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POSITION STATEMENT

Recommendations for estrogen and progestogen use in peri- and postmenopausal women: October 2004 position statement of The North American Menopause Society

Clinical use of estrogens and progestogens in women through and beyond the menopause transition continues to be a source of ongoing debate and confusion. The plethora of new clinical trial data regarding postmenopausal hormone therapy (HT) published over the last few years prompted The North American Menopause Society (NAMS) to develop reports on HT use in October 2002 (*Menopause* 2003;10:6-12) and September 2003 (*Menopause* 2003;10:497-506). The overall objective of these reports has been to make recommendations to both clinicians and the lay public about the appropriate role of HT for peri- and postmenopausal women. During 2004, the NAMS Board of Trustees convened a third HT Advisory Panel to develop a new report. As with the previous analyses, all relevant published evidence was considered. After approval from the 2003-2004 NAMS Board of Trustees, this position statement was released on October 6, 2004.

Panel Members

The 2004 HT Advisory Panel was composed of acknowledged clinical and research experts (both NAMS members and nonmembers) from relevant areas of menopause-related health care, including investigators from the Women's Health Initiative (WHI) and other key trials. All Panel members provided disclosure of interests during the past 2 years (presented at the end of the paper).

NAMS is grateful to the following individuals who served on the Panel, advising the NAMS Board of Trustees.

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Methodology

The 2004 Panel utilized the 2002 and 2003 reports as a starting point. A comprehensive literature search was conducted to identify all new papers published subsequent to the 2003 report. Panelists also submitted relevant papers. Considering all the evidence, Panelists were asked to provide their current view of all items of consensus and nonconsensus from the 2003 report. Each Panelist provided comments independently (ie, unaware of the responses of the other Panelists). All responses were collated in the NAMS Central Office into two lists: those with consensus and those without. All responses were distributed to the entire Panel. The Panel reviewed all of the responses by telephone conference call in an attempt to reach consensus. Further development of the report through multiple drafts was conducted through the Internet. The clinical recommendations indicate where consensus was achieved as well as where opinions differed. The latter clearly indicates some of the areas needing future research.

The primary clinical question was to differentiate the risk-benefit ratio of postmenopausal estrogen therapy (ET) and estrogen-progestogen therapy (EPT) for both disease prevention and treatment of specific menopause-related symptoms.

This position statement focuses on the use of government-approved prescription ET/EPT products available in the United States and Canada, not custom ET/EPT preparations, selective estrogen-receptor modulators (SERMs), or hormones available without a prescription (including phytoestrogens).

The position statement was reviewed and approved by the NAMS 2003-2004 Board of Trustees.

A list of the most current references regarding HT use is listed at the end of this report. The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented at the end of the reference list.

Introductory Comments

Because of absence of direct evidence in many circumstances, the Panel took into account all the variables in attempting to reach a general consensus on the current evidence-based role of ET/EPT use through the menopause transition and beyond. The ultimate purpose was to provide a direction for the current best practice of medicine. The recommendations that follow thus fall into two distinct categories, namely, those where there was a Panel consensus and those where consensus could not be reached.

Further, in developing recommendations, the Panel recognized that a woman's willingness to accept certain risks of ET/EPT will vary depending upon her individual situation such as when therapy is used to treat existing symptoms as opposed to long-term use to prevent a future problem that may or may not occur. Moreover, recognition had to be given to the fact that incidence of disease outcomes is also dependent on age. That is, ET/EPT is more likely to be acceptable for symptom reduction when therapy is planned to be short-term in a population that is younger with lower prevalence of risk outcomes. In contrast, the absolute risks of either use in older women or long-term therapy may make ET/EPT less acceptable. Moreover, premature hypoestrogenism (premature menopause, premature oophorectomy, or hypothalamic amenorrhea) may be associated with an increased risk of osteoporosis and cardiovascular disease based on epidemiologic observational studies. It therefore cannot be assumed that benefits and risks apply to all age ranges and all durations of therapy. All of these issues had to be taken into consideration by the Panel when developing its recommendations.

The Panel also recognized that a significant contributor to the confusion regarding the appropriate use of hormones after menopause is the actual time of onset of HT in relation to menopause (final menstrual period). There is a real difference between perimenopausal initiation for symptom relief and initiation of systemic

HT several years beyond menopause for non-symptom-related reasons. Moreover, a deficiency of randomized prospective study data was noted on the consequences of long-term use of HT on long-term disease outcomes when prescribed for symptom management.

The Panel was also faced, as so often happens in clinical practice, with the dilemma of defining and measuring the likely level of individual risk and its context in clinical decision making. Significant confusion has resulted from caregivers, researchers, and the media misinterpreting terms such as relative risk, absolute risk, or number needed to treat. Panelists recognized the confusion that can arise when discussing risk. Key risk-related definitions are as follows:

- Rate – The number of events per number of individuals per time interval.
  Example: 44 per 10,000 per year
- Relative Risk (RR) – Incidence in exposed divided by incidence in unexposed.
  Example: (44 per 10,000 per year) divided by (22 per 10,000 per year) = 2.0
- Attributable Risk (AR) – Incidence in exposed minus incidence in unexposed.
  Example: (44 per 10,000 per year) minus (22 per 10,000 per year) = 22 per 10,000 per year
- Number Needed to Treat (NNT) – Number of individuals who must be treated with an intervention for a specific period of time to prevent 1 bad outcome or result in 1 good outcome.
  Example: 1 divided by (incidence in exposed minus incidence in unexposed) = 1 divided by 0.0022 = 454

To many women, and even to health professionals, these numbers are often difficult to place in practical perspective. In recognition of this problem, the World Health Organization convened a panel of experts to develop standardized nomenclature for the description of risk for adverse events. The Council for International Organizations of Medical Sciences (CIOMS) task force released its report in 1998, providing a strict form of risk categorization to assist healthcare professionals and the public when interpreting risk. In this context, risks are considered as follows:

- ≤1/1,000 = rare
- ≤1/10,000 = very rare

The decision to use long-term HT for prevention of disease or enhancement of quality of life is in part a lifestyle choice, and needs to be considered both in the context of risk versus benefit of the HT itself, as well as in comparison to other therapies or lifestyle choices. Another effective way to present risk is to consider the known risk in comparison with other risks of other frequently used medications. Here a good example is the risk that can be attributable to aspirin use. Aspirin utilized for myocardial infarction (MI) prophylaxis is associated with an absolute increase in the risk of hemorrhagic stroke of 12/10,000 individuals. But benefit is considered to outweigh the risks with an absolute risk reduction of 137 MIs per 10,000, and 39 ischemic strokes per 10,000.

