr>
</tbody>
</table>

n = 886; age range 45–65 years; 19% of women surveyed were using HT and some form of alternative therapy.

- In this survey, 886 women between the ages of 45 and 65 years were questioned about their use of alternative therapies for some symptoms that occur during the menopause, including trouble sleeping. Among respondents, 71% were classified as postmenopausal (having no periods for 12 months, post-hysterectomy, or taking HT), 8% were perimenopausal (having irregular periods, but at least one period within 12 months, and not taking HT), and 21% were considered premenopausal (still having regular periods and not using HT).

- Investigators asked about a limited number of menopause symptoms, and collected data in such a way as to avoid linking use of alternative therapies with symptoms.

- Approximately one-third of women who were having moderate to severe trouble sleeping used some forms(s) of alternative therapy. The most commonly reported therapies for these women were herbal or homeopathic remedies and stress management. For women reporting mild problems sleeping, use of herbal/homeopathic remedies (10%), stress management (9%), and dietary soy products (9%) was almost equivalent.

- Overall, sleep disturbances were associated with a 4-fold increased use of body work (including massage), a 3-fold increase in use of stress management, and a 2-fold increase in use of dietary soy to improve sleep, compared with use by women who were not reporting trouble sleeping.

Quality of Life, Menopausal Changes, and Hormone Therapy

Section 2c: Urogenital Changes
Physiology of Vulvovaginal Changes: Structure and Histology

- Loss of collagen and adiposity in vulva
- Clitoral glans loses protective covering
- Vaginal surface thinner, less elastic; more friable


- Significant physiological changes occur to the female anatomy during menopause due to estrogen loss.
- The vulva loses most of its collagen and adipose tissue in response to estrogen loss. Oriba and Maibach showed that, when lipids in the stratum corneum are lost, the barrier function they provide is lost, and vulvar tissue loses its ability to retain water. It becomes flattened and thin. Glandular secretions also diminish.
- The prepuce of the clitoris atrophies, exposing the glans to irritation from clothing, prolonged sitting, and sexual contact.
- The vaginal surface becomes thinner, less elastic, and more friable. Fewer secretions are produced, and production is delayed longer during sexual stimulation.
Menopausal Changes and Quality of Life

Presenting Genital Symptoms and Physical Signs of Vaginal Atrophy

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs on Physical Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dryness</td>
<td>Pale, smooth, or shiny vaginal epithelium</td>
</tr>
<tr>
<td>Itching</td>
<td>Loss of elasticity or turgor of skin</td>
</tr>
<tr>
<td>Burning</td>
<td>Sparsity of pubic hair</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>Dryness of labia</td>
</tr>
<tr>
<td></td>
<td>Fusion of labia minora</td>
</tr>
<tr>
<td></td>
<td>Introital stenosis</td>
</tr>
<tr>
<td></td>
<td>Friable, unrugated epithelium</td>
</tr>
<tr>
<td>Burning leukorrhea</td>
<td>Pelvic organ prolapse</td>
</tr>
<tr>
<td>Vulvar pruritus</td>
<td>Rectocele</td>
</tr>
<tr>
<td>Feeling of pressure</td>
<td>Vulvar dermatoses</td>
</tr>
<tr>
<td>Yellow malodorous discharge</td>
<td>Vulvar lesions</td>
</tr>
<tr>
<td></td>
<td>Vulvar patch erythema</td>
</tr>
<tr>
<td></td>
<td>Petechiae of epithelium</td>
</tr>
</tbody>
</table>


- If sexual history taking uncovers bothersome symptoms and problems such as dyspareunia, physical findings such as vaginal atrophy may be confirmed during the physical exam.
- The presenting symptoms of vaginal atrophy are often dryness, itching, and burning. Other symptoms may include dyspareunia, burning leukorrhea, vulvar pruritus, feeling of pressure, or yellow malodorous discharge.¹

These images illustrate vaginal histologic changes that occur during the postmenopause, and the effect of unopposed E on these changes. The image on the left shows vaginal atrophy evidenced by obliteration of rugal folds and lack of a discernable basement membrane. After one month of unopposed E (image on the right), damage to the epithelial layer is reversed. Efficacy has been demonstrated with low-dose topical estrogen as well as systemic therapy.
In a longitudinal, population-based study of 438 women aged 45 to 55 years, Dennerstein et al\textsuperscript{1} found that the percentage of women reporting vaginal dryness increased progressively as women approached and passed through menopause.

In premenopause, only 3\% of women reported vaginal dryness compared with 25\% of women postmenopausal by 1 year and 47\% of women postmenopausal by 3 years.

Vulvovaginal atrophy and dyspareunia are often associated with menopause. Dyspareunia can be further described as being either superficial or deep. Superficial dyspareunia refers to pain around the entrance to the vagina, whereas deep dyspareunia refers to pain deeper within the vagina or pelvic area.¹

In this study of 285 peri- and postmenopausal women, Versi et al² found that the percentage of women showing both superficial dyspareunia and signs of vulvovaginal atrophy increased with menopausal age.

Among perimenopausal women, 15% reported superficial dyspareunia, but this number increased to 28% for postmenopausal women. There was no trend indicating an increase in prevalence of deep dyspareunia with menopausal age.

Additionally, 40% of sexually active women reported dyspareunia; however, the increase in vulvovaginal atrophy was more pronounced than that of dyspareunia.

In this preliminary report, Santen and colleagues evaluated low-dose estradiol regimens to determine the lowest dose that would effectively relieve urogenital symptoms without significantly increasing plasma estradiol levels.

The 7 participants were all ≥2 years postmenopausal with signs of urogenital atrophy. Participants completed a urogenital symptoms questionnaire to report subjective vaginal and urethral symptoms; vaginal and urethral cytology, and measurement of vaginal pH were among the objective measurements used to determine response to therapy. Additionally, clinician-observed improvement was also documented. Endometrial biopsy was performed to assess endometrial changes.

Measurements were obtained on Day 1 of treatment with either placebo or estradiol, and again after 3 weeks and 9 weeks (study Week 12) of treatment. The following doses of vaginally administered estradiol were evaluated: 1.25 μg, 2.5 μg, 5.0 μg, and 10.0 μg. Investigators reported data for the 10-μg dose only.

The figure above illustrates average total, vaginal, and urethral symptom severity scores. Compared with baseline, total symptom severity score and urethral symptom severity score both improved significantly by 12 weeks (P = .01), but not at 3 weeks. Vaginal symptom severity score did not differ significantly from baseline at any time.

At week 3 and again at week 9, vaginal pH scores were improved compared with baseline (P < .01). On vaginal cytology, superficial cells increased in all patients. Symptoms of urethral atrophy improved in all women receiving the 10-μg dose, and vaginal atrophy symptoms improved in 42% of women receiving this dose. Of the 22 symptoms reported at baseline, 82% improved by at least one grade by the end of the 12-week study.

The authors reported no endometrial stimulation after 12 weeks of therapy, and they estimated that 3% of vaginally administered estradiol was absorbed systemically.

Although this was a small, single-blind study and the results reported are preliminary, the authors conclude that 10 μg of vaginal estradiol administered twice weekly relieved urogenital symptoms and vaginal atrophy with only minimal influence on plasma estradiol levels.

This study evaluated the efficacy of both CEE and CEE plus MPA in relieving symptoms of vaginal atrophy in 2,673 women enrolled in the Women’s HOPE study.¹

Vaginal atrophy was assessed by vaginal maturation index (VMI), which was reported as the proportion of vaginal superficial cells, relative to the number of parabasal and intermediate cells, in a lateral vaginal wall smear.

The percentage of superficial cells was increased significantly from baseline at cycles 6 and 13 in all CEE and CEE/MPA groups (P < .001), but not in placebo.

Changes from baseline were significantly greater in the CEE 0.625 group compared with the CEE 0.625/MPA 2.5 group (P < .05), the CEE 0.45 group (P < .05), and the CEE 0.3 group (P < .001).

No differences in median changes in VMI were detected between the CEE 0.45 and the CEE 0.45/MPA 1.5 groups or between the CEE 0.3 and CEE 0.3/MPA 1.5 groups.

The values for the median change from baseline in VMI were similar in the CEE 0.625/MPA 2.5 and CEE 0.45/MPA 1.5 groups.

