Oregon State University College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | **Fax** 503-947-1119

Oregon Health Authority

Hormone Replacement Therapies

Month/Year of Review: November, 2012
PDL Class: Hormone Replacement Therapy (HRT)
End date of literature search: August, 2012

Date of Last Review: April 2008
Source Document: HRC Report

Current Preferred Agents	Current Non-Preferred Agents
Oral HRT - Estrogen	
Estradiol	Conjugated Estrogens, Synthetic B (Enjuvia®)
Conjugated Estrogens, Synthetic A (Cenestin®)	Esterified Estrogens/methyltestosterone
Estropipate	Esterified estrogens (Menest®)
Norethindrone acetate/Ethinyl Estradiol (Femhrt®)	Estradiol/norethindrone (Activella®)
	Drospirenone/estradiol (Angeliq®)
	Norethindrone acetate/ethinyl estradiol (Jinteli®)
	Estradiol/norethindrone acetate (Mimvey®)
	Estradiol/norgestimate (Prefest®)
	Conjugated estrogens/Medroxyprogesterone (Prempro®, Premphase®)
Topical HRT - Estrogen	
Estradiol patch	Estradiol gel packet (Divigel®)
Estradiol (Alora®) patch	Estradiol gel pump (Elestrin®)
Estradiol (Climara®)	Estradiol patch (Estraderm®)
	Estradiol patch (Estrasorb®)
	Estradiol gel pump (EstroGel®)
	Estradiol spray (Evamist®)
	Estradiol patch (Vivelle-dot®)
	Estradiol/norethindrone acetate patch (Combipatch®)
	Estradiol/levonorgestrel patch (Climara Pro®)
Vaginal HRT - Estrogen	
Estradiol (Estring®) vaginal ring	Estradiol vaginal cream (Estrace®)
Estradiol (Vagifem®) tablet	Estradiol vaginal ring (femring®)
Conjugated Estrogen (Premarin®) cream	

Previous Conclusions:[1]

- Estrogens reduce some menopausal symptoms and have been shown to improve bone density and reduce fracture risk.
- Decreasing doses of conjugated equine estrogen (CEE) with or without medroxyprogesterone acetate (MPA) resulted in decreasing preservation of bone density however it is unclear if lower doses of estrogen will sufficiently preserve bone density in a manner to affect outcomes.
- The majority of studies are of estradiol and CEE. For many estrogen preparations, clinical trials are few and evidence is insufficient to conclude they are equal to estrogens that have been studied more extensively.
- For the comparison of the estradiol ring to CEE vaginal cream there was more improvement in pruritus with the ring. For the comparison of estradiol ring versus estradiol tablet, vaginal dryness was improved more with tablets
- CEE cream caused more side effects compared to estradiol tablets (uterine bleeding, breast pain, and perineal pain) or estradiol vaginal ring (endometrial overstimulation).
- There are conflicting results for Breast cancer rates and cardiovascular events.
- At the present time there is no comparative evidence to evaluate estrogen use in subgroup populations of race or ethnicity.
- An increased incidence of probable dementia among participants taking CEE (+/- MPA) starting after 4 years, was positively related to increasing age and lower Mini Mental State exam scores at baseline.

Issues:

- Is there any new comparative evidence of different hormone therapy preparations for reducing symptoms of menopause, preventing low bone density and fractures?
- Is there any new comparative safety evidence of different therapy preparations?
- Are there subgroups of patients for which one medication or preparation is more effective or associated with fewer adverse effects?

Conclusions:

- Estrogen plus progestin and estrogen alone decreased risk for fractures but increased risk for stroke, thromboembolic events, gallbladder disease, and urinary incontinence.
- Estrogen plus progestin increased risk for breast cancer and probable dementia, whereas estrogen alone decreased risk for breast cancer.
- There are insufficient data to assess the risk of long term hormone therapy use in perimenopausal women or postmenopausal women younger than 50 years of age.
- Hormone therapy for postmenopausal women with an intact uterus should comprise both estrogen and progestin to reduce the risk of endometrial hyperplasia.
- There were no consistent differences by age and comorbidities in subgroup analyses.
- Despite of lacking randomized clinical trials evidence for potential favorable thromboembolic risks using transdermal formulation of hormone therapy, several national guidelines recommended transdermal route of administration over oral route.

Recommendation:

- Evaluate price comparisons of individual agents for topical HRT and consider including a topical estrogen plus progestin product.

