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This e-newsletter presents reviews of important, recently published scientific articles selected by The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women's health and quality of life through an understanding of menopause. Each has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Peter F. Schnatz, DO, Chair, 2009-2010 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Schnatz. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

Chronic fatigue syndrome and retrovirus XMRV

Lombardi VC, Ruscetti FW, Das Gupta J, et al. Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. *Science* 2009;326:585-589. **Level of evidence: III.**

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Chronic fatigue syndrome (CFS) is a debilitating disease of unknown etiology that is estimated to affect 17 million people worldwide. Studying peripheral blood mononuclear cells (PBMCs) from CFS patients, we identified DNA from a human gammaretrovirus, xenotropic murine leukemia virus-related virus (XMRV), in 68 of 101 patients (67%) compared to 8 of 218 (3.7%) healthy controls. Cell culture experiments revealed that patient-derived XMRV is infectious and that both cell-associated and cell-free transmission of the virus are possible. Secondary viral infections were established in uninfected primary lymphocytes and indicator cell lines following exposure to activated PBMCs, B cells, T cells, or plasma derived from CFS patients. These findings raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS.

Comment: Retroviruses are RNA viruses that replicate using DNA genes that have been inserted into the host cell genome. The infecting viral RNA is reverse transcribed to double strand DNA (termed the provirus), which is then incorporated into the host cell genome. After the viral code is included in the host cell genome, viral replication can proceed, or the viral genes can be silent for an extended period, and be activated at a later time in response to change in the internal cell milieu or to external signals received by the cell. There are several retroviruses known to be pathogens in humans (eg, human immunodeficiency virus, human T-lymphotropic virus [HTLV]-I) and an ever-growing list of retroviruses that have been identified in humans but which have not yet been associated with a specific disease (eg, HTLV-II, HTLV-IV). Retroviruses are associated with cancer and immune dysfunction in animals (eg, rous sarcoma virus, feline immunodeficiency virus). Retroviruses can also infect host germline cells (where they are termed endogenous retroviruses) with the provirus being passed to succeeding generations of the host. Endogenous retroviruses are common in mammals and birds, and have a long evolutionary history in humans, remnants of which comprise up to 8% of the human genome.

In a careful and thorough set of experiments, Lombardi et al demonstrate an association between a mouse retrovirus, XMRV, and a group of patients with CFS. The association of XMRV with CFS was statistically greater than with an uncharacterized control group. In the same issue of *Science*, Coffin and Stoye¹ discuss the propensity of xenotrophic murine retroviruses to contaminate human cell lines in the laboratory and concur with the evidence that contamination was unlikely to be an issue in the Lombardi study.

XMRV is not the first virus hypothesized to be the cause of CFS. Associations with several herpes viruses (Epstein-Barr virus, cytomegalovirus, herpesvirus 6), and retroviruses (HTLV-II) have been proposed and refuted.^{2,3} Similarly, XMRV in prostate cancer patients has been reported, but Hohn et al⁴ were unable to detect it in 589 German prostate cancer patients. Although the laboratory support for the author's conclusions is strong, a conspicuous omission from the paper is the absence of any clinical description of the patient or control populations. Without additional knowledge about how the patients and controls were selected, what definition of CFS was used, and how the patient and control specimens were collected and stored, the association between XMRV and CFS is speculative. Confirmation of this finding by an independent, blinded laboratory using carefully collected specimens from well-characterized populations of CFS patients and matched controls will be required to confirm or refute the relationship between XMRV and CFS.

Although XMRV has not been proved to be a cause of CFS, thousands of patients suffering from CFS may hope for treatment. Temptation might be great to embark on treatment trials, particularly because there are dozens of approved antiretroviral agents that have been developed for treating HIV/AIDS. Only after independent confirmation of the findings in this study should treatment trials be considered. Such trials will also require the development and validation of screening and confirmatory serologic tests, and quantifying virologic tests (such as a viral load)

to diagnose and track the infection. High-precision diagnostic tests for XMRV will be required, as the clinical diagnosis of CFS is controversial. Millions of individuals in the general population have symptoms that overlap with CFS. Even a test with 99.9% specificity (1 in 1,000 tests being false positive) would label thousands of patients with false-positive results if it were applied to such a population.