Many large randomized controlled trials (RCTs) and observational studies of postmenopausal hormonal therapies have been published in recent years. The Panel recognized that no trial is perfect, and no single trial should be used to make public health recommendations. Evidence-based medicine implies that recommendations should be limited only to the women for whom the studies are relevant. While this is ideal in principle, it is impossible in practice, given that there will never be adequate RCTs covering all populations, eventualities, drugs, and regimens. The practice of medicine is ultimately based on the interpretation at any one time of the entire body of evidence currently available.

Although the majority opinion was that it is not possible to extrapolate conclusions from the study of one compound, dose, and route of administration directly to another, in the absence of specific safety and efficacy evidence for any one specific compound, estrogens and progestogens must be considered as specific drug classes for purposes of therapeutic indications. The Panel thus acknowledged that estrogen and progesterone agonists share some common features and effects, and the only way to establish definitively the net clinical outcome for any given agent (alone or in combination) is through randomized clinical trials. In the absence of clinical trial data for each estrogen and progestogen, the clinical trial results for one agent probably should be generalized to all agents within the same family, especially with regard to adverse effects. Where data suggest differences, this will be reported in the consensus statements.

The same proviso also needs to be recognized with regard to dose, when a different dose of the same compound is reported in previous randomized controlled trials. In the WHI, for example, the dose of conjugated equine estrogens (CEE) was 0.625 mg per day, and currently lower doses are being prescribed in clinical practice, particularly for new starters.

Another area of confusion in clinical practice is the utilization of so-called “bioidentical hormones.” As a

result of concerns about safety issues with use of traditional HT, there is escalating utilization of alternatives to pharmaceutical dosage forms of estrogens and/or progestogens, including hormonal substances prepared in unique individualized dosage forms as gels, suppositories, sublingual tablets, oral tablets, etc. The scientific evidence for these forms of usage was also reviewed and it was concluded that the same proviso applies, namely, that in the absence of specific safety and efficacy data for any specific product, the generalized risk and benefit data will apply.

The Panel acknowledged that the potential absolute risks published thus far regarding ET/EPT are small, particularly for the ET arm of the WHI which provided evidence of considerable safety for 0.625 mg of CEE per day. The risks in the EPT arm were small and by CIOMS criteria rare, as are the likely benefits. For women younger than 50 or those at low risk for coronary heart disease (CHD), stroke, osteoporosis, breast cancer, or colon cancer, the absolute risk or benefit from ET or EPT is likely to be even smaller than demonstrated in WHI, although the relative risk may be similar. An individual risk profile is essential for every woman contemplating any regimen of EPT or ET. Women should be informed of known risks.

Finally, the Panel concluded that there is always a need to recognize that even in the absence of HT use, there is risk of development of all the diseases under consideration. In randomized controlled studies, that background inherent risk is represented by the rate of occurrence of the problem in the placebo group. Differences in relative risk between active drug and placebo can result from increased or decreased incidence of the event in either study group.

Recommendations for Clinical Practice: Areas of Consensus

The Panel agreed on the following clinical recommendations for postmenopausal hormone therapy.

- A strong recommendation was made for uniform and consistent terminology for menopause-related therapies, as indicated below:

ET	estrogen therapy
EPT	combined estrogen-progestogen therapy
HT	hormone therapy (encompassing both ET and EPT)
CC-EPT	continuous-combined estrogen-progestogen therapy (daily administration of both estrogen and progestogen)
CS-EPT	continuous-sequential estrogen-progestogen therapy (estrogen daily, with progestogen added on a set sequence)
systemic ET/EPT	preparations of ET or EPT that have a systemic, not solely vaginal, effect
local ET	preparations of ET that have a predominantly vaginal, not systemic, effect
progestogen	encompassing both progesterone and progestin

- Treatment of moderate to severe menopause symptoms (ie, vasomotor symptoms, sleep disruption from vasomotor symptoms) remains the primary indication for systemic ET and EPT. Every systemic ET/EPT product is government-approved for this indication.
- Every systemic and local ET/EPT product is government-approved for treating moderate to severe symptoms of vulvar and vaginal atrophy, such as vaginal dryness, dyspareunia, and atrophic vaginitis. When hormones are considered solely for this indication, local ET is generally recommended.
- The primary menopause-related indication for progestogen use is endometrial protection from unopposed ET. For all women with an intact uterus who are using estrogen therapy, clinicians are advised to prescribe adequate progestogen, in either a CC-EPT or CS-EPT regimen. Postmenopausal women without a uterus should not be prescribed a progestogen.
- Some women with an intact uterus who choose EPT may experience undesirable side effects from the progestogen component. However, there is insufficient evidence regarding endometrial safety to recommend use of long-cycle progestogen (ie, progestogen every 3-6 months for 12-14 days), a progestin-containing intrauterine device, or low-dose estrogen without progestogen as an alternative to standard EPT regimens. If utilizing any of these approaches, close surveillance of the endometrium is recommended, pending more definitive research. There are encouraging data on the efficacy of lower-dose therapies with reduction of side effects.
- ET and EPT did not reduce coronary heart disease (CHD) incidence in the WHI study. The role of ET/EPT in primary prevention of coronary heart disease (CHD) remains unclear when considered for peri- and early postmenopausal women if started early and continued for a number of years,

and needs further evaluation. Until that evidence is forthcoming, no ET or EPT regimen should be used for primary or secondary prevention of CHD.