Methods:

A MEDLINE Ovid search was conducted using hormone replacement therapy (HRT), menopause, estradiol and estrogen. The search was limited to meta-analysis, English language, and to studies conducted in humans since last HRT review. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA) and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Treatment Guidelines

American Association of Clinical Endocrinologists (AACE) Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Menopause[2] key recommendations (2011 Task force revisions):

- Menopausal hormone therapy (MHT) may be appropriate for the relief of severe menopausal symptoms in selected postmenopausal women, on the basis of an individually determine benefit-versus-risk profile. (Grade A)
- MHT may be prescribed during the perimenopause and early menopause for relief of menopausal symptoms and treatment of vulvovaginal atropy. (Grade A)
- The use of transdermal route of estrogen administration should be considered in order to avoid the hepatic "first-pass effect," which may theoretically reduce the risk of thromboembolic disease. (Grade B)
- The use of transvaginal estrogen may be considered to provide topical effects with less systemic absorption. (Grade B)
- Progestatonal agents should be used for minimum 10 to 14 days per month in women treated with estrogen who have an intact uterus. (Grade A)
- MHT should be used in the lowest dose and for the shortest period necessary to control menopausal symptoms. (Grade A)
- MHT should be used for the prevention and treatment of osteoporosis within the context of the overall benefit-versus-risk analysis of each patient. (Grade A)
- MHT should be prescribed to women in conjunction with a thorough discussion of the possible relationship of MHT to breast cancer. Current evidence suggests that estrogen + progesterone regimens are associated with a possible higher risk of breast cancer than is therapy with estrogen alone. (Grade A)
- Women should be advised that smoking increases the risk of cardiovascular and venous thromboembolic disease when taking estrogen, and aggressive smoking cessation programs should be advised. (Grade A)
- Women should be advised that cerebrovascular accidents occur with increased frequency in patients taking estrogen alone or estrogen +progesterone combination therapies in an age-dependent manner (Grade A)
- Women should be advised that there may be an increase in ovarian epithelial tumors with the use of estrogen for more than 10 years. (Grade B)

- Women may be advised that several studies including the Women's Health Initiative (WHI) have demonstrated a lower risk of colon cancer in women treated with estrogen + progesterone combination. (Grade B)

The 2012 Hormone Therapy Position Statement of the North American Menopause Society (NAMS)[3]

The position statement updated the 2010 evidence-based statement published by the NAMS regarding recommendations for hormone therapy (HT) for postmenopausal women. The 2012 updated statement concluded that recent data support the initiation of HT around the time of menopause to treat menopause -related symptoms and to prevent osteoporosis in women at high risk of fracture. The more favorable benefit-risk ratio for estrogen (ET) allows more flexibility in extending the duration of use compared with combined estrogen-progestogen therapy (EPT), where the earlier appearance of increased breast cancer risk precludes a recommendation for use beyond 3 to 5 years. (See Appendix A for key recommendations)

Venous thromboembolism (VTE) and Hormone Replacement Therapy by NICE[4] **(May 2011)**

This is the 3rd edition of this guideline on VTE risk associated with HRT and treatment recommendations on duration, types of HRT, and preparations of different HRT. (See Appendix A for Key conclusions and recommendations)

Menopause and Osteoporosis Update 2009 by the Society of obstetricians and Gynaecologists of Canada[5] **(SOGC)**

The guidelines provided the updated recommendations on the management of menopause in asymptomatic healthy women as well as in women presenting with vasomotor symptoms or with urogenital, mood, or memory concerns, and on considerations related to cardiovascular disease, breast cancer and bone health, including the diagnosis and clinical management of postmenopausal osteoporosis. Lifestyle interventions, prescription medications, and complementary and alternative therapies are presented according to their efficacy in the treatment of menopausal symptoms. See Appendix A for key HRT related recommendations.

New Systematic Reviews (See Appendix B for Review Abstracts)

Nelson el al.[6] published a systematic review in July 2012 to update the evidence about the effectiveness of hormone therapy in reducing risk of chronic conditions and adverse effects, and to examine whether outcomes vary among women in different subgroups. Randomised placebo-controlled trials of postmenopausal therapy versus placebo for prevention of chronic conditions for postmenopausal women were eligible for inclusion. Women with known thrombotic disorders, hormone sensitive cancer or coronary heart disease were excluded. The review was concerned with primary prevention of new conditions rather than effects on pre-existing conditions. Outcomes of interest were coronary heart disease, stroke, deep vein thrombosis, pulmonary embolism, cancer (breast, colon, lung, endometrium or ovaries), fracture at various sites, cognition and dementia, disease-specific and all-cause mortality and any new findings reported by the trials. Intervention drugs included conjugated equine estrogen with or without medroxyprogesterone acetate, estradiol valerate, 17-beta estradiol plus norethindrone and unopposed transdermal estradiol. The main analysis was based on participants aged 60 to 69. Nine randomized placebo controlled trials were included in the review. The longest follow-up was 11 years (Women's Health Initiative trials). All trials were rated of fair quality. The most common problems across the trials were high attrition and low adherence. The results of review show estrogen plus progestin reduced fractures (HR 0.76, 95% CI 0.69 to 0.83) but increased invasive breast cancer (HR 1.25, 95% CI 1.07 to 1.46), stroke (HR 1.34, 95% CI 1.05 to 1.71),