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2. DeFreitas E, Hilliard B, Cheney PR, et al. Retroviral sequences related to human T-lymphotropic virus type II in patients with chronic fatigue immune dysfunction syndrome. *Proc Natl Acad Sci USA* 1991;88:2922-2926.
3. Heneine W, Woods TC, Sinha SD, et al. Lack of evidence for infection with known human and animal retroviruses in patients with chronic fatigue syndrome. *Clin Infect Dis* 1994;18:S121-S125.
4. Hohn O, Krause H, Barbarotto P, et al. Lack of evidence for xenotropic murine leukemia virus-related virus (XMRV) in German prostate cancer patients. *Retrovirology* 2009;6:92.

Hearing decline and menopause

Hederstierna C, Hultcrantz M, Collins A, Rosenhall U. The menopause triggers hearing decline in healthy women. *Hear Res* 2009 Sep 23. [Epub ahead of print]
Level of evidence: II-2.

Study authors hypothesize that menopause triggers auditory deterioration, perhaps because of reduced levels of endogenous estrogens, which are known to protect the auditory system. Studies have shown that women have better high-frequency thresholds than men in all age groups, and decline in hearing related to aging starts after 30 years in men and after 50 years in women, coinciding with menopause for most women. In this trial, at an average interval of 7.5 years, 104 women with a mean age of 51.2 years at baseline were tested with pure tone audiometry twice. All women reported their age at the final menstrual period

(FMP). Researchers calculated hearing decline at individual frequencies. Women with an FMP 0-4 years previously had a rate of high-frequency hearing decline of 0.9-1.5dB/year in the left ear; women with an FMP 5-7 years previously had a rate of 1.1-1.5dB/year in the right ear; 8-13 years after the FMP, decline was 0.7-1.1dB/year in both ears. Researchers concluded that menopause appears to act as a trigger of a relatively rapid age-related hearing decline in healthy women, starting in the left ear.

Comment: As we manage women during menopause, it is easy to be caught up in narrow discussions about hormone therapy (HT). Hot flashes, breast issues, and cardiac issues get the most press, but a decline in estrogen levels affect many more tissues and organ systems. Quality of life is frequently linked to maintaining normal day-to-day function and the ability to interact with the world around us.

My introduction to the topic of declining estrogen levels and hearing loss was with an article from South Korea with 1,830 women.¹ Women with estrogen levels below 10 pg/ml had five times the hearing loss compared to those with levels over 30 pg/ml. They were unable to show a difference with HT, but only 3% of the women used some form of HT. The authors point out that 30% of patients over age 65 and 50% over age 75 suffer hearing loss.

Much of the research into estrogen and hearing loss has been done in mice. In mice, both estrogen-receptor alpha (ER- α) and estrogen-receptor beta (ER- β) have been found, but in specific locations within the inner ear. In the ER- β knockout mouse model, there is absence of hair cells, loss of the whole organ of Corti, and the spiral ganglion lacks many of its neurons. These changes mimic the changes seen with human age-related hearing loss. As expected, these mice were deaf at 1 year.² Several other studies have tried to demonstrate a relationship between bone density changes and hearing loss, suggesting a mechanical reason for presbycusis. With multivariate analysis, this relationship remains weak.

A recent prospective study of breast cancer patients undergoing chemotherapy demonstrated high-frequency hearing loss 6 months following therapy. The pattern of loss is similar to that seen in menopausal patients. The authors concluded that the most likely explanation for the loss is the reduction in serum estrogen levels due to chemotherapy.³

This current longitudinal study comes from one of the leading institutions in hearing research, the Karolinska Institute in Stockholm, Sweden. Hederstierna et al have been able to quantify the dramatic degree of hearing loss associated with the menopause. Losing a full decibel per year is greater than previous models and studies have suggested. The finding of the left-right difference is significant from a research standpoint, but I am unsure of the clinical relevance at this point.

Now that there are good data with the levels of serum estradiol associated with hearing loss, and a quantified degree of loss, the stage is set for a larger scale study to evaluate the effect of HT on hearing loss in the perimenopausal patient.

Although this may not be compelling enough data to encourage widespread use of HT to prevent hearing loss, it is an essential piece of information for clinicians.

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3. Kim SH, Kang BM, Chae HD, Kim CH. The association between serum estradiol level and hearing sensitivity in postmenopausal women. *Obstet Gynecol* 2002;99:726-730.

Bazedoxifene and the metabolic profile

Lobo RA, Pinkerton JV, Gass ML, et al. Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. *Fertil Steril* 2009;92:1025-1038.

