BlueCross BlueShield of New Mexico

Medicare Part D News Update
Why is estrogen replacement therapy considered a potentially high risk medication?

Introduction: A basic tenet of recent efforts to reform healthcare is promoting improved quality of care and clinical outcomes while also decreasing overall healthcare costs. A popular strategy to accomplish these goals is to link positive patient care outcomes with increased reimbursement. The Centers for Medicare and Medicaid Services (CMS) is a major driver of this initiative and has developed a 5-Star Quality Ratings program for its Medicare Advantage and Part D programs. The quality rating system outlines quality rating metrics and corresponding bonus payments. The star rating program was developed as a result of the passage of the Patient Protection and Affordable Care Act in March 2010.

One of CMS' most heavily weighted pharmacy measures is the utilization of potentially high-risk medications (HRMs) in the elderly population. Beginning with the 2012 reports, CMS began utilizing the Pharmacy Quality Alliance (PQA) HRM list which was based on the 2012 American Geriatrics Society (AGS) updated BEERs criteria. In communicating to healthcare providers about the use of potentially inappropriate medications in the elderly we often receive feedback about the inclusion of estrogen replacement therapy on these HRM lists. So what is the identified risk of utilizing these medications in the elderly population and what data is it based on?

AGS BEERs Criteria recommendations: The updated 2012 BEERs Criteria current recommendation is to avoid the use of oral and topical patches in the elderly population due to evidence (high quality, strong recommendation) of a higher risk potential for both breast and endometrium cancer while lacking the benefit of a cardio-protective effect and/or cognitive protection in older women as once believed.

Position Statement – North American Menopause Society: In March of 2012 The North American Menopause Society released a position statement regarding the uses of hormone therapy. The position statement is designed to update the evidence-based position statement by the North American Menopause Society (NAMS) in 2010 on the recommendations for hormone therapy (HT) for postmenopausal women. The new 2012 position statement also addresses emerging differences in therapeutic benefit to risk ratio regarding estrogen therapy (ET) and combined estrogen-progestogen (EPT).[1]

An advisory panel of expert clinicians and researchers in the field of women's health were invited to review the 2010 NAMS position statement, evaluate new evidence, and reach consensus on recommendations. The updated recommendations were reviewed and approved by the NAMS Board of Trustees as an official NAMS position statement.[1]

Below is the information provided by the NAMS 2012 position statement regarding endometrial cancer, breast cancer, ovarian cancer, and duration of use. Information regarding osteoporosis, cardiovascular health, and other conditions can also be found in the 2012 position statement.

Unopposed systemic ET in postmenopausal women with an intact uterus is associated with an increase cancer risk related to the dose and duration of ET use. A meta-analysis summary report showed a RR of 2.3 (95% CI, 2.1-2.5) overall and a RR of 9.5 if used for more than 10 years.[2] To mitigate this risk the use of adequate concomitant progesterone is recommended for women with an intact uterus using systemic ET.

The potential risk of developing breast cancer increases with EPT use beyond 3 to 5 years.[3] According to the Women's Health Initiative (WHI) this risk, in absolute terms, is equal to eight additional breast cancers per 10,000 women who utilize EPT for 5 or more years. Studies have shown that EPT, and to a lesser extent, ET increases breast cell proliferation, breast pain, and mammographic density, and EPT may impede the diagnostic interpretation of mammograms therein delaying the diagnosis of breast cancer.[3,4] The WHI also showed that users of EPT had increased breast cancer mortality when followed for 11 years and had an HR of 2.75 for breast cancer when used for more than 5 years.[5,6] It is worth mentioning that

the WHI showed no increased risk of breast cancer when ET was used. The Million Women Study reported an increased risk in women initiating HT shortly after menopause.[7] However, the Nurse Health Study (NHS) showed an increased risk for breast cancer when ET was extended past 5 years.[8-10]

In the National Institutes of Health American Association of Retired Persons Diet and Health Cohort there was no elevated risk of ovarian cancer seen with less than 10 years of ET, but significantly increased risk was seen after 10 years of use.[11] In the WHI, EPT was not associated with statistically significant increase in ovarian cancer after a mean of 5.6 years.[12]

Long term follow-up data from the WHI have clarified the increased risk of breast cancer and endometrial cancer mortality with 4 to 5 years of EPT use at the time of menopause and a slightly later onset of breast cancer if a hiatus in estrogen exposure is used.[3,5] Regarding ET, there appears to be no increased risk of breast cancer with early postmenopausal use in the WHI or the NHS, and there was a decrease in breast cancer incidence when used after a hiatus in estrogen exposure in the WHI.[4,5] Long term use of ET (15-20 years in the NHS) can be expected to increase the risk of developing breast cancer, but to a lesser degree than EPT.[9]

This information is not intended to replace your clinical judgment. Only you, in direct consultation with your patient, may determine if drug therapy benefits outweigh the potential risks. If a change is warranted please advise your patient directly.

References:

1. North American Menopause Society. The 2012 hormone therapy position statement of: The North American Menopause Society. Menopause. 2012 Mar; 19(3):257-71. Doi: 10.1097/gme.0b013e31824b970a. PubMed PMID: 22367731
2. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol. 1995; 85:304–313. [PubMed: 7824251]
3. 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. [PubMed:12824205]
4. Stefanick ML, Anderson GL, Margolis KL, et al. for the WHI Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA. 2006; 295:1647–1657. [PubMed: 16609086]
5. Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA. 2010; 304:1684–1692. [PubMed: 20959578]
6. Prentice RL, Chlebowski RT, Stefanick ML, et al. Conjugated equine estrogens and breast cancer risk in the Women's Health Initiative Clinical Trial and Observational Study. Am J Epidemiol. 2008; 167:1407–1415. [PubMed: 18448442]
7. Beral V, Reeves G, Bull D, Green J, for the Million Women Study Collaborators. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. J Natl Cancer Inst. 2011; 103:296–305. [PubMed: 21278356]
8. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med. 1995; 332:1589–1593. [PubMed:7753136]
9. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol. 2000; 152:950–964. [PubMed:11092437]
10. Chen W, Manson J, Hankinson S, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. Arch Intern Med. 2006; 166:1027–1032. [PubMed: 16682578]
11. Lacey JV Jr, Brinton LA, Leitzmann, et al. Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study Cohort. J Natl Cancer Inst. 2006; 98:1397–1405. [PubMed: 17018786]
12. 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. [PubMed:14519708]