deep venous thrombosis (HR 1.88, 95% CI 1.38 to 2.55), pulmonary embolism (HR 1.98, 95% CI 1.36 to 2.87), lung cancer death (HR 1.71, 95% CI 1.16 to 2.52), gallbladder disease (HR 1.61, 95% CI 1.30 to 2.00), probable dementia (HR 2.05, 95% CI 1.21 to 3.48) and urinary incontinence (HR 1.39, 95% CI 1.27 to 1.52). There were no statistically significant reductions in colorectal cancer, lung cancer, endometrial, ovarian and cervical cancers, coronary heart disease, pulmonary embolism, all-cause mortality, probable dementia and mild cognitive impairment. Estrogen-only therapy reduced fractures (HR 0.70, 95% CI 0.63 to 0.79), invasive breast cancer incidence (HR 0.77, 95% CI 0.62 to 0.95) and breast cancer death (HR 0.37, 95% CI 0.13 to 0.91) but increased stroke (HR 1.36, 95% CI 1.08 to 1.71), deep venous thrombosis (HR 1.47, 95% CI 1.06 to 2.05), gallbladder disease (HR 1.79, 95% CI 1.44 to 2.22) and urinary incontinence (HR 1.53, 95% CI 1.37 to 1.71). There were no statistically significant reductions in diabetes, colorectal cancer, lung cancer, coronary heart disease, pulmonary embolism, all-cause mortality, probable dementia and mild cognitive impairment. Among the subgroup analyses, there were no consistent differences by age and comorbidities. Other subgroup analyses were not performed due to lack of data.

The review addressed a clear question and was supported by appropriate inclusion criteria. Several relevant data sources were searched. The review was restricted to studies in English (the authors reported that they did not identify any relevant trials from journals in other languages). Study quality was assessed. The authors appropriately highlighted weaknesses in the evidence such as high drop-out rates and differential adherence rates. Two reviewers were involved in study selection, data extraction and quality assessment, which minimized potential for error and bias. The restriction of results to those of the Women's Health Initiative trials appeared justified. The conclusions were based on the evidence presented and appear reliable.

Another recent systematic review by **Marjoribanks et al**[7] assessed the effects of long term HT on mortality cardiovascular outcomes, cancer, gallbladder disease, fractures, cognition and quality of life in perimenopausal and postmenopausal women, both during HT use and after cessation of HT use. Twenty-three studies involving 42,830 women were included. Seventy per cent of the data were derived from two studies (WHI 1998 and Heart and Estrogen/progestin Replacement Study (HERS) 1998 Research Group). Most participants were postmenopausal women with at least some degree of co-morbidity, and the mean participant age in most studies was over 60 years. None of the studies focused on perimenopausal women. In relatively healthy postmenopausal women (that is generally fit, without overt disease) combined continuous HT significantly increased the risk of a coronary event (after one year's use: AR 4 per 1000, 95% CI 3 to 7), venous thromboembolism (after one year's use: Absolute risk (AR) 7 per 1000, 95% CI 4 to 11), stroke (after three years' use: AR 18 per 1000, 95% CI 14 to 23), breast cancer (after 5.6 years' use: AR 23 per 1000, 95% CI 19 to 29), gallbladder disease (after 5.6 years' use: AR 27 per 1000, 95% CI 21 to 34) and death from lung cancer (after 5.6 years' use plus 2.4 years' additional follow-up: AR 9 per 1000, 95% CI 6 to 13). Estrogen-only HT significantly increased the risk of venous thromboembolism (after one to two years' use: AR 5 per 1000, 95% CI 2 to 10; after 7 years' use: AR 21 per 1000, 95% CI 16 to 28), stroke (after 7 years' use: AR 32 per 1000, 95% CI 25 to 40) and gallbladder disease (after seven years' use: AR 45 per 1000, 95% CI 36 to 57) but did not significantly increase the risk of breast cancer. Among women aged over 65 years who were relatively healthy and taking continuous combined HT, there was a statistically significant increase in the incidence of dementia (after 4 years' use: AR 18 per 1000, 95% CI 11 to 30). Among women with cardiovascular disease, long term use of combined continuous HT significantly increased the risk of venous thromboembolism (at one year: AR 9 per 1000, 95% CI 3 to 29). Women taking HT had a significantly decreased incidence of fractures with long term use (after 5.6 years of combined HT: AR 86 per 1000, 95% CI 79 to 84; after 7.1 years' use of estrogen-only HT: AR 102 per 1000, 95% CI 91 to 112). Risk of fracture was the only outcome for