In summary, lower doses of CEE alone and CEE/MPA were effective in improving the VMI in postmenopausal women. There was no change in VMI in the placebo group.

Vaginal Lubricants and Moisturizers

- Multiple vaginal moisturizers and lubricants are available over the counter.
- Selection of product is based on individual preference.

- There are a variety of vaginal moisturizers and vaginal lubricants containing various ingredients available over the counter.
- Lubricants, in general, are thinner and dry more quickly than moisturizers. Both are used to protect the delicate vaginal tissue and facilitate penetration.
- Product selection is based on a woman’s individual preference.
Menopausal Changes and Quality of Life

HT and Urinary Incontinence: Conflicting Findings

- Diagnose cause of incontinence
  - Atrophic urethritis
  - Stress
  - Urge
- Check for irritative and atrophic factors
- Measurements must include subjective & objective modalities
- Vaginal estrogen superior to oral estrogen in most cases
- Progesterone may decrease action of estrogen

- There are three major types of incontinence:
  - Incontinence associated with atrophic urethritis is usually characterized by urgency and occasionally by a sense of scalding dysuria.¹
  - Stress incontinence is an involuntary loss of urine that occurs during physical activity, such as coughing, sneezing, laughing, or exercise.²
  - Urge incontinence involves a strong, sudden need to urinate immediately followed by a bladder contraction, resulting in an involuntary loss of urine.³
- The vagina should be inspected for signs of atrophic vaginitis, characterized by mucosal friability, petechiae, telangiectasia, or vaginal erosions.⁴
- When evaluating incontinence, measurements should include both subjective modalities (eg, voiding difficulties), as well as objective modalities (eg, urodynamic measurements).
- A recent Cochrane review concluded that treating urinary incontinence with E alone is associated with perceived improvement or cure compared with placebo, but that larger trials were needed.⁵ However, a recent WHI study found that both CEE alone and CEE+MPA increased risk of new onset urinary incontinence among continent women and worsened the characteristics among symptomatic women.⁶

Menopausal Changes and Quality of Life

HT and Self-Reported Urinary Incontinence

Nurses’ Health Study (N = 39,436)
- Elevated risk of incontinence with HT vs never-users
- Risk similar for E alone and E+P

HERS (N = 2,763)
- Incontinence improved by 26% with placebo vs 21% with E+P

WHI (N = 27,347)
- E-alone and E+P increased risk among asymptomatic women


- The purpose of the Nurses’ Health Study was to prospectively assess the relationship between HT and the development of urinary incontinence in 39,436 continent women aged 50-75 years who did not report leaking urine. They were followed for 4 years to identify incident cases of incontinence.
  - There were 5,060 incident cases of occasional incontinence (1-3 times/month) and 2,495 incident cases of frequent incontinence (leaking at least weekly)
  - The risk of incontinence was elevated among women taking postmenopausal HT vs those who were never-users
    - Oral E alone: RR = 1.54  95% CI = 1.44–1.65
    - Transdermal E alone: RR = 1.68  95% CI = 1.41–2.00
    - Oral E+P: RR = 1.34  95% CI = 1.24–1.44
    - Transdermal E+P: RR = 1.46  95% CI = 1.16–1.84
  - There was little risk after stopping HT (RR = 1.46; 95% CI = 1.06–1.23)
  - 10 years after stopping, the risk was identical to never users (RR = 1.02; 95% CI = 0.91–1.14)
- In the Heart and Estrogen/progesterin Replacement Study (HERS), the authors sought to determine whether HT improves the severity of urinary incontinence in 2,763 postmenopausal women (mean age, 67 ± 7 years).
  - Incontinence improved in 26% of the women assigned to placebo compared with 21% assigned to HT (P = .001).
  - 27% of the placebo group worsened compared with 39% of the hormone group (P = .001).
    - This difference was evident by 4 months of treatment and was observed for both urge and stress incontinence.
  - The number of incontinent episodes per week increased an average of 0.7 in the HT group and decreased by 0.1 in the placebo group (P < .001).
- In the Women’s Health Initiative study, menopausal HT increased the incidence of all types of incontinence at 1 year in women who were continent at baseline.

Efficacy of Low-dose Vaginal Estriol on Urogenital Symptoms

- 88 women with stress incontinence were treated with estriol (n = 44) or placebo (n = 44)
  - Estriol ovule (1 mg) once daily for 2 weeks, then 2 mg once weekly for a total of 6 months
- Vaginal pH, colposcopy, vaginal and urethral smears, and urodynamics were studied
- 68% subjective improvement in incontinence
- Statistical improvement in MUP, MUCP, and PTR

MUP = maximum urethral pressure; MUCP = mean maximum urethral closure; PTR = abdominal pressure transmission ratio.

- The purpose of this prospective, randomized, double-blind, placebo-controlled study\(^1\) was to assess the efficacy and safety of intravaginal estriol administration on urinary incontinence, urogenital atrophy, and recurrent urinary tract infections in postmenopausal women. Before starting therapy, all of the women presented symptoms of stress incontinence ranging from mild to severe.

- The study enrolled 88 women, who were randomly divided into 2 groups:
  - Intravaginal estriol ovules – 1 ovule (1 mg) once daily for 2 weeks followed by 2 ovules once weekly for a total of 6 months as maintenance therapy.
  - Inert placebo vaginal suppositories in a similar regimen.

- Urogenital symptomatology, urine cultures, colposcopic findings, urethral cytologic findings, urethral pressure profiles, and urethrocystometry were evaluated before and after 6 months of treatment.
  - The urethral pressure profile and urethrocystometry were evaluated using the Phoenix Plus videourodynamic machine. Urethral and intravesical pressures were measured in the supine position by a catheter equipped with a microtransducer two-way standard. Vesical filling was performed with saline solution at a constant speed of 50 mL/min and the urethral pressure profile was measured after vesical filling to 250 mL. By three reproducible urethral pressure profiles, the mean maximum urethral pressure (MUP), the mean maximum urethral closure (MUCP), and the mean functional urethral length (FUL) were calculated. Abdominal pressure transmission ratio (PTR) to the urethra was also calculated.

- After 6 months, 30 (68.2%) of the participants who received estriol registered subjective improvement of their incontinence (7 totally continent, 23 significantly improved), compared with only 7 (16%) in the placebo group (\(P < .01\)).

- In the treated participants, there were statistically significant increases in mean MUP, MUCP, and mean PTR in comparison with the control participants.

- Note that this is a controversial topic, as several studies have shown estrogen to have little or no effect on urinary stress incontinence and pelvic floor relaxation\(^2,3\); this topic requires further confirmation. A number of studies reporting no effect, such as the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial\(^3\), did not use urodynamics to assess outcomes.

Efficacy of Low-dose Vaginal Estriol on Urogenital Symptoms continued

<table>
<thead>
<tr>
<th>Variables</th>
<th>Treatment Group (n = 44)</th>
<th>Control Group (n = 44)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Treatment</td>
<td>After Treatment</td>
<td>Before Treatment</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>100%</td>
<td>20.5%</td>
<td>100%</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>86.4%</td>
<td>20.5%</td>
<td>84.1%</td>
</tr>
<tr>
<td>Urogenital atrophy</td>
<td>100%</td>
<td>27.3%</td>
<td>100%</td>
</tr>
<tr>
<td>Urodynamic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUP (cm H₂O)</td>
<td>50.82 ± 6.15</td>
<td>62.15 ± 8.64</td>
<td>52.35 ± 6.30</td>
</tr>
<tr>
<td>MUCP (cm H₂O)</td>
<td>45.25 ± 7.20</td>
<td>56.87 ± 9.23</td>
<td>44.77 ± 6.86</td>
</tr>
<tr>
<td>PTR (%)</td>
<td>72.52 ± 10.31</td>
<td>88.85 ± 9.66</td>
<td>70.75 ± 9.08</td>
</tr>
</tbody>
</table>

*P-value is comparison between the treatment and control groups.
MUP = maximum urethral pressure; MUCP = mean maximum urethral closure; PTR = abdominal pressure transmission ratio.