- ET and EPT may increase the risk of ischemic stroke in postmenopausal women, but randomized controlled trial data are not consistent in this regard. The WHI EPT and ET arms demonstrated an increased risk while other large trials have not. The attributable absolute increased risk of stroke based on WHI data, under the CIOMS classification, falls into the rare category. The Panel concluded that no HT regimen should be used for primary stroke prevention. In women with a history of CHD or ischemic cerebrovascular disease, ET does not significantly influence stroke risk (secondary prevention). It is therefore important to reduce the risk of stroke regardless of HT use in these women.
- Breast cancer risk probably increases with EPT use beyond 5 years. In absolute terms, this increased risk is small in the WHI, being 4 to 6 additional invasive cancers per 10,000 women who use it for 5 or more years and of possible statistical significance. There is no mortality difference between EPT users and nonusers. Studies have not clarified whether the risk differs between continuous or sequential use of progestogen. Women in the estrogen-only (CEE) arm of the WHI demonstrated no increase in risk of breast cancer after an average of 6.8 years of use, and there was a nonsignificant trend toward reduction of breast cancer in women overall, with this trend strongest in women under age 60 (7 fewer breast cancers per 10,000 women using ET). Available evidence also suggests that estrogen alone for fewer than 5 years has little impact on breast cancer risk, although this question persists despite the WHI results. A large observational study has shown that 25 years of ET use is not associated with breast cancer risk. Specific subgroups may be affected in different ways. There are no substantial data reporting any increase in mortality with HT. EPT and, to a lesser extent, ET increase breast cell proliferation, breast pain, and mammographic density, and EPT may impede the diagnostic interpretation of mammograms. Evidence suggests that unopposed CEE is unlikely to have a significant effect on mammography.
- There is definitive evidence for ET and EPT efficacy in reducing risk for postmenopausal osteoporosis fracture. Many EPT and ET products are government-approved for prevention of postmenopausal osteoporosis (ie, loss of bone mineral density) through long-term treatment. For women who require drug therapy for osteoporosis risk reduction (including women at high risk of fracture in the next 5-10 years), ET/EPT can still be considered, weighing its risks and benefits as well as those of alternate therapies.
- Initiating EPT after age 65 should not be recommended for primary prevention of dementia as it may increase the risk of dementia during the ensuing 5 years in this population. The evidence is insufficient to either support or refute the efficacy or harm of ET/EPT for primary prevention of dementia when therapy is initiated during the menopause transition or early postmenopause. ET does not appear to convey direct benefit or harm for treatment of dementia due to Alzheimer's disease.
- The effects of ET/EPT on risk for breast cancer and osteoporotic fracture in perimenopausal women with moderate to severe menopause symptoms have not been established in randomized clinical trials. The findings from trials in different populations (eg, WHI) should, therefore, be extrapolated with caution.
- Data from studies such as the WHI and the Heart and Estrogen/progestin Replacement Study (HERS) should not necessarily be extrapolated to symptomatic postmenopausal women younger than 50 years of age who initiate HT as these women were not studied in these trials. WHI and HERS involved predominantly asymptomatic postmenopausal women aged 50 years and over (with mean ages of 63 and 67, respectively), the majority of whom were 10 years or more beyond menopause, and HERS was conducted solely among women with known coronary artery disease. The data should not be extrapolated to women experiencing premature menopause ($\leq$ 40 years of age) and initiating HT at that time.
- Premature menopause and premature ovarian failure are conditions associated with earlier onset of osteoporosis and CHD, but there are no clear data as to whether ET or EPT will reduce morbidity or mortality from these conditions. The benefit-risk ratio may be more favorable for younger women who initiate therapy at an early age.
- Use of ET and EPT should be consistent with treatment goals, benefits, and risks for the individual woman, taking into account symptoms and domains (eg, sexuality, sleep) that may have an impact on quality of life.
- Lower-than-standard doses of ET and EPT should be considered (ie, daily doses of 0.3 mg oral conjugated estrogens, 0.25-0.5 mg oral micronized 17β-

estradiol, 0.025 mg 17β-estradiol patch, or the equivalent). Many studies have demonstrated nearly equivalent vasomotor and vulvovaginal symptom relief and preservation of bone mineral density. However, some women may need additional local therapy for persistent vaginal symptoms. Lower ET and EPT doses are better tolerated and may have a better benefit-risk profile than standard doses. However, lower doses have not been tested in long-term trials.

- Nonoral routes of administration of ET/EPT may offer advantages and disadvantages, but the long-term benefit-risk ratio has not been demonstrated. Differences would be related to the role of the first-pass hepatic effect, the hormone concentrations in the blood achieved by a given route, and the biologic activity of active component ingredients. There is some evidence that transdermal 17β-estradiol may be associated with lower risk of deep venous thrombosis than oral estrogen and to a nonsignificant increase in CHD risk relative to placebo. A large observational study has shown similar increased risks for breast cancer with both oral and transdermal estrogens.
- Extended use of the lowest effective dose for treatment goals of ET or EPT is acceptable under the following circumstances, provided the woman is well aware of the potential risks and benefits and that there is clinical supervision.
  - For the woman for whom, in her opinion, benefits of menopause symptom relief outweigh risks, notably after failing an attempt to withdraw HT.
  - For women who are at high risk for osteoporotic fracture and also have moderate to severe menopause symptoms.
  - For further prevention of bone loss in women with established reduction in bone mass when alternate therapies are not appropriate for that woman, cause side effects, or when the outcomes of the extended use of alternate therapies are unknown.
- Prior to consideration of any therapeutic regimen, including ET/EPT, all women should have a complete health evaluation, including a comprehensive history, physical examination, and mammography. Other specific examinations, such as bone densitometry, should be considered on a case-by-case basis.
- The Panel concluded that with regard to duration of use, a general guiding principle should be for the lowest effective dose and time consistent with treatment goals. The Panel recognized that symptoms can recur when therapy is discontinued, independent of age and duration of ET/EPT use. The Panel agreed that the decision to continue HT should be individualized based on severity of symptoms, current risk-benefit considerations, and that the woman in consultation with her healthcare provider believes that continuation of therapy is warranted.
- The Panel concluded that an improvement in health-related quality of life (HQOL) can result through decreased menopause symptoms and possible elevation of mood that leads to a feeling of well-being. There is a lack of consensus on the impact of HT on overall quality of life (QOL) and HQOL in asymptomatic women. In part this is due to a lack of agreement regarding how best to obtain an appropriate evaluation of QOL in women after menopause, including the domains to be incorporated into any survey instruments. There is consensus that validated instruments for determining the impact of HT, or indeed any menopause-related therapy, on both overall QOL and HQOL should be incorporated into future studies.
- The Panel recognized that specific compounds, dose, and route of administration may have different outcomes. Nonetheless, in the absence of clinical trial data for each specific product, the clinical trial results for one agent should be generalized to all agents within the same family. This proviso also applies to the so-called bioidentical products.