Level of evidence: I.

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OBJECTIVE: To evaluate the effects of a tissue-selective estrogen complex (TSEC) composed of bazedoxifene/conjugated estrogens (BZA/CE) on menopausal symptoms, metabolic parameters, and overall safety. **DESIGN:** Multicenter, double-blind, placebo- and active-controlled phase 3 trial (Selective estrogens, Menopause, And Response to Therapy [SMART]-1). **SETTING:** Outpatient clinical. **PATIENT(S):** Healthy, postmenopausal women (n = 3,397) age 40 to 75 with an intact uterus. **INTERVENTION(S):** Single tablets of BZA (10, 20, or 40 mg), each with CE (0.625 or 0.45 mg); raloxifene 60 mg; or placebo taken daily for 2 years. **MAIN OUTCOME MEASURE(S):** Hot flashes, breast pain, vaginal atrophy, metabolic parameters, and adverse events. **RESULT(S):** BZA (20 mg)/CE (0.625 or 0.45 mg) significantly reduced the frequency and severity of hot flashes and improved measures of vaginal atrophy compared with placebo. At week 12, the daily number of hot flashes decreased by 51.7% to 85.7% with all BZA/CE doses vs. 17.1% for placebo. BZA/CE improved lipid parameters and homocysteine levels, did not significantly change carbohydrate metabolism, and had only minor effects on some coagulation parameters. The incidences of breast pain and adverse events were similar between BZA/CE and placebo. **CONCLUSION:** The TSEC composed of BZA (20 mg)/CE (0.625 or 0.45 mg) is an effective and safe treatment for menopausal symptoms.

Comment. The publication of the SMART-1 trial reminds us of the complexity of the ligand-estrogen receptor-gene interaction and the need for careful clinical evaluation of each new selective estrogen-receptor modulator (SERM).

In this case, a SERM, BZA, has been coupled with CE at doses of 0.45 mg or 0.625 mg/day. The actions of the TSEC, as the new combination is called, cannot be presumed to simply reflect the sum of the parts. Appropriately, several doses of BZA (10 mg, 20 mg, and 40 mg/d) combined with the two doses of CE were compared to placebo and raloxifene therapy. The results, as reported in this paper and several companion papers, illustrate the yin and yang of the varied doses and effects of the two compounds constituting the TSEC. As specified in the conclusions, the TSEC composed of BZA 20 mg with CE of 0.625 mg or 0.45 mg seemed to strike the right balance when hot flashes, vaginal atrophy, metabolic parameters, and adverse events were tallied.

The good news for recently postmenopausal women looking for symptom relief is that the combination of BZA/CE reduces both hot flashes and vaginal dryness with rates of breast tenderness and vaginal bleeding similar to that of placebo therapy.¹ Women with a uterus, particularly those who do not tolerate or wish to avoid progestogens, might prefer the TSEC combination.

A number of metabolic parameters changed favorably with BZA/CE. Lipid changes primarily reflect those anticipated with oral estrogen therapy (ET), as does the decline in homocysteine levels. Changes in coagulation parameters were consistent with those of raloxifene. Of note, neither fasting glucose nor fasting insulin changed as anticipated with oral estrogens. Neither did C-reactive protein levels increase, as in trials with oral ET.

How the metabolic changes described with TSEC therapy ultimately affect clinical outcomes is largely unknown at this time. Though no differences in adverse events were reported, the study was not designed to fully evaluate endpoints such as cardiovascular effects, cognitive change, or cancer incidence. (Each group contained ~425 women followed for 2 y). It will be interesting (and imperative)

to see in larger and longer trials the cumulative effects of this unique combination on the bone, the breast, the cardiovascular system, and the brain. Meanwhile, the TSEC concept provides a welcome new mode of “combination” therapy for symptomatic postmenopausal women with a uterus.

Note: BZA has not been tested with other estrogen formulations. Careful evaluation in clinical trials would be necessary to delineate effects. Similarly, the safety of concomitant use of raloxifene with systemic estrogens has not been established and its use is not recommended (raloxifene package insert).

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Reference:

1. Archer DF, Lewis V, Carr BR, et al. Bazedoxifene/conjugated estrogens (BZA/CE): incidence of uterine bleeding in postmenopausal women. *Fertil Steril* 2009; 92:1039-1044.