which there was strong evidence of clinical benefit from HT. There was no strong evidence that HT has a clinically meaningful impact on the incidence of colorectal cancer. One trial analyzed subgroups of 2839 relatively healthy 50 to 59 year old women taking combined continuous HT and 1637 taking estrogen-only HT versus similar-sized placebo groups. The only significantly increased risk reported was for venous thromboembolism in women taking combined continuous HT: their absolute risk remained low, at less than 1/500. However, other differences in risk cannot be excluded as this study was not designed to have the power to detect differences between groups of women within 10 years of the menopause. The authors concluded HT is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for preventing deterioration of cognitive function in postmenopausal women. Although HT is considered effective for the prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-estrogen therapies are unsuitable. There are insufficient data to assess the risk of long term HT use in perimenopausal women or postmenopausal women younger than 50 years of age.

Lin et al[8] conducted a meta-analysis to summarize the relative risks (RR) of colorectal cancer CRC due to estrogen (ET) versus combined estrogen-progestogen therapy (EPT) among peri- or postmenopausal women. From a total of 2,661 articles, four randomized controlled trials, eight cohort and eight case-control studies were included. Variables assessed included study characteristics, duration and recency of menopausal hormone therapy (HT) use, method of assessment of HT use, outcome definition and its ascertainment method. RRs were synthesized by random-effects models. The authors found that EPT ever use was associated with a decreased risk of CRC (RR 0.74, 95% CI 0.68-0.81), and so was ET ever use (RR 0.79, 95% CI 0.69-0.91). While current use of ET was associated with a significantly reduced risk of CRC (RR 0.70, 95% CI 0.57-0.85), former use was not (RR 0.86, 95%CI 0.67-1.11). Recency did not significantly modify the association between EPT and CRC risk. EPT former use was associated with a lower RR of CRC compared to ET former use (p = 0.008) but no such difference was observed between EPT and ET current use (p = 0.12). Overall, authors found consistent evidence supporting the association between EPT and CRC risk reduction, regardless of recency. While literature for the association between ET and CRC risk is heterogeneous, authors' analyses suggest only current use of ET is associated with a decreased CRC risk.

Furness et al[9] conducted a systematic review to assess which hormone therapy regimens provide effective protection against the development of endometrial hyperplasia or carcinoma. The main results of the review indicated that unopposed estrogen is associated with increased risk of endometrial hyperplasia at all doses, and durations of therapy between one and three years. For women with a uterus the risk of endometrial hyperplasia with hormone therapy comprising low-dose estrogen continuously combined with a minimum of 1 mg norethisterone acetate (NETA) or 1.5 mg medroxyprogesterone acetate (MPA) is not significantly different from placebo at two years (1 mg NETA: OR 0.04; 95% confidence interval (CI) 0 to 2.8; 1.5 mg MPA: no hyperplasia events). The authors concluded hormone therapy for postmenopausal women with an intact uterus should comprise both estrogen and progestogen to reduce the risk of endometrial hyperplasia.

References:

1.HRC-2008-04-HRT Update.pdf. Available at: http://cms.oregon.gov/oha/pharmacy/therapeutics/docs/hrc-2008-01-hrt.pdf. Accessed August 28, 2012.

2. National Guideline ClearingHouse. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of menopause. Available at: http://www.guideline.gov/content.aspx?id=35238&search=hormone+replacement+therapy#Section420. Accessed August 29, 2012.

3. National Guideline ClearingHouse. The 2012 hormone therapy position statement of The North American Menopause Society. Available at: http://www.guideline.gov/content.aspx?id=36195&search=hormone+replacement+therapy#Section432. Accessed August 29, 2012.

4. National Guideline ClearingHouse. Venous thromboembolism and hormone replacement therapy. Available at: http://www.guideline.gov/content.aspx?id=34965&search=hormone+replacement+therapy#Section420. Accessed August 29, 2012.

5. National Guideline ClearingHouse. Hormone therapy and breast cancer. In: Menopause and osteoporosis update 2009. Available at: http://www.guideline.gov/content.aspx?id=13611&search=hormone+replacement+therapy#Section420. Accessed August 29, 2012.

6. Nelson HD, Walker M, Zakher B, Mitchell J. Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: A Systematic Review to Update the U.S. Preventive Services Tas Force Recommendations. *Ann Intern Med*. 2012;157(2):104–113.

7. Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. In: *Cochrane Database of Systematic Reviews 2012*. Issue 7. Art. No.: CD004143. DOI: 10.1002/14651858.CD004143.pub4. John Wiley & Sons, Ltd; 2012. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004143.pub4/abstract. Accessed August 28, 2012.