Areas Where Insufficient or Conflicting Evidence Precludes Consensus

The Panel could not reach consensus on the following issues:

- *Is HT associated with early risk of CHD?* Panelists were divided on the issue as to whether there is definitive evidence for early increased risk of CHD with HT. For women similar to participants in the EPT arm of WHI (average age 63 years; range from 50 to 79 years), the WHI data are the best estimate of early harm from EPT. The WHI demonstrated that EPT may increase the risk of CHD during the first year of hormone use among generally healthy postmenopausal women in whom HT is initiated up to 20 or more years after menopause. The attributable risk in this instance, under the CIOMS classification, falls into the rare category. In addition, in HERS the increased risk of CHD in the first year due to EPT use was not observed in women who

were concomitantly using statin therapy. There is also evidence that early harm within the first year of use may not pertain to healthy postmenopausal women using ET/EPT for menopause symptom management. Increased risk of CHD in the first year was not observed in the ET arm of the WHI or any other ET-only study.

- *Should women who are doing well on long-term HT discontinue?* The Panelists were divided in opinion as to whether women on well established long-term therapy should be advised to discontinue at a specific duration of therapy. No recommendation is made, but there is agreement that the risks and benefits must be discussed on an individualized basis.
- *Is there a best way to discontinue HT?* When a decision is made to discontinue therapy, Panelists were divided in their recommendations regarding abrupt therapy cessation versus tapering the dose. Past history of severe symptoms may favor tapering, but no specific protocols could be recommended. Some gradually decrease the dose, while others lengthen the time between doses. Matrix transdermal HT patches can be trimmed to provide smaller doses. Current data are inadequate to suggest that one method is better than the other.
- *Does a continuous-combined EPT regimen (CC-EPT) have an effect different from continuous estrogen with sequential progestogen (CS-EPT)?* There are some indications that continuous progestogen in the dosages administered in studies such as WHI and HERS may be related to these trials' adverse breast cancer and cardiovascular outcomes, but conflicting data preclude a consensus.

Need for Future Research

On the basis of this review, the Panelists identified the following areas requiring further research.

Further study of the positive and negative effects of hormone therapy and the mechanisms by which they occur.

- Timing of initiation of HT relative to menopause with regard to cardiovascular, cognitive, and other health outcomes.
- Compare different formulations, regimens, and doses of both estrogens and progestogens.
- Determine whether HT should be based on manipulating endogenous hormone levels to premenopausal physiological concentrations rather than traditional single dosing for all women.
- Effects of endogenous levels of estradiol and/or estrone on benefit and/or risk.
- Determine whether the combination of ET/EPT and statin therapy could result in amelioration of potential CHD risks while preserving and possibly enhancing the benefits of HT.
- Long-term benefits/risks of ET and EPT, including different preparations, lower than standard dosages, and different regimens and routes of administration other than oral CEE and oral medroxyprogesterone acetate.
- Cause for the probable increase in stroke with ET, and for probable increased stroke, CHD, and breast cancer with EPT, in order to better understand the pathophysiology of these events, identify potential new treatments and ways to prevent their occurrence, and to identify a subgroup for whom HT would be less toxic.
- How to factor other health outcomes including QOL issues into the composite benefit-risk profile for ET/EPT.
- Health outcomes for HT over the long term (greater than 10 years).
- The benefit-risk profile of CS-EPT compared with CC-EPT or other HT regimens.
- Endometrial effects from alternatives to standard progestogen regimens, such as a progestin-releasing intrauterine device or long-cycle progestogen regimens.
- Long-term effects of ET/EPT on Alzheimer's disease risk and other forms of dementia, particularly when therapy is initiated before age 65.
- Short- and long-term effects of ET/EPT on neuropsychiatric disorders, such as Parkinson's disease, sleep apnea, depression, and schizophrenia.
- Effects of estrogen on mood and interactions of estrogens with mood-altering drugs.
- Long-term effects of ET/EPT on primary and secondary prevention and progression of ophthalmologic disorders, such as cataract and age-related macular degeneration.
- Health outcomes with ET/EPT for women experiencing early or premature menopause.
- Health outcomes with osteoporosis drugs over the long term (>10 years).
- Role of progestogens (eg, type, regimen) in breast cancer and cardiovascular risk.
- Efficacy of nonpharmacologic methods of managing hot flashes.
- The benefit-risk profile associated with an abrupt versus a tapering discontinuation of HT regimens, including impact on bone density in the first 2 or 3 years after termination.

- Effects of HT discontinuation on health outcomes influenced by HT.
- Role of estrogen and progestogen in postmenopausal women with underlying disease such as diabetes mellitus and hypertension to evaluate the effects of HT on the adverse events associated with the disease itself.
- How women can best be identified for risk of deep venous thrombosis and pulmonary embolism, as well as hypercoagulability responsiveness to estrogens in general.
- Identification of subgroups of women for whom ET or EPT might be beneficial with regard to cardiovascular, cognitive, and overall health outcomes.

Further study of the natural history of the menopause transition.

- Incidence and course of CHD, breast cancer, dementia, and other health outcomes in women experiencing early or premature menopause.
- Stricter evaluation of domains of QOL through the menopause transition.

