NAMS
THE NORTH AMERICAN MENOPAUSE SOCIETY

FIRST TO KNOW®

Released August 27, 2013

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 and healthy aging. Each review has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Chrisandra L. Shufelt, MD, MS, NCMP, Chair-elect of the 2012-2013 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Shufelt.

Hot flashes start in the brainstem

Research shows sequence and areas of brain activation during hot flashes

Diwadkar VA, Murphy ER, Freedman RR. Temporal sequencing of brain activations during naturally occurring thermoregulatory events. *Cereb Cortex.* June 19, 2013. [Epub ahead of print] **Level of evidence: III.**

Summary. Researchers conducted functional magnetic resonance imaging (fMRI) in a group of postmenopausal women to measure neuronal activity in the brainstem, insula, and prefrontal cortex around the onset of a hot flash. They found that brainstem activity increased before detection of onset of a hot flash, perhaps indicating the functional origins of hot flashes. Activations also occurred in the anterior cingulate cortex and the basal ganglia. Prefrontal and striatal brain activity may be associated with the phenomenological correlates of hot flashes.

Comment. Little is known about the neurophysiologic events underlying hot flashes, which affect more than 75% of midlife women.[1] The lack of a clear understanding comes in part from limitations in animal models of hot flashes.[2] Neuroimaging, however, has the potential to provide important new information on the mechanisms underlying hot flashes in women. These may also provide insights into new therapeutics and illuminate mechanisms linking hot flashes to adverse health outcomes.[3]

Strengths of this study include careful measurement of hot flashes using validated psychophysiologic methods and precise detection of the time course of individual hot flashes. Thermal blankets were used to initiate hot flashes, which were measured with monitors to ensure appropriate timing. Brain activation patterns were assessed in 20-second windows at three different times around baseline, preceding a hot flash, and during a hot flash. The focus on the period immediately preceding a hot flash was novel and provided new insights into the role of the brainstem, particularly the substantia nigra, in triggering hot flashes. Although it can be challenging to identify specific brainstem nuclei in fMRI studies, the involvement of the substantia nigra suggests that the neurotransmitter dopamine may be critical in triggering hot flashes. The insula and prefrontal cortex were active during the hot flash but not immediately preceding it, suggesting that these cortical regions are involved in experiencing hot flashes but not in triggering them.

It is surprising that hypothalamic activation was not detected before the hot flash, although it is challenging to detect in fMRI. A recent positron emission tomography study by Joffe and colleagues also implicated the insula and hypothalamus in hot flashes.[4] Glucose uptake, a

measure of neuronal activity, was lower in the hypothalamus and insula of women who had hot flashes after adjuvant endocrine therapies (eg, tamoxifen) than in women who did not have hot flashes. Notably, those alterations were related to CYP2D6 polymorphisms, which predict risk for tamoxifen-induced hot flashes.[5] Thus, neuroimaging studies have the potential to shed light on genetically linked neurobiologic traits that predispose certain women to hot flashes and on the time course of brain events underlying individual hot flashes.

Pauline M. Maki, PhD
Professor of Psychiatry and Psychology
Director, Women's Mental Health Research
Research Director, UIC Center for Research in Women and Gender
University of Illinois at Chicago
Chicago, IL

References
1. Kronenberg F. Hot flashes: epidemiology and physiology. *Ann N Y Acad Sci.* 1990;592:52-86; discussion 123-33.
2. Cosmi S, Pawlyk AC, Alfinito PD, Roman J, Zhou T, Deecher DC. Simultaneous telemetric monitoring of tail-skin and core body temperature in a rat model of thermoregulatory dysfunction. *J Neurosci Methods*. 2009;178(2):270-275.
3. Thurston RC, Joffe H. Vasomotor symptoms and menopause: findings from the Study of Women's Health across the Nation. *Obstet Gynecol Clin North Am.* 2011;38(3):489-501.
4. Joffe H, Deckersbach T, Lin NU, et al. Metabolic activity in the insular cortex and hypothalamus predicts hot flashes: an FDG-PET study. *J Clin Endocrinol Metab.* 2012;97(9):3207-3215.
5. Henry NL, Rae JM, Li L, et al. Association between CYP2D6 genotype and tamoxifen-induced hot flashes in a prospective cohort. *Breast Cancer Res Treat.* 2009;117(3):571-575.

Bone resorption varies during the menopause transition

SWAN study shows differences according to BMI and ethnicity

Sowers MR, Zheng H, Greendale GA, et al. Changes in bone resorption across the menopause transition: effects of reproductive hormones, body size, and ethnicity. *J Clin Endocrinol Metab*. 2013;98(7):2854-2863. **Level of evidence: II-3.**

Summary. Researchers examined how changes in bone resorption relate to the final menstrual period (FMP), reproductive hormones, body mass index (BMI), and ethnicity by measuring urinary type 1 collagen N-telopeptide (NTX), estradiol, and follicle-stimulating hormone levels annually for up to 8 years of the menopause transition in 918 women (classified as African American, Chinese, Japanese, or Caucasian). They found that urinary NTX began to increase sharply about 2 years before the FMP, peaking about 1 to 1.5 years after the FMP. From 2 to 6 years after the FMP, NTX levels declined but stayed about 20% higher than before menopause.