- Before starting therapy, all 88 women had presented with urogenital atrophy ranging from moderate to severe, and most (38 in the treatment group and 37 in the control group) reported symptoms of dyspareunia.
- After 6 months, vaginal dryness, dyspareunia, and urogenital atrophy improved in the estriol group compared with the placebo group.
- In the treated participants, there were statistically significant increases in mean MUP, MUCP, and mean PTR in comparison with the control participants.
  - Note that $P < .05$ is possibly significant for the urodynamic variables.
- As noted on the previous slide, this is a controversial topic, as several studies have shown estrogen to have little or no effect on urinary stress incontinence and pelvic floor relaxation$^{2,3}$; this topic requires further confirmation. A number of studies reporting no effect, such as the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial$^3$, did not use urodynamics to assess outcomes.

Quality of Life, Menopausal Changes, and Hormone Therapy

Section 2d: Sexual Well-Being
One of the difficulties of assessing sexual problems in the postmenopausal women is the barrier in communication between physicians and their patients.

A survey on physician-patient communication regarding sexual problems showed most women think the following:\(^1,^2:\)

- There is no medical treatment for their problem.
- Their physician would dismiss their problem.
- Their doctor would be embarrassed to even talk to them about sexual problems.

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Validated Inventories for Assessing Sexual Complaints

- Female Sexual Function Index (FSFI)¹
- Brief Index of Sexual Function for Women (BISF-W)²
- McCoy Female Sexual Questionnaire³
- Derogatis Sexual Function Inventory⁴
- Arizona Sexual Experience Scale⁵
- Personal Experience Questionnaire⁶

- M. Freedman, personal communication.

This slide provides a list of commonly used, validated, self-administered questionnaires for assessing sexual complaints:
- Female Sexual Function Index¹
- Brief Index of Sexual Functioning for Women²
- McCoy Female Sexuality Questionnaire³
- Derogatis Sexual Function Inventory⁴
- Arizona Sexual Experience Scale⁵
- Personal Experiences Questionnaire⁶
Two models of the sex response cycle have received attention in the literature. Masters and Johnson were among the early researchers to scientifically study the human sexual response cycle from a physiological standpoint.¹ They postulated that the sexual response cycle consisted of four successive phases: excitement, plateau, orgasm, and resolution.

In 1979, Kaplan proposed adding the aspect of desire as shown here.² This model is somewhat simplistic and does not factor in the more complex emotions involved in a woman’s sexual response.

More recently, an intimacy-based model of a women’s sexual response cycle has been proposed.³ This model reflects the key roles of emotional intimacy and sexual stimuli. Earlier models tended to neglect the importance of emotional intimacy.

Even in the presence of emotional intimacy and responsiveness, sexual arousal and desire, women can suffer a negative sexual outcome from factors such as chronic dyspareunia, partner dysfunction, insufficient sexual skills, or side effects of medication.

Sexual Response: Male vs Female
An estimated 20% to 43% of women report sexual dysfunction or complaints. The same risk factors associated with male erectile dysfunction (aging, hypertension, smoking, hypercholesterolemia) are associated with sexual dysfunction in women.

Just as sexual functioning is multifactorial, so is sexual dysfunction, combining biological, psychological, and interpersonal factors.

Female sexual dysfunction has a major impact on QOL and interpersonal relationships. It can be physically and emotionally distressing to women as well as socially disruptive.
• Age can have a profound effect on sexual activity in women.

• Findings from the National Health and Social Life Survey show a sharp increase in sexual inactivity around age 50 to 54 years, coincident with the average age of menopause.
Female Sexual Dysfunction

Definition and Classification*

- **I: Sexual desire disorders**
  - Hypoactive sexual desire disorder
  - Sexual aversion disorder

- **II: Sexual arousal disorders**
  - Genital arousal disorder
  - Subjective arousal disorder
  - Combined genital and subjective
  - Persistent arousal disorder

- **III: Orgasmic disorder**

- **IV: Sexual pain disorders**
  - Dyspareunia
  - Vaginismus

*International Consensus Development Conference on Female Sexual Dysfunction.

• Because sexual complaints are reported by nearly 50% of American women,¹ there is a need for comprehensive, up-to-date definitions for and classification of female sexual dysfunction.

• The 1998 International Consensus Development Conference on Female Sexual Dysfunction proposed four categories of sexual dysfunction:
  - Sexual desire disorders.
  - Sexual arousal disorder.
  - Orgasmic disorder.
  - Sexual pain disorders.

• The following revisions were recently made to these classifications in response to inaccuracies and limitations of existing definitions of female sexual dysfunction²
  - Subcategories were added to “sexual arousal disorder”
  - ”Noncoital sexual pain disorder” was removed from category IV

• The National Health and Social Life Survey found overall that 43% of women had complaints of sexual dysfunction compared with 31% of men.¹

• A subanalysis of sexual complaints for both men and women is shown here. Lack of interest in sex was the most frequently reported problem for women.² Other reported problems included:
  – Trouble lubricating.
  – Pain during sex.
  – Difficulty achieving orgasm.

• There are numerous contributions to consider when counseling a postmenopausal woman with sexual complaints:
  – There are biological/hormonal factors to consider; these include androgen and estrogen levels, medications she may be taking, and concomitant illness or fatigue.
  – Due to a history of disappointing sex, her complaints could be based on the expectation of a negative outcome.
  – There may be contextual factors to consider, such as a lack of privacy, safety, or emotional rapport.
  – Intrapersonal factors could be the cause of her complaints, including a history of trauma (sexual, physical, or medical), as well as negative emotions associated with sex (e.g., anxiety, fear, shame, and guilt).
  – There are also interpersonal factors, such as discord in the relationship or an absence of emotional intimacy.
  – There could also be a lack of appropriate stimuli from her partner.
• In order to further understand sexual dysfunction, it is necessary to have knowledge of both the biological and psychological risk factors involved.
• Biological risk factors include gender, age, and hormone levels as well as the presence of depression, cardiovascular disease, diabetes, alcohol abuse, or medication use.
• Psychosocial risk factors include such things as emotional and stress-related problems, a history of sexual abuse, and relationship conflict.
• Women are especially at risk for sexual dysfunction and lack of sexual satisfaction due to societal constraints and gender-role socialization.
The Massachusetts Women’s Health Study II was conducted to determine if menopausal status influences some aspects of sexual functioning.

Participants included 200 women between the ages of 51 and 61 years who were in menopausal transition and not using HT. As noted above, 39% were postmenopausal, 35% were premenopausal, and 26% were perimenopausal. All participants had partners, and none were surgically menopausal. Other baseline characteristics of participants are listed above on the left.

The Sexual Activity Questionnaire administered to participants evaluated several sexual function issues including satisfaction with current sexual relationship, desire, frequency of intercourse, and level of arousal compared with level at a younger age, difficulty reaching orgasm, and pain.

Several outcomes are listed above on the right. Mean score for sexual satisfaction was 23.3 (range of possible scores = 6 to 30), indicating that women were generally satisfied with their sexual relationships. Mean score for sexual desire was 10 (range = 0 to 20). On average, participants had intercourse on 58 days per year (slightly more often than once per week), and 39% reported less arousal compared with the levels experienced when they were in their 40’s. Sixty-three percent of the participants reported no difficulty reaching orgasm, and most (77.5%) did not experience pain during intercourse.

Overall, postmenopausal women reported a lower level of sexual desire compared with that of premenopausal women ($P < .05$). Also, peri- and postmenopausal women reported less arousal compared with levels experienced when they were in their 40s ($P < .05$ compared with premenopausal women).

Although some sexual function parameters are influenced by menopause, investigators concluded that health and other factors tended to have a larger effect.
Menopause status has a direct relationship to several aspects of sexual functioning.

- Sexual dysfunction was measured in HT nonusers from the Massachusetts Women’s Health Study II. Women were stratified into 3 groups: pre-, peri-, and postmenopausal.
- The postmenopausal women had: (1) significantly lower sexual desire; (2) belief that interest in sex declined with age; and (3) decreased arousal.
- Women were asked to compare their current level of arousal to when they were in their 40s. Results were rated on a 3-point scale:
  - More now than then
  - About the same
  - Less now than then
- About 45% of the postmenopausal women said their arousal was less than it was when they were in their 40s.