8. Lin KJ, Cheung WY, Lai JY-C, Giovannucci EL. The effect of estrogen vs. combined estrogen-progestogen therapy on the risk of colorectal cancer. *International Journal of Cancer*. 2012;130(2):419–430.

9. Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. In: *Cochrane Database of Systematic Reviews 2012*. Issue 8. Art. No.: CD000402. DOI: 10.1002/14651858.CD000402.pub4. John Wiley & Sons, Ltd; 2012. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000402.pub4/abstract. Accessed August 28, 2012.

10. Salpeter SR, Cheng J, Thabane L, Buckley NS, Salpeter EE. Bayesian Meta-analysis of Hormone Therapy and Mortality in Younger Postmenopausal Women. *The American Journal of Medicine*. 2009;122(11):1016–1022.e1.

Appendix A

The 2012 Hormone Therapy Position Statement of the North American Menopause Society (NAMS) Conclusions and Recommendations:

- Individualization is of key importance in the decision to use HT and should incorporate the woman's health and quality of life priorities as well as her personal risk factors, such as risk of venous thrombosis, CHD, stroke, and breast cancer.
- The recommendation for duration of therapy differs for EPT and ET. For EPT, duration is limited by the increased risk of breast cancer and breast cancer mortality associated with 3 to 5 years of use; for ET, a more favorable benefit-risk profile was observed during a mean of 7 years of use and 4 years of follow-up, a finding that allows more flexibility in duration of use.
- ET is the most effective treatment of symptoms of vulvar and vaginal atrophy; low-dose, local vaginal ET is advised when only vaginal symptoms are present.
- Women with premature or early menopause who are otherwise appropriate candidates for HT can use HT at least until the median age of natural menopause (age 51 y). Longer duration of treatment can be considered if needed for symptom management.
- Although ET did not increase breast cancer risk in the WHI, there is a lack of safety data supporting the use of ET in breast cancer survivors, and one RCT reported a higher increase in breast cancer recurrence rates.
- Both transdermal and low-dose oral estrogen have been associated with lower risks of VTE and stroke than standard doses of oral estrogen, but RCT evidence is not yet available.

Venous thromboembolism (VTE) and Hormone Replacement Therapy key Conclusions and Recommendations by NICE

- All women commencing HRT should be counseled about the risk of VTE and the signs and symptoms of VTE. All women should be advised to access medical help rapidly if they suspect that they have developed a thrombosis. (Evidence level 1+)
- Women starting or continuing HRT should be counseled with regard to the perceived benefits and possible risks for their individual situations, including consideration of alternative therapies. (Evidence level 1+)
- The risk of VTE may be less with esterfied estrogens compared with conjugated equine estrogen. (Evidence level 2+)
- There may be a greater risk of VTE with combination therapy and definitive information on individual estrogen types is still lacking. However, the results to date suggest that therapy with estrogen alone is associated with a significant VTE risk. (Evidence level 2++)
- There is some evidence that the effect of estrogen therapy may be dose related. Transdermal preparations are associated with a substantially lower risk of VTE than oral preparations. (Evidence level 2+)
- The risk of VTE is highest in the first year of HRT use, with no evidence of continuing risk on stopping HRT. (Evidence level 2++)
- A personal history of thrombosis is a contraindication to oral HRT. If it is considered that quality of life is so severely affected that the benefits of HRT outweigh the risks, a transdermal preparation should be used. (Evidence level 2+)

Menopause and Osteoporosis Update 2009 by the Society of obstetricians and Gynaecologists of Canada key HRT Related Recommendations

- Health care providers should offer HT (estrogen alone or EPT) as the most effective therapy for the medical management of menopausal symptoms. (Evidence level IA)
- Progestins alone or low-dose oral contraceptives can be offered as alternatives for the relief of menopausal symptoms during the menopausal transition. (Evidence level IA)
- HT should be offered to women with premature ovarian failure or early menopause (IA), and it can be recommended until the age of natural menopause. (IIIC)
- Estrogen therapy can be offered to women who have undergone surgical menopause for the treatment of endometriosis. (IA)
- Health care providers should not initiate or continue HT for the sole purpose of preventing coronary artery disease and stroke. (IA)
- Health care providers should abstain from prescribing HT in women at high risk for VTE. (IA)
- Health care providers may prescribe HT to diabetic women for the relief of menopausal symptoms. (IA)
- Health care providers should periodically review the risks and benefits of prescribing HT to a menopausal woman in light the association between duration of use and breast cancer risk. HT may be prescribed for menopausal symptoms in women at increased risk of breast cancer with appropriate counseling and surveillance. (IA)
- Conjugated estrogen cream, and intravaginal sustained-release estradiol ring, or estradiol vaginal tablets are recommended as effective treatment for vaginal atrophy. (IA)
- Routine progestin cotherapy is not required for endometrial protection in women receiving vaginal estrogen therapy in appropriate dose. (IIIC)
- Estrogen therapy should not be recommended for the treatment of postmenopausal urge or stress urinary incontinence but may be recommended before corrective surgery. (IA)
- Vaginal estrogen therapy can be recommended for the prevention of recurrent urinary tract infections in postmenopausal women. (IA)
- Usual-dosage HT should be prescribed for symptomatic postmenopausal women as the most effective therapy for menopausal symptom relief (1A) and a reasonable choice for the prevention of bone loss and fracture. (1A)
- Physicians may recommend low- and ultralow-dosage estrogen therapy to symptomatic women for relief of menopausal symptoms (1A) but should inform their patients that despite the fact that such therapy has demonstrated a beneficial effect in osteoporosis prevention (1A), no data are yet available on reduction of fracture risk.
- Estrogen can be prescribed to enhance mood in women with depressive symptoms. The effect appears to be greater for perimenopausal symptomatic women than for postmenopausal women. (IA)
- Estrogen therapy is not currently recommended for reducing the risk of dementia developing in postmenopausal women or for retarding the progression of diagnosed Alzheimer's disease, although limited data suggest that early use of HT in the menopause may be associated with diminished risk of later dementia. (IB)