The magnitude of the increase in bone resorption was inversely associated with BMI. Ethnic differences in bone resorption changes were weakened but not wholly eliminated by adjusting for BMI. Thus, ethnic differences in BMI appear to account for much of the ethnic variation in bone loss during perimenopause.

Comment. Over the past 10 years, the Study of Women's Health Across the Nation (SWAN) has provided us with an astonishing number and variety of studies based on observation of 3,302 women transitioning from premenopausal to postmenopausal status. In the area of skeletal health, prior SWAN reports have described how falling serum estradiol levels signal an increase in bone turnover that, in turn, accelerates age-related bone loss. SWAN defines transmenopause as the period 1 to 2 years before 2 years after the FMP.

Quantitatively, these transmenopausal changes have been shown to be modest and brief—specifically, about a 30% increase in bone turnover, with a resulting increase in the annual rate of bone mineral density (BMD) loss of about 2%. SWAN has also shown us that over the long term, the median annual bone loss is approximately 1% (ie, a cumulative 11% in the spine and 9% in the hip).[1]

The current SWAN report assesses bone turnover in 918 women undergoing a natural menopause at a median age of 51.3 years. Data on these women were available for about 6 years before and 6 years after the FMP. During the 2- to 3-year transmenopausal period, the bump in bone turnover was greater among thinner women (BMI <25) than heavier women (BMI >30). However, these differences dissipated within a few years after the FMP. Additionally, differences in bone turnover among different ethnicities were largely explained by BMI.

Should these findings alter our management of women transitioning through menopause? The simple answer is no—for the following reasons:

1. The modest and self-limited changes in bone turnover and BMD should allay concerns about catastrophic bone loss occurring in otherwise healthy women transitioning through menopause.
2. Given the variability in bone turnover markers and BMD, small changes in bone turnover and BMD would be difficult to reliably detect in individual women.

Should these findings alter our perspective on preventing bone loss? I would like to tentatively say yes, for the following reasons:

1. To return a transitioning or postmenopausal woman's bone turnover to premenopausal levels requires only a modest antiresorptive drug effect.
2. When prevention of bone loss is appropriate, I suggest we avoid potent antiresorptive treatments that typically suppress bone turnover by 60% to 80% and instead consider those with milder effects, in the range of 30%. That would fit the profile of low-dose hormone therapy or selective estrogen-receptor modulators.
3. With accumulating evidence of harm (atypical femoral fractures) linked to excessive suppression of bone turnover, it would be prudent in the setting of prevention to seek physiologic restoration of premenopausal bone turnover rates.

Bruce Ettinger, MD, NCMP
Emeritus Clinical Professor of Medicine
University of California, San Francisco
San Francisco, CA

Reference

1. Greendale GA, Sowers M, Han W, et al. Bone mineral density loss in relation to the final menstrual period in a multiethnic cohort: results from the Study of Women's Health Across the Nation (SWAN). *J Bone Miner Res.* 2012;27(1):111-118.

Timing of weight gain and breast cancer risk

Gain before and around menopause associated with most breast cancer risk

Alsaker MDK, Janszky I, Opdahl S, Vatten LJ, Romundstad PR. Weight change in adulthood and risk of postmenopausal breast cancer: the HUNT study of Norway. *Br J Cancer.* July 23, 2013. [Epub ahead of print] **Level of evidence: II-3.**

Summary. Researchers studied weight changes and postmenopausal breast cancer risk in 28,153 Norwegian women over up to 30 years. They found that weight gain in adulthood was associated with increased breast cancer risk (hazard ratio [HR], per kg per y, 1.31; 95% confidence interval [CI], 1.11-1.54), as was weight gain before menopause (HR per kg per y, 1.38; 95% CI, 1.09-1.75), and weight gain around menopause (HR per keg per y, 1.69; 95% CI, 1.32-2.16). No clear risk associated with later weight gain (HR per kg per y, 0.92; 95% CI, 0.73-1.18). Researchers concluded that weight gain before and around menopause may be particularly important for breast cancer risk in post-menopausal women.

Comment. This observational study provides more insight into the relationship of post-menopausal obesity versus adult weight gain and the risk for postmenopausal breast cancer. Unlike other snapshot studies, this observation reports serial weight changes over 30 years. As with many observations in medicine, conflicting

and incomplete data are difficult for patients and physicians who counsel patients on possible modifiable lifestyle changes.