Panelist Disclosures

Chair, Wulf H. Utian, MD, PhD, FACOG – Industry consulting fees: Berlex, Eli Lilly, Endeavor, GSK, Johnson & Johnson Pharmaceutical Research, Merck-Theramex, Pfizer, Roche, Warner Chilcott. Direct industry lecture fees: None disclosed. Industry research support: Amylin, 3M, Barr, Berlex, Bristol-Myers Squibb, Eli Lilly, Endeavor, Forest, Galen, GlaxoSmithKline, Neurocrine Biosciences, Novartis, Novo Nordisk, Organon, Pfizer, Pharmacia, Procter & Gamble, Roche, Sepracor, Solvay, Wyeth, Yamanouchi. *David F. Archer, MD* – Industry consulting fees: Agile Therapeutics, Berlex, Endeavor, Genentech, Galen, Lilly, Novo Nordisk, Organon, Schering, Solvay, Watson, Wyeth. Direct industry lecture fees: Berlex, Novo Nordisk, Solvay, Wyeth. Industry research support: Amylin, Barr, Berlex, Galen, Insmed, Lilly, Organon, Parke-Davis, Pharmacia, Solvay, Wyeth, Yamanouchi. *J. Chris Gallagher, MD* – Industry consulting fees: Aventis, Endeavor, Lilly, Pfizer, Roche, Wyeth. Direct industry lecture fees: Aventis, Organon, Pfizer, Roche, Wyeth. Industry research support: Endeavor, Organon, Pfizer, Roche, Solae, Wyeth. *Margery L.S. Gass, MD* – Industry consulting fees: Eli Lilly, GlaxoSmithKline, Merck, Procter & Gamble. Direct industry lecture fees: Aventis. Industry research support: Eli Lilly, GlaxoSmithKline, Merck, Pfizer, Procter & Gamble, Wyeth. *Morrie M. Gelfand, CM, MD* – Industry consulting fees: Procter & Gamble. Industry lecture fees: None disclosed. Industry research support: Pfizer. *Victor W. Henderson, MD, MS* – Industry consulting fees: None disclosed. Direct industry lecture fees: None disclosed. Industry research support: None disclosed. *Howard N. Hodis, MD* – Industry consulting fees: None disclosed. Direct industry lecture fees: None disclosed. Industry research support: None disclosed. *Rogerio A. Lobo, MD* – Industry consulting fees: Berlex, Merck, Novartis, Ortho-McNeil, Pfizer, Solvay, Wyeth. Direct industry lecture fees: None disclosed. Industry research support: Novartis, Wyeth. *Michael McClung, MD* – Industry consulting fees: Amgen, Aventis, Lilly, Merck, Novartis, NPS, Pfizer, Procter & Gamble, Roche, Wyeth. Direct industry lecture fees: Aventis, Merck. Industry research support: Amgen, Aventis, Lilly, Merck, Novartis, NPS, Pfizer, Procter & Gamble, Roche. *Robert Reid, MD* – Industry consulting fees: Lilly Canada. Direct industry lecture fees: Wyeth Canada. Industry research support: Wyeth. *Peter E. Schwartz, MD* – Industry consulting fees: None disclosed. Direct industry lecture fees: None disclosed. Industry research support: None disclosed. *Marcia L. Stefanick, PhD* – Industry consulting fees: None disclosed. Direct industry lecture fees: None disclosed. Industry research support: None disclosed. *Nancy Fugate Woods, PhD, RN, FAAN* – Industry consulting fees: None disclosed. Direct industry lecture fees: None disclosed. Industry research support: None disclosed.

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Barnabei VM, Grady D, Stovall DW, et al. Menopausal symptoms in older women and the effects of treatment with hormone therapy. *Obstet Gynecol* 2002;100:1209-1218. Level of evidence: I.

Nurses' Health Study

Grodstein F, Lifford K, Resnick NM, Curhan GC. Postmenopausal hormone therapy and risk of developing urinary incontinence. *Obstet Gynecol* 2004;103:254-260. Level of evidence: II-2.

Women's Health Initiative (WHI)

Anderson GL, Limacher M, Assaf AR, et al, for the Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial *JAMA* 2004;291:1701-1712. Level of evidence: I.

Hays J, Ockene JK, Brunner RL, et al, for the Women's Health Initiative Investigators. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med* 2003;348:1839-1854. Level of evidence: I.

Other Studies

Gordon S, Walsh BW, Ciaccia AV, Siddhanti S, Rosen AS, Plouffe L. Transition from estrogen-progestin to raloxifene in postmenopausal women: effect on vasomotor symptoms. *Obstet Gynecol* 2004;103:267-273. Level of evidence: I.

Salpeter SR, Walsh JME, Greyber E, Ormiston TM, Salpeter EE. Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis. *J Gen Intern Med* 2004;19:791-804. Level of evidence: III. Meta-analysis.

Utian WH, Janata JW, Kingsberg SA, Schluchter M, Hamilton JC. The Utian Quality of Life (UQOL) Scale: development and validation of an instrument to quantify quality of life through and beyond menopause. *Menopause* 2002;9:402-410. Level of evidence: II-3.

Review Articles

Bachmann GA, Leiblum SR. The impact of hormones on menopausal sexuality: a literature review. *Menopause* 2004;11:120-130. Level of evidence: review.

MacLennan A, Lester S, Moore V. Oral oestrogen replacement therapy versus placebo for hot flushes (Cochrane Review). *Cochrane Database Syst Rev* 2001;1:CD002978. Level of evidence: III.

Soares CN, Poitras JR, Prouty J. Effect of reproductive hormones and selective estrogen receptor modulators on mood during menopause. *Drugs Aging* 2003;20:85-100. Level of evidence: Review.

Epidemiology and Demographics

Brett KM, Reuben CA. Prevalence of estrogen or estrogen-progestin hormone therapy use. *Obstet Gynecol* 2003;102:1240-1249. Level of evidence: II-3.

Ettinger B, Grady D, Tosteson AN, Pressman A, Macer JL. Effect of the Women's Health Initiative on women's decisions to discontinue postmenopausal hormone therapy. *Obstet Gynecol* 2003;102:1225-1232. Level of evidence: Telephone survey.

Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and responses to recent evidence. *JAMA* 2004;291:47-53. Level of evidence: Database review.

Effects of Low-Dose Hormones

Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial

Archer DF, Dorin M, Lewis V, Schneider DL, Pickar JH. Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on endometrial bleeding. *Fertil Steril* 2001;75:1080-1087. Level of evidence: I.

Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH. Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. *JAMA* 2002;287:2668-2676. Level of evidence: I.

Pickar JH, Yeh I-T, Wheeler JE, Cunnane MF, Speroff L. Endometrial effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate: two-year substudy results. *Fertil Steril* 2003;80:1234-1240. Level of evidence: I.

Utian WH, Gass MLS, Pickar JH. Body mass index does not influence response to treatment, nor does body weight change with lower doses of conjugated estrogens and medroxyprogesterone acetate in younger, postmenopausal women. *Menopause* 2004;11:306-314. Level of evidence: I.

Utian WH, Shoupe D, Bachmann G, Pinkerton JV, Pickar JH. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril* 2001;75:1065-1079. Level of evidence: I.

Other Studies

Brynhildsen J, Hammar M. Low dose transdermal estradiol/norethisterone acetate treatment over 2 years does not cause endometrial proliferation in postmenopausal women. *Menopause* 2002;9:137-144. Level of evidence: I.