Appendix B

Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: A Systematic Review to Update the U.S. Preventive Services Task Force Recommendations

Heidi D. Nelson, MD, MPH; Miranda Walker, MA; Bernadette Zakher, MBBS; and Jennifer Mitchell, BA *Ann Intern Med*. 17 July 2012;157(2):104-113

Abstract

Background: Menopausal hormone therapy to prevent chronic conditions is currently not recommended because of its adverse effects.

Purpose: To update evidence about the effectiveness of hormone therapy in reducing risk for chronic conditions and adverse effects, and to examine whether outcomes vary among women in different subgroups.

Data Sources: MEDLINE (January 2002 to November 2011), Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the 3rd quarter of 2011), Scopus, and reference lists.

Study Selection: Randomized, placebo-controlled trials of menopausal hormone therapy published in English since 2002 that assessed primary prevention of chronic conditions.

Data Extraction: Investigators extracted data on participants, study design, analysis, follow-up, and results; 2 investigators independently rated study quality by using established criteria.

Data Synthesis: 9 fair-quality trials met the inclusion criteria. The Women's Health Initiative reported most of the results, had 11 years of follow-up, and had data most applicable to postmenopausal women in the United States. It showed that estrogen plus progestin therapy reduced fractures (46 fewer per 10 000 woman-years) and increased invasive breast cancer (8 more per 10 000 woman-years), stroke (9 more per 10 000 woman-years), deep venous thrombosis (12 more per 10 000 woman-years), pulmonary embolism (9 more per 10 000 woman-years), lung cancer death (5 more per 10 000 woman-years), gallbladder disease (20 more per 10 000 woman-years), dementia (22 more per 10 000 woman-years), and urinary incontinence (872 more per 10 000 woman-years). Estrogen-only therapy reduced fractures (56 fewer per 10 000 woman-years), invasive breast cancer (8 fewer per 10 000 woman-years), and death (2 fewer per 10 000 woman-years) and increased stroke (11 more per 10 000 woman-years), deep venous thrombosis (7 more per 10 000 woman-years), gallbladder disease (33 more per 10 000 woman-years), and urinary incontinence (1271 more per 10 000 woman-years). Outcomes did not consistently differ by age or comorbid conditions.

Limitation: Limitations of the trials included low adherence, high attrition, inadequate power to detect risks for some outcomes, and evaluation of few regimens.

Conclusion: Estrogen plus progestin and estrogen alone decreased risk for fractures but increased risk for stroke, thromboembolic events, gallbladder disease, and urinary incontinence. Estrogen plus progestin increased risk for breast cancer and probable dementia, whereas estrogen alone decreased risk for breast cancer.

Primary Funding Source: Agency for Healthcare Research and Quality.

Long term hormone therapy for perimenopausal and postmenopausal women

Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD004143. DOI: 10.1002/14651858.CD004143.pub4.

Abstract

Background: Hormone therapy (HT) is widely used for controlling menopausal symptoms and has also been used for the management and prevention of cardiovascular disease, osteoporosis and dementia in older women. This is an updated version of a Cochrane review first published in 2005.

Objectives: To assess the effects of long term HT on mortality, cardiovascular outcomes, cancer, gallbladder disease, fractures, cognition and quality of life in perimenopausal and postmenopausal women, both during HT use and after cessation of HT use.

Search methods: We searched the following databases to February 2012: Cochrane Menstrual Disorders and Subfertility Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO.