Uterine bleeding and bazedoxifene

Archer DF, Lewis V, Carr BR, Olivier S, Pickar JH. Bazedoxifene/conjugated estrogens (BZA/CE): incidence of uterine bleeding in postmenopausal women. *Fertil Steril* 2009;92:1039-1044. **Level of evidence: I.**

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OBJECTIVE: To evaluate the effect of bazedoxifene/conjugated estrogens (BZA/CE), a tissue selective estrogen complex, on uterine bleeding in postmenopausal women. **DESIGN:** International, multicenter, randomized, double-blind, placebo- and active-controlled, phase III study (Selective estrogen Menopause And Response to Therapy [SMART]-1). **SETTING:** Outpatient clinical. **PATIENT(S):** Healthy, postmenopausal women (N = 3,397) aged 40 to 75 years with an intact uterus. **INTERVENTION(S):** Daily oral therapy with

BZA 10, 20, or 40 mg, each with CE 0.625 or 0.45 mg, raloxifene 60 mg, or placebo. **MAIN OUTCOME MEASURE(S):** Cumulative amenorrhea profiles and the incidence of bleeding or spotting over 2 years. **RESULT(S):** Treatment with BZA 20 or 40 mg with CE 0.625 or 0.45 mg was associated with rates of cumulative amenorrhea (>83% during cycles 1-13 and >93% during cycles 10-13) and bleeding or spotting that were comparable to those with placebo. Subjects who received BZA 10 mg/CE 0.625 mg experienced slightly lower cumulative amenorrhea rates throughout the study compared with placebo-treated subjects. **CONCLUSION(S):** Postmenopausal women treated with BZA 20 or 40 mg with CE 0.625 or 0.45 mg had high rates of cumulative amenorrhea that were similar to those reported with placebo. This new menopausal therapy may offer a favorable bleeding and tolerability profile.

Comment: The SMART -1 trial was a 2-year double-blind, randomized, placebo-controlled study. This phase III clinical trial compared daily bazedoxifene (BZA; 10 mg, 20 mg, or 40 mg) combined with conjugated estrogens (CE, 0.45 or 0.625 mg) to daily raloxifene (60 mg) or placebo. All study participants took calcium (1,000-1,600 mg) daily. Eligible women were between ages 40 and 75 and postmenopausal for 1 or more years. The primary endpoint was the incidence of endometrial hyperplasia, and the secondary endpoint was the effect on bone mineral density (BMD). Groups assigned to BZA/CE doses of 40 mg/0.625 mg and 40 mg/0.45 mg, raloxifene 60 mg, or placebo, showed 0% incidence of endometrial hyperplasia at 2 years. BZA administered with CE has demonstrated a safe endometrial profile and is an acceptable alternative to progestogen for protecting the endometrium from estrogen stimulation. In this paper, the amenorrhea rate was similar to placebo, and BZA at 20 mg was the lowest effective dose for preventing endometrial hyperplasia.

BZA is a selective estrogen-receptor modulator that competitively inhibits binding of 17β-

estradiol to ER- α and ER- β . BZA demonstrates both agonist and antagonist properties. It is effective in the prevention and treatment of postmenopausal osteoporosis. Clinical studies have demonstrated estrogen-like prevention of bone loss in postmenopausal women without osteoporosis and reduction of vertebral fracture risk in postmenopausal women with osteoporosis. BZA has no agonist activity on endometrial cell proliferation, and the higher the dose, the greater the antagonist effect on the endometrium. However, BZA may increase the risk of deep vein thrombosis compared to placebo, as well as cardiovascular events.

Tissue-selective estrogen complex (TSEC) combines estrogens with one or more SERMs. The ideal TSEC will reduce menopausal symptoms (vasomotor symptoms and urogenital atrophy), increase BMD, but not increase risk for endometrial or breast cancer, breast pain, or uterine bleeding. BZA/CE is the first TSEC investigated, and more long-term studies for safety are ongoing.

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Editor's picks from November-December *Menopause*

NAMS spotlights the most recent issue of the Society's official journal, *Menopause*, selected by its Editor-in-Chief, Dr. Isaac Schiff.

Stewart JW, Alekel DL, Ritland LM, Van Loan M, Gertz E, Genschel U. Serum 25-hydroxyvitamin D is related to indicators of overall physical fitness in healthy postmenopausal women. *Menopause* 2009;16:1093-1101.