Hashimoto M, Miyao M, Akishita M, et al. Effects of long-term and reduced-dose hormone replacement therapy on endothelial function and intima-media thickness in postmenopausal women. *Menopause* 2002;9:58-64. Level of evidence: II-1.

Prestwood KM, Kenny AM, Kleppinger A, Kulldorff M. Ultralow-dose micronized 17β-estradiol and bone density and bone metabolism in older women: a randomized controlled trial. *JAMA* 2003;290:1042-1048. Level of evidence: I.

Speroff L, Whitcomb RW, Kempfert NJ, Boyd RA, Paulissen JB, Rowan JP. Efficacy and local tolerance of a low-dose, 7-day matrix estradiol transdermal system in the treatment of menopausal vasomotor symptoms. *Obstet Gynecol* 1996;88:587-592. Level of evidence: I.

Utian WH, Burry KA, Archer DF, et al. Efficacy and safety of low, standard, and high dosages of an estradiol transdermal system (Esclim) compared with placebo on vasomotor symptoms in highly symptomatic menopausal patients: the Esclim Study Group. *Am J Obstet Gynecol* 1999;181:71-79. Level of evidence: I.

Progestogen Added to ET

Review Articles

The North American Menopause Society. Role of progestogen in hormone therapy for postmenopausal women: position statement of The North American Menopause Society. *Menopause* 2003;10:113-132. Level of evidence: III.

Warren MP. A comparative review of the risks and benefits of hormone replacement therapy regimens. *Am J Obstet Gyncol* 2004;190:1141-1157. Level of evidence: Review.

Hormone Effects on CHD, Venous Thromboembolism, Stroke, Diabetes

EStrogen and THromboembolism Risk (ESTHER) study

Scarabin P-Y, Oger E, Plu-Bureau G, for the EStrogen and THromboEmbolism Risk (ESTHER) Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428-432. Level of evidence: II-2.

Estrogen in the Prevention of Atherosclerosis Trial (EPAT)

Hodis HN, Mack WJ, Lobo RA, et al, for Estrogen in the Prevention of Atherosclerosis Trial Research Group. Estrogen in the prevention of atherosclerosis: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;135:939-953. Level of evidence: I.

Estrogen in the Prevention of Reinfarction Trial (ESPRIT)

Cherry N, Gilmour K, Hannaford P, et al, for The ESPRIT team. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomized placebo controlled trial. *Lancet* 2002;360:2001-2008. Level of evidence: I.

Estrogen Replacement and Atherosclerosis (ERA) trial

Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;343:522-529. Level of evidence: I.

Mack WJ, Hameed AB, Xiang M, et al. Does elevated body mass modify the influence of postmenopausal estrogen replacement on atherosclerosis progression: results from the estrogen in the prevention of atherosclerosis trial. *Atherosclerosis* 2003;168:91-98. Level of evidence: I.

Heart and Estrogen/progestin Replacement Study (HERS)

Herrington DM, Vittinghoff E, Lin F, et al, for the HERS Study Group. Statin therapy, cardiovascular events, and total mortality in the Heart and Estrogen/Progestin Replacement Study (HERS). *Circulation* 2002;105:2962-2967. Level of evidence: I.

Hsia J, Simon JA, Lin F, et al. Peripheral arterial disease in randomized trial of estrogen with progestin in women with coronary heart disease: the Heart and Estrogen/Progestin Replacement Study. *Circulation* 2000;102:2228-2232. Level of evidence: I.

Simon JA, Hsia J, Cauley JA, et al. Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen-progestin Replacement Study (HERS). *Circulation* 2001;103:638-642. Level of evidence: I.

Heart and Estrogen/progestin Replacement Study follow-up (HERS II)

Grady D, Herrington D, Bittner V, et al, for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002;288:49-57. Level of evidence: II-2.

Hulley S, Furberg C, Barrett-Connor E, et al, for the HERS Research Group. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002;288:58-66. Level of evidence: II-2.

Vittinghoff E, Shlipak MG, Varosy PD, et al, for the Heart and Estrogen/progestin Replacement Study research group. Risk factors and secondary prevention in women with heart disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2003;138:81-89. Level of evidence: II-2.

Nurses' Health Study

Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal

hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000;133:933-941. Level of evidence: II-2.

Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996;335:453-461. Level of evidence: II-2.

Papworth HRT Atherosclerosis study (PHASE)

Clarke SC, Kelleher J, Lloyd-Jones H, Slack M, Schofiel PM. A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT atherosclerosis study. *Br J Obstet Gynaecol* 2002;109:1056-1062. Level of evidence: I.

Postmenopausal Estrogen/Progestin Interventions (PEPI) study

Barrett-Connor E, Slone S, Greendale G, et al. The Postmenopausal Estrogen/Progestin Interventions Study: primary outcomes in adherent women. *Maturitas* 1997;27:261-274. Level of evidence: I.

The Writing Group for the PEPI trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial [erratum in: *JAMA* 1995;274:1676]. *JAMA* 1995;273:199-208. Level of evidence: I.

THromboEmbolism Risk (THER) study

Scarabin PY, Oger E, Plu-Bureau G, for the Estrogen and THrombo-Embolism Risk Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428-432. Level of evidence: II-2.

Women's Angiographic Vitamin and Estrogen (WAVE) trial

Waters DD, Alderman EL, Hsia J, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *JAMA* 2002;288:2432-2440. Level of evidence: I.

Women's Estrogen for Stroke Trial (WEST)

Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243-49. Level of evidence: I.

Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELLHART)

Hodis HN, Mack WJ, Azen SP, et al, for the Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial Research Group. Hormone therapy and the progression of coronary artery atherosclerosis in postmenopausal women. *N Engl J Med* 2003;349:535-545. Level of evidence: I.

Women's Health Initiative (WHI)

Manson JE, Hsia J, Johnson KC, et al, for the Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523-534. Level of evidence: I.

Margolis KL, Bonds DE, Rodabough RJ, et al, for the Women's Health Initiative Investigators. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia* 2004;47:1175-1187. Level of evidence: I.

Wassertheil-Smoller S, Hendrix SL, Limacher M, et al, for the WHI Investigators. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* 2003;289:2673-2684. Level of evidence: I.

Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333. Level of evidence: I.

Studies on Premature Hypoestrogenism as an Epidemiologic Risk Factor of CHD

Bairey Merz CN, Johnson BD, Sharaf BL, et al, for the WISE Study Group. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE Study. *J Am Coll Cardiol* 2003;41:413-419. Level of evidence: II-2.