Evaluation of Postmenopausal Patients With Complaints of Sexual Dysfunction

Classes of Medications That May Interfere With Sexual Function

- Antihypertensive agents
- Antidepressant medications (eg, SSRIs)
- Chemotherapeutic agents
- Central nervous system agents
- Agents that affect hormones


- The clinical evaluation of postmenopausal patients with complaints of sexual dysfunction should include a medical/physiologic evaluation and a psychosocial/psychosexual assessment.1
- Numerous medications adversely affect sexual functioning—several drug classes with examples are shown here.
- In some cases, switching or adjusting medications may be all that is required to alleviate the problem.
Menopausal Changes and Quality of Life

Effect of Menopausal Transition on Parameters of Sexual Functioning

Cross-sectional Data Reported From a Longitudinal, Population-based Cohort of Australian Women, 45–55 Years of Age

- Dennerstein et al. found significant changes in sexual functioning in a prospective observational study of 438 Australian-born women ages 45 to 55 years.
- From a personal-experiences questionnaire, women reported decreases in sexual responsivity, decreases in sexual frequency, decreases in libido, increases in vaginal dyspareunia, and increases in partner problems.
- Longitudinal analysis showed a significant decline in sexual functioning with both age and menopausal transition.

\[ n = 438; \text{SPEQ} = \text{Shortened version of the Personal Experiences Questionnaire.} \]

\[ P < .05 \text{ for postmenopausal compared with perimenopausal women.} \]


\[ 1 \text{Dennerstein L, Dudley E, Burger H. Are changes in sexual functioning during midlife due to aging or menopause? Fertil Steril. 2001;76:456-460.} \]
Comparative Efficacy of Oral EE With or Without MT in Postmenopausal Women With Hypoactive Sexual Desire

- Double-blind, randomized, 16-week study
- EE + MT vs EE alone
- 218 women receiving HT, 20 centers
- Postmenopausal ≥6 months, age 40–65 years
- Adequate desire before menopause
- Onset of low desire with menopause
- No mood disorder

EE = esterified estrogens; MT = methyltestosterone.

- The purpose of this double-blind, randomized, 16-week study\(^1\) was to examine the effect of oral EE with and without MT on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire.
- The study included 218 healthy postmenopausal women who experienced hypoactive sexual interest or desire. The women met the following criteria:
  - Postmenopausal (natural or surgical) for ≥6 months
  - 40-65 years old
  - History of adequate sexual interest before the onset of menopause
  - Had received the equivalent of 0.625 mg CEE for ≥3 months
  - In a stable, monogamous, heterosexual relationship
  - No overt mood disorders
- Participants were randomized to the combination of EE + MT (0.625 mg + 1.25 mg; n = 107) or EE alone (n = 111) for 4 months.
- The Brief Index of Sexual Functioning for Women (BISF-W) and the Sexual Interest Questionnaire (SIQ) were administered at baseline and after 4, 8, 12, and 16 weeks of treatment.
  - The SIQ is a unidimensional scale that measures desire and sexual responsiveness.
  - The BISF-W is a 22-item, validated instrument to measure sexual functioning and satisfaction.

Comparative Efficacy of Oral EE With or Without MT in Postmenopausal Women With Hypoactive Sexual Desire continued

Mean Change in Sexual Desire Scores

- This graph depicts the mean change in sexual desire scores, as measured by item 1 of the Sexual Interest Questionnaire (SIQ), for women receiving EE alone and those receiving EE + MT.
- Improvements in sexual desire were seen in both groups as early as Week 4. However, the combination of EE + MT led to greater improvements compared with EE alone, with the treatment difference reaching statistical significance at Week 16 ($P < .02$).

Comparative Efficacy of Oral EE With or Without MT in Postmenopausal Women With Hypoactive Sexual Desire

Results

- Also improved sexual interest and responsiveness for EE + MT (3.29 ± 5.5) vs EE (1.28 ± 4.65; \( P = .002 \))
- Significant association between changes in women’s sexual interest and bioavailable testosterone


- In addition to improving sexual desire, as demonstrated on the previous slide, the authors found that the combination of EE + MT also improved sexual interest and responsiveness compared with EE alone (\( P = .002 \)).
- The authors concluded that the improved sexual functioning in women receiving EE + MT might be due to increased circulating levels of testosterone, as there was a significant association between changes in sexual interest and bioavailable testosterone.

Effect of Testosterone on Low Libido

- 75 women who had undergone bilateral salpingo-oophorectomy and hysterectomy
  - All treated with CEE
- Randomized to transdermal testosterone 150 mg/d or 300 mg/d, or placebo
- Testosterone therapy increased scores for frequency of sexual activity and pleasure-orgasm
- Testosterone/CEE increased serum concentrations of testosterone to normal range


- Participants in this randomized, placebo-controlled, crossover trial by Shifren et al\(^1\) were already receiving at least 0.625 mg/d of oral CEE at baseline.
- All 75 participants had undergone bilateral salpingo-oophorectomy and hysterectomy, and had evidence of impaired sexual function. Subjects received (in random order) either placebo, transdermal testosterone (150 mg/d), or transdermal testosterone (300 mg/d) for 12 weeks each.\(^1\)
- Despite an appreciable placebo response, the 300 mg/d testosterone dose resulted in increases in scores for frequency of sexual activity and pleasure-orgasm in the Brief Index of Sexual Functioning ($P = .03$ compared with placebo).
- At the higher dose, the percentages of women who had sexual fantasies, masturbated, or engaged in sexual intercourse at least once a week increased two to three times from baseline.
- Treatment with the higher dose of testosterone improved sexual function and psychological well-being better than placebo. Testosterone therapy may be useful for surgically menopausal women, who often complain of decreased sexual desire or libido.

• The purpose of this randomized, double-blind, multicenter study was to compare the effect of a testosterone transdermal patch (TTP) vs placebo on sexual function in surgically menopausal women with hypoactive sexual desire disorder.
  – 562 surgically menopausal women on stable doses of oral or transdermal estrogen were enrolled (mean age, 49 years; mean time since oophorectomy, 8.5 years).
  – Patients were randomized to TTP (300 mcg/day by patch twice weekly) or placebo for 24 weeks; all patients continued their previous estrogen therapy.
• Overall, TTP significantly improved sexual functioning; these improvements were seen as early as 4 weeks.
  – Sexual desire was assessed from the Profile of Female Sexual Function instrument (PFSF).
    • Statistically significant improvements in sexual desire were observed at Weeks 4, 12, and 24.
    • As shown on this slide, at 24 weeks there was a statistically significant 56% improvement in sexual desire with TTP compared with 29% in the placebo group ($P = .0006$).
  – Total satisfying sexual activity was assessed with the Sexual Activity Log.
    • There were statistically significant increases in total satisfying sexual activity at Weeks 5–8 and were sustained through Weeks 21–24.
  – Distress was measured by the Personal Distress Scale (PDS).
    • Statistically significant decreases in personal distress were observed at Weeks 4, 8, 12, and 24.
• Please note that TTP is not FDA approved for the treatment of hypoactive sexual desire disorder in postmenopausal women.

Nachtigall L. Presented at NAMS 15th Annual Meeting; October 7, 2004; Washington, DC. Personal communication.
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  - At 24 weeks there was a statistically significant 56% improvement in sexual desire with TTP compared with 29% in the placebo group ($P = .0006$).
  - This slide shows some of the data from other PFSF domains. Every domain improves significantly with TTP compared with placebo.

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Overall, TTP significantly improved sexual functioning; these improvements were seen as early as 4 weeks.

As shown on this side, the adverse event profile was similar between the placebo and TTP groups.

- There were small numbers of dropouts due to adverse events; this was consistent between the treatment groups.
- There were small numbers of serious AEs, and only 2 cases were possibly related to study drug: TIA and flushing, tachycardia, chest pain, sweating, diarrhea.
- Most of the application site reactions were mild; 13 women in the placebo group and 9 in the testosterone group discontinued treatment for this reason.
- The risk of a patient experiencing at least 1 type of androgenic AE was lower in the testosterone group vs placebo (12.7% vs 15.8%). Most of these events were mild, and only 3 in the testosterone group and 1 in placebo discontinued treatment.

Please note that TTP is not FDA approved for the treatment of hypoactive sexual desire disorder in postmenopausal women.