So what do we recommend to patients regarding modifiable lifestyle risk factors and breast cancer? The growing body of data suggests that maintaining a normal body mass index, moderating weekly alcohol consumption, and reducing postmenopausal body weight gain may help to reduce the incidence of breast cancer, but none of these variables has been subjected to testing in the gold-standard prospective randomized clinical trial. It is quite likely that randomized studies may help to eliminate bias from family history and other untested variables. Finally, although it seems likely that these suggestions would be helpful in reducing breast cancer recurrences in our 3 million US breast cancer survivors, randomized studies are lacking in this specific population, too.

We should remember that both the incidence and survival from breast cancer has improved since 2000, and this improvement is in large part attributed to reducing prolonged use of combined hormone replacement therapy. We owe thanks to the thousands of women who have participated in studies such as the Women's Health Initiative, Nurses' Health Study, and the Nord-Trondelag Health Study. Therefore, our most important recommendation is to participate in observational and randomized clinical studies which can provide new insight into new risk reduction strategies for breast cancer.

Elyse E. Lower, MD
Director, University of Cincinnati Cancer Institute
Comprehensive Breast Cancer Center
Director, Breast Medical Oncology
Professor of Hematology-Medical Oncology
University of Cincinnati
Cincinnati, Ohio

Improve your marriage in 30 minutes or less!

In a randomized trial, a very brief program reduced marital dissatisfaction

Finkel EJ, Slotter EB, Luchies LB, Walton GM, Gross JJ. A brief intervention to promote conflict reappraisal preserves marital quality over time. *Psychol Sci.* June 26, 2013. [Epub ahead of print]

Summary. Normatively, marital happiness decreases over time. Because depression is linked to marital discord and divorce rates hover near 50%, interventions that reduce marital dissatisfaction have clinical and public health merit. For this Internet-based, controlled study, investigators recruited a community-based convenience sample of 120 heterosexual married couples (mean age, 40; mean marriage length, 11 years). Participants were assessed for relationship satisfaction, love, intimacy, trust, passion, and commitment every 4 months for 2 years (7 waves of assessments). For waves 2 through 7, each spouse also provided "fact-based," behavior-focused summaries of their most significant disagreements and rated conflict-related distress.

At 12 months, the couples underwent randomization. The intervention was a 7-minute task in which the couples individually reappraised the conflicts they had just identified and wrote about them from the perspective of a neutral third party. They repeated the writing task during the next two assessments and were encouraged to apply these third-party perspectives during other disagreements. Midway between each subsequent wave, the intervention couples received email reminders of the task, and control couples received friendly email check-ins.

As predicted, marital quality deteriorated during the study. After year 1, however, the intervention group reported less conflict-related distress starting with the first reappraisal and no longer reported declining marital quality.

The lengths of the marriages did not moderate the findings.

Comment. A briefly sustained, prompted intervention may prevent progressive decline in marital quality. Additional fine-grained research is necessary to identify the characteristics of the couples most and least amenable to such interventions and to examine dosing, timing, duration, implementation, and mechanisms of action. Whether these interventions might actually preserve marriages and help clinical populations remains to be seen.

Joel Yager, MD
Professor, Department of Psychiatry
School of Medicine
University of Colorado
Emeritus Professor, Department of Psychiatry
University of New Mexico School of Medicine
Emeritus Professor, Department of Psychiatry
and Biobehavioral Sciences
David Geffen School of Medicine, UCLA
Los Angeles, CA

Originally published in Journal Watch Women's Health *at http://womens-health.jwatch.org/ July 24, 2013. Reprinted with permission.*

Menopause Editor's picks from August 2013

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

Impact of brisk walking on perceived health evaluated by a novel short questionnaire in sedentary and moderately obese postmenopausal women.
Sophie Garnier, PhD, Isabelle Gaubert, MSc, Sandra Joffroy, PhD, Gerard Auneau, PhD, and Pascale Mauriege, PhD.

♦

Significance of bladder trabeculation in postmenopausal women with severe pelvic organ prolapse: clinical and urodynamic assessments.
Ching-Chung Liang, MD, Yao-Lung Chang, MD, Yi-Hao Lin, MD, and Shuenn-Dhy Chang, MD..

♦

Aging, obesity, and multimorbidity in women 50 years or older: a population-based study.
Vanessa de S. Santos Machado, MD, MSc, Ana Lucia Ribeiro Valadares, MD, PhD, Lucia H. Costa-Paiva, MD, PhD, Maria J. Osis, PhD, Maria H. Sousa, PhD, and Aarão M. Pinto-Neto, MD, PhD.

5900 Landerbrook Drive, Suite 390 • Mayfield Heights, OH 44124 • USA
Tel 440/442-7550 • Fax 440/442-2660 • info@menopause.org • www.menopause.org

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.