Hu FB, Grodstein F, Hannekens CH, et al. Age at natural menopause and risk of cardiovascular disease. *Arch Intern Med* 1999;159:1061-1066. Level of evidence: II-2.

Other Studies

Angerer P, Kothny W, Störk S, von Schacky C. Hormone replacement therapy and distensibility of carotid arteries in postmenopausal women: a randomized, controlled trial. *J Am Coll Cardiol* 2000;36:1786-1796. Level of evidence: I.

Angerer P, Störk S, Kothny W, Schmitt P, von Schacky C. Effect of oral postmenopausal hormone replacement on progression of atherosclerosis: a randomized, controlled trial. *Arterioscler Thromb Vasc Biol* 2001;21:262-268. Level of evidence: I.

Chilvers CE, Knibb RC, Armstrong SJ, Woods KL, Logan RF. Post menopausal hormone replacement therapy and risk of acute myocardial infarction: a case control study of women in the East Midlands, UK. *Euro Heart J* 2003;24:2197-2205. Level of evidence: II-2.

Ferrara A, Quesenberry CP, Karter AJ, Njoroge CW, Jacobson AS, Selby JV, for the Northern California Kaiser Permanente Diabetes Registry. Current use of unopposed estrogen and estrogen plus progestin and the risk of acute myocardial infarction among women with diabetes: the Northern California Kaiser Permanente Diabetes Registry, 1995-1998. *Circulation* 2003;107:43-48. Level of evidence: II-3.

Lobo RA. Evaluation of cardiovascular event rates with hormone therapy in healthy early postmenopausal women. *Arch Intern Med* 2004;164:482-484. Level of evidence: I.

Review Articles

Humphrey LL, Chan BK, Sox HC. Postmenopausal hormone replacement therapy and the primary prevention of cardiovascular disease. *Ann Intern Med* 2002;137:273-284. Level of evidence: Review.

Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism. *Arch Intern Med* 1998;158:585-593. Level of evidence: Database review.

Hormone Effects on the Skeleton

Heart and Estrogen/progestin Replacement Study follow-up (HERS II)

Hulley S, Furberg C, Barrett-Connor E, et al, for the HERS Research Group. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002;288:58-66. Level of evidence: I.

Million Women Study

Banks E, Beral V, Reeves G, Balkwill A, Barnes I, for the Million Women Study Collaborators. Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women. *JAMA* 2004;291:2212-2220. Level of evidence: II-2.

National Osteoporosis Risk Assessment (NORA) study

Barrett-Connor E, Wehren LE, Siris ES, et al. Recency and duration of postmenopausal hormone therapy: effects on bone mineral density and fracture risk in the National Osteoporosis Risk Assessment (NORA) study. *Menopause* 2003;10:412-419. Level of evidence: II-2.

Yates J, Barrett-Connor E, Barlas S, Chen YT, Miller PD, Siris ES. Rapid loss of hip fracture protection after estrogen cessation: evidence from the National Osteoporosis Risk Assessment. *Obstet Gynecol* 2004;103:440-446. Level of evidence: II-2.

Postmenopausal Estrogen/Progestin Interventions (PEPI) study

Greendale GA, Espeland M, Slone S, Marcus R, Barrett-Connor E, for the PEPI Safety Follow-up Study (PSFS) Investigators. Bone mass response to discontinuation of long-term hormone replacement therapy: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) safety follow-up study. *Arch Intern Med* 2002;162:665-672. Level of evidence: I.

Greendale GA, Wells B, Marcus R, Barrett-Connor E, for the Postmenopausal Estrogen/Progestin Interventions trial investigators. How many women lose bone mineral density while taking hormone replacement therapy? Results from the Postmenopausal Estrogen/Progestin Interventions trial. *Arch Intern Med* 2000;160:3065-3071. Level of evidence: I.

The Writing Group for the PEPI trial. Effects of hormone therapy on bone mineral density: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. *JAMA* 1996;276:1389-1396. Level of evidence: I.

Prospective Epidemiologic study focusing on Risk Factors (PERF) for osteoporosis and CHD

Bagger YZ, Tanko LB, Alexandersen P, et al. Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study. *Bone* 2004;34:728-735. Level of evidence: II-2.

Women's Health Initiative (WHI)

Cauley JA, Robbins J, Chen Z, et al, for the Women's Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA* 2003;290:1729-1738. Level of evidence: I.

Other Studies

Gallagher JC, Rapuri PB, Haynatzki G, Detter JR. Effect of discontinuation of estrogen, calcitriol, and the combination of both on bone density and bone markers. *J Clin Endocrinol Metab* 2002;87:4914-4923. Level of evidence: I.

Greenspan SL, Emkey RD, Bone HG, et al. Significant differential effects of alendronate, estrogen, or combination therapy on the rate of bone loss after discontinuation of treatment of postmenopausal osteoporosis: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002;137:875-883. Level of evidence: I.

Review Articles

Delmas PD. Treatment of postmenopausal osteoporosis. *Lancet* 2002; 359:2018-2026. Level of evidence: Review.

The North American Menopause Society. Management of postmenopausal osteoporosis: position statement of The North American Menopause Society. *Menopause* 2002;9:84-101. Level of evidence: III.

Wells G, Tugwell P, Shea B, et al, for the Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. *Endocr Rev* 2002;23:529-539. Level of evidence: III.

Hormone Effects on the Brain

Cache County Study

Zandi PP, Carlson MC, Plassman BL, et al, for the Cache County Memory Study Investigators. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. *JAMA* 2002;288:2123-2129. Level of evidence: II-3.

Heart and Estrogen/progestin Replacement Study follow-up (HERS II)

Grady D, Yaffe K, Kristof M, Lin F, Richards C, Barrett-Connor E. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. *Am J Med* 2002;113: 543-548. Level of evidence: I.

Melbourne Women's Midlife Health Project

Henderson VW, Guthrie JR, Dudley EC, Burger HG, Dennerstein L. Estrogen exposures and memory at midlife: a population-based study of women. *Neurology* 2003;60:1369-1371. Level of evidence: II-2.

Multi-Institutional Research on Alzheimer Genetic Epidemiology (MIRAGE) study

Henderson VW, Benke KS, Green RC, Cupples LA, Farrer LA. Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. *J Neurol Neurosurg and Psychiatry* 2004 [in press]. Level of evidence: II-2.