Selection criteria: We included randomised double-blind studies of HT versus placebo, taken for at least one year by perimenopausal or postmenopausal women. HT included oestrogens, with or without progestogens, via oral, transdermal, subcutaneous or intranasal routes.

Data collection and analysis: Two authors independently assessed study quality and extracted data. We calculated risk ratios (RRS) for dichotomous data and mean differences (MDs) for continuous data, with 95% confidence intervals (CIs). Where findings were statistically significant, we calculated the absolute risk (AR) in the intervention group (the overall risk of an event in women taking HT).

Main results: Twenty-three studies involving 42,830 women were included. Seventy per cent of the data were derived from two studies (WHI 1998 and HERS 1998). Most participants were postmenopausal American women with at least some degree of co-morbidity, and the mean participant age in most studies was over 60 years. None of the studies focused on perimenopausal women. In relatively healthy postmenopausal women (that is generally fit, without overt disease) combined continuous HT significantly increased the risk of a coronary event (after one year's use: AR 4 per 1000, 95% CI 3 to 7), venous thrombo-embolism (after one year's use: AR 7 per 1000, 95% CI 4 to 11), stroke (after three years' use: AR 18 per 1000, 95% CI 14 to 23), breast cancer (after 5.6 years' use: AR 23 per 1000, 95% CI 19 to 29), gallbladder disease (after 5.6 years' use: AR 27 per 1000, 95% CI 21 to 34) and death from lung cancer (after 5.6 years' use plus 2.4 years' additional follow-up: AR 9 per 1000, 95% CI 6 to 13). Oestrogen-only HT significantly increased the risk of venous thrombo-embolism (after one to two years' use: AR 5 per 1000, 95% CI 2 to 10; after 7 years' use: AR 21 per 1000, 95% CI 16 to 28), stroke (after 7 years' use: AR 32 per 1000, 95% CI 25 to 40) and gallbladder disease (after seven years' use: AR 45 per 1000, 95% CI 36 to 57) but did not significantly increase the risk of breast cancer. Among women aged over 65 years who were relatively healthy and taking continuous combined HT, there was a statistically significant increase in the incidence of dementia (after 4 years' use: AR 18 per 1000, 95% CI 11 to 30). Among women with cardiovascular disease, long term use of combined continuous HT significantly increased the risk of venous thrombo-embolism (at one year: AR 9 per 1000, 95% CI 3 to 29). Women taking HT had a significantly decreased incidence of fractures with long term use (after 5.6 years of combined HT: AR 86 per 1000, 95% CI 79 to 84; after 7.1 years' use of oestrogen-only HT: AR 102 per

1000, 95% CI 91 to 112). Risk of fracture was the only outcome for which there was strong evidence of clinical benefit from HT. There was no strong evidence that HT has a clinically meaningful impact on the incidence of colorectal cancer. One trial analyzed subgroups of 2839 relatively healthy 50 to 59 year old women taking combined continuous HT and 1637 taking oestrogen-only HT versus similar-sized placebo groups. The only significantly increased risk reported was for venous thrombo-embolism in women taking combined continuous HT: their absolute risk remained low, at less than 1/500. However, other differences in risk cannot be excluded as this study was not designed to have the power to detect differences between groups of women within 10 years of the menopause.

Authors' conclusions: HT is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for preventing deterioration of cognitive function in postmenopausal women. Although HT is considered effective for the prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-oestrogen therapies are unsuitable. There are insufficient data to assess the risk of long term HT use in perimenopausal women or postmenopausal women younger than 50 years of age.

The effect of estrogen *vs.* combined estrogen-progestogen therapy on the risk of colorectal cancer

Lin, K. J., Cheung, W. Y., Lai, J. Y.-C. and Giovannucci, E. L. (2012). The effect of estrogen *vs.* combined estrogen-progestogen therapy on the risk of colorectal cancer. Int. J. Cancer, 130: 419–430. doi: 10.1002/ijc.26026

Abstract

Studies suggest that estrogen therapy (ET) and combined estrogen-progestogen therapy (EPT) may have different associations with colorectal cancer (CRC) risk, but data are conflicting. Prior meta-analyses did not distinguish between ET and EPT. We conducted a meta-analysis to summarize the relative risks (RR) of CRC due to ET versus EPT among peri- or postmenopausal women. From a total of 2,661 articles, four randomized controlled trials, eight cohort and eight case-control studies were included. Variables assessed included study characteristics, duration and recency of menopausal hormone therapy (HT) use, method of assessment of HT use, outcome definition and its ascertainment method. RRs were synthesized by random-effects models. We found that EPT ever use was associated with a decreased risk of CRC (RR 0.74, 95% CI 0.68-0.81), and so was ET ever use (RR 0.79, 95% CI 0.69-0.91). While current use of ET was associated with a significantly reduced risk of CRC (RR 0.70, 95% CI 0.57-0.85), former use was not (RR 0.86, 95%CI 0.67-1.11). Recency did not significantly modify the association between EPT and CRC risk. EPT former use was associated with a lower RR of CRC compared to ET former use (p = 0.008) but no such difference was observed between EPT and ET current use (p = 0.12). Overall, we found consistent evidence supporting the association between EPT and CRC risk reduction, regardless of recency. While literature for the association between ET and CRC risk is heterogeneous, our analyses suggest only current use of ET is associated with a decreased CRC risk.

Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD000402. DOI: 10.1002/14651858.CD000402.pub4.

Abstract

Background: Reduced circulating estrogen levels around the time of the menopause can induce unacceptable symptoms that affect the health and well-being of women. Hormone therapy (both unopposed estrogen and estrogen/progestogen combinations) is an effective treatment for these symptoms, but is associated with risk of harms.

Guidelines recommend that hormone therapy be given at the lowest effective dose and treatment should be reviewed regularly. The aim of this review is to identify the minimum dose(s) of progestogen required to be added to estrogen so that the rate of endometrial hyperplasia is not increased compared to placebo.

Objectives: The objective of this review is to assess which hormone therapy regimens provide effective protection against the development of endometrial hyperplasia or carcinoma.

Search methods: We searched the Cochrane Menstrual Disorders and Subfertility Group trials register (searched January 2012), The Cochrane Library (Issue 1, 2012), MEDLINE (1966 to January 2012), EMBASE (1980 to January 2012), Current Contents (1993 to May 2008), Biological Abstracts (1969 to 2008), Social Sciences Index (1980 to May 2008), PsycINFO (1972 to January 2012) and CINAHL (1982 to May 2008). Attempts were made to identify trials from citation lists of reviews and studies retrieved, and drug companies were contacted for unpublished data.

Selection criteria: Randomised comparisons of unopposed estrogen therapy, combined continuous estrogen-progestogen therapy, sequential estrogen-progestogen therapy with each other or placebo, administered over a minimum period of 12 months. Incidence of endometrial hyperplasia/carcinoma assessed by a biopsy at the end of treatment was a required outcome. Data on adherence to therapy, rates of additional interventions, and withdrawals owing to adverse events were also extracted.

Data collection and analysis: In this update, 46 studies were included. Odds ratios (ORs) were calculated for dichotomous outcomes. The small numbers of studies in each comparison and the clinical heterogeneity precluded meta-analysis for many outcomes.

Main results: Unopposed estrogen is associated with increased risk of endometrial hyperplasia at all doses, and durations of therapy between one and three years. For women with a uterus the risk of endometrial hyperplasia with hormone therapy comprising low-dose estrogen continuously combined with a minimum of 1 mg norethisterone acetate (NETA) or 1.5 mg medroxyprogesterone acetate (MPA) is not significantly different from placebo at two years (1 mg NETA: OR 0.04; 95% confidence interval (CI) 0 to 2.8; 1.5 mg MPA: no hyperplasia events).

Authors'conclusions: Hormone therapy for postmenopausal women with an intact uterus should comprise both estrogen and progestogen to reduce the risk of endometria hyperplasia.

Bayesian Meta-analysis of Hormone Therapy and Mortality in Younger Postmenopausal Women

Shelley R. Salpeter, MD, Ji Cheng, MSc,c Lehana Thabane, PhD, Nicholas S. Buckley,Edwin E. Salpeter, PhD *The American Journal of Medicine* (2009) 122, 1016-1022

Abstract

Background: There is uncertainty over the risks and benefits of hormone therapy. We performed a Bayesian meta-analysis to evaluate the effect of hormone therapy on total mortality in younger postmenopausal women. This analysis synthesizes evidence from different sources, taking into account varying views on the issue.

Methods: A comprehensive search from 1966 through January 2008 identified randomized controlled trials of at least 6 month's duration that evaluated hormone therapy in women with mean age < 60 years and reported at least one death, and prospective observational cohort studies that evaluated the relative risk of mortality associated with hormone therapy after adjustment for confounding variables.

Results: The results were synthesized using a hierarchical random-effects Bayesian meta-analysis. The pooled results from 19 randomized trials, with 16,000 women (mean age 55 years) followed for 83,000 patient-years, showed a mortality relative risk of 0.73 (95% credible interval 0.52-0.96). When data from 8 observational studies were added to the analysis, the resultant relative risk was 0.72 (credible interval 0.62-0.82). The posterior probability that hormone therapy reduces total mortality in younger women is almost 1.

Conclusions: The synthesis of data using Bayesian meta-analysis indicates a reduction in mortality in younger postmenopausal women taking hormone therapy compared with no treatment. This finding should be interpreted taking into account the potential benefits and harms of hormone therapy.