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**300-mcg Testosterone Transdermal Patch: Similar Adverse Event Rate to Placebo**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Placebo (n = 279)</th>
<th>TTP (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any AEs</td>
<td>79.6</td>
<td>77.7</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Withdrawals due to AEs</td>
<td>6.8</td>
<td>8.5</td>
</tr>
</tbody>
</table>

**AEs of special interest**

- **Application site reaction**: 39.1 | 31.1
- **Upper respiratory infection**: 9.3 | 9.9
- **Headache**: 7.5 | 9.9
- **Acne**: 6.1 | 6.0
- **Alopecia**: 3.2 | 3.2
- **Hirsutism**: 6.5 | 5.7
- **Voice deepening**: 2.9 | 2.5
- **Breast tenderness**: 2.5 | 2.5
- **Hot flushes**: 2.2 | 1.8

Possible Dose-Related Adverse Effects With Testosterone Treatment

- Hirsutism and acne
- Voice changes
- Lipid and cardiovascular changes
- Clitoromegaly


- Women treated with testosterone should be observed for possible adverse effects, including signs of virilization (deepening of the voice, hirsutism, acne, and clitoromegaly) and lipid changes.
Princeton Consensus Statement on Female Androgen Insufficiency

- Female androgen insufficiency consists of a pattern of clinical symptoms in the presence of
  - Decreased bioavailable testosterone
  - Normal estrogen status
  - Clinical symptoms
    - Impaired sexual function
    - Mood alterations
    - Diminished energy and well-being


- Androgen therapy has frequently been proposed to ameliorate arousal and desire dysfunction in postmenopausal women.
- An international consensus conference on androgen deficiency in women was convened in Princeton, New Jersey, on June 28 and 29, 2001, under the auspices of the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School. The conference included participants representing epidemiology, endocrinology, pharmacology, obstetrics and gynecology, urology, psychology, psychiatry, and women’s health.
- Female androgen deficiency was defined as “consisting of a pattern of clinical symptoms in the presence of decreased bioavailable testosterone and normal estrogen status”.1

Princeton Consensus Statement on Female Androgen Insufficiency continued

◆ Female androgen deficiency may occur from the decline in androgen levels with age

◆ Androgen insufficiency should only be diagnosed in women who are adequately estrogenized because of the strong association of estrogen levels and sexual function

◆ Large, randomized, controlled trials are needed to determine normal levels of androgen in women of different ages and reproductive states


• On the basis of the evidence presented, the following consensus statements were promulgated:\(^1\):
  – Female androgen deficiency may occur from the decline in androgen levels with age.
  – Androgen insufficiency should only be diagnosed in women who are adequately estrogenized.
  – Androgen therapies (eg, testosterone supplements, 17β-hydroxysteroid dehydrogenase) are not currently approved for treatment of sexual dysfunction, and their safety and efficacy have not been established.

### Treatment Options for Sexual Dysfunction/Complaints

- **Sex therapy/couples’ therapy**
- **Hormone therapy**
  - Topical estrogen
  - Systemic estrogen
  - Estrogen ± progestin
  - Estrogen/androgen*
  - Androgens*
- **Lubricants/moisturizers**

*Not FDA approved for treatment of sexual complaints.

- The major treatments for female sexual dysfunction include therapy, hormone replacement therapy, and nonhormonal therapies.
- Despite the presence or absence of organic disease, psychological counseling can help women with emotional and relational issues affecting sexual function. Counseling can build self-esteem, improve body image, and address partner issues. Depression and mood disorders should be treated appropriately, noting that antidepressants can have sexual side effects.
- Hormone replacement (estrogen and estrogen/progesterone) is often the most logical therapy for alleviation of female sexual dysfunction. Some women may also benefit from the addition of testosterone. Indications for testosterone replacement include premature ovarian failure, and symptomatic testosterone deficiency following surgical, natural, or chemotherapy-induced menopause.
- Women with vaginal dryness may benefit from the use of vaginal lubricants and moisturizers.
- Local administration of estrogen may also be an option. Vaginal creams and tablets containing estrogen have demonstrated efficacy for treating vaginal atrophy; the estradiol vaginal ring also has FDA approval for treatment of vaginal atrophy and lower urinary tract symptoms.

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Menopausal Changes and Quality of Life

Postmenopausal Sexual Health: Summary

- Sexual dysfunction affects many postmenopausal women
- Physicians and patients may be reluctant to discuss sexual issues
- Genital atrophy is a major consequence of estrogen deficiency
- HT is effective in preventing and reversing genital atrophy and associated dyspareunia

- Sexual problems in menopausal women are highly prevalent and have profound effects on mood, self-esteem, QOL, and interpersonal relationships.
- Unfortunately, both physicians and patients may be reluctant to discuss sexual issues.
- A major cause of female sexual dysfunction is genital atrophy, its symptoms, and consequences due to estrogen deficiency.
- HT is effective in preventing and reversing genital atrophy and its associated dyspareunia.
Quality of Life, Menopausal Changes, and Hormone Therapy

Section 2e:
Skin Changes
Menopausal Changes and Quality of Life

QOL Impact of Skin Appearance

◆ Preserving physical appearance confers psychological benefits¹
  – Physically attractive older women have better self-image than less attractive women²
  – Physically attractive women rate themselves more favorably with regard to mental, physical, and social well-being²

◆ Dermatologic conditions (eg, psoriasis) can negatively affect QOL³


• Physical appearance, especially of the face, is a powerful factor in human transactions. As a result, aging skin can have a negative impact on both physical and mental health.¹

• The loss of so-called “good looks” with advancing years is thought to be particularly damaging for women.¹

• A study by Graham and Kligman² compared two groups of older, age-matched women (aged 60 to 96 years) and used neutral observers to rate the physical attractiveness of the women. The individuals themselves filled out a questionnaire related to self-perceptions of their health, appearance, etc. The researchers found that physically attractive, older women had a better self-image than less attractive women. In addition, the physically attractive women rated themselves more favorably with respect to mental, physical, and social well-being.

• Due to its psychosocial role, skin can profoundly affect QOL. For example, skin problems such as acne or psoriasis have been shown to negatively impact QOL measures.³
Appearance of Skin: A Major and Costly Concern

- Natural, healthy appearance coveted by most women
- $36.6 billion in cosmetics and toiletries were sold to consumers in 2000\(^1\)
- In 2001, rhytidectomies ("facelifts") were the most common cosmetic procedure in adults \(\geq 51\) years old\(^2\)
- Total number of facelifts increased 74% from 1992 to 2001\(^3\)


- Most women covet a natural, healthy appearance, and to that end spent close to $40 billion in cosmetics and toiletries in 2000.\(^1\)
- In addition to cosmeceuticals, interest in facial cosmetic surgery is high. In 2001, eyelid surgeries, face lifts, and forehead lifts were the 3 most frequently performed cosmetic procedures in adults 51 years of age and older, with facelifts being the most common procedure.\(^2\)
- The trend toward choosing cosmetic procedures is increasing. Data from the American Society of Plastic Surgeons show a 74% increase in facelifts from 1992 to 2001.\(^3\)
Menopausal Changes and Quality of Life

The Physical Impact of Intrinsic Aging on Skin

- Altered barrier function of skin
- Increased rate of skin disorders, such as actinic keratoses and skin cancer
- Impaired wound healing
- Deterioration in physical appearance
- Decreased blood flow


- Factors that contribute to aging skin in women are categorized as extrinsic, intrinsic or chronological, and changes in skin that are exacerbated by the loss of estrogen at menopause.
- Extrinsic influences are mainly environmental factors, the most significant being sun exposure. Intrinsic aging refers to skin changes that result from largely unknown internal bodily and genetic factors associated with a person’s chronological age. In other words, intrinsic changes are “programmed changes” that occur naturally with age, including those associated with hormonal changes. Skin changes that occur following the loss of estrogen/menopause have been termed hormonal aging.
- With age there is a decline in the skin’s barrier function and wound-healing ability. Therefore, elderly skin has a higher propensity to tear or blister, and there is an increased rate of skin disorders such as actinic keratoses and contact dermatoses.
- In addition, there is an increased incidence of skin cancers both in sun-exposed and non–sun-exposed skin, although the non–sun-exposed skin tends toward far fewer malignant lesions.
- With age, there is a decrease in the immunologic responsiveness of skin and the thermoregulatory ability of skin. The latter may predispose older patients to hypothermia and heat stroke.
- Deterioration in appearance is an obvious physical manifestation of aging skin.
- Also, a 30% decrease in the cross-sectional area of dermal venules in aged skin and a 60% decrease in basal and peak cutaneous blood flow has been reported.