Study of Women Across the Nation (SWAN)

Meyer PM, Powell LH, Wilson RS, et al. A population-based longitudinal study of cognitive functioning in the menopausal transition. *Neurology* 2003;61:801-806. Level of evidence: II-2.

Women's Health Initiative Memory Study (WHIMS)

Espeland MA, Rapp SR, Shumaker SA, et al, for the Women's Health Initiative Memory Study Investigators. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291:2959-2968. Level of evidence: I.

Rapp SR, Espeland MA, Shumaker SA, et al, for the WHIMS Investigators. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003;289:2663-2672. Level of evidence: I.

Shumaker SA, Legault C, Kuller L, et al, for the Women's Health Initiative Memory Study Investigators. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004:291:2947-2958. Levels of evidence: I.

Shumaker SA, Legault C, Thal L, et al, for the WHIMS Investigators. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003;289: 2651-2662. Level of evidence: I.

Other Studies

den Heijer T, Geerlings MI, Hofman A, et al. Higher estrogen levels are not associated with larger hippocampi and better memory performance. *Arch Neurol* 2003;60:213-220. Level of evidence: II-2.

Morrison MF, Kallan MJ, Ten Have T, Katz I, Tweedy K, Battistini M. Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biol Psychiatry* 2004;55:406-412. Level of evidence: I.

Thal LJ, Thomas RG, Mulnard R, Sano M, Grundman M, Schneider L. Estrogen levels do not correlate with improvement in cognition. *Arch Neurol* 2003;60:209-212. Level of evidence: II-2.

Review Articles

Henderson VW. Hormone therapy and Alzheimer's disease: benefit or harm? *Expert Opin Pharmacother* 2004;5:389-406. Level of evidence: Review.

Hormone Effects on Breast and Gynecologic Cancer

Hormonal replacement therapy After Breast cancer – Is It Safe? (HABITS) study

Holmberg L, Anderson H, for the HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer – is it safe?), a randomized comparison trial stopped. *Lancet* 2004;363:453-455. Level of evidence: I (no placebo).

Million Women Study

Beral V, for the Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;362:419-427. Level of evidence: II-2.

Postmenopausal Estrogen/Progestin Interventions (PEPI) study

Greendale GA, Reboussin BA, Sie A, et al. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators. *Ann Intern Med* 1999;130:262-269. Level of evidence: I.

Women's Health Initiative (WHI)

Anderson GL, Judd HL, Kaunitz AM, et al, for the Women's Health Initiative Investigators. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA* 2003;290:1739-1748. Level of evidence: I.

Chlebowski RT, Hendrix SL, Langer RD, et al, for the WHI Investigators. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA* 2003;289:3243-3253. Level of evidence: I.

McTiernan A, Kooperberg C, White E, Wilcox S, Coates R, Adams-Campbell LL, Woods N, Ockene J. Women's Health Initiative Cohort Study. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. *JAMA. 2003;*290:1331-1336. Level of evidence: II-2.

Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333. Level of evidence: I.

Other Studies

Lacey JV Jr, Mink PJ, Lubin JH, et al. Menopausal hormone replacement therapy and risk of ovarian cancer [erratum in: *JAMA* 2002;288: 2544]. *JAMA* 2002;288;334-341. Level of evidence: II-2.

Li CI, Malone KE, Porter PL, et al. Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. *JAMA* 2003;289:3254-3263. Level of evidence: 11-2.

Olsson HL, Ingvar C, Bladström A. Hormone replacement therapy containing progestins and given continuously increases breast carcinoma risk in Sweden. *Cancer* 2003;97:1387-1392. Level of evidence: II-2.

Weiss LK, Burkman RT, Cushing-Hauger KL, et al. Hormone replacement therapy regimens and breast cancer risk. *Obstet Gynecol* 2002;100:1148-1158. Level of evidence: II-2.

Review Articles

Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiologic studies of 52,705 women with breast cancer and 108,411 women without breast cancer [erratum in: *Lancet* 1997;350: 1484]. *Lancet* 1997;350:1047-1059. Level of evidence: III.

Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst* 2002;94:606-616. Level of evidence: III.

Montgomery BE, Daum GS, Dunton CJ. 2004. Endometrial hyperplasia: a review. *Obstet Gynecol Survey* 59:368-78. Level of evidence: Review.

Hormone Effects on Colon Cancer

Women's Health Initiative (WHI)

Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al, for the Women's Health Initiative Investigators. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med* 2004;250: 991-1004. Level of evidence: I.

Other Studies

Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med* 1999;106:574-582. Level of evidence: III.

MacLennan SC, MacLennan AH, Ryan P. Colorectal cancer and oestrogen replacement therapy: a meta-analysis of epidemiological studies. *Med J Aust* 1995;162:491-493. Level of evidence: III.

Nanda K, Bastian LA, Hasselblad V, Simel DL. Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis. *Obstet Gynecol* 1999;93:880-888. Level of evidence: III.

Review Articles

Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. *N Engl J Med* 2003;348:645-650. Level of evidence: III.

Bioidentical Hormones

Boothby LA, Doering PL, Kipersztok S. Bioidentical hormone therapy: A review. *Menopause* 2004;11:356-367. Level of evidence: Review.

Risks Associated with Aspirin

He J, Whelton PK, Vu B, Klag MJ. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials. *JAMA* 1998;280: 1930-1935. Level of evidence: III.

WHO CIOMS Classification of Risk for Adverse Events

Council for International Organizations of Medical Sciences (CIOMS). **Guidelines for Preparing Core Clinical-Safety Information of Drugs**, 2nd ed. Geneva, Switzerland: CIOMS; 1998, Level of evidence: review.

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*Description of the levels of evidence**

Level I	Properly randomized controlled trial.
Level II-1	Well-designed controlled trial but without randomization.
Level II-2	Well-designed cohort or case-control analytic study, preferably from more than one center or research group.
Level II-3	Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies); uncontrolled experiments with dramatic results could also be regarded as this type of evidence.
Level III	Opinions of respected authorities that are based on clinical experience; descriptive studies and case reports; reports from expert committees.

* Preventive Services Task Force. *Guide to Clinician Preventive Services: Report of the US Preventive Services Task Force.* 2nd ed. Baltimore, MD: Williams & Wilkins; 1996.