The purpose of this cross-sectional analysis was to examine the relationship between serum 25(OH)vitamin D, taking into account a variety of key factors and indicators of physical fitness in healthy postmenopausal women. Serum 25(OH)vitamin D was the common contributor to physical fitness indices (androidal fat mass, lean body mass, balance, hand grip strength) in healthy postmenopausal women.



Pinkerton JV, Archer DF, Utian WH, et al. Bazedoxifene effects on the reproductive tract in postmenopausal women at risk for osteoporosis. *Menopause* 2009;16:1102-1108.

Treatment with bazedoxifene for 2 years was associated with a favorable endometrial, ovarian, and breast safety profile in healthy, recently postmenopausal women at risk for osteoporosis.



Archer DF, Pinkerton JV, Utian WH, et al. Bazedoxifene, a selective estrogen receptor modulator: effects on the endometrium, ovaries, and breast from a randomized controlled trial in osteoporotic postmenopausal women. *Menopause* 2009;16:1109-1115.

Treatment with bazedoxifene for 3 years was associated with a favorable endometrial, ovarian, and breast safety profile in postmenopausal women with osteoporosis.



Pinkerton JV, Utian WH, Constantine GD, Olivier S, Pickar JH. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial. *Menopause* 2009;16:1116-1124.

Postmenopausal women aged 40 to 65 years with 7 or more moderate to severe hot flashes per day or 50 per week enrolled in a 12-week placebo controlled, double-blind hot flash efficacy trial. Bazedoxifene 20 mg paired with conjugated estrogens 0.45 or 0.625 mg was found to be

effective and safe in this trial for treating vasomotor symptoms.



Reed SD, Buist DSM, Anderson ML, et al. Short-term (1-2 mo) hormone therapy cessation before mammography. *Menopause* 2009;16:1125-1131.

In a randomized controlled trial of hormone therapy cessation 1 to 2 months before screening mammogram, nonparticipants were compared with participants. Nonparticipants were older, were less educated, and had lower body mass index; among estrogen and progestin therapy users, participants were more likely to have a first-degree relative with breast cancer.



Beutel ME, Glaesmer H, Decker O, Fischbeck S, Brahler E. Life satisfaction, distress, and resiliency across the life span of women. *Menopause* 2009;16:1132-1138.

Personal and social resources and the absence of anxiety and depression are of crucial importance for the maintenance of life satisfaction in aging women.



Blumel JE, Chedraui P, Baron G, for the Collaborative Group for Research of the Climacteric in Latin America (REDLINC). Sexual dysfunction in middle-aged women: a multicenter Latin American study using the Female Sexual Function Index. *Menopause* 2009;16:1139-1148.

This cross-sectional study analyzing data from 7,243 middle-aged Latin American women determined that the prevalence of sexual dysfunction was high and that decreased vaginal lubrication was the most important associated risk factor.

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 below.

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.
Level II-3	Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies).
Level III	Meta-analyses; reports from expert committees; descriptive studies and case reports.

NAMS IS HERE, THERE, AND EVERYWHERE

NAMS has been busy partnering with organizations that boast far-reaching audiences of either clinicians or consumers including Medscape, Penn State College of Medicine, and *MORE* Magazine. Additional collaborations are scheduled for the coming year!

Medscape

To date, NAMS has posted 12 interactive activities on Medscape.com, the most popular online destination for healthcare professionals. Some offer CME and some do not, discussing such topics as the benefits and risks of hormone therapy, counseling patients, coronary heart disease, and breast cancer. For more, go to www.menopause.org/MS.aspx.

EMPREss

“EMPREss: Enhancing Menopause management through understanding the Physiology of Receptors of Estrogen” is a CME collaboration between NAMS, Penn State Medical College, and Indicia Medical Education for concise information about SERMs through cases, journal and conference summaries, confidence-based learning, and an office poster. For more, go to www.menopause.org/empress.aspx.

MORE Magazine

NAMS has thus far posted two articles on MORE.com (which celebrates women 40+) on bioidentical hormones and sex around the time of menopause. Next month’s article is a postmenopause health quiz. Tell your patients! For more, go to [www.http://www.menopause.org/MORE.aspx](http://www.menopause.org/MORE.aspx)

And don’t forget to explore the redesigned NAMS Web site (www.menopause.org) for the latest scientific and Society news.

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