The structural changes that occur as skin ages include thinning, dryness, slight scaliness, fine wrinkling, laxity, hair color changes, hair loss, and decreased sweating.\(^1\,^2\)

- In the epidermis, there is flattening of the dermal-epidermal junction and a decrease in the density of melanocytes, resulting in irregular and mottled pigmentation.\(^2\)
- In the dermis, overall thickness decreases along with cellularity and vascularity.\(^1\) There are also decreases in dermal collagen, elastin, and proteoglycan content.
- Overall, aging skin undergoes an increase in dryness, changes in hair number and color, decreased collagen fiber content, decreased skin thickness, decreased glycosaminoglycans (and therefore decreased water-binding capacity), and a decrease in elasticity.

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The skin typically thins as people age. In the absence of photoaging, unexposed older skin can appear clear and almost transparent.

Thinning is due to cumulative changes in all layers of the skin, but is largely due to thinning and structural changes in the dermis. The aging dermis has fewer fibroblasts, which results in a decreased production of elastin, collagen, and the supportive glycosaminoglycans.1

The thinning of skin is also accompanied by a loss of integrity between the epidermis and the dermis due to flattening of the dermal-epidermal junction, making aging skin more susceptible to simple trauma and to shearing forces.1

Dyspigmentation or blotchiness of older aging skin occurs because of a decreased number of melanocytes. Melanocyte density decreases 10% to 20% per decade.2 These changes result in irregular, mottled pigmentation. Surprisingly, sun exposure does not accelerate the decline in melanocyte density. Although sun-exposed skin has a higher melanocyte density at all ages, the decline in melanocytes is similar in rate for both unexposed and exposed skin.

Skin Is Estrogen Responsive

- ERs have been identified in:
  - Epidermal keratinocytes
  - Dermal fibroblasts
  - Blood vessels
  - Hair follicles

- Both aromatase and 17β-hydroxysteroid dehydrogenase type I expressed in skin

- In order for a tissue to be considered estrogen responsive, the existence of ERs in the particular tissue needs to be established.
- Indeed, the skin contains ERs in the epidermal keratinocytes, dermal fibroblasts, blood vessels, and hair follicles. The density of ERs is highest in the genitalia, face, and lower limbs; this correlates to areas of the body where aging significantly affects skin parameters.
- In addition, both aromatase and 17β-hydroxysteroid dehydrogenase type I are expressed in skin. These enzymes are involved in the synthesis of biologically active estrogens. Due to the presence of these enzymes, the skin is probably an important site for peripheral estradiol formation in postmenopausal women.

Menopausal Changes and Quality of Life

Skin Collagen and Estrogen Loss

◆ Collagen loss is associated with decreased estrogen

– 30% of skin collagen is lost in the first 5 years after menopause

– Average rate of loss = 2.1% per postmenopausal year

*Women were monitored for up to 20 years postmenopause.

- Atrophy of the dermis after menopause is due to a decrease in dermal skin collagen content.
- There is evidence of an inverse relationship between skin collagen content and years since menopause, independent of a woman’s age.
- In early work, Brincat and colleagues reported as much as a 30% loss in collagen in the first 5 years after menopause.
- The average rate of collagen loss was determined to be 2.1% per postmenopausal year.

In this landmark study, Brincat and coworkers compared skin collagen content in 52 postmenopausal women (mean age, 50.5 years) who had been treated with estradiol and testosterone implants for 2 to 10 years with that in a group of postmenopausal women (mean age, 50.3 years) who had never received sex hormone therapy. Punch biopsy specimens of the skin, 3 mm in diameter, were taken from the thigh and hydroxyproline content was determined.

These data clearly show the decrease in skin collagen with time after menopause. In addition, this study demonstrated that HT can protect against the loss in collagen.

E+P Increases the Skin Collagen Content of Upper Arm of Postmenopausal Women

![Graph showing mean collagen fibers comparison between Placebo and E+P at baseline and 6 months](image)

E+P = valerate estradiol 2 mg/d for 21 d/mo combined with cyproterone acetate 1 mg/d for 10 d/mo.

*P < .05 versus baseline and placebo; bars represent standard deviations.


• An example of recent data regarding collagen content and E+P is shown here.

• Forty-one postmenopausal women who enrolled in this double-blind, placebo-controlled study were randomly allocated to receive either HT (2 mg valerate estradiol and 1 mg cyproterone acetate) or placebo for 6 months. Histologic analysis of skin biopsies from the medial part of the left arm (approximately 4 cm above the pleat of the elbow) demonstrated that collagen content of the left upper arm increased in the hormonal group but not in the placebo group. No average age was specified for the participants.1

• It has been reported elsewhere that collagen loss can be prevented when postmenopausal estrogen use is initiated early.2-4

• To date, of 11 clinical trials assessing the effect of HT on collagen levels, only 1 has failed to show a beneficial effect.5 The majority have demonstrated that deficiencies in skin collagen can be corrected by estrogen treatment. The only study that did not report a positive effect6 examined the effect of HT in very early menopausal women. Brincat3 has shown that estrogen only has a demonstrable effect when collagen levels are low, possibly explaining why no effect was seen in early menopausal women. The author suggests that postmenopausal skin changes, like bone changes, take time to progress to a measurable level.4

• In early work, Brincat and colleagues2 demonstrated that estrogen use can maintain premenopausal levels of collagen. Further, by preventing the loss of collagen, estrogens are of prophylactic value when initiated in the early postmenopausal years.3

A complete list of references for this slide can be found in the accompanying document titled "Menopausal Symptoms and QOL References."
Menopausal Changes and Quality of Life

HT Maintains Skin Thickness in Postmenopausal Women

- Consistent with clinical increases in collagen, studies have indicated that HT can significantly increase skin thickness. Data from a recent study of HT and skin thickness are shown here.

- This cross-sectional observational study was carried out at a menopause and gynecology outpatient clinic. A total of 84 women took part; 34 postmenopausal HT users (no age specified, but at least 1 year since last menses), 25 postmenopausal nonusers (no age specified, but at least 1 year since last menses), and 25 premenopausal controls. The HT preparations used varied by individual. Each volunteer was scanned using diagnostic ultrasound on the arm, and skin thickness measures were made from each scan by computerized image analysis.¹

- HT-induced increases in thickness were detected in the dermis²-⁴ but not the epidermis²-⁵

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Menopausal Changes and Quality of Life

Early Intervention With Estrogen Prevents Collagen Loss

- Deficiencies in skin collagen can be corrected by estrogen treatment\(^1,2\)
- Estrogens are of prophylactic value when initiated in the early postmenopausal years\(^2\)
- An increase in collagen with estrogen depends on the collagen content at the start of treatment\(^1,3\)


- Studies have shown that collagen loss can be prevented when postmenopausal estrogen use is initiated early\(^1-3\).
- To date, of 11 clinical trials assessing the effect of HT on collagen levels, only 1 has failed to show a beneficial effect\(^4\). The majority have demonstrated that deficiencies in skin collagen can be corrected by estrogen treatment. The only study that did not report a positive effect\(^4\) examined the effect of HT in very early menopausal women. Brincat\(^2\) has shown that estrogen only has a demonstrable effect when collagen levels are low, explaining why no effect was seen in early menopausal women. The author suggests that postmenopausal skin changes, like bone changes, take time to progress to a measurable level\(^3\).
- In early work, Brincat and colleagues\(^1\) demonstrated that estrogen use can maintain premenopausal levels of collagen. Further, by preventing the loss of collagen, estrogens are of prophylactic value when initiated in the early postmenopausal years\(^2\).

Summary: Skin Changes With Menopause

- **Skin is estrogen responsive**

- **Postmenopausal skin**
  - Atrophy, dryness, and wrinkles
  - Impaired wound healing

- **Hormone therapy**
  - Increases skin thickness
  - Enhances wound repair

- The skin has been shown to contain ERs in several areas, supporting the hypothesis that the skin is estrogen responsive, and an important site for peripheral estradiol formation in postmenopausal women.1,2

- Changes in skin that result from estrogen loss at menopause have been called climacteric skin aging3 or hormonal aging.4 The thinning and increased wrinkling of older skin is also associated with impaired wound healing and results in an increased frequency of chronic ulcers.

- Augmentation of estrogen levels may enhance wound healing properties in skin5 and increase skin thickness.6

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Quality of Life, Menopausal Changes, and Hormone Therapy

Section 2f:
Osteoporosis and QOL
Menopausal Changes and Quality of Life

Osteoporosis and QOL

◆ Osteoporosis-related events negatively impact QOL through
  – Incident vertebral fractures
  – Pain
  – Loss of mobility and independence

◆ QOL may impact development and outcome of osteoporosis through
  – Level of activity and exercise
  – Adherence to therapy
  – Healthy diet


• There is considerable evidence that the complications of osteoporosis (eg, incident vertebral fractures, pain, and loss of mobility and independence) have a negative impact on QOL.

• A woman with good global QOL may be more likely to impact the development and outcome of osteoporosis by exercising, eating a healthy diet, and being adherent to therapy.
Quality of Life, Menopausal Changes, and Hormone Therapy

Section 3:
Recent Evidence and Critical Review of QOL in Menopause
Global and Health-Related QOL

◆ Global QOL
  – “Sense of well-being” that is impacted by experience of symptoms but not solely determined by symptoms
  – Patient’s own subjective appraisal of overall life satisfaction/sense of well-being

◆ Health-related QOL
  – Patient’s perceptions of their physical, cognitive, and mental health


• In discussing the topic of QOL, a distinction needs to be made between global QOL and health-related QOL.
  – Global QOL refers to a sense of well-being that is impacted by the experience of symptoms, but is not solely determined by them; it is a subjective appraisal of life satisfaction.
    • For example, one person may objectively be experiencing severe symptoms but perceive their life as having excellent quality, while another person may be symptom-free but perceive their life to have poor quality.
  – Health-related QOL, on the other hand, specifically refers to a patient’s perceived physical and mental health over time.
Menopausal Changes and Quality of Life

Problems With QOL Construct

- Minimal definitional agreement
- Objective measurement difficult
- Current publications have oversimplified QOL as health status
- Cultural differences are often minimized or ignored


- Perceived QOL is difficult to define and measure because there is no universal agreement on what it is and how it can be quantified.
- QOL instruments based on a biomedical definition of QOL may actually assess a woman’s health status rather than QOL. The vast majority do not accurately assess a patient’s global sense of well-being.
HERS: QOL-Related Instruments

- Physical function—*Duke Activity Status Index*
- Energy/fatigue—*RAND scale*
- Mental health—*RAND Mental Health Inventory-5*
- Depressive symptoms—*Burnam screening scale*

None of these inventories are validated to measure global QOL


- To assess QOL, participants in the HERS study completed questionnaires that assessed functional capacity, emotional health, vitality, and depression.
  - Physical function was assessed using the 12-item Duke Activity Status Index.
  - Energy/fatigue was measured using a 4-item RAND scale.
  - Mental health was assessed by the RAND Mental Health Inventory, which is a 5-item scale that assesses anxiety and depression.
  - Depressive symptoms were measured using an 8-item scale developed by Burnam et al to screen for depression in the National Study of Medical Outcomes.
- None of the inventories used in HERS are validated to measure menopause-related QOL.

HERS and QOL

- Reported no benefits on QOL except for flushes
- Study considerations:
  - No sexual function included
  - No urogenital problems included
  - No skin aspects studied
  - Few vasomotor symptoms in older age group (mean age, 68 years old)
- For this age group, no true QOL issues were measured

HERS = Heart and Estrogen/progestin Replacement Study.

- The Heart and Estrogen/progestin Replacement Study (HERS)\(^1\)—a randomized, double-blind, placebo-controlled trial—was a secondary prevention trial, conducted to determine if estrogen plus progestin therapy changes the risk for second CHD events (fatal or nonfatal myocardial infarction) in postmenopausal women with established coronary disease.
- The study included 2,763 women with established CHD. On average, women enrolled in HERS were almost 68 years old and postmenopausal for 18 years.
- QOL parameters, such as sexual function, urogenital problems, and skin changes were not addressed in this trial. A separate subgroup analysis also did not address QOL issues.\(^2\) It should be noted that fewer vasomotor symptoms are generally reported for women in this age group. However, the other QOL factors mentioned are likely to occur in women of this age group, but these QOL issues were not measured or addressed.

• The HERS investigators also evaluated the effect of CEE/MPA on QOL measures among >400 postmenopausal women who reported hot flushes “all,” “most,” “a good bit,” or “some of the time.”
  – Note that the HERS population included primarily older women (mean age, 67 years) with documented coronary artery disease.
• All four QOL variables assessed (physical function, energy/fatigue, mental health, and depressive symptoms) were worse at baseline and throughout the 3-year follow-up period for women with hot flushes compared with asymptomatic women (P < .001; data not shown).
• As shown, mental health and depression scores were significantly improved over 3 years for HT users who reported hot flushes at baseline compared with symptomatic women in the placebo group.
• Over 3 years, physical function and energy/fatigue scores were not significantly different for symptomatic women in the HT group compared with those in the placebo group (data not shown).

Women’s Health Initiative (WHI): QOL Evaluation

<table>
<thead>
<tr>
<th><strong>Study Design</strong></th>
<th>Randomized, double-blind, placebo-controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects</strong></td>
<td>16,608 postmenopausal women 50 to 79 years old (mean age, 63.3 years)</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>CEE 0.625 mg + MPA 2.5 mg daily (n = 8506) or placebo (n = 8102)</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Assessments* made at baseline, 1 year (all women), and 3 years (subgroup of 1511 women)</td>
</tr>
</tbody>
</table>

*Assessments did not include any of the most commonly accepted, validated instruments for measuring menopause-related QOL.


- Recently, the WHI investigators reported findings on the effect of HT on health-related QOL in postmenopausal women of mean age 63.3 years.
- The WHI is the first randomized primary prevention trial of conjugated equine estrogens (CEE) and CEE/medroxyprogesterone acetate (MPA) evaluating the long-term risks and benefits of postmenopausal HT. The QOL study evaluated the relationship between use of HT and QOL-related variables.¹
- For the CEE/MPA arm of the WHI, 16,608 women aged 50 to 79 years with an intact uterus at baseline were randomized to CEE/MPA or placebo.
- Quality-of-life–related measures were evaluated at baseline and at 1 year in all participants, and again at 3 years in a subgroup of 1,511 women.²
- The QOL measures used by the WHI investigators did not include any of the most commonly accepted, validated instruments for assessing menopause-related QOL.

Menopausal Changes and Quality of Life

WHI: Surrogate Measures NOT Validated for Assessment of Menopause-Related QOL

- Health and functional status—RAND-36
- Depression—CES-D
- Sleep quality—WHI Insomnia Rating Scale
- Satisfaction with sexual functioning—1 item with 4-point response scale
- Cognitive functioning—mMMSE
- Menopausal symptoms—5-item checklist

CES-D = Center for Epidemiological Studies-Depression; mMMSE = modified Mini-Mental State Examination.

- Variables assessed in the WHI QOL study\(^1\) included health-related functioning, depression, sleep quality, sexual functioning, cognitive functioning, and menopausal symptoms.
- The RAND-36 survey was the primary instrument used to assess health and functional status. Although this instrument measures health-related functioning, it was not designed to assess some other variables (like sense of well-being) that help determine QOL in postmenopausal women.
- Depression was assessed by using the Center for Epidemiological Studies-Depression (CES-D) scale, which is a validated scale for evaluating depressive disorders. Sleep functioning, however, was assessed by using a 5-item scale developed for the WHI (the WHI Insomnia Rating Scale) that included questions relating to sleep initiation, maintenance, and quality, but did not address measurable variables such as duration of REM sleep.
- Sexual functioning was assessed with a single question with a 4-point response scale ranging from 1 (very unsatisfied) to 4 (very satisfied). Such a method is unlikely to adequately evaluate sexual functioning, which is both multidimensional and multifactorial. Additionally, marital status of the participants was not reported.
- The modified Mini-Mental State Examination (mMMSE) was administered to participants ≥65 years of age to assess cognitive functioning.
- The investigators assessed menopausal symptoms using 5 items from the symptom checklist that was used in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial.\(^2\) Symptoms assessed were hot flushes, night sweats, mood swings, forgetfulness, and difficulty concentrating. Each item had 4 response categories: none, mild, moderate, and severe. No assessment of vaginal symptoms (an indication for HT) was made.
- While some of the instruments used in this study are validated, none have been validated for the measurement of menopause-related QOL.

### WHI QOL: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CEE/MPA (n = 8506)</th>
<th>Placebo (n = 8102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate or severe vasomotor symptoms (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12.7</td>
<td>12.2</td>
</tr>
<tr>
<td>No</td>
<td>87.3</td>
<td>87.8</td>
</tr>
<tr>
<td>Number of years since menopause (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>17.1</td>
<td>16.3</td>
</tr>
<tr>
<td>5 to &lt;10 years</td>
<td>19.1</td>
<td>19.8</td>
</tr>
<tr>
<td>10 to &lt;15 years</td>
<td>21.0</td>
<td>20.9</td>
</tr>
<tr>
<td>≥15 years</td>
<td>42.8</td>
<td>43.0</td>
</tr>
</tbody>
</table>


- This table lists some additional baseline characteristics for women in the CEE/MPA and placebo groups. There were no significant differences between groups at baseline.
- Only 12% of the women in the WHI reported having moderate or severe vasomotor symptoms at baseline. In fact, the investigators noted in the methods section of their report that women with moderate or severe symptoms were discouraged from participating, although they were not excluded from the study.
- Number of years since menopause may also have been a factor that influenced outcome variables. Close to 2/3 of the women in the WHI (64%) had been postmenopausal for ≥10 years, and more than 80% had been postmenopausal for >5 years. Other studies have suggested that hot flushes are most common during the first 2 to 4 years of menopause.\(^2\) Early postmenopausal women with severe symptoms, who are most likely to initiate HT, were not well-represented in this study.

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WHI QOL: Study Considerations

- Unclear how “moderate” and “severe” vasomotor symptoms were defined
- Moderate or severe vasomotor symptoms were reported by only 12% of participants
- Vaginal symptoms were not evaluated
- Scores were high at baseline, limiting potential for therapy to increase them further
- 63% of the participants were ≥10 years postmenopausal
- No validated QOL tools used


• In interpreting the results of this study, some important factors should be taken into consideration:
  - The methods used to determine which women had moderate or severe vasomotor symptoms at baseline remains unclear.
  - At the start of the study, moderate or severe symptoms were reported by only 12% of the participants. Because vasomotor symptoms can have a significant effect of QOL, a study that includes more women with moderate or severe symptoms might have different outcomes.
  - No specific changes in vaginal symptoms, which are a known indication for HT, were assessed.
  - Scores on almost all of the QOL-related assessments were high at baseline for both placebo and treatment groups, which suggests that any therapeutic intervention would have been unlikely to increase these scores further.
  - Because the mean age of participants was 63 years and most of the women were at least 10 years postmenopausal, the study population does not represent early postmenopausal women who are more likely to have moderate to severe vasomotor symptoms, or other menopausal symptoms that may affect QOL.
  - While a number of accepted, validated tools exist for assessing QOL in postmenopausal women, the WHI investigators did not use any of them in their evaluation of QOL and HT.

• In summary, this analysis from the WHI did not address the question of whether HT improves QOL in women with moderate to severe menopausal symptoms. Similarly, it does not address how important a QOL benefit might be to symptomatic women and how QOL benefits may affect the overall risk-benefit assessment for HT in symptomatic women.

Menopausal Changes and Quality of Life

WHI and HERS QOL: Summary of Findings

- WHI\(^1\) found
  - No significant clinical QOL benefit on any of the outcomes, including general health, vitality, mental health, or sexual satisfaction
  - A statistically—but not clinically—significant benefit in sleep disturbance, physical functioning, and body pain at 1 year
- Findings were similar to HERS\(^2\)
  - No improvement in QOL was seen with HT use in older, asymptomatic, postmenopausal women utilizing instruments that have not been validated for menopause-related QOL*  

* Duke Activity Status Index, RAND scale, Burnam screening scale.

• In summary:
  - The report from the WHI on QOL benefits associated with HT use found no significant clinical QOL benefit on any of the QOL-related outcomes assessed, including general health, vitality, mental health and depressive symptoms, or satisfaction with sexual functioning.
  - The WHI investigators did find that HT use was associated with a statistically significant but not clinically significant benefit in sleep disturbance, physical functioning, and body pain at one year but not at 3 years.
• The results from this WHI\(^1\) analysis are comparable to findings from HERS\(^2\): no improvement in QOL was observed in older asymptomatic postmenopausal women using HT.

Conclusions

◆ QOL is a multi-dimensional construct
◆ QOL is more than presence/absence of symptoms
◆ QOL is useful as complement to symptom inventory
◆ UQOL and the Greene symptom profile are sound instruments to follow patient progress in clinical practice


• Quality of life, as it relates to menopausal women, is a multi-dimensional construct that includes physical health and functioning, emotional functioning, role limitations, and social functioning.
• Unfortunately, menopause-related QOL is commonly used to refer to only symptoms, such as severe hot flushes, night sweats, and vaginal dryness or pain. While these symptoms may negatively affect QOL and are improved with use of HT, it is important to recognize other more global aspects of QOL, including health status, life satisfaction, coping, and psychological functioning.
• Instruments that measure menopause-related QOL should be modern, reliable, and comparable to other validated instruments, and be responsive to changes in clinical symptoms or with different interventions. Simple use of a symptom checklist can introduce bias since patients may respond positively to symptoms on a checklist, but report declines if frequency or degree of bother is queried. Failure to use adequately validated assessment tools has been a common problem in menopause research.
• The Utian QOL scale is strongly based on perception of sense of well-being as distinct from menopausal symptoms, and is a valuable new tool for use in clinical research and practice.
• The ideal practical assessment in clinical practice would be to combine the UQOL with a validated menopause-related symptom inventory, such as the Greene Climacteric Scale.

Quality of Life, Menopausal Changes, and Hormone Therapy

Section 4:
Summary and Conclusions
HT and Menopausal Symptoms: Benefit/Risk Assessment

- Benefit is significant and consistent
  - Vasomotor symptom relief
  - Vulvovaginal atrophy
  - Skin changes
  - Indirect measures contributing to improved QOL
  - Decreased fractures

- Although the WHI study did not assess the benefits of HT use for menopausal and urogenital symptom relief, other studies have reported efficacy of HT for alleviating these symptoms and improving QOL.
Menopausal Changes and Quality of Life

HT and Menopausal Symptoms: Benefit/Risk Assessment continued

Assessment of risk in newly menopausal women

- Breast cancer—generally no increased relative risk observed with short-term use
- CHD—absolute risk is generally low in newly postmenopausal women, dependent on background rate and risk factors¹
- Must consider other potential risks (ie, DVT, PE, stroke, gallbladder)

For many newly menopausal women with moderate to severe symptoms, benefits will outweigh risks

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

• WHI findings did not suggest increased breast cancer risk associated with short-term HT use. In fact, Kaplan-Meier cumulative hazard functions for HT and placebo were comparable through the first 4 years of the trial. Additionally, the overall hazard ratio for risk of invasive breast cancer among HT users was 1.26 with a 95% nominal CI of 1.00 to 1.59, a finding that is not statistically significant.

• The absolute excess risk or benefit attributable to HT use was low for several reported WHI outcomes. WHI findings predict that over 1 year, 10,000 women taking CEE/MPA compared with placebo might be expected to experience 7 more coronary heart disease events, 8 more strokes, 8 more invasive breast cancers, 18 more pulmonary embolisms, 6 fewer colorectal cancers, 5 fewer hip fractures, and 44 fewer total fractures.
Menopausal Changes and Quality of Life

“I would embrace the aging process if I could lift